Responses to Subpoena
"Roundup Products Liability Litigation -- Civil Action No. 3:16-MD-2741-VC"
Served on Roger O. McClellan on November 26, 2018

The Subpoena identified above was served on November 26, 2018 on Roger O. McClellan, Editor-in-Chief of Critical Reviews in Toxicology, an international journal published by Taylor and Francis. Attachment A to the Subpoena contains a section identified as "Documents and Things to be Produced" including a list of 19 items.

This document is a summary of the responses to the 19 items.

(1) All agreements and contracts between YOU and Monsanto

Response:

There are no past or current agreements or contracts between Roger O. McClellan and Monsanto.

(2) All invoices from You to Monsanto

Response:

There are no invoices from Roger O. McClellan to Monsanto.

(3) All communications and documents related to unrestricted research grants from Monsanto to You

Response:

There are no communications or documents related to unrestricted research grants from Monsanto to Roger O. McClellan

(4) All communications and documents related to unrestricted research grants from Monsanto to Critical Reviews in Toxicology

Response:

Roger O. McClellan is not aware of any communications or documents related to unrestricted research grants from Monsanto to Critical Reviews in Toxicology.

(5) All communications and documents related to peer-review reports for Monsanto-sponsored and/or authored manuscripts related to the potential adverse human health effects of GBFs, AMPA, ad/or surfactants for GBF's published in Critical Reviews in Toxicology during your tenure at the journal.

Response:

I have served as Editor-in-Chief of Critical Reviews in Toxicology since 1987 (see attached Biography). Most recently, Critical Reviews in Toxicology has been published by Taylor and Francis and earlier by Informa Healthcare, both a part of Informa UK Limited.

I have not searched issues of Critical Reviews in Toxicology published prior to 2013 to determine if any papers on GBFs, AMPA, and/or surfactants for GBFs were published in Critical Reviews in Toxicology prior to 2013.

From 2013 to the present time, 9 manuscripts, authored by Monsanto scientists and/or scientists funded directly or indirectly by Monsanto, have been published in Critical Reviews in Toxicology. The 9 papers and a Foreword to a Special Supplement are listed below and copies are provided with this response.

Kimmel, G.L., C.A. Kimmel, A.L. Williams and J.M. DeSesso (2013). Evaluation of Developmental Toxicity Studies of Glyphosate with Attention to Cardiovascular Development. Crit. Rev. in Toxicology 43(2): 79-95.

Kier, L.D. and D.I. Kirkland (2013). Review of Genotoxicity Studies of Glyphosate and Glyphosate-Based Formulations. Crit. Rev. in Toxicology 43(4): 283-315.

Greim, H., D. Saltmiras, V. Mostert and C. Strupp (2015) Evaluation of the Carcinogenic Potential of the Herbicide Glyphosate Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies. Crit. Rev. in Toxicol 45(3): 185-208.

Kier, L.D. (2015). Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations. Crit. Rev. Toxicol. 45(3): 209-218.

McClellan, Roger O. (2016). Foreword: Evaluating the Potential Carcinogenic Hazard of Glyphosate. Crit. Rev. Toxicol. 46(S1): 1-2. [Prepared independently in Roger O. McClellan's role as Editor-in-Chief of Critical Reviews in Toxicology]

Williams, Gary, Marilyn Aardena, John Acquavella, Sir Colin Berry, David Brusick and Michele M. Burns (2016). A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels & Comparison to IARC Assessment. Crit. Rev. Toxicol. 46(S1): 3-20.

Solomon, Keith R. (2016). Glyphosate in the General Population and in Applications: A Critical Review of Studies on Exposures. Crit. Rev. Toxicol. 46(S1): 21-27.

Acquavella, John, David Garabrant, Gary Marsh, Tom Sorahan and Douglas L. Weed. (2016). Glyphosate Epidemiology Expert Panel Review: A Weight of Evidence Systematic Review of the Relationship Between Glyphosate Exposure and Non-Hodgkin's Lymphoma or Multiple Myeloma. Crit. Rev. Toxicol. 46(S1): 28-43.

Williams, Gary, Colin Berry, Michele Burns, Joao LauroViana de Camargo and Helmut Greim. (2016). Glyphosate Rodent Carcinogenicity Bioassay Expert Panel Review. Crit. Rev. Toxicol. 46(S1): 44-55.

Brusick, David, Marilyn Aardema, Larry Kier, David Kirkland and Gary Williams. (2016). Genotoxicity Expert Panel Review: Weight of Evidence Evaluation of the Genotoxicity of Glyphosate, Glyphosate-Based Formulations, and Aminomethylphosphonic Acid. Crit. Rev. Toxicol. 46(S1): 56-74.

All of these manuscripts, excluding my Foreword to the Supplement, were submitted to Critical Reviews in the same manner as the 100 or so manuscripts received by the journal each year. The entry point for manuscripts is an electronic manuscript management review system [Manuscript Central/Scholar One] provided by the publisher. The system may be accessed at https://mc.manuscriptcentral.com/btxc.

This electronic system has provision for:

(1) authors to submit manuscripts in an electronic format,
(2) the Editor to identify potential reviewers and solicit review comments,
(3) reviewers to return comments to the Editor,
(4) the Editor to send review comments (blind as to identity) to the author(s),
(5) the author to return revised manuscript to the Editor,
(6) the Editor to make a decision on the revised manuscript (accept, further revisions or reject),
(7) the Editor to advise author of the editorial decision, and
(8) the Editor to forward accepted manuscripts to the publisher.

The integrity of the manuscript management and review system and its successful use is dependent upon all parties recognizing the confidential nature of the communications between authors, Editor, reviewers and the publisher.

The following material taken from the Manuscript Central/Scholar One instructions to reviewers illustrates the emphasis given to ensuring confidentiality.

"Agreeing to review an article for this Journal implies that you as the reviewer will adhere to the accepted ethical standards of scientific, medical and academic publishing.

Material submitted for peer review is a privileged communication that should be treated in confidence. Material under review should not be shared or discussed with anyone outside the designated review process, unless approved by the editor. All communications relating to the paper in review should also be treated in confidence. Any breach of confidentiality in the review process is taken seriously by the journal and will be investigated according to the advice of COPE (http://publicationethics.org). Any conflict of interest, suspicion of duplicate publication, fabrication of data, plagiarism or other ethical concerns must immediately be reported to the Editor. By agreeing to review this manuscript, you are stating that you are the person completing this review. If you wish to collaborate with a colleague and/or trainee to perform this review, or wish to assign this review to a trainee for completion under your guidance, please contact the Editor for permission before sharing the manuscript. If the Editor agrees please provide the name, affiliation and e-mail address for the trainee/colleague so he or she may be assigned as a reviewer directly. If you have any conflict of interest (for example, collaborate with the author(s) or are currently working on a similar study), please decline to review this manuscript and, if possible, suggest appropriate alternate reviewers."

The publisher uses a second electronic system to manage the production and publication of the accepted manuscripts; that system operated by Taylor and Francis is called the Central Article Tracking System (CATS).

(14) All communications with any of the authors of Williams, et al., *A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels and Comparison to the IARC Assessment* 46 Crit. Rev. Toxicol. 3-20 (2016), including all communications with any of the authors of the four companion papers by the Intertek Expert Panel, related to GBs, AMPA, and/or surfactants for GBFs.

Response:

As noted above, the primary communications between authors and the Editor are initially conducted electronically using the Manuscript Central/Scholar One system provided by the publisher, Taylor and Francis. After critical review and acceptance by the Editor-in-Chief , the accepted manuscripts are electronically transferred to the Central Article Tracking System (CATS) operated by Taylor and Francis. The CATS system is used for processing of the accepted manuscripts, including production of galley proofs for review and approval by the authors before proceeding to on-line publication. CATS is maintained and used by Taylor and Francis to publish the approximate 2600 journals in its portfolio.

As Editor-in-Chief, I do not maintain files to duplicate the CATS system.

BIOGRAPHY -- 2018

ROGER O. McCLELLAN, DVM, MMS, DSc (Honorary),
Dipl-ABT and ABVT;
Fellow-ATS, SRA, HPS, AAAR, IARA, ATS and AAAS
Member – National Academy of Medicine
Advisor: Inhalation Toxicology and Human Health Risk Analysis
13701 Quaking Aspen NE Albuquerque, NM 87111-7168, USA
Tel: [redacted] Fax: [redacted]
e-mail: roger.o.mcclellan[redacted]

ROGER O. McCLELLAN serves as an advisor to public and private organizations on issues of air quality in the ambient environment and work place using his expertise in inhalation toxicology, comparative medicine, aerosol science and human health risk analysis. He received his Doctor of Veterinary Medicine degree with Highest Honors from Washington State University in 1960 and a Master of Management Science degree from the University of New Mexico in 1980. He is a Diplomate of the American Board of Toxicology and the American Board of Veterinary Toxicology and a Fellow of the Academy of Toxicological Sciences.

He served as Chief Executive Officer and President of the Chemical Industry Institute of Toxicology (CIIT) in Research Triangle Park, NC from September 1988 through July 1999. During his tenure, the organization achieved international recognition for the development of scientific information under-girding important environmental and occupational health decisions and regulations. Prior to his appointment as President of CIIT, Dr. McClellan was Director of the Inhalation Toxicology Research Institute, and President and Chief Executive Officer of the Lovelace Biomedical and Environmental Research Institute, Albuquerque, New Mexico. The Institute continues operation today as a core element of the Lovelace Respiratory Research Institute. During his 22 years with the Lovelace organization, he provided leadership for development of one of the world's leading research programs concerned with the health effects of airborne radioactive and chemical materials. Prior to joining the Lovelace organization, he was a scientist with the Division of Biology and Medicine, U.S. Atomic Energy Commission, Washington, DC (1965-1966), and Hanford Laboratories, General Electric Company, Richland, WA (1957-1964). In these assignments, he conducted and managed research directed toward understanding the human health risks of internally deposited radionuclides.

Dr. McClellan is an internationally recognized authority in the fields of inhalation toxicology, aerosol science, comparative medicine, and human health risk analysis. He has authored or co-authored over 400 scientific papers and reports and edited 10 books. In addition, he frequently speaks on risk assessment and air pollution issues in the United States and abroad. He is active in the affairs of a number of professional organizations, including past service as President of the Society of Toxicology and the American Association for Aerosol Research. He serves in an editorial role for a number of journals, including service since 1987 as Editor of Critical Reviews in Toxicology. He serves or has served on the Adjunct Faculty of 8 universities.

Dr. McClellan has served in an advisory role to numerous public and private organizations. He has served on senior advisory committees for eight major federal agencies concerned with human health. This included service as Chairman of the Clean Air Scientific Advisory Committee, Environmental Health Committee, Research Strategies Advisory Committee, and Member of the Executive Committee, Science Advisory Board, U. S. Environmental Protection Agency; Member for 30 years, National Council on Radiation Protection and Measurements; Member, Advisory Council for Center for Risk Management, Resources for the Future; a former Member, Health Research Committee, Health Effects Institute; and service on National Academy of Sciences/National Research Council Committee on Toxicology (served as Chairman for 7 years), Risk Assessment for Hazardous Air Pollutants, Health Risks of Exposure to Radon, Research Priorities for Airborne Particulate Matter, as well as the Committee on Environmental Justice of the Institute of Medicine. He has served on the Board of Scientific Councilors for the Center for Environmental Health Research of the Centers for Disease Control and Prevention and the Agency for Toxic Substances and Disease Registry and on the National Institutes of Health Scientific Advisory Committee on Alternative Toxicological Methods. He served on the National Aeronautics and Space Administration Lunar Airborne Dust Toxicity Advisory Group.

Dr. McClellan's contributions have been recognized by receipt of a number of honors, including election in 1990 to membership in the National Academy of Medicine. He is a Fellow of the Society for Risk Analysis, the American Association for Aerosol Research, the Health Physics Society, the International Aerosol Research Assembly, and the American Association for the Advancement of Science and American Thoracic Society Fellow. In 1985, he received the American Conference of Governmental industrial hygienist Herbert Stokinger Award for pioneering research on the health effects of exposure to diesel engine exhaust. In 1997, he received the Thomas T. Mercer Prize for research on inhalable materials from the International Society for Aerosols in Medicine and the American Association for Aerosol Research. In 1998, he received the International Achievement Award of the International Society of Regulatory Toxicology and Pharmacology for outstanding contributions to improving the science used for decision making on chemical safety and the International Aerosol Fellow Award of the International Aerosol Research Assembly for outstanding contributions to aerosol science and technology. In 2002, he was inducted into the University of New Mexico Anderson School of Management Hall of Fame for contributions to the effective management of multi-disciplinary research organizations. He received the Society of Toxicology Arnold J. Lehman Award in 1992 for contributions to chemical safety, the Society's Merit Award in 2003 for a distinguished career in toxicology, the Society's Founders Award in 2009 for contributions to science-based safety/risk decision-making and the Society's Distinguished Toxicology Scholar Award in 2018 for contributions to understanding the toxicity of inhaled radionuclides. In 2012, he received a career achievement award from the International Dose-Response Society and the American Association for Aerosol Research. and in 2014 from the Academy of Toxicological Sciences. In 2016, he received the American Veterinary Medical Association Meritorious Service Award for public service. In 2018, he was designated as an American Thoracic Society Fellow. In 2005, The Ohio State University awarded him an Honorary Doctor of Science degree for his contributions to comparative medicine and the science under-girding improved air quality. In 2006, he received the New Mexico Distinguished Public Service Award. In 2008, Washington State University presented Dr. McClellan the Regents Distinguished Alumnus Award, the highest recognition the University can bestow on an Alumnus.

Dr. McClellan has a long-standing interest in environmental and occupational health issues, especially those involving risk assessment and air quality and in the management of multidisciplinary research organizations. He is a strong advocate of science-based decision-making and the need to integrate data from epidemiological, controlled clinical, laboratory animal and cell studies to assess human health risks of exposure to toxic materials and to inform policy makers in developing standards and guidance to protect public health. He is internationally recognized for his knowledge of the health issues associated with a range of energy technologies, including nuclear power, coal combustion, oil/gas extraction and internal combustion engines, including the transition from traditional to clean diesel technology.

Critical Reviews in Toxicology

http://informahealthcare.com/txc
ISSN: 1040-8444 (print), 1547-6898 (electronic)

Crit Rev Toxicol, 2013; 43(2): 79–95
© 2013 Informa Healthcare USA, Inc. DOI: 10.3109/10408444.2012.749834

informa
healthcare

REVIEW ARTICLE

Evaluation of developmental toxicity studies of glyphosate with attention to cardiovascular development

Gary L. Kimmel[1], Carole A. Kimmel[1], Amy L. Williams[1], and John M. DeSesso[1,2]

[1]*Exponent Inc, Alexandria, VA, and* [2]*Georgetown University School of Medicine, Washington, DC, USA*

Abstract

The herbicide glyphosate has undergone multiple safety tests for developmental toxicity in rats and rabbits. The European Commission's 2002 review of available glyphosate data discusses specific heart defects observed in several individual rabbit developmental toxicity studies, but describes the evidence for a potential causal relationship as equivocal. The present assessment was undertaken to analyze the current body of information generated from seven unpublished rabbit studies in order to determine if glyphosate poses a risk for cardiovascular malformations. In addition, the results of six unpublished developmental toxicity studies in rats were considered. Five of the seven rabbit studies (dose range: 10–500 mg/kg/day) were GLP- and testing guideline-compliant for the era in which the studies were performed; a sixth study predated testing and GLP guidelines, but generally adhered to these principles. The seventh study was judged inadequate. In each of the adequate studies, offspring effects occurred only at doses that also caused maternal toxicity. An integrated evaluation of the six adequate studies, using conservative assumptions, demonstrated that neither the overall malformation rate nor the incidence of cardiovascular malformations increased with dose up to the point where severe maternal toxicity was observed (generally ≥150 mg/kg/day). Random occurrences of cardiovascular malformations were observed across all dose groups (including controls) and did not exhibit a dose–response relationship. In the six rat studies (dose range: 30–3500 mg/kg/day), a low incidence of sporadic cardiovascular malformations was reported that was clearly not related to treatment. In summary, assessment of the entire body of the developmental toxicity data reviewed fails to support a potential risk for increased cardiovascular defects as a result of glyphosate exposure during pregnancy.

Keywords

Cardiac, heart, interventricular septal defect, rabbit, rat

History

Received 22 June 2012
Revised 12 November 2012
Accepted 12 November 2012
Published online 31 December 2012

Introduction

Glyphosate, the active ingredient in popular herbicide formulations such as Roundup, AquaMaster and Vision branded products, is the most commonly used herbicide in the US (Grube, 2011). Specific usage statistics are not readily available for Europe, but are assumed to mirror those of the US. Glyphosate acts by targeting the enzyme enolpyruvylshikamate phosphate synthase in plants (Williams et al., 2012). Although this enzyme is important in the synthesis of several essential amino acids in plants, it is not found in animals. For this reason, glyphosate is considered to be generally safe to people and other mammals when used according to the manufacturer's instructions. Nevertheless, due to its widespread use and the large number of glyphosate manufacturers, glyphosate has been subjected to numerous safety tests to protect health. In a monograph developed to support the European Commission's 2002 review of glyphosate (BBA, 1998–2000; European Commission, 2002), the authors discuss specific heart defects observed in individual rabbit developmental toxicity studies of glyphosate, however they describe the evidence for a potential causal relationship as equivocal. Based on data selected from these studies, others have alleged there is evidence of teratogenicity and have called for a new risk assessment of glyphosate (Antoniou et al., 2012).

The present critical analysis assesses the glyphosate developmental toxicity database available to European regulatory agencies in order to determine if there is, in fact, a cause for concern for cardiovascular defects or other malformations. Rabbit and rat developmental toxicity studies on glyphosate conducted by member companies of the European Union (EU) Glyphosate Task Force were made available to the authors of this paper for the purpose of this analysis. These included seven developmental toxicity studies conducted in rabbits as well as six developmental toxicity studies conducted in rats. A PubMed search of the peer-reviewed literature through May 2012 was also conducted in an attempt to identify other studies of developmental glyphosate exposure and heart/cardiovascular malformations. No studies were

Address for correspondence: John M. DeSesso, Ph.D., Exponent Inc, 1800 Diagonal Road, Suite 500, Alexandria, VA 22314, USA. Tel: 571-227-7261. E-mail: jdesesso@exponent.com

found to be focused on cardiovascular defects as a result of *in utero* glyphosate treatment. A few published studies examined the effects on the fetal development of *in utero* exposure to glyphosate-based herbicide formulations (Dallegrave et al., 2003, 2007; Daruich et al., 2001); none of these studies, however, addressed visceral malformations. Therefore, the focus of the present analysis is on developmental toxicity studies of glyphosate that were conducted to fulfill regulatory requirements, particularly those in the rabbit. Each of the seven rabbit developmental toxicity studies has been critically evaluated with attention to whether the database as a whole is of sufficient quality to determine glyphosate's teratogenic potential in rabbits, particularly for the cardiovascular system. Details of these analyses are found in the Appendix. The findings from six rat developmental toxicity studies conducted with glyphosate for regulatory purposes are also addressed, paying particular attention to heart and cardiovascular defects. Finally, the rabbit and rat data are briefly discussed in the context of the available epidemiological data for glyphosate.

Rabbit developmental toxicity database

A total of seven developmental toxicity studies of glyphosate have been conducted in the rabbit, the designs of which are summarized in Table 1. These studies, which are critically evaluated in the Appendix, involved testing in three different rabbit strains (New Zealand white, Japanese white and Dutch belted) and covered a wide range of glyphosate doses, from 10 to 500 mg/kg/day. This range includes doses that caused overt maternal toxicity (150 mg/kg/day and above); in some cases, the maternal toxicity observed was substantial. Two of these studies (Suresh, 1993; Tasker, 1980a) had insufficient numbers of fetuses available for assessment at the high dose (500 and 350 mg/kg/day, respectively).

The seven rabbit developmental toxicity studies vary considerably in their quality: the numbers of animals per dose group, the spacing of doses, the extent of documentation and detail provided and the specific types of data reported. Five of the studies stated that they followed good laboratory practices (GLP) specific to the time period in which they were conducted (Brooker et al., 1991a; Coles and Doleman, 1996; Hojo, 1995; Moxon, 1996; Suresh, 1993). Another study was conducted prior to the establishment of GLP requirements, but appears to have generally adhered to GLP principles (Tasker et al., 1980a). In the seventh study (Bhide & Patil, 1989), it is not clear to what extent GLP practices were followed, but it is unlikely that this study was fully GLP-compliant because the description of study results is extremely limited and inappropriate animals appear to have been included in the calculations for certain endpoints. All these studies were conducted according to developmental toxicity testing guideline requirements current at the time they were initiated and provided quality assurance audits.

As these studies were all done in different laboratories, there is considerable disparity across studies in the classification of various anomalies as major malformations, minor malformations or variations and in the terminology used to describe these findings. Further, three of the studies (Bhide & Patil, 1989; Hojo, 1995; Suresh, 1993) did not report anomalies by individual fetus. Therefore, for these studies, it is not possible to determine whether certain fetuses showed multiple anomalies or if anomalies occurred in combination. The study by Suresh (1993) also used some terminology that is not standard for heart defects in developmental toxicity studies (e.g. seal-shaped heart, dilated heart), which makes interpretation of the findings difficult. Certain cardiovascular changes reported in the Brooker et al. (1991a) study (e.g. retroesophageal right subclavian artery) are considered variations in other laboratories (Appendix), these are discussed in more detail below. Because of inappropriate methods and the poor reporting of data, the Bhide & Patil (1989) study was considered inadequate for assessing glyphosate's potential for developmental toxicity in rabbits. The remaining six rabbit studies formed the basis for our analysis. While the individual studies may fall short of current guidelines (mainly because the desired number of rabbits per group has increased and the exposure period has been extended beyond GD18), these shortcomings are overcome when one considers the overall database. More specifically, the exposure period in each of these studies extends well before and after the period of organogenesis for the cardiovascular system. Additionally, the studies cover a broad and well-distributed range of 15 different glyphosate exposures ranging from 10 to 500 mg/kg/day. Finally, the combined database from these studies includes evaluation of 347 total litters (99 controls and 247 treated) and 2990 fetuses (834 controls and 2156 treated). Based on these elements, the overall database of six adequate rabbit developmental studies is considered to be robust for the purposes of risk assessment.

To address whether the six adequate studies exhibited evidence of selective offspring sensitivity to glyphosate

Table 1. Maternal and developmental NOAELs from six sufficient rabbit developmental toxicity studies of glyphosate.

Study	No. of animals per group	Exposure period	Doses (mg/kg/day)	Maternal NOAEL (mg/kg/day)	Offspring NOAEL (mg/kg/day)
Moxon (1995)	20	GD 7–19†	0, 100, 175, 300	100	175
Coles & Doleman (1996)	18	GD 7–19	0, 50, 200, 400	200	>400
Brooker et al. (1991a)	16–20	GD 7–19	0, 50, 150, 450	50	150
Hojo (1995)	18	GD 7–19†	0, 10, 100, 300	100	>300
Tasker et al. (1980a)	16–17	GD 6–27	0, 75, 175, 350	75	>175
Suresh (1993)	15–26	GD 6–18	0, 20, 100, 500	100	>100
Bhide & Patil (1989)	15	GD 6–18	0, 125, 250, 500	–‡	–‡

†Moxon (1995) designated the day of insemination as GD 1 and Hojo (1995) designated the day after insemination as GD 0. The exposure periods here have been adjusted to be comparable to the other studies which used GD 0 as the day of insemination.
‡Due to significant limitations in study design and data reporting, this study was considered inadequate for determining NOAELs.

treatment *in utero*, the no observed adverse effect levels (NOAELs) for maternal toxicity and developmental effects were determined (Table 1). Maternal toxicity was most commonly evidenced in the rabbit studies by diarrhea and reduced food intake, which generally occurred at doses of 150 mg/kg/day or higher. Additionally, maternal weight loss and deaths generally occurred at the highest doses. Table 1 also shows that offspring effects due to glyphosate, when observed in a particular rabbit developmental toxicity study, always occurred at the same dose or doses as those associated with maternal toxicity. This does not mean that injury to the fetus necessarily occurred as a direct result of maternal toxicity, but rather, when exposures to glyphosate were kept below the doses that cause maternal toxicity, the developing offspring did not exhibit any adverse effects. Therefore, selective offspring sensitivity to glyphosate is not apparent from these studies.

Post-implantation loss was quite variable across studies. Four of the six adequate studies (Hojo, 1995; Moxon, 1996; Suresh, 1993; Tasker, 1980a) reported no statistically significant increase in post-implantation loss in three different strains of rabbits at exposure levels as high as 500 mg/kg/day. In comparison, Coles & Doleman (1996) reported an increase in post-implantation loss at 200 mg/kg/day, but not at 400 mg/kg/day; consequently, a dose–response pattern was not established in this study. Brooker et al. (1991a) reported increased post-implantation loss at doses of 50 mg/kg/day and above (mean = 19.5 ± 19.8%, 15.3 ± 17.2% and 21.0 ± 11.8% for the 50, 150 and 450 mg/kg/day dose groups, respectively), but noted that post-implantation loss in the concurrent control group (5.7 ± 7.2%) was lower than in historical controls (mean: 12.9%; range: 6.5–17.5%), while post-implantation loss in treated litters was within or slightly higher than the historical control range. Post-implantation loss has a high degree of variability as demonstrated by the standard deviations around this endpoint in the six studies reviewed. This variability is common in the rabbit. Other historical control databases have reported mean percent post-implantation loss in the rabbit of 8.1% (range: 2.8–17.7%) and 9.1% (range: 0.6–23.4%) (Holson et al., 2006 and MARTA, 1997, respectively). Consequently, without a clear dose–response pattern established across the six studies reviewed, it is unlikely that these findings are biologically significant.

As previously noted, the rabbit developmental toxicity data for glyphosate have been previously described as equivocal with regard to cardiovascular defects (BBA, 1998–2000; European Commission, 2002). To address this issue, data were extracted from each study for malformations and variations (Appendix). Two of the studies (Brooker et al., 1991a; Suresh, 1993) suggested a possible association of cardiovascular anomalies with treatment, but the data were not clear-cut; these are discussed in more detail in the Appendix. In addition, two studies (Hojo, 1995; Moxon, 1996) reported an increase in skeletal defects at the high dose of 300 mg/kg/day. These anomalies appeared to be the result of reduced ossification, which is likely related to delayed development (evidenced by reduced fetal body weights observed at the high dose), or were not clearly dose-related. Based on this information and our evaluation of the combined data, we concluded that glyphosate treatment was not associated with an increase in malformations in rabbits. The remaining discussion focuses on cardiovascular defects only.

Examination of the data from the six rabbit studies showed a variety of malformations of the heart and great vessels. These included: dilated aorta/narrow pulmonary artery; narrow aorta/dilated pulmonary artery; hypoplasia of the pulmonary artery; interventricular (IV) septal defect; cardiomegaly; single ventricle, thickened ventricle walls; dilated ventricle; retro-esophageal right subclavian artery; interrupted aorta; right subclavian artery arising from aortic arch; "seal-shaped" heart. If glyphosate treatment was associated with congenital heart defects and malformation of the great vessels in rabbits, then the prevalence of these defects would be anticipated to increase with dose and the overall malformation rate would also be anticipated to increase. However, as can be seen from the malformation incidence tables in the Appendix, cardiovascular malformations generally occurred in the rabbit studies at a low incidence across all dose groups. Further, in most studies, they did not exhibit a positive dose–response, and oftentimes, clusters of malformations occurred in the same fetuses.

In order to further discern whether there might be an association between exposure of rabbits to glyphosate and cardiovascular malformations, the following conservative assumptions were made so that the malformation data from the six adequate studies could be combined. First, all three rabbit strains (Japanese white, New Zealand white and Dutch belted) were assumed to be equally sensitive to glyphosate. Second, small differences in treatment duration across studies were assumed not to affect the incidence of cardiovascular malformations because all treatment paradigms covered the critical period of heart and great vessel development (i.e. GD 8–17; DeSesso, 2012). Third, cardiovascular malformations were categorized depending on the type of cardiovascular defect and what is known about the underlying morphogenetic processes. For instance, several defects are related to development of the aorticopulmonary septum and are grouped together. As an example, Brooker et al. (1991a) reported that many fetuses with IV septal defects exhibited other cardiovascular defects that included enlarged aorta/stenotic pulmonary artery or the converse (stenotic aorta/enlarged pulmonary artery). During formation of the outflow tract from the ventricles, neural crest cells migrate from the hindbrain region into the truncus arteriosus where they contribute to and direct the growth of the aorticopulmonary septum (Hutson & Kirby, 2003; Kirby et al., 1983; Sadler, 2011). The aorticopulmonary (spiral) septum (Figure 1) grows as a pair of ridges that divide the truncus arteriosus into equally sized halves: the aorta and the pulmonary artery (DeSesso & Venkat, 2010). At its inferior end, the aorticopulmonary septum forms the upper portion (membranous portion) of the IV septum. Consequently, malformations relating to a disproportionately sized aorta and pulmonary septum, as well as IV septal defects of the upper region, are all related to displacement of the developing aorticopulmonary septum (DeSesso & Venkat, 2010).

Based on this information, those cardiac defects that involved perturbations of aorticopulmonary septum development were combined based on the premise that glyphosate

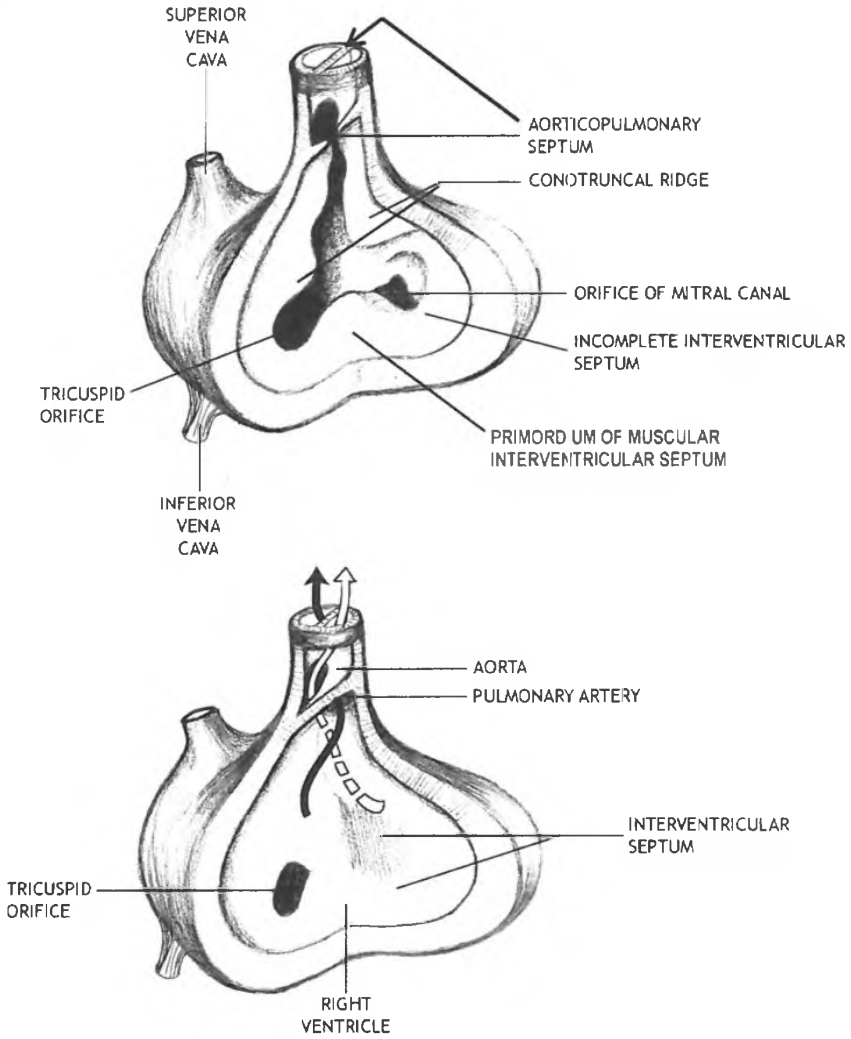


Figure 1. Division of the outflow tract by the aorticopulmonary (spiral) septum. In the top diagram, the aorticopulmonary septum is forming by the growth and merging of the conotruncal ridges in the walls of the outflow tract. This process divides the outflow tract into the atrioventricular canals (precursors of the aorta and pulmonary artery). In the lower diagram, the spiral septum has completed the separation of the outflow tract into the equally sized aorta (for systemic circulation) and pulmonary artery (for the pulmonary circulation). The most inferior part of the spiral septum will contribute to the upper membranous portion of the IV septum. (Modified from DeSesso & Venkat, 2010).

might cause all or any of these defects by acting on a single developmental process. Data from all numerically similar dose groups (e.g. data from all three studies that treated rabbits at 100 mg/kg/day) were combined into a single entry.

Evaluation of the resulting tabulation (Table 2) shows that there was no increase in cardiovascular malformations at doses that were not overtly toxic to the pregnant rabbits (i.e. generally at doses over 150 mg/kg/day). The two most commonly observed malformations involved the aorticopulmonary septum and dilated heart. The incidence of aorticopulmonary septum-related defects in the combined control groups was 1/770 (0.1%); in the combined glyphosate-treated groups the incidence was 6/1939 (0.3%). More than half of these affected fetuses were found in litters exposed to one of the highest doses (450 mg/kg/day). Doses of 150 mg/kg/day and above were generally associated with maternal toxicity, including severe weight loss and death. If doses of 300 mg/kg/day and above are not considered because of the confounding maternal toxicity issues, then the incidence of the defects in glyphosate-treated animals is 2/1388 (0.1%). Thus, these data show that the overall incidence of aorticopulmonary septum-related defects in offspring from mothers exposed to glyphosate at doses below those that cause severe maternal toxicity is similar to that seen in non-exposed rabbits.

The other prevalent cardiovascular malformation reported was dilated heart. All observations of this finding occurred in a single study (Suresh, 1993). There was also one case of cardiomegaly at 100 mg/kg/day in the same study. None of the other five adequate studies reported dilated hearts or cardiomegaly. Furthermore, neither the criteria used to diagnose dilated heart nor measurements of the hearts were provided in the study report, so it is not possible to directly

Table 2. Combined and grouped (number and percentage) cardiovascular malformations from six rabbit developmental toxicity studies.

Dose (mg/kg/day)	0	10	20	50	75	100	150	175	200	300	350	400	450	500
Total number of fetuses evaluated at each dose	770	130	78	261	114	374	112	200	119	256	38	134	95	28
Defects related to displaced aorticopulmonary (spiral) septum including ventricular septal defects	1[B] (0.1%)					1[H] (0.3%)	1[B] (0.9%)						4[B] (5.0%)	
Dilated heart			4[S] (5.1%)			4[S] (1.1%)								2[S] (7.1%)
Dilated ventricles	1[S] (0.1%)					1[S] (0.2%)								1[S] (3.6%)
Cardiomegaly						1[S] (0.2%)								
Single heart ventricle. thickened ventricle walls						1[M] (0.2%)				1[M] (0.4%)				
Retroesophageal right subclavian artery							3[B] (2.7%)						2[B] (2.1%)	
"Seal-shaped" heart	1[S] (0.1%)					1[S] (0.2%)								
Acephalic animal with heart defects				1[B] (0.4%)					1[C] (0.8%)					
Cebocephalic animal with heart defects	1[M] (0.1%)													

B = Brooker et al. (1991a); C = Coles & Doleman (1996); H = Hojo (1995); M = Moxon (1996); S = Suresh (1993).

Table 3. Maternal and developmental NOAELs from six sufficient rat developmental toxicity studies of glyphosate.

Study	No. of animals per group	Exposure period	Doses (mg/kg/day)	Maternal NOAEL (mg/kg/day)	Offspring NOAEL (mg/kg/day)
Moxon (2002)	22–24	GD 6–15†	0, 250, 500, 1000	≥1000	≥1000
Wood (1996)	22–25	GD 6–15	0, 100, 500, 1000	≥1000	≥1000
Hatakenaka (1995)	22–24	GD 6–15	0, 30, 300, 1000	300	≥1000
Brooker et al. (1991a)	23–25	GD 6–15	0, 300, 1000, 3500	1000	1000
Suresh (1991)	20–30	GD 6–15	0, 1000	≥1000	≥1000
Tasker et al. (1980b)	20–23	GD 6–19	0, 300, 1000, 3500	1000	1000

†Moxon (1995) designated the day of finding sperm as GD 1. The exposure period here has been adjusted to be comparable to the other studies which used GD 0 as the day of insemination.

compare the dilated heart findings to the hearts of the more than 2500 fetuses in the other studies.

Finally, an examination of the overall rate of cardiac malformations across the six studies did not support a dose–response correlation with glyphosate exposure. Based on this analysis, it appears that prenatal glyphosate exposure is not associated with increased cardiovascular defects in rabbits.

Rat developmental toxicity database

The six developmental toxicity studies of glyphosate conducted in the rat are discussed in the Appendix and summarized in Table 3. These studies involved testing in two different rat strains (Wistar and Sprague–Dawley) and covered a wide range of glyphosate doses up to 3500 mg/kg/day, which is well above the current limit dose for toxicity studies of 1000 mg/kg/day. With the exception of Tasker et al. (1980b), all studies conformed to internationally accepted general principles of GLPs and were conducted according to OECD 414 (1981) and US EPA 83-3 guideline requirements. The study by Tasker et al. (1980b) predated the establishment of US EPA and OECD guidelines, but it received quality assurance audits by the testing facility and appeared to be well-conducted and essentially guideline-compliant. As with the rabbit studies, the rat developmental toxicity studies of glyphosate varied in the numbers of animals per dose group, the spacing of doses, the extent of documentation and detail provided, and the specific types of data reported. Nevertheless, for the purposes of this evaluation, all six rat studies were considered adequate for assessing the developmental toxicity potential of glyphosate.

The NOAELs for maternal toxicity and developmental effects as assessed for the six rat developmental toxicity studies are shown in Table 3. Maternal body weight was not affected in any of the studies at exposure levels lower than 3500 mg/kg/day. Further, there were no dose-related effects on intrauterine parameters at doses of 1000 mg/kg/day and below. Maternal NOAELs were determined to be ≥1000 mg/kg/day for all studies except Hatakenaka (1991) (Table 3), which reported loose stools in a few dams at that exposure. No treatment-related effects were observed in the offspring at doses of 1000 mg/kg/day and below. Consequently, the offspring NOAELs for these studies were ≥1000 mg/kg/day and equal to or greater than the maternal

NOAELs in each study (Table 3). Further, no treatment-related effects of glyphosate on structural development of the offspring were observed (Table A10). Generally, malformations (including cardiovascular malformations) were limited to 1–3 fetuses in 1–2 litters in the exposed groups and occurred at incidences as low as or lower than those in the control group. Overall, the rat developmental toxicity studies do not show any evidence of cardiovascular or other types of malformations as a result of glyphosate exposure at doses of up to 3500 mg/kg/day.

Discussion and conclusions

The 13 developmental toxicity studies summarized above and discussed in detail in the Appendix have been submitted to regulatory agencies in support of the registration of glyphosate. Analyses by the regulatory agencies have not supported the claim that glyphosate causes cardiovascular defects or other developmental effects (BBA, 1998–2000; EPA, 1993; European Commission, 2002). At the time of the US EPA's assessment, only the studies by Tasker et al. (1980a,b) were available for evaluation. The European Commission's review (European Commission, 2002), however, included the examination of four of the rabbit studies (Bhide & Patil, 1989; Brooker et al., 1991a; Suresh, 1993; Tasker et al., 1980a) and three of the rat studies (Brooker et al., 1991b; Suresh 1991; Tasker et al., 1980b) discussed herein. In a related monograph (BBA, 1998–2000), the results from two of the rabbit studies reviewed by the European Commission were characterized as equivocal for cardiovascular developmental effects. None of the three rabbit developmental toxicity studies that were not evaluated by the European Commission (Coles & Doleman, 1996; Hojo, 1995) showed a potential for cardiovascular defects.

Based on our assumptions underlying the integrated assessment of data across studies (equal strain sensitivity, insignificant differences in timing of exposure and shared morphogenetic processes of certain defects), the overall conclusion of our analysis of the potential for glyphosate to cause malformations, and cardiovascular defects in particular, is that there is no increased risk at the levels of exposure below those that caused maternal toxicity. This conclusion is in agreement with that of regulatory agency reviews as well as the limited data available from epidemiology studies showing no increased risk of congenital defects with exposure (Bell et al., 2001a,b,c; Garry et al., 2002; Rull et al., 2006; reviewed in Williams et al., 2012). It should be noted, however, that these studies investigated exposures to several pesticides and were not specific to glyphosate. More recently, a detailed review of epidemiology studies of glyphosate and non-cancer endpoints found no evidence of a causal relationship between glyphosate exposures and malformations (Mink et al., 2011). Finally, a review of the available biomonitoring data demonstrates that human exposure as a result of normal glyphosate application practices is extremely low, often below the limits of analytical detection (Williams et al., 2012). In conclusion, this analysis of the developmental toxicity data available for glyphosate exposure confirms that there is no evidence of an increased risk of cardiovascular defects as a result of glyphosate exposure.

Acknowledgements

The authors would like to acknowledge member companies of the EU Glyphosate Task Force who shared their unpublished developmental toxicity study reports with us for the purposes of this assessment. Member companies on the task force are listed at www.glyphosatetaskforce.org.

Declaration of interest

The authors affiliation is as shown on the cover page. Exponent is a consulting firm that provides scientific analysis and advice in areas that include toxicology and risk assessment; Georgetown University School of Medicine is a provider of medical education. Funding for this work was supplied by the European Glyphosate Task Force. Although none of the authors on this assessment have previously consulted for the European Glyphosate Task Force, two authors (A. L. Williams and J. M. DeSesso) have addressed other issues related to glyphosate in work funded by Monsanto. The authors are solely responsible for the analyses and preparation of this manuscript; the opinions and conclusions are those of the authors and are not necessarily those of the sponsoring entity.

References

Antoniou M, Habib MEM, Howard CV, et al. (2012). Teratogenic effects of glyphosate-based herbicides: divergence of regulatory decisions from scientific evidence. J Environ Anal Toxicol, Suppl 4, 1–13.

BBA (Federal Biological Center for Agriculture and Forestry – Germany). (1998–2000). Monograph on the active substance glyphosate and its IPA-, Na- and NH4-salts. Annex to the European Commission report for the active substance glyphosate.

Bell EM, Hertz-Picciotto I, Beaumont JJ. (2001a). A case-control study of pesticides and fetal death due to congenital anomalies. Epidemiology, 12, 148–56.

Bell EM, Hertz-Picciotto I, Beaumont JJ. (2001b). Case-cohort analysis of agricultural pesticide applications near maternal residence and selected causes of fetal death. Am J Epidemiol, 154, 702–10.

Bell EM, Hertz-Picciotto I, Beaumont JJ. (2001c). Pesticides and fetal death due to congenital anomalies: implication of an erratum (letter). Epidemiology, 12, 595–6.

Berko NS, Jain VR, Godelman A, et al. (2009). Variants and anomalies of vasculature on computed tomographic angiography in adults. J Comput Assist Tomogr, 33, 523–8.

Bhide MB, Patil UM. (1989). Rabbit teratology study with glyphosate technical. Study No. IIT Project No. 1086.

Brooker AJ, Brennan C, John DM, et al. (1991a). The effect of glyphosate on pregnancy of the rabbit (incorporates preliminary investigations). Study/Project No. CHV 45 & 39 & 40/901303.

Brooker AJ, John DM, Anderson A, Dawe IS. (1991b). The effect of glyphosate on pregnancy of the rat (incorporates preliminary investigation). Study No. CHV 43 & 41/90716.

Coles RJ, Doleman N. (1996). Glyphosate technical: oral gavage teratology study in the rabbit. SPL Project No. 434/020.

Dallegrave E, Mantese FD, Coelho RS, et al. (2003). The teratogenic potential of the herbicide glyphosate-roundup in wistar rats. Toxicol Lett, 142, 45–52.

Dallegrave E, Mantese FD, Oliveira RT, et al. (2007). Pre- and postnatal toxicity of the commercial glyphosate formulation in Wistar rats. Arch Toxicol, 81, 665–73.

Daruich J, Zirulnik F, Gimenez MS. (2001). Effect of the herbicide glyphosate on enzymatic activity in pregnant rats and their fetuses. Environ Res, 85, 226–31.

DeSesso JM. (2012). Comparative gestational milestones in vertebrate development. In: Hood RD, ed. Developmental and reproductive toxicology: a practical approach. 3rd ed. New York: Informa Healthcare, 93–138.

DeSesso JM, Venkat AG. (2010). Cardiovascular development and malformation. In: Kapp RW, Tyl RW, eds. Reproductive toxicology. 3rd ed. Chap 13. New York: Informa Healthcare. 223–48.
Epstein DA, DeBord JR. (2002). Abnormalities associated with aberrant right subclavian arteries: a case report. Vasc Endovascular Surg. 36. 297–303.
European Commission (2002). Review report for the active substance glyphosate, Directive 6511/VI/99-final. 21 January 2002. Available from: http:ec.europe.eu/food/plant/protection/evaluation/existactive/list1_glyphosate_en.pdf [last accessed 12 Dec 2012]
Fazan VPS, Riberio RA, Riberio JAS, Filho OAR. (2003). Right retroesophageal subclavian artery. Acta Cir Bras, 18, 54–6.
Garry VF, Harkins ME, Erickson LL, et al. (2002). Birth defects, season of conception, and sex of children born to pesticide applicators living in the Red River Valley of Minnesota, USA. Environ Health Persp. 110, 441–9.
Grube A, Donaldson D, Kiely T, Wu L. (2011). Pesticide industry sales and usage: 2006 and 2007 market estimates. Biological and Economic Analysis Division, Office of Pesticide Programs, Office of Chemical Safety and Pollution Prevention, U.S. Environmental Protection Agency. February 2011. Available from: www.epa.gov/opp00001/pestsales/07pestsales/market_estimates2007.pdf [last accessed 12 Dec 2012]
Hatakenaka N. (1995). HR-001: teratogenicity study in rats. Study No. IET 94-0152.
Hoffman JIE, Kaplan S. (2002). The incidence of congenital heart disease. J Am Coll Cardiol, 39, 1890–900.
Hojo H. (1995). HR-001: a teratogenicity study in rabbits. Study No. IET 94-0153.
Holson JF, Nemec MD, Stump DG, et al. (2006). Significance, reliability, and interpretation of developmental and reproductive toxicity findings. In: Hood RD, ed. Developmental and reproductive toxicology: a practical approach. 2nd ed. Boca Raton: CRC Press. 329–424.
Hutson MR, Kirby ML. (2003). Neural crest and cardiovascular development. Birth Defects Res C: Embryo Today, 69, 2–13.
Kirby ML, Gale TF, Stewart DE. (1983). Neural crest cells contribute to normal aorticopulmonary septation. Science, 220. 1059–61.
MARTA (Middle Atlantic Reproduction and Teratology Association). (1997). Historical control data. In: Hood RD, ed. Appendix B in Handbook of developmental toxicology. Boca Raton: CRC Press. 713–33.
Mink PJ, JS Mandel, JI Lundin, Sceurman BK. (2011). Epidemiologic studies of glyphosate and non-cancer health outcomes: a review. Regul Toxicol Pharmacol, 61, 172–84.
Moxon ME. (1996). Glyphosate acid: developmental toxicity study in the rabbit. Report No. CTL/P/5009.
Moxon ME. (2002). Glyphosate acid: developmental toxicity study in the rat. Report No. CTL/P/4819/Amendment – 001.
Rull RP, Ritz B, Shaw GM. (2006). Neural tube defects and maternal residential proximity to agricultural pesticide applications. Am J Epidemiol, 163, 743–53.
Sadler TW. (2011). Selective serotonin reuptake inhibitors (SSRIs) and heart defects: potential mechanisms for the observed associations. Reprod Toxicol, 32. 484–9.
Stump DG, Nemec MD, Parker GA, et al. (2012). Significance, reliability, and interpretation of developmental and reproductive toxicity study findings. In: Hood RD, ed. Developmental and reproductive toxicology: a practical approach. 3rd ed. Chap 9. New York: Informa Healthcare. 229–301.
Suresh TP. (1991). Teratogenicity study in wistar rats – test compound: glyphosate technical (FSG 03090 H/05 March 90). Study No. TOXI: ES.883.TER-R.
Suresh TP. (1993). Teratogenicity study in rabbits – test compound: glyphosate technical (FSG 03090 H/05 March 1990). Study No. TOXI: 884-TER-RB.
Tasker EJ, Rodwell DE, Jessup DC. (1980a). Technical glyphosate: teratology study in rabbits. Report No. IR-79-018.
Tasker EJ, Rodwell DE, Jessup DC. (1980b). Technical glyphosate: teratology study in rats. Report No. IR-79-016.
US Environmental Protection Agency (US EPA). (1993). Re-registration Eligibility Decision (RED) Glyphosate. Report No. EPA-738-R-93-014. Washington, DC: U.S. Environmental Protection Agency, Office of Pesticide Programs and Toxic Substances, 291pp.
Williams AL, Watson RE, DeSesso JM. (2012). Developmental and reproductive outcomes in humans and animals after glyphosate exposure: a critical analysis. J Toxicol Environ Health. Pt B. 15, 39–96.
Wood E. (1996). Glyphosate technical: oral gavage teratology study in the rat. SPL Project No. 434/018.

Appendix

Rabbit developmental toxicity studies

A total of seven developmental toxicity studies of glyphosate have been conducted in the rabbit and are summarized in detail below. The studies vary considerably in their quality, the extent of documentation and detail provided and the specific types of data reported. They have been ordered on the basis of quality, with studies of higher quality, and therefore greater relevance to the overall evaluation, detailed first. Although some of these studies reported the results of preliminary range-finding experiments, only the results of the definitive studies are detailed here for the purposes of this review. Typically, doses for the definitive studies were selected based on maternal toxicity observed in the preliminary range-findings studies. Five of the studies stated that they followed GLP specific to the time period in which they were conducted (Brooker et al., 1991a; Coles & Doleman, 1996; Hojo, 1995; Moxon, 1996; Suresh, 1993). Another study was conducted prior to the establishment of GLP requirements, but generally adhered to GLP principles (Tasker et al., 1980a). In the seventh study (Bhide & Patil, 1989), it is not clear to what extent GLP practices were followed, but it appears that this study was not fully GLP-compliant because the description of study results is extremely limited and inappropriate animals appear to have been included in the calculation of certain endpoints. All the studies were conducted according to current testing guideline requirements at the time of the study and provided quality assurance audits. The animal supply and husbandry were described, although detailed husbandry data were not provided in the study reports. No other deviations were detailed by the study authors. In the summaries that follow, we address issues of data quality where appropriate. In two cases (Brooker et al., 1991a; Suresh, 1993), we have tabulated the malformations reported in some detail. This was done because these two studies reported increases in malformations which appeared to be related to increases in cardiovascular defects. All other studies had very low levels of cardiovascular malformations, so no further details were given.

Moxon (1996)

This study was conducted according to OECD 414 (1981) and US EPA 83-3 testing guideline requirements. Female virgin New Zealand White rabbits (age unknown) were paired with males (day of insemination = gestational day [GD] 1) and delivered to the testing laboratory on either GD 2 or 3. The designation of the day of insemination as GD 1 is different than that for the majority of the rabbit studies, which designated the day of insemination as GD 0. For the purposes of comparing to other studies, the day of mating has been corrected to GD 0 in the following discussion with succeeding gestational days changed accordingly. The maternal animals were assigned by a randomized design to minimize (but not necessarily to prevent) the number of animals in the same group that were sisters or mated to the same male. Glyphosate acid (purity: 95.6%) was formulated in deionized water, was stable over the test period and was shown to have an adequate homogeneity. The achieved concentrations were within 12% of the target concentrations. The does were administered 0, 100, 175 or 300 mg/kg/day by oral gavage on GD 7–19 (20 rabbits per group). The dosing volume was 2 mL/kg body weight; the dosing vehicle was deionized water. The rabbits were evaluated daily for mortality, behavior and clinical signs of toxicity. Body weights were recorded on GDs 3, 7–19, 22, 25 and 29. Food consumption was recorded every 3–4 days from GD 3 to GD 25. Does were sacrificed on GD 29 and the uteri and ovaries were examined for the numbers of corpora lutea, implantations, live and dead fetuses, and intra-uterine deaths (both early and late). The does were further evaluated for any gross pathological changes. Fetuses were weighed and examined for external, visceral (via fresh dissection) and skeletal (by means of alizarin red S staining) anomalies. The degree of bone ossification was scored visually based on the extent of alizarin staining.

Clinical symptoms of toxicity observed in the 175 and 300 mg/kg/day dose groups included diarrhea, few feces and/or staining in the genital

Table A1. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 7–19† (Moxon 1996).

	0 mg/kg/day	100 mg/kg/day	175 mg/kg/day	300 mg/kg/day
Maternal data				
No. animals on study	20	20	20	20
No. non-gravid	2	0	1	1
No. gravid does dead or sacrificed *in extremis*	1	2	2	2
No. that aborted	1	2	1	2
Embryo/fetal data				
Total No. litters examined‡	17	18	17	17
Mean No. corpora lutea	10.8 ± 2.2	11.0 ± 1.6	11.1 ± 1.3	11.2 ± 1.4
Mean No. implantations	9.65 ± 2.06	9.00 ± 1.78	9.12 ± 2.50	9.82 ± 1.88
Mean % pre-implantation loss	10.7 ± 11.0	18.2 ± 11.1	18.1 ± 20.8	12.8 ± 11.9
Mean No. embryo/fetal death	NR	NR	NR	NR
Mean No. viable fetuses	8.41 ± 1.80	8.17 ± 2.20	7.94 ± 2.19	8.47 ± 2.32
Mean % post-implantation loss	11.7 ± 12.0	9.5 ± 16.7	12.1 ± 9.7	13.6 ± 16.6
Mean fetal body weight (g)	44.4 ± 4.3	43.3 ± 3.9	43.2 ± 5.7	40.7 ± 7.8*
Total fetuses (litters) with malformations				
Major external/visceral	2 (2)	1 (1)	0 (0)	2 (2)
Minor external/visceral	12 (8)	7 (5)	9 (8)	11 (7)
Major skeletal	3 (2)	0 (0)	0 (0)	1 (1)
Minor skeletal	58 (16)	82 (18)**	59 (16)	79 (17)**
Total fetuses (litters) with variations				
External/visceral	0	0	0	0
Cardiovascular	1 (1)	1 (1)	0	1 (1)
Skeletal	119 (17)	129 (18)	116 (17)	132 (17)**

NR = Not reported.
†Moxon (1995) designated the day of insemination as GD 1. The exposure period here has been adjusted to be comparable to the other studies which used GD 0 as the day of insemination. See text for details.
‡Includes litters that were aborted in the analysis.
*$p < 0.05$. ANOVA; litter is statistical unit.
**$p < 0.05$. Fisher's exact test.

area. Dose-dependent reductions in food consumption and body weight gains were observed in these two dose groups as well.

Pregnancy outcome and delivery data are shown in Table A1. Two does died or were sacrificed *in extremis* in each dose group except the control, in which there was a single animal death. Abortions occurred in 1, 2, 1 and 2 rabbits in the 0, 100, 175 and 300 mg/kg/day dose groups, respectively. All animals that aborted or had total litter resorptions died or were sacrificed *in extremis*. No macroscopic findings related to treatment were found in does at necropsy.

Glyphosate treatment had no effect on the number of corpora lutea, implantations, viable fetuses per litter or the incidences of pre- and post-implantation loss. Mean fetal body weights were significantly reduced at the high dose of 300 mg/kg/day compared to controls; this difference was attributed to two litters for which fetal weights were particularly low. The fetal sex ratio was skewed toward males at the intermediate dose of 175 mg/kg/day. Since this endpoint tends to be highly variable and no dose response trend was evident, the difference was not considered to be treatment-related.

Table A1 also shows the number of fetuses and litters in each dose group with major and minor external/visceral and skeletal defects and the incidence of fetuses with variations in each. The only changes that appeared to increase with dose were minor skeletal defects and variants, and these were increased almost exclusively in the 300 mg/kg/day group. The increase in minor skeletal defects and variants can be attributed to reduced ossification in several bones, including transverse processes of cervical and lumbar vertebrae, sternebrae and bones of the hindpaw. These are likely related to the reduced fetal body weights seen at the highest dose level.

The type and incidence of major malformations within individual fetuses did not increase with dose. Only five fetuses in the entire study had major malformations, two in the control group, one at 100 mg/kg/day and one at 300 mg/kg/day. Three fetuses had heart defects involving effects on septation of the heart, one in the controls, one at 100 mg/kg/day and one at 300 mg/kg/day. Thus, none of the malformations noted were associated with exposure to glyphosate.

Based on clinical signs of toxicity and on reduced food intake and body weight gain, the NOAEL for maternal toxicity is considered to be 100 mg/kg/day. Based on reduced fetal weights observed at the high dose, the NOAEL for developmental toxicity is considered to be 175 mg/kg/day.

Coles & Doleman (1996)

This study was conducted according to OECD 414 (1981) and US EPA 83-3 (1984) testing guideline requirements. Female New Zealand White rabbits (2.7–4.1 kg) of 17–19 weeks of age were mated with "stud" males by the supplier and delivered to the test facility at or before GD 3. The day of mating was considered GD 0. Glyphosate technical (purity: 95.3%) was formulated in 1% carboxymethyl cellulose, was stable over the test period and was shown to have an adequate homogeneity. The averaged achieved concentrations were within 11% the target concentrations over the test period. Although doses were described as "mg/kg" in the study report, based on the dosing description, it is assumed that these are daily doses (i.e. mg/kg/day). The does were administered 0, 50, 200 or 400 mg/kg/day by oral gavage on GD 7–19 (18 rabbits per group). The dosing volume was 5 mL/kg body weight. Individual dose volumes were based on the most recent body weight. Animals were examined at least once daily for mortality and clinical signs. Body weights were recorded on GD 3, 7, 10, 13, 16, 19, 22, 25 and 29 (body weight change was based on BW at GD 7); food consumption was measured using the same time intervals (e.g. GD 3–7, 7–10). All surviving animals were sacrificed on GD 29 and the uteri and ovaries were examined. The numbers of corpora lutea, implantations, and live and dead fetuses were recorded. The does were further evaluated for gross pathological changes. All fetuses were sexed, weighed and examined for external and internal abnormalities. The heads of alternate fetuses were fixed and examined separately. The skeletons were stained with alizarin red and examined.

No dose-related clinical signs were reported except soft/liquid feces and mucus in the feces. This was observed most frequently in the 400 mg/kg/day group, but was also observed at 50 and 200 mg/kg/day. During the treatment period, maternal food consumption was reduced from that of controls at 400 mg/kg/day (GD 10–19). In the post treatment period, food consumption in the treated groups tended to be higher than the controls; however, the differences did not attain statistical significance. There was a statistically significant reduction in body weight gain (GD 7–29) at 400 mg/kg/day, and a non-statistically significant reduction at 200 mg/kg/day.

Pregnancy outcome and delivery data are presented in Table A2. The numbers of non-pregnant animals were 3, 0, 2 and 1 in the 0, 50, 200 and 400 mg/kg/day groups, respectively. The numbers of does dead or

Table A2. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 7–19 (Coles & Doleman, 1996).

	0 mg/kg/day	50 mg/kg/day	200 mg/kg/day	400 mg/kg/day
Maternal data				
No. animals on study	18	18	18	18
No. non-gravid	3	0	2	1
No. gravid does dead or sacrificed *in extremis*	1	0	1	2†
No. that aborted	0	0	0	0
Embryo/fetal data				
Total No. litters examined	14	18	15	15
Mean No. corpora lutea	10.9 ± 2.2	10.5 ± 2.4	10.7 ± 2.1	11.5 ± 1.8
Mean No. implantations	9.5 ± 2.5	9.1 ± 2.3	8.9 ± 2.5	10.3 ± 2.3
Mean % pre-implantation loss	12.5 ± 18.2	13.6 ± 9.4	16.4 ± 15.5	9.3 ± 12.5
Mean No. embryo/fetal death	0.36 ± 0.63	0.33 ± 0.77	1.00 ± 1.00*	1.40 ± 2.35
Mean No. viable fetuses	9.1 ± 2.5	8.7 ± 2.4	7.9 ± 2.5	8.9 ± 2.6
Mean % post-implantation loss	3.7 ± 6.5	3.6 ± 8.5	11.5 ± 11.4*	12.1 ± 18.6
Mean fetal body weight (g)	41.5 ± 5.5	39.4 ± 5.6	41.7 ± 4.5	38.2 ± 5.2
Total fetuses (litters) with malformations	1 (1)	3 (2)	2 (2)	1 (1)
Total fetuses (litters) with cardiovascular malformations	0	0	1 (1)	0
Total fetuses (litters) with variations‡	41 (13)	50 (17)	39 (15)	51 (14)

†At least one of these deaths/sacrifices at 400 mg/kg/day was likely treatment-related.
‡Fetuses with both malformations and variations are included in the malformations tally; fetuses with only variations are captured here.
*$p < 0.05$, Kruskal–Wallis followed by the Mann–Whitney U test; litter was the statistical unit.

sacrificed *in extremis* were 1, 0, 1 and 2 in the 0, 50, 200 and 400 mg/kg/day groups, respectively. At least one maternal death at 400 mg/kg/day appeared to be treatment-related; deaths in the control and mid-dose groups were attributed to dosing technical errors. None of the animals aborted.

The total litters included in the data evaluation were 14, 18, 15 and 15 for the 0, 50, 200 and 400 mg/kg/day groups, respectively. Compared to controls, glyphosate treatment exerted no effects on the numbers of corpora lutea, implantations, pre-implantation loss, fetal sex ratios or fetal weights. There was a statistically significant increase in embryo/fetal death and post-implantation loss at 200 mg/kg/day, and a non-statistically significant increase at 400 mg/kg/day. The standard deviations within these data are considerable and Coles & Doleman (1996) point out that at 200 mg/kg/day, there was a preponderance of "early fetal deaths", and at 400 mg/kg/day, the increase could be attributed to one animal with nine late deaths or a post-implantation loss of 69.2%. If the one litter with high implantation loss is excluded, the mean ± standard deviation for post-implantation loss in the remaining litters is 8.0 ± 10.2. With no consistent, statistically significant dose-response pattern, the biological significance of these data is questionable. No historical control data were provided in Coles & Doleman (1996) to compare with these results.

Table A2 also shows the number of fetuses and litters in each dose group with external/visceral and skeletal malformations and variations. There was no apparent increase in morphological findings with increasing dose in any group. There was a variety of malformations seen, but no particular pattern of malformations and no apparent dose–response relationship. Only one case of a heart and great vessel defect was seen in the 200 mg/kg/day group in a fetus with a number of other severe abnormalities. A number of skeletal variations were noted, but there did not appear to be a dose-related increase.

Based on clinical signs and a decrease in maternal weight gain at 400 mg/kg/day, the NOAEL for maternal toxicity is considered to be 200 mg/kg/day. It is possible that similar treatment-related clinical signs were observed at exposures lower than 400 mg/kg/day, but there was no clear dose–response. Assuming that the increase in post-implantation loss discussed above is not biologically significant, the NOAEL for developmental toxicity is >400 mg/kg/day.

Brooker et al. (1991a)

This study was conducted according to OECD 414 (1981) and US EPA 83-3 (1984) guideline requirements. Female New Zealand White rabbits of 11–24 weeks of age were used; there did not appear to be a period of acclimatization. The females were mated with proven males, followed by an injection of luteinizing hormone to promote ovulation. The day of mating (sperm positive) was considered GD 0. Glyphosate acid (purity: 95.3%) was formulated in 1% methylcellulose, was stable over the test period and was shown to have an adequate homogeneity. The achieved concentrations were within 6% of the target concentrations, with the exception of a single measurement in Group 2 which was 19% below the target concentration. It is unclear how often samples for analysis were taken during the study. The does were administered 0, 50, 150 or 450 mg/kg/day by oral gavage on GD 7-19 (16–20 rabbits per group). The reason for including different numbers of animals per dose group was not reported. The dosing volume was 5 mL/kg body weight. Individual dose volumes were based on individual body weights on GD 7 and adjusted according to body weights on GD 9, GD 11 and GD 15. Animals were examined daily for mortality and signs of toxicity. Body weights were recorded on GD 1, 7, 9, 11, 15, 20, 24 and 29; food consumption was measured using the same time intervals (e.g. GD 1–7, 7–9). Does that did not survive until the end of the study were weighed and necropsied. All surviving animals were sacrificed on GD 29, and the ovaries and uteri were examined for the numbers of corpora lutea, implantations, and live and dead fetuses. The does were further evaluated for gross pathological changes. All fetuses were weighed and examined for external abnormalities, then dissected to examine for visceral abnormalities and to determine sex. The heads were fixed and examined separately. The skeletons were stained with alizarin red and examined. Structural changes were reported by study investigators as malformations (defined as rare and/or probably lethal changes), anomalies (defined as relatively frequent minor differences from "normal") and variants (defined as alternative structures occurring regularly in the control population).

There were no dose-related clinical signs except soft/liquid feces: this finding was observed at all exposure levels, but not in the controls, and was substantially increased at the high dose (450 mg/kg/day). During the treatment period, maternal food consumption was reduced from that of controls at 150 mg/kg/day (GD 11–19) and 450 mg/kg/day (GD 7–19). In the post-treatment period, both of these groups demonstrated a rebound and food consumption was greater than that in controls. No dose-related differences in maternal body weights were observed.

Pregnancy outcome and delivery data for this study are shown in Table A3. Two does were excluded from the study for non-experimental reasons (one control doe was found with a congenital malformation of the uterus at autopsy; one 450 mg/kg/day doe[1] was found to have a broken leg prior to treatment). The numbers of non-pregnant animals were 0, 6, 1 and 5 in the 0, 50, 150 and 450 groups, respectively; there did not appear to be a correlation between age of the animals (assumed based on body weights) and the occurrence of non-pregnancy. One

[1]The authors state that this animal was replaced, but this does not appear to be the case from Appendix 1 in Brooker et al. (1991a).

Table A3. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 7–19 (Brooker et al., 1991a).

	0 mg/kg/day	50 mg/kg/day	150 mg/kg/day	450 mg/kg/day
Maternal data				
No. animals on study	19	19	16	20
No. excluded from study	1	0	0	1
No. non-gravid	0	6	1	5
No. gravid does dead or sacrificed *in extremis*	0	0	0	1
No. that aborted	0	1	0	0
Embryo/fetal data				
Total No. litters examined	18	12†	15‡	13
Mean No. corpora lutea¶	11.5	12.4	11.7	11.3
Mean No. implantations¶	9.7	10.5	9.0	9.2
Mean % pre-implantation loss¶	14.6	15.4	23.4	18.8
Mean No. embryo/fetal death¶	0.6	1.8*	1.5*	1.8**
Mean No. viable fetuses¶	9.1	8.7	7.5	7.3
Mean % post-implantation loss§	5.7 ± 7.2	19.5 ± 19.8*	15.3 ± 17.2*	21.0 ± 11.8**
Mean fetal body weight (gms)¶	43.9	43.3	44.0	44.5
Total fetuses (litters) with malformations	3 (3)	3 (3)	5 (3)	6 (5)
Total fetuses (litters) with cardiovascular malformations‖	1 (1)	1 (1)	4 (3)	5 (4)
Total fetuses (litters) with variations "anomalies"	29 (13)	26 (9)	26 (11)	16 (10)

†Analysis does not includes the one litter that was aborted at this dose.
‡Includes one female which aborted one embryonic death – referred to as "partial abortion".
¶Standard deviation was not provided.
§Standard deviation values calculated from individual animal data in Brooker et al. (1991a).
‖Exclusion of retroesophageal right subclavian artery reduces the numbers to 1 (1), 1 (1), 1 (1) and 4 (4) for 0, 50, 150 and 450 mg/kg/day, respectively.
*$p < 0.05$; **$p < 0.01$., Kruskal–Wallis test followed by non-parametric equivalent of Williams' test; litter was the statistical unit.

Table A4. Types and incidence of malformations by individual fetus (Brooker et al., 1991a).

	0 mg/kg/day	50 mg/kg/day	150 mg/kg/day	450 mg/kg/day
No. fetuses examined	163	104	112	95
Narrow ascending aorta, dorsally displaced pulmonary trunk, IV septal defect	1		1	1
Dilated ascending aorta/aortic arch, narrow pulmonary trunk; IV septal defect with enlarged left, reduced right ventricle				2
Retroesophageal right subclavian artery† (1 fetus at 150 mg/kg/day also had forelimb flexure: 1 fetus at 450 mg/kg/day with IV septal defect)			3	2
Acephaly; single dilated arterial trunk and carotid artery; right-sided descending aorta; IV septal defect, forelimb flexure and hindlimb brachydactyly		1		
Sacral meningocoele occulta with slightly flattened cranium and minimal protrusion in occipital region	1			
Bilateral small eye (areas of retinal folding and dysplasia)		1		
Hydrocephaly and cebocephaly with fused and reduced nasals and premaxillae, fused nares, absent upper incisors			1	
Cleft palate; forelimb flexure and brachydactyly				1
Reduced and fused thoracic vertebral arches with absent centrum; connected, branched and absent ribs	1			
Spina bifida with lumbar kyphosis and flattened cranium; malrotated hindlimb		1		

†Retroesophageal right subclavian artery is considered a variation by other laboratories. Removing this endpoint as a malformation would reduce the number of fetuses in this group to one fetus with forelimb flexure at 150 mg/kg/day and one fetus with IV septal defect at 450 mg/kg/day.

maternal death occurred at 450 mg/kg/day following abortion, gastrointestinal disturbances, reduced food intake and body weight loss. One doe aborted in the 50 mg/kg/day group.

The total litters included in the data evaluation were 18, 12, 15 and 13 for the 0, 50, 150 and 450 mg/kg/day groups, respectively. Compared to controls, glyphosate treatment exerted no marked effects on the numbers of corpora lutea, implantations, pre-implantation loss, fetal sex ratios or fetal weights. There was a statistically significant increase in embryo/fetal death and post-implantation loss at all exposure levels. The study investigators questioned the biological significance of these findings for several reasons: (1) No dose–response pattern was evident; (2) the control value was at the lower end of the historical control range, while those of the exposed groups were at the higher end and (3) the values in all groups were within or slightly above the historical control range. The latter two statements are supported by the historical control data provided in the study report. There was also considerable variance around the mean for post-implantation loss.

A dose-related increase in malformations (fetuses and litters) was observed with 3, 3, 5 and 6 fetuses malformed at 0, 50, 150 and 450 mg/kg/day, respectively. The increase at 450 mg/kg/day appeared to be due to an increase in IV septal and other heart defects, which were seen in 1, 1, 4 and 5 fetuses in the 0, 50, 150 and 450 mg/kg/day groups, respectively (Table A4).

Although the authors indicated retroesophageal right subclavian artery as a malformation in three fetuses at 150 mg/kg/day and in two at 450 mg/kg/day, other laboratories suggest that this is a fairly common

Table A5. Maternal and fetal outcome data for Japanese white rabbits treated with glyphosate on gestational days 7–19† (Hojo, 1995).

	0 mg/kg/day	10 mg/kg/day	100 mg/kg/day	300 mg/kg/day
Maternal data				
No. animals on study	18	18	18	18
No. non-gravid	0	0	0	0
No. gravid does dead or sacrificed *in extremis*	0	0	0	1
No. that aborted	0	2	0	2
No. with only resorptions	0	1	2	1
Embryo/fetal data				
Total No. litters examined‡	18	15	16	14
Mean No. corpora lutea	10.2 ± 2.0	11.7 ± 2.2	12.1 ± 2.0	10.1 ± 2.3
Mean No. implantations	8.5 ± 2.8	9.8 ± 2.9	10.4 ± 2.9	8.6 ± 3.3
Mean % pre-implantation loss¶	17.8 ± 22.4	16.6 ± 17.0	15.2 ± 18.0	14.6 ± 25.2
Mean No. embryo/fetal death¶	0.7	1.1	1.0	0.6
Mean No. viable fetuses	7.8 ± 2.4	8.7 ± 3.2	9.4 ± 2.7	8.0 ± 3.2
Mean % post-implantation loss§	7.1 ± 8.8	13.8 ± 14.1	8.7 ± 10.5	6.5 ± 9.8
Mean fetal body weight (g) MALES	35.8 ± 8.1	37.3 ± 5.4	36.7 ± 3.3	36.2 ± 5.4
Mean fetal body weight (g) females	35.7 ± 6.7	36.1 ± 5.1	36.0 ± 3.9	34.9 ± 4.4
Malformations and variations				
Total # litters (%) with malformations	1 (5.6)	3 (20.0)	3 (18.8)	5* (35.7)
Total # litters (%) with variations	16 (88.9)	14 (93.3)	16 (100.0)	8* (57.1)
Total # Fetuses (%) with malformations				
External	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)
Visceral	0 (0.0)	1 (0.8)	3 (2.0)	0 (0.0)
Cardiovascular	0	0	1 (1)	0
Skeletal	1 (0.7)	4 (3.1)	6 (4.0)	5 (5.4)
Total # Fetuses (%) with variations				
Visceral	4 (2.9)	5 (3.8)	5 (3.3)	1 (0.9)
Skeletal	40 (28.6)	32 (24.6)	61* (40.7)	31 (27.7)

†Day of insemination adjusted to GD0 for comparison with other studies. See text for details.
‡Analysis does not include the litters that were aborted.
¶Mean and standard deviations not reported. Calculated from individual animal data in Hojo (1995).
§Standard deviations calculated from individual animal data in Hojo (1995).
*$p < 0.05$, Fisher's exact test; litter is the statistical unit.

variation in rabbits (MARTA, 1997; Stump et al., 2012) and it occurs in 0.5–2.0% of humans (Berko et al., 2009; Epstein & DeBord, 2002; Fazan et al., 2003). The historical control data provided by Brooker et al. (1991a) indicate that various studies have included 1–3 of such defects in control groups. Removing this defect as a malformation would reduce the total incidence of malformed fetuses to 3, 3, 3 and 5, and the incidence of fetuses with cardiovascular defects to 1, 1, 1 and 4 in the 0, 50, 150 and 450 mg/kg/day dose groups, respectively. Glyphosate treatment had no significant effect on the incidence of fetuses with variations when compared to the control group.

Based on clinical signs and decreased food consumption at 150 and 450 mg/kg/day, the NOAEL for maternal toxicity is considered to be 50 mg/kg/day. There was a slight increase in fetuses with malformations at 450 mg/kg/day. Several of the cardiovascular malformations that were observed, particularly in the high dose group, occurred in the same animals (Table A4) and are related to a single morphogenetic mechanism (i.e. displacement of the developing aorticopulmonary septum), which may adjust during the postnatal period as some of these improve during the first few months of life in humans (Hoffman and Kaplan, 2002). These mechanistically related findings, which often cluster together, include dilated/narrow aorta and narrow/dilated pulmonary artery; IV septal defect and disproportionately sized right and left ventricles. These malformations and the associated morphogenetic mechanism are discussed in greater detail in the integrated assessment below. These findings in the heart were also observed (often in clusters) in the historical control data provided by Brooker et al. (1991a). Overall, the malformation data showed an increase at 450 mg/kg/day (not statistically significant) and all findings in the glyphosate-treated groups were within historical control ranges. Although there were statistically significant increases in embryo/fetal death and post-implantation loss at 50 mg/kg/day and above, this was due to unusually low values in the concurrent control group. Although embryo/fetal death was within the historical control range, post-implantation loss was above historical control values in the high dose group, and both of these parameters were highly statistically significant at the high dose. Based on these data, the developmental NOAEL is 150 mg/kg/day.

Hojo (1995)

This study was conducted according to OECD 414 (1981) and US EPA 83-3 (1984) guideline requirements. Female Japanese White rabbits (3.3–3.8 kg) of 17 weeks of age were acclimatized for 10 days, and then impregnated by artificial insemination with sperm from breeder males of the same strain, followed by 25 units of human chorionic gonadotropin. The day after insemination was considered GD 0; this designation is different than that used in most of the other rabbit studies. Days of gestation have been adjusted for this study by designating the day of insemination as GD 0 to compare with other studies reviewed here. Glyphosate acid (purity: 97.6%, referred to in the report as HR-001) was formulated in 0.5% carboxymethyl cellulose, was stable over the test period and was shown to have an adequate homogeneity. The achieved concentrations were within 5% of the target concentrations. Impregnated does were administered 0, 10, 100 or 300 mg/kg/day by oral gavage on GD 7–19 (18 rabbits per group). The dosing volume was 5 mL/kg body weight, based on the individual body weights on each day of dosing. Animals were examined at least once daily for mortality and clinical signs. Body weights were recorded on GDs 1, 7–19 (daily), 25 and 28. Body weight gains were based on the GD 1 body weight; adjusted weight was not reported, but was calculated herein by subtracting the gravid uterine weight from the body weight on GD 28. Daily food consumption was based on the average consumption over 2-day periods. All surviving animals were sacrificed on GD 28 and the uteri and ovaries were weighed and examined for the numbers of corpora lutea, implantations, resorptions and live and dead fetuses. Uteri without apparent implants were stained to detect possible early resorptions. All fetuses were sexed, weighed and examined for external and internal abnormalities. The skeletons were stained with alizarin red and examined.

The only dose-related clinical sign reported was soft/liquid feces at 300 mg/kg/day. There were no dose-related effects on food consumption, maternal body weight or body weight gain.

Pregnancy outcome and delivery data are presented in Table A5. All of the animals on study were reported to be pregnant. One animal in the 300 mg/kg/day group died on GD 21. In the 10 and 300 mg/kg/day

groups, one doe in each group aborted and one doe in each group had a premature delivery. The authors reported all of these events as abortions (as shown in Table A5).

The total numbers of litters included in the data evaluation were 18, 15, 16 and 14 for the 0, 10, 100 and 300 mg/kg/day groups, respectively. Compared to controls, glyphosate treatment exerted no effect on the numbers of corpora lutea, implantations, pre-implantation loss, post-implantation loss, embryo/fetal deaths, fetal sex ratios or fetal weights.

Table A5 also shows the number and percentage of fetuses and litters in each dose group with external/visceral and skeletal malformations and variations. There was a statistically significant increase in total litters with malformations and variations at 300 mg/kg/day. The increased malformation rate was due to an increase in litters with fetuses showing skeletal malformations, as no external or visceral malformations were noted in fetuses from the high dose group. A change in the number of litters showing defects can be misleading because a litter is counted whether only one or all fetuses are affected. The specific alterations were not available on an individual fetus basis, so it was impossible to determine whether external, visceral or skeletal defects occurred in the same or different fetuses. Even so, the malformations seen were considered to be sporadic in nature rather than related to glyphosate treatment. Further, a dose–response in the number of fetuses showing skeletal malformations was not evident across dose groups. The number of litters with variations was significantly decreased at 300 mg/kg/day, and the incidence of fetuses with skeletal variations was significantly increased at 100 mg/kg/day. Overall, the incidence of fetuses with visceral or skeletal variations did not show a treatment-related change. With regard to malformations of the heart, only one fetus had heart-related defects at 100 mg/kg/day (hypoplasia of the pulmonary artery and ventricular septal defect).

Based on clinical signs at 300 mg/kg/day, the NOAEL for maternal toxicity is considered to be 100 mg/kg/day. The lack of a dose-related increase in fetuses with external, visceral or skeletal defects indicates a lack of biological significance for the total litter finding. Overall, these data support a developmental toxicity NOAEL of $\geq$300 mg/kg/day.

Tasker et al. (1980a)

Although this study was conducted prior to the establishment of GLPs and EPA or OECD study guidelines, it generally adhered to GLP practices and satisfies the general requirements of OECD 414 (1981). Female Dutch belted rabbits of age 7 months were acclimated for at least 30 days prior to being inseminated on GD 0 using semen from only four proven male rabbits. Glyphosate technical (purity: 98.7%) was formulated in 0.5% aqueous Methocel* solution (Dow Chemical Company, Midland, MI). No additional information on formulation was provided. Impregnated does were administered 0, 75, 175, or 350 mg/kg/day by oral gavage on GD 6–27 (16 rabbits per group). The dosing volume was 1 mL/kg body weight. Doses were based on individual body weights on GD 6. Animals were examined once daily for behavior, mortality and clinical signs of toxicity. Body weights were recorded on GDs 0, 6, 12, 18, 24 and 28. Food consumption rates were not recorded. Does that did not survive until the end of the study were necropsied to determine the cause of death. All surviving animals were sacrificed on GD 28. The uteri and ovaries were examined and the numbers of corpora lutea, implantations, resorptions, live and dead fetuses were recorded. The does were further evaluated for gross pathological changes. All fetuses were weighed, sexed internally, examined for external and visceral malformations (via dissection) and prepared for skeletal examination using alizarin red. External malformations were not reported separately from visceral malformations in this study.

Soft stools and diarrhea were noted in all treatment groups, but showed a dose-dependent rise in incidence in does treated with 175 and 350 mg/kg/day glyphosate compared to controls. Animals at 350 mg/kg/day also demonstrated an increase in nasal discharge. Maternal body weight changes were highly variable across groups throughout the study and no significant differences in body weights or body weight gains were noted compared to controls.

Pregnancy outcome and delivery data are shown in Table A6. Abortions occurred in two rabbits from the control group, and in one rabbit in each of the 175 and 350 mg/kg/day treatment groups. The numbers of rabbits that died before the end of study were 0, 1, 2 and 10 in the control, 75, 175 and 350 mg/kg/day glyphosate treatment groups, respectively. Mortality rates were greater than 10% in the intermediate and high dose groups. The causes of maternal death were determined for five of the 13 animals (pneumonia, respiratory disease, enteritis or gastroenteritis), but were not consistent across the groups. No macroscopic findings related to treatment were observed in the does.

Compared to controls, glyphosate treatment exerted no marked effects on the numbers of corpora lutea, implantations, resorptions (early or late), fetal sex ratios or fetal weights. There was also considerable variance around the mean for post-implantation loss. A statistically significant elevation in the number of viable fetuses per doe treated with 75 mg/kg/day was noted, but this result was considered to be a random occurrence because it was not observed in the two higher treatment groups. The total numbers of fetuses with malformations were 0, 3, 2 and 2 in the control, 75, 175 and 350 mg/kg/day dose groups, respectively. External and visceral defects occurred in two fetuses at the high dose

Table A6. Maternal and fetal outcome data for Dutch belted rabbits treated with glyphosate on gestational days 6–27 (Tasker et al., 1980a).

	0 mg/kg/day	75 mg/kg/day	175 mg/kg/day	350 mg/kg/day
Maternal data				
No. animals on study	16	16	16	17
No. non-gravid	2	0	2	0
No. gravid does dead or sacrificed *in extremis*	0	1	2	10
No. that aborted	2	0	1	1
Embryo/fetal data				
Total No. litters examined†	12	15	11	6
Mean No. corpora lutea	9.0 ± 2.13	10.1 ± 1.64	10.5 ± 3.45	8.5 ± 1.87
Mean No. implantations	5.9 ± 2.39	8.0 ± 1.81	6.1 ± 2.84	7.2 ± 2.93
Mean % pre-implantation loss	NR	NR	NR	NR
Mean No. embryo/fetal deaths	NR	NR	NR	NR
Mean No. viable fetuses/litter	5.3 ± 2.73	7.6 ± 1.84*	5.9 ± 2.77	6.3 ± 2.25
Mean % post-implantation loss‡	16.7 ± 23.0	4.9 ± 8.0	2.5 ± 5.8	18.7 ± 13.5
Mean fetal body weight (g)	33.4 ± 7.27	30.9 ± 4.43	29.9 ± 7.21	29.3 ± 4.82
Total fetuses (litters) with malformations¶				
External and visceral	0	0	0	2 (1)
Cardiovascular	0	0	0	0
Skeletal	0	3 (3)	2 (2)	0

NR = Not reported.
†Analysis does not include the litters that were aborted.
‡Calculated from individual animal data in Tasker et al. (1980a).
¶ The incidences of variations were not reported in this study.
*$p < 0.05$. ANOVA followed by t-test for multiple comparisons; litter is the statistical unit.

level. Only skeletal malformations were observed in the low- and mid-dose groups, with no defects seen in controls. One fetus at the high-dose level had multiple malformations, including acrania with gastro-thoracoschisis, bilateral carpal flexures, fetal anasarca, absent diaphragm, reduced diameter of carotids and associated skeletal changes, while another had a single finding of carpal flexure. Neither the type nor the incidence of these malformations suggests an adverse effect of glyphosate. Although total fetuses and litters with variations were not specifically reported, the types and incidence of fetuses with variations were primarily reduced ossification and there was no indication of a dose-related change. With respect to the heart and cardiovascular system, only the fetus with acrania had carotid stenosis.

Based on mortality and clinical signs at 175 and 350 mg/kg/day, the NOAEL for maternal toxicity is considered to be 75 mg/kg/day. The large number of maternal deaths at the high dose makes interpretation of the overall study data difficult. Since no treatment-related increase in developmental toxicity was observed, ≥175 mg/kg/day is considered the NOAEL for developmental toxicity. Because the study was limited by having too few fetuses available at the high dose of 350 mg/kg/day for adequate morphological assessment, the NOAEL for developmental toxicity could not be established for doses higher than 175 mg/kg/day.

Suresh (1993)

This study was conducted according to OECD 414 (1981). Female New Zealand White rabbits of at least 6 months of age (≥2.5 kg) were acclimatized for at least 10 days, and then mated. The day of mating was considered GD 0. Glyphosate technical (purity: 96.8%) was formulated in 0.5% carboxymethyl cellulose and Tween 80. No additional information on formulation was provided. Doses were described as "mg/kg" in the study report, but based on the dosing description it is assumed that these were daily doses (i.e. mg/kg/day). Impregnated does were administered 0, 20, 100 or 500 mg/kg/day by oral gavage on GD 6–18 (16–26 rabbits per group). The reason for including different numbers of animals per dose group was not reported. The dosing volume was 2 mL/kg body weight. Individual dose volumes were based on animal body weights. Animals were examined twice daily for mortality and clinical signs. Body weights were recorded on GDs 0, 6–18 (daily) and 27. Body weight gain was based on the intervals between body weights (e.g. GDs 0–6, 6–18). Absolute body weight was not reported by the authors, but was calculated here by subtracting the gravid uterine weight from the body weight on GD 28. Food consumption was calculated for GDs 0–6, 6–19, 19–28 and 0–28. All surviving animals were sacrificed on GD 28 and the uteri and ovaries were weighed and examined for the numbers of corpora lutea, implantations, resorptions, and live and dead fetuses. Uteri without apparent implants were stained to detect possible early resorptions. All fetuses were sexed, weighed and examined for external and internal abnormalities. The skeletons were stained with alizarin red and examined.

The major dose-related clinical signs included soft/liquid feces and mucus in the feces; these were observed in 0, 0, 1 and 14 does in the 0, 20, 100 and 500 mg/kg/day groups, respectively. No dose-related effects on maternal food consumption or body weight gain were reported. Maternal body weight, however, was statistically significantly decreased in the 500 mg/kg/day group on GD 0, 6 and 28, indicating that the animals in this group were below the weights of animals in other groups at the beginning of the study.

The pregnancy outcome and delivery data are presented in Table A7. The numbers of non-pregnant animals were 4, 4, 0 and 1 in the 0, 20, 100 and 500 mg/kg/day groups, respectively. Animals that died or were sacrificed *in extremis* were 2, 0, 4 and 8 in the 0, 20, 100 and 500 mg/kg/day groups, respectively. Various findings at gross necropsy were noted in the lungs and trachea for the 100 and 500 mg/kg/day dose groups; these findings suggest possible gavage errors to which the deaths at these doses may be attributed. The number of animals that aborted in each group was not reported.

Table A7. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 6–18 (Suresh, 1993).

	0 mg/kg/day	20 mg/kg/day	100 mg/kg/day	500 mg/kg/day
Maternal data				
No. animals on study	26	17	16	15
No. non-gravid	4	4	0	1
No. gravid does dead or sacrificed *in extremis*	2	0	4	8
No. that aborted	NR	NR	NR	NR
No. with only resorptions	0	0	0	1
Embryo/fetal data				
Total No. litters examined	20	13	12	6†
Mean No. corpora lutea	11 ± 2.8	10 ± 2.4	10 ± 1.9	9 ± 2.0
Mean No. implantations	8 ± 2.0	8 ± 1.5	9 ± 1.8	6 ± 2.4
Mean % pre-implantation loss‡	48	29	20	37
Mean No. embryo/fetal death‡	0.90	1.38	2.00	1.67
Mean No. viable fetuses	6.7	6.1	6.4	5.6
Mean % post-implantation loss¶	13.5 ± 14.3	18.6 ± 13.1	23.4 ± 23.8	23.2 ± 39.0
Mean fetal body weight (g)	32 ± 5.3	35 ± 3.7#	35 ± 2.4#	33 ± 4.9
"Abnormal fetuses" (*n*; %)	1 (1)	2 (3)	0	0
Total fetuses (litters) with malformations				
External	2 (2)	2 (1)	1 (1)	0 (0)
Visceral	4 (3)	6 (3)	6 (4)	8 (2)*
Cardiovascular	2 (2)	4 (3)	6 (4)	6 (2)
Skeletal	11 (4)	5 (3)	0 (0)	1 (1)
Total fetuses (litters) with minor malformations and variations§				
External	0	0	1 (1)	0
Visceral	NR (9)	NR (5)	NR (7)	NR (2)
Skeletal	NR (20)	NR (13)	NR (11)	NR (5)

NR = Not reported.

†Only five litters were evaluated for developmental toxicity at 500 mg/kg/day; includes single litter that was aborted at this dose in the analysis.

‡Standard deviation not reported.

¶Calculated from data provided in Suresh, 1993; values do not exactly match those presented in the study report.

§Incidence was not reported by individual fetus; rather, the incidence of each type of defect was reported, but more than one may have been seen in the same fetus.

#Significantly higher than control by ANOVA followed by Dunnett's test; litter is the statistical unit.

*Significantly different from control by chi-square test.

Table A8. Types and incidence of individual malformations† (Suresh, 1993).

	0 mg/kg/day	20 mg/kg/day	100 mg/kg/day	500 mg/kg/day
No. fetuses examined	133‡	78	77	28
Acephaly, abdominal hernia, external nares absent, shortened upper jaw, tail short & kinky, dorsal displacement of genital tubercle; multiple associated skeletal malformations	1 (1)			
Acrania, open eyelids, kinky tail, arthrogryposis and adactyly (one with microglossia, short upper jaw, thoracic and abdominal hernia, hemimelia, malformed skull, missing cervical centrum and arch; one with cleft palate and oligodactyly)		2 (1)		
Seal-shaped heart	1 (1)			
Cardiomegaly and seal-shaped-heart			1 (1)	
Dilated heart		4 (3)*	4 (2)*	5 (2)*
Dilated ventricle¶	1 (1)		1 (1)	1 (1)
Cleft palate	1 (1)			
Forelimb arthyrogryposis			1 (1)	
Liver hematoma				1 (1)
Gall bladder absent				1 (1)
Hydronephrosis	1 (1)	1 (1)		
Dilated ureter		1 (1)		
Fused sternebrae		1 (1)		
Malformed sternebrae	1 (1)	1 (1)		
Displaced sternebrae	1 (1)			
Missing ribs	4 (3)			
Bifurcated ribs	2 (2)			
Missing thoracic arch and centrum	3 (3)			
Extra lumbar arch and centrum				1 (1)

†Single fetuses may be represented more than once.
‡One fetus was not examined for skeletal malformations.
¶It is unclear from the study report if the dilated ventricles are of the heart or brain. For the purposes of this review, it is assumed that this description relates to the ventricles of the heart.
*Significantly different from control by chi-square test.

The total numbers of litters included in the data evaluation were 20, 13, 12 and 5 for the 0, 20, 100 and 500 mg/kg/day groups, respectively. Compared to controls, glyphosate treatment exerted no effect on the numbers of corpora lutea, implantations or pre-implantation loss. Although there was no effect on pre-implantation loss, it seems high across groups and especially high in the controls (48%). There were no historical control data provided for this endpoint. There was no effect on post-implantation loss, embryo/fetal death or fetal sex ratios. Although fetal body weights in the 20 and 100 mg/kg/day dose groups were reported to be significantly different from control, the weights were increased, the changes were less than 10% of control values and no dose–response across treatment groups was evident. Thus, the fetal body weight differences observed in these two dose groups are biologically inconsequential with respect to adverse effects.

There were no significant treatment-related increases in minor malformations or variations (Table A7). The incidence of visceral malformations appeared to increase with dose, but only 28 fetuses were available for examination in the high-dose group and the incidence in the low, mid and high dose groups was similar.

Major visceral malformations primarily affected the heart, but occurred in single incidences and showed no dose-response (Table A8). The exception was dilated heart, which was reported in 0, 4, 4 and 5 fetuses (0, 3, 2 and 2 litters) in the control, 20, 100 and 500 mg/kg/day dose groups, respectively. The terminology used to describe the heart malformations in this study is difficult to interpret (e.g. dilated heart, seal-shaped heart, cardiomegaly). For example, "dilated heart" was not defined in the study report, and how this malformation might relate to other heart defects (i.e. dilated right ventricle, seal-shaped heart, cardiomegaly) was not reported. Neither the criteria used to diagnose dilated heart nor measurements of the hearts were provided, so it is not possible to directly compare the dilated heart findings to the hearts of the fetuses in other studies. It is possible that the observation of dilated hearts was due to overly stringent inspection compared to criteria used by other laboratories. Only two litters exhibited major visceral malformations in the high dose group: one fetus in one litter and an unknown number in another (individual fetus data were not reported). It should be noted that the high-dose group findings were seen in the presence of extensive maternal toxicity, evidenced by clinical signs and a substantial number of maternal deaths.

This developmental toxicity study in rabbits had several weaknesses including a small number of litters available for examination due to low pregnancy rates and maternal deaths in the mid- and high-dose groups; these weaknesses severely limit the conclusions that can be drawn at these dose levels. It is especially difficult to extract data from the report to confirm the findings. Based on clinical signs and deaths at 500 mg/kg/day, it appears that the high dose in this study significantly exceeded the maximum tolerated dose. Therefore, the NOAEL for maternal toxicity is considered to be 100 mg/kg/day. Since no apparent developmental toxicity was observed at any dose, ≥100 mg/kg/day is considered the NOAEL for developmental toxicity. Because the study is limited by having too few fetuses available at the high dose of 500 mg/kg/day for adequate morphological assessment, the NOAEL for developmental toxicity could not be established for doses higher than 100 mg/kg/day.

Bhide & Patil (1989)

This study was conducted according to OECD 414 (1981). It is not clear to what extent this study followed GLP practices, but it appears to be only partially GLP-compliant at most. Female New Zealand white pregnant rabbits of age 24–28 weeks (1.5–2.0 kg) were used; they were acclimatized for six days. The females were mated with "adult vigorous males". The day of mating was considered GD 0. Doses were described as mg/kg doses in the study report, but based on the dosing description it is assumed that these were daily doses. Impregnated does were administered 0, 125, 250 or 500 mg/kg/day glyphosate technical (purity: 95%) by oral gavage on GD 6–18 (15 rabbits per group). The dosing volume was 5 mL/kg body weight; the test material was suspended in 0.1% gum acacia in water. Animals were observed twice daily for clinical signs, general behavior and body weight gain. Body weights were recorded on GDs 0, 6, 12, 18, 23 and 29. Food consumption was measured using the weight day intervals (e.g. GD 0–6, 6–12). The females were "delivered by caesarian section 1 day before expected delivery". The does were sacrificed on GD 29 and the uteri and ovaries examined for the numbers of corpora lutea, uterine weight, implantations, live and dead fetuses. Uteri from non-gravid animals were stained to examine for implantation sites (early resorptions). The does were further evaluated for gross pathological changes. All fetuses were

Table A9. Maternal and fetal outcome data for New Zealand white rabbits treated with glyphosate on gestational days 6–18† (Bhide & Patil, 1989).

	0 mg/kg/day	125 mg/kg/day	250 mg/kg/day	500 mg/kg/day
Maternal data				
No. animals on study	15	15	15	15
No. non-gravid	2	1	1	3
No. gravid does dead or sacrificed *in extremis*	0	0	0	0
No. that aborted	0	0	0	2
Embryo/fetal data				
Total No. litters examined	13	14	14	12‡
No. litters with no live fetuses	0	0	0	2
Mean No. corpora lutea	10.0 ± 1.69	10.1 ± 1.60	10.3 ± 1.44	9.8 ± 1.57
Mean No. implantations	9.0 ± 1.20	9.3 ± 1.33	9.4 ± 1.12	8.5 ± 1.05
Mean No. early resorptions	1.7 ± 3.22	1.1 ± 2.53	1.0 ± 2.56	1.9 ± 2.43
Mean % pre-implantation loss	21.3 ± 32.4	14.9 ± 24.09	14.7 ± 24.38	13.1 ± 6.34
Mean No. embryo/fetal death	0.07 ± 0.26	0.13 ± 0.35	0.27 ± 0.59	1.4 ± 2.20
Mean No. viable fetuses	7.3 ± 3.10	8.0 ± 2.59	8.0 ± 2.48	5.2 ± 3.03
Mean % post-implantation loss	NR	NR	NR	NR
Mean fetal body weight (gms) ¶	40.6 ± 16.6	47.1 ± 0.95	47.5 ± 1.38	48.7 ± 1.87
Total fetuses (litters) with malformations§				
Total fetuses (litters) with malformations‖	3 (3)	6 (6)	10 (10)	20 (14)
External	1 (1)	2 (2)	3 (3)	3 (3)
Visceral	1 (1)	4 (4)	5 (5)	12 (9)
Cardiovascular	0	1 (1)	1 (1)	2 (2)
Skeletal	1 (1)	0	2 (2)	5 (2)

NR = Not reported.

†Body weights, maternal endpoints and some developmental endpoints for all 15 animals in each group appear to be included in the data. It appears that only the gravid animals were included for data on sex ratio and fetal body weight.

‡The two litters that were aborted at this dose were included in the analysis.

¶Fetal body weight data are as reported in the study report; it is unclear if all 15 does were included in this calculation.

§The incidences of variations were not reported in this study.

‖The total number appears to be the sum of the fetuses and litters with external, visceral and skeletal malformations. Thus, the number of litters in the 500 mg/kg/day dose group is reported as 14 when there were only 12 litters in the group.

weighed and examined for external abnormalities, then processed by a fresh visceral dissection technique to determine sex and to examine for visceral abnormalities, including those of the heart and great vessels. The heads were removed, decalcified, fixed in Bouin's solution and examined separately. The remainder of each skeleton was prepared for the examination of osseous tissue using alizarin red.

The pregnancy outcome and delivery data for this study are shown in Table A9. The authors did not describe any statistical methods and there were no designations of statistical significance in their tables. The description of the results provided in Bhide & Patil (1989) was very limited. The numbers of non-pregnant animals were 2, 1, 1 and 3 in the 0, 100, 250 and 500 groups, respectively. There were no maternal deaths. Two does aborted in the 500 mg/kg/day group and were also included in the "No. Litters examined" endpoint. Data are given in the report for fetuses from 12 individual litters, but it is not clear which litters aborted.

The total number of litters included in the data evaluation for various endpoints was not explained in detail in the report and appear to be different for different endpoints. From the tables in the report, it appears that all 15 animals from each exposure group were evaluated for clinical signs, food consumption, maternal body weight gain, corpora lutea counts, implantations, resorptions and embryo/fetal viability. Consequently, these endpoints would appear to include data from animals that were non-pregnant or which aborted. For sex ratio, fetal body weights, and malformations, it appears that only the gravid animals were included (i.e. 13, 14, 14 and 12 in the 0, 100, 250 and 500 groups, respectively).

There were no dose-related clinical signs reported at any exposure level. Maternal food consumption and body weight gain appear to be reduced from that of controls at 500 mg/kg/day (food consumption, GDs 6–29; body weight gain, GDs 12–29). However, with the inclusion of animals that were non-pregnant or aborted, it is not possible to determine if this is a biologically significant result. There were no differences from control for the number of corpora lutea, implantations or pre-implantation loss. Embryo/fetal deaths were slightly higher and viability was slightly lower than controls. Post-implantation loss was not reported.

The incidences of external, visceral and skeletal malformations as well as total malformations are also shown in Table A9. Data were not reported for individual litters or fetuses, and the numbers for total fetuses and litters appear to be the sum of the number with external, visceral and skeletal defects. As a result, the authors reported 14 litters with malformations in the high-dose group when only 12 litters were examined. The numbers of fetuses and litters with variations are not reported.

The number of types of malformations reported was low in this study. Several malformations appeared to be increased in the high-dose group, including abnormal tail, missing kidney(s), absent postcaval lung lobe and rudimentary 14th rib. The latter two defects are typically considered variations. The only cardiovascular changes reported as malformations were IV septal defects; these were observed in 0, 1, 1 and 2 fetuses in the 0, 125, 250 and 500 mg/kg/day dose groups. A number of variations were reported, some of which have been included as malformations by other authors; for example, globular heart, small right ventricle, dilated lateral cerebral ventricles and fused thoracic centra. Other variations reported are commonly seen in rabbits (e.g. incomplete septation of lung lobes, irregular palatal rugae, blunt-tipped tail, irregular-shaped liver, globular-shaped kidneys, bilobed vertebral centra, reduced ossification of centra, sternebrae, pubis and skull). Several of these were increased in the high-dose group. In summary, there were a number of changes reported in the high-dose group, but the actual number of fetuses and litters affected is likely to be lower. However, this could not be determined because of the inadequate reporting of data.

This developmental toxicity study in rabbits is limited by the study design (e.g. the number of pregnant does surviving to term in each dose group, especially the high-dose group) and inadequate reporting of data (e.g. the inclusion of inappropriate animals in the calculation of some endpoints, insufficient description of study results). These limitations raise concern about using the results in any evaluation of glyphosate developmental toxicity and NOAELs are not proposed because of these limitations.

Rat developmental toxicity studies

The six rat developmental toxicity studies of glyphosate are summarized below and in Table A10. As in the rabbit studies, we have focused only on the results of the definitive studies. Because the impetus for concern regarding cardiovascular development was the rabbit studies and not the rat studies, these studies were not reviewed in the same level of detail as the rabbit studies. Rather, these studies are addressed in a combined discussion.

Table A10. Maternal and fetal outcome data from the developmental toxicity studies of glyphosate in rats.

Strain (#/group)	Duration of Treatment	Dose (mg/kg/day)	No. gravid females	No. maternal deaths	No. litters examined	Mean % post-implantation loss	Mean No. live fetuses	Mean fetal body wts (gms)	No. malformed fetuses (litters)	Cardiovascular malformations	Maternal toxicity	Ref.
Wistar (24)	GD 6–15[†]	0	22	0	22	9.9 ± 15.5	12.9 ± 2.4	4.86 ± 0.29	1 (1)	None	None	Moxon (2002)
		250	24	0	24	4.0 ± 5.1	12.4 ± 3.4	5.02 ± 0.33	1 (1)	None	None	
		500	23	0	23	7.8 ± 10.8	13.1 ± 2.7	4.95 ± 0.29	1 (1)	None	None	
		1000	24	0	23	5.8 ± 8.3	12.9 ± 2.9	4.96 ± 0.27	2 (2)	None	None	
Sprague–Dawley (25)	GD 6–15	0	23	0	23	4.9 ± 5.6	14.1 ± 3.3	3.81 ± 0.32	3 (3)	One IV septal defect and persistent truncus arteriosis, 1 retro-esophageal right-sided aortic arch	None	Wood (1996)
		100	24	0	24	4.4 ± 4.7	13.8 ± 2.2	3.99 ± 0.47	1 (1)	One IV septal defect	None	
		500	22	0	22	6.1 ± 7.0	14.0 ± 1.8	3.76 ± 0.29	0	None	None	
		1000	25	0	25	5.2 ± 6.8	14.0 ± 3.1	3.79 ± 0.40	0	None	None	
Sprague–Dawley Crj:CD (24)	GD 6–15	0	23	0	23	7.0 ± 6.1	13.7 ± 4.1	M: 3.6 ± 0.4 F: 3.3 ± 0.3	2 (1)	None	None	Hatakenaka (1995)[‡]
		30	24	0	24	6.8 ± 7.8	15.0 ± 2.1	M: 3.6 ± 0.2 F: 3.4 ± 0.3	1 (1)	None	None	
		300	24	0	24	7.4 ± 8.0	14.9 ± 2.8	M: 3.5 ± 0.4 F: 3.4 ± 0.4	3 (2)	One right aortic arch, 1 IV septal defect	None	
		1000	22	0	22	8.4 ± 9.1	15.4 ± 2.1	M: 3.6 ± 0.2 F: 3.4 ± 0.2	5 (2)	One IV septal defect	Loose stool	
Sprague–Dawley (25)	GD 6–15	0	23	0	23	6.1	13.7	3.96	1 (1)	None[*]	None	Brooker et al. (1991b)[§]
		300	23	0	23	7.3	12.7	3.90	2 (2)	None	None	
		1000	25	0	25	5.7	13.2	3.89	1 (1)	One IV septal defect	None	
		3500	25	3	22	3.6	13.1	3.71[‖]	3 (2)	One IV septal defect	Salivation, loose feces, noisy respiration, wet coats, gasping	
Wistar	GD 6–15	0	30	0	30	8	8.7	3.6 ± 0.4	External/visceral 5 (5) Skeletal 17 (8)[#]	None	None	Suresh (1991)
		1000	20	0	20	11	7.9	3.7 ± 0.3	External/Visceral 0 Skeletal 10 (6)[#]	None	None	
Sprague–Dawley COBS CD rats (25)	GD 6–19	0	22	0	22	4.2 ± 5.7	14.4 ± 1.3	3.5 ± 0.2	3 (3)	None	None	Tasker et al. (1980b)[$]
		300	20	0	20	1.4 ± 3.5	11.9 ± 4.4*	3.7 ± 0.7	0	None	None	
		1000	21	0	21	3.1 ± 5.6	14.3 ± 2.1	3.6 ± 0.2	0	None	None	
		3500	23	6	16	14.3 ± 24.0[¶]	11.5 ± 4.1*	3.2 ± 0.3**	10 (3)[%]	None	6/25 deaths: various signs of clinical toxicity; decreased weight gain due to weight loss on GD 6–9	

[†]Moxon (2002) designated the day of finding sperm as GD1. The exposure period listed here was adjusted using GD 0 as the day of finding sperm.
[‡]Hatakenaka (1995) did not report a combined mean fetal weight, but rather reported the mean fetal weight for males (M) and females (F) separately. Individual animal data were not available to calculate the combined mean fetal weight. Mean post-implantation loss also was not reported but was calculated by the present authors based on data provided in the study report.
[*]One small IV septal defect was considered a variation by the authors.
[§]Brooker et al. (1991b) did not provide standard deviation values for mean post-implantation loss, mean number of live fetuses, or mean fetal body weights.
[‖]Undescended testis and unascended kidneys were considered minor malformations by the authors but are included here.
[#]Several bilobed vertebral centra and delayed ossification of various bones were reported as major malformations, but none fit the author's definition of a major malformation. Individual fetal data were incompletely reported, so it is difficult to determine which type of defects which fetus and litter. The number of fetuses (litters) given here is taken from Table A9 in Suresh (1991).
[$]Post-implantation loss percentages and standard deviations calculated from individual animal data in Tasker et al. (1980b); statistical significance was not calculated.
[%]Includes six fetuses in one litter with a syndrome of bent tail, open eyelids, missing kidneys and ureters, and various skeletal defects and three fetuses in another litter with dwarfism. All malformations were seen in the historical controls.
[¶]$p < 0.01$, Kruskal–Wallis followed by distribution-free Williams' test; litter was the statistical unit.
*$p < 0.05$, ANOVA followed by Dunnett's test; statistical unit was not specified.
**$p < 0.01$, ANOVA followed by Dunnett's test; statistical unit was not specified.

In the rat studies, the day of finding sperm was designated as GD 0,[2] except in the study by Moxon (2002), which referred to it as GD 1. For the purpose of discussing the timing of exposure and outcome measurements in the rat studies in an integrated fashion, the day of mating and succeeding gestational days have been corrected to GD 0 for Moxon (2002). With the exception of Suresh (1991), all of the studies used a randomized (block) design to assign the impregnated females to treatment groups ($n = 20$–25 animals/group). In contrast, Suresh (1991) had only one exposure level (1000 mg/kg/day) and it is unclear how the females were assigned to the control and treated groups. Each study included a vehicle control group (0 mg/kg/day). Glyphosate exposure levels ranged from 30 to 3500 mg/kg/day across the studies and were administered as glyphosate technical (i.e. glyphosate acid). The exposure was via oral gavage on GDs 6–15, except in Tasker et al. (1980b), in which animals were exposed on GDs 6–19. Regular observations of the females for mortality, clinical signs and body weight measurements were made in all studies; food consumption was measured in most studies.

In several cases, females were euthanized during the course of the study due to issues that were not associated with glyphosate exposure (e.g. mis-dosing, intubation error). At exposure levels lower than 1000 mg/kg/day, no maternal toxicity was observed over the course of the studies. In Wood (1996), lethargy was reported in two animals on 2 days during treatment; this finding was not considered sufficient evidence of maternal toxicity. Also, in Brooker et al. (1991b), noisy respirations were reported in two animals on a single day. Again, due to the transient nature of the finding, it was not considered evidence of maternal toxicity. At 1000 mg/kg/day and higher, animals in three of the six studies showed signs of lethargy, as well as respiratory and gastrointestinal distress. At 1000 mg/kg/day and lower, there were no maternal deaths. In the two studies that used doses as high as 3500 mg/kg/day (Brooker et al., 1991b; Tasker et al., 1980b), there were three (two considered treatment-related) and six deaths, respectively.

For the most part, exposure levels less than 1000 mg/kg/day did not affect food consumption except during short intervals at the beginning of treatment (Hatakenaka, 1995; Wood, 1996) or post-dosing (Hatakenaka, 1995). At 3500 mg/kg/day, Brooker et al. (1991b) reported a treatment-related decrease in food consumption during the exposure period (GD 6–15); Tasker et al. (1980b) also tested 3500 mg/kg/day, but did not report food consumption values.

Maternal body weight was not affected in any of the studies at exposure levels lower than 3500 mg/kg/day. At 3500 mg/kg/day, Brooker et al. (1991b) reported that maternal body weight and body weight gain were reduced (GD 6–20); in contrast, Tasker et al. (1980b) did not observe a similar effect at this dose.

Maternal animals were sacrificed on GD 20, except in Moxon (2002) where the animals were sacrificed on GD 21. Standard endpoints of reproductive and developmental toxicity were evaluated (Table A10). There were no dose-related effects on the numbers of corpora lutea, implantations, live and dead fetuses, fetal weight or fetal sex ratio at 1000 mg/kg/day and below. At 3500 mg/kg/day, Brooker et al. (1991b) reported reduced mean fetal weight. At this same dose, Tasker et al. (1980b) reported a statistically significant increased number of resorptions, significantly decreased mean numbers of implantations and viable fetuses per dam, and diminished mean fetal body weights compared to controls. Tasker et al. (1980b) also reported statistically significant decreased mean numbers of implantations and viable fetuses per dam in the 300 mg/kg/day treatment group, but this effect was not observed at 1000 mg/kg/day. Consequently, there was no clear dose–response effect for this parameter.

Glyphosate did not produce adverse effects on structural development (Table A10). Tasker et al. (1980b) reported 10 fetuses with malformations in three litters at 3500 mg/kg/day. Six of these fetuses were in one litter and showed a syndrome of bent tail, open eyelids, missing kidneys and ureters, and various skeletal defects. Three fetuses in another litter were reported to have dwarfism. All these effects were within the historical control range. With respect to specific cardiovascular malformations, three of the six studies reported no effects (Moxon, 2002; Suresh, 1991; Tasker et al., 1980b). The other three studies (Brooker et al., 1991b; Hatakenaka, 1995; Wood, 1996) reported single incidences of specific defects; in two studies, they were observed in the controls as well as in the exposed fetuses. These results indicate that of glyphosate exposure of pregnant rats at doses of up to 3500 mg/kg/day does not produce any evidence of cardiovascular malformations.

[2]Brooker (1991b) & Suresh (1991) refer to it as Day 0 of Pregnancy.

Critical Reviews in Toxicology

http://informahealthcare.com/txc
ISSN: 1040-8444 (print), 1547-6898 (electronic)

Crit Rev Toxicol, 2015; 45(3): 185–208
© 2015 Informa Healthcare USA, Inc. DOI: 10.3109/10408444.2014.1003423

informa
healthcare

REVIEW ARTICLE

Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies

Helmut Greim[1], David Saltmiras[2,6], Volker Mostert[4,5], and Christian Strupp[3,6]

[1]*Technical University Munich, Arcisstr. 21, 80333 Munich, Germany,* [2]*Monsanto Company, 800 North Lindbergh Blvd., 63167 St. Louis, MO, USA,* [3]*ADAMA MAH BV Amsterdam NL Schaffhausen Branch, Spitalstrasse 5, 8200 Schaffhausen, Switzerland,* [4]*Knoell Consult GmbH, Dynamostr. 19, 68165 Mannheim, Germany,* [5]*Extera, Nelly-Sachs-Str. 37, 40764 Langenfeld, Germany, and* [6]*Glyphosate Task Force, http://www.glyphosatetaskforce.org/*

Abstract

Glyphosate, an herbicidal derivative of the amino acid glycine, was introduced to agriculture in the 1970s. Glyphosate targets and blocks a plant metabolic pathway not found in animals, the shikimate pathway, required for the synthesis of aromatic amino acids in plants. After almost forty years of commercial use, and multiple regulatory approvals including toxicology evaluations, literature reviews, and numerous human health risk assessments, the clear and consistent conclusions are that glyphosate is of low toxicological concern, and no concerns exist with respect to glyphosate use and cancer in humans. This manuscript discusses the basis for these conclusions. Most toxicological studies informing regulatory evaluations are of commercial interest and are proprietary in nature. Given the widespread attention to this molecule, the authors gained access to carcinogenicity data submitted to regulatory agencies and present overviews of each study, followed by a weight of evidence evaluation of tumor incidence data. Fourteen carcinogenicity studies (nine rat and five mouse) are evaluated for their individual reliability, and select neoplasms are identified for further evaluation across the data base. The original tumor incidence data from study reports are presented in the online data supplement. There was no evidence of a carcinogenic effect related to glyphosate treatment. The lack of a plausible mechanism, along with published epidemiology studies, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans.

Keywords

amino acid, carcinogenicity, epidemiology, glyphosate, herbicide, mouse, neoplasm, phosphonomethylglycine, Roundup, rat, regulatory, tumor

History

Received 6 November 2014
Revised 19 December 2014
Accepted 28 December 2014
Published online 24 February 2015

Table of Contents

Address for correspondence: David Saltmiras, Monsanto Company, 800 North Lindbergh Blvd., 63167 St. Louis, MO, USA. Tel: + 1 (314) 684-8856. E-mail: david.a.saltmiras@monsanto.com

Introduction

Glyphosate (Figure 1), an aminophosphonic analog of the natural amino acid glycine, is widely used as an herbicide for the control of annual and perennial grasses and broadleaved weeds. Glyphosate inhibits 5-enolpyruvateshikimate-3-phosphate synthase (EPSPS), an enzyme of the aromatic acid biosynthesis pathway, which is not present in the animal kingdom. Glyphosate-based herbicide formulations (GBFs) were introduced in 1974 and are formulated with

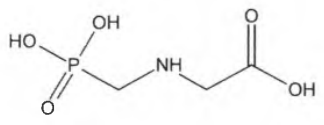


Figure 1. Structure of glyphosate acid.

sodium-, potassium-, ammonium- and isopropyl ammonium-salt forms of the active ingredient. The bulk-manufactured active herbicide glyphosate has the synonyms glyphosate technical acid, technical grade glyphosate and glyphosate acid.

The economic importance of glyphosate for growers is high. It has been estimated that a hypothetical ban of glyphosate would lead to decreases in the production of wheat, fodder, maize and oilseeds, by 4.3–7.1%, with the result of an estimated annual welfare loss of 1.4 billion USD to society in the European Union alone (Schmitz and Harvert 2012). Furthermore, glyphosate plays an important role in integrated pest management strategies, and affords the environmental benefit of substantially reduced soil erosion resulting from of no-till and reduced-till agriculture.

The long-term toxicity and carcinogenicity of glyphosate has been investigated by multiple entities including academia, registrants, and regulatory authorities, and the data generated have been evaluated in support of herbicide regulatory approvals in many world regions including the USA (US EPA 1993) and the European Union (EC 2002), and several scheduled reevaluations are currently ongoing in the USA, Canada, Japan and Europe (Germany Rapporteur Member State 2015a), with imminent conclusions.

Studies of appropriate scientific quality are the basis for regulatory decision making. Mandatory testing guidelines (TGs) exist for toxicological studies submitted for regulatory review of active substances for plant protection in many regions of the world. Such TGs have been released, *inter alia*, by the United States Environmental Protection Agency (US EPA 2012), the European Union (EU 2008), the Japanese Ministry of Agriculture, Forestry and Fisheries (JMAFF 2000), and the Organization of Economic Co-operation and Development (OECD 2012b). These TGs set quality standards for each type of study by giving guidance regarding test species, strains, and number of animals to be used, the choice of dosing, exposure duration, and parameters to be measured and observed, as well as for the reporting of results. Due to the lack of effective legal and regulatory provisions for the sharing of vertebrate study data in the past, and to guarantee the safety of technical glyphosate obtained from different processes of synthesis, several manufacturers of glyphosate had to initiate toxicological testing programs of their own. Occasionally, regulatory studies had to be repeated to reflect major changes in the underlying TG. In the case of glyphosate, this has given rise to a multitude of studies for the same toxicological endpoints, leading to the availability of an extraordinarily robust scientific study database that can be considered unique among pesticides, industrial chemicals, and pharmaceuticals. Such a remarkable volume of studies addressing the same endpoints, conducted over the last 40 years by several independent companies and laboratories while toxicology test guidelines have evolved, warrants investigation for consistency, reliability, and application to their intended purpose: identifying potential human health hazards and setting appropriate endpoints for human health risk assessment. Studies conducted with equivalent test substances using the same TG are readily comparable and can be evaluated by regulators following standardized schemes. Minor differences in the findings reported by such repetitive studies are attributable to statistical chance, natural biological variability, type of basal diet, rate of feed consumption, animal strain differences, choice of dose levels, inter-strain genetic drift over time due to varying vendor breeding practices, changes in animal care and husbandry practices across laboratories over the years, inter-laboratory variations in clinical measurements, and differences between individual pathologist evaluation and interpretation of tissue specimens.

Glyphosate is under significant political pressure due to its widespread use, particularly in association with use on genetically modified crops. One focus area of contention has been the human safety of glyphosate, which has been repeatedly challenged by interest groups via the media, as well as select research publications in the scientific literature (Antoniou et al. 2012, Aris and Leblanc 2011, Aris and Paris 2010, Benachour and Seralini 2009, Gasnier et al. 2010, Paganelli et al. 2010, Romano et al. 2012, Romano et al. 2010). To that end, one specific publication by Seralini et al. (2012, retracted) drew significant criticism from both the toxicology and broader scientific communities (Barale-Thomas 2013, Berry 2013, de Souza and Oda 2013, Grunewald and Bury 2013, Hammond et al. 2013, Langridge 2013, Le Tien and Le Huy 2013, Ollivier 2013, Panchin 2013, Sanders et al. 2013, Schorsch 2013, Tester 2013, Trewavas 2013, Tribe 2013). After a special review of the investigators' raw data by a mutually agreed-upon expert panel, the manuscript was retracted by *Food and Chemical Toxicology* (FCT), for reasons of inconclusive data and unreliable conclusions (Hayes 2014). The Editor of the *International Journal of Toxicology* highlighted this manuscript as an example of possible failure of the peer review process in a well-respected toxicology journal with an editorial board of well-known and respected toxicologists (Brock 2014). The manuscript was later republished without peer-review in an open access journal (Seralini et al. 2014), but will not be addressed in this data evaluation due to the inappropriate study design, insufficient reporting of tumor incidence data, and the lack of a data supplementary to the manuscript.

The chronic/carcinogenicity studies discussed in this paper have been submitted to and evaluated by a variety of agencies over time, including the World Health Organization (WHO/FAO 2004b, WHO/FAO 2004a), the United States Environmental Protection Agency (US EPA 1993), the European Rapporteur Member State Germany for the initial glyphosate Annex I listing (EC 2002) and the recent European re-evaluation (Germany Rapporteur Member State 2015a), as well as the ongoing reevaluations in the USA, Canada and Japan. These regulatory bodies, drawing upon internal and/or external expertise, have consistently concluded that glyphosate is devoid of carcinogenic risk to humans.

The purpose of this article is to provide the broader scientific community with insight into this large body of carcinogenicity data on glyphosate, originally generated for

regulatory purposes. Each study discussed in this review has been assigned a reliability score in Tables 3–19, following the Klimisch scoring system (Klimisch et al. 1997). In this system, a score of 1 is assigned to studies that are fully reliable based on compliance with Good Laboratory Practice (GLP) and adherence to appropriate study guidelines. A score of 2 is appropriate if some guideline requirements are not met, but if these deficiencies do not negatively affect the validity of the study for its regulatory purpose. Studies with a reliability of 3 employ a test design that is not fit for the scientific purpose of the study, due to significant scientific flaws, or the objective of the study not covering the regulatory endpoints, or both. Such studies can provide supplemental information but do not allow a stand-alone appraisal of a regulatory endpoint. No studies were assigned a reliability of 4, since each report contained sufficient information to judge the validity of the study.

This manuscript presents the robust glyphosate carcinogenicity data generated by industry. Study summaries will focus on carcinogenicity evaluation, to allow third parties the opportunity to independently evaluate the carcinogenicity data presented alongside other relevant data on carcinogenicity, i.e. genotoxicity testing and epidemiology, and facilitate a multidisciplinary carcinogenicity assessment as proposed in the literature, by recognized experts in the fields of toxicology and human health risk assessment (Adami et al. 2011).

Absorption, distribution, metabolism and excretion of glyphosate

A number of absorption, distribution, metabolism, and excretion studies (ADME) have been conducted on glyphosate for evaluation in regulatory submissions (EC 2002, US EPA 1993, WHO/FAO 2004a) and also by academic institutions (Anadon et al 2009). Glyphosate consistently demonstrates low gastrointestinal absorption (20–40%). Its metabolism is very limited, whereby only small quantities of a single metabolite, aminomethylphosphonic acid (AMPA), are eliminated in feces. AMPA is likely produced by the limited metabolism of glyphosate by the gastrointestinal microflora, rather than via mammalian metabolism. Glyphosate is structurally akin to a phase II metabolite, a glycine-conjugate of methyl phosphonate, and thus avails itself to rapid urinary excretion. Systemic elimination is biphasic, with alpha-phase half-lives in the range of 6–14 h (Anadon et al. 2009, WHO/FAO 2004a).

Toxicological properties of glyphosate

Table 1 contains a short overview of toxicological endpoints of glyphosate that have been published in the List of Endpoints identified for glyphosate by the Rapporteur in the European Union under Regulation 1107/2009 (Germany Rapporteur Member State 2015c). Glyphosate is of low acute toxicity via all routes of exposure. Glyphosate's active ingredient, an organic acid, has an irritating effect on mucosa which is evidenced by eye irritation and effects on oral and gastrointestinal mucosa; final formulated products contain more neutral pH salt forms, as reflected in the tabulated eye irritation data reported in Table 11, on page 109 of the 2004 JMPR Toxicological Evaluation (WHO/FAO 2004a). Glyphosate is not mutagenic, not neurotoxic, and has no effect on pre-natal development and fertility at doses not exceeding the maximum tolerated dose (MTD).

Genotoxicity

Very recently, a review of the vast body of genotoxicity studies on glyphosate and GBFs has been published (Kier and Kirkland 2013), including an online data supplement presenting detailed data from 66 separate *in vitro* and *in vivo* genotoxicity assays. The authors incorporated these studies and published genotoxicity data into a weight-of-evidence analysis. The vast majority (over 98%) of the available bacterial reversion and *in vivo* mammalian micronucleus and chromosomal aberration assays were negative. Negative results for *in vitro* gene mutation and a large majority of negative results for clastogenic effect assays in mammalian cells support the conclusion that glyphosate is not genotoxic for these endpoints in mammalian test systems. DNA damage effects are reported in some instances for glyphosate at high or toxic dose levels. The compelling weight of evidence is that glyphosate and typical GBFs are negative in core assays, indicating that the reported high-dose effects are secondary to toxicity and are not due to DNA-reactive mechanisms. Mixed results were observed for micronucleus assays in non-mammalian systems and DNA damage assays of GBFs. These effects of GBFs may also be associated with surfactants present in the formulated products. Kier and Kirkland conclude that glyphosate and its typical formulations do not present significant genotoxic risk under normal conditions of human or environmental exposures.

Epidemiology

Available epidemiological studies of glyphosate and cancer endpoints were recently reviewed (Mink et al. 2012). Seven cohort studies and fourteen case-control studies examining a potential association between glyphosate and one or more cancer outcomes were subjected to a qualitative analysis. The review found no consistent pattern of positive associations between total cancer (in adults or children) or any site-specific cancer, and exposure to glyphosate. A recent review article (Alavanja et al. 2013) cites one epidemiology study associating glyphosate use with non-Hodgkin's lymphoma (NHL), and accepts the study findings *prima facie*. However, Alavanja et al. (2013) did not highlight six other published epidemiology studies which evaluated glyphosate use and NHL, noting that any association between NHL and glyphosate use was null or not statistically significant. All seven studies were scrutinized by Mink et al. (2012). NHL is not a specific disease, as mentioned in both the epidemiology review publications above, but is rather multiple presentations of lymphoma which are simplistically classified as not being Hodgkin's lymphoma (HL). This dichotomous classification of HL/NHL was rejected by the World Health Organization in 2001, whereby 43 different lymphomas of various etiologies were precisely characterized (Berry 2010). The Bradford Hill criteria are often applied in efforts to determine whether an association between a health effect and human exposure may be deemed causal. However, an important premise often overlooked from Sir Austin Bradford Hill's famous speech of 1965, is that before applying these criteria, the observations should "reveal an association between two variables, perfectly clear-cut and beyond what we care to attribute to the play of chance" (Bradford Hill 1965). This predicate of the association being "perfectly clear-cut"

Table 1. Summary of toxicological endpoints for glyphosate (Germany Rapporteur Member State 2015c).

Endpoint	Value	Remark
Oral absorption	*ca* 20%	Rat, *in vivo*
Dermal absorption	< 1%	Human, *in vitro*, 0.015 g glyphosate/L
Rat LD50 oral	> 2000 mg/kg bw	
Rat LD50 dermal	> 2000 mg/kg bw	
Rat LC50 inhalation	> 5 mg/L	4-h exposure
Skin irritation	Not irritating	
Eye irritation	Acid: moderately to severely irritating Salts: slight or non-irritating	
Skin sensitization	Not sensitizing (LLNA, Magnusson-Kligmant, and Buehler test)	
Genotoxicity	Not genotoxic (*in vitro* and *in vivo*)	
Chronic toxicity	BW gain, liver (organ weight ↑, clinical chemistry, histology); salivary glands (organ weight ↑, histology); stomach mucosa and bladder epithelium(histology); eye (cataracts), caecum (distention, organ weight ↑) NOAEL = 100 mg/kg bw/day (2-yr rat)	Critical study used for ADI setting
Reproductive toxicity	Reduced pup weight at parentally toxic doses. NOAEL = 300 mg/kg bw/day	
Developmental toxicity	Post-implantation loss, fetal BW & ossification ↓; effects confined to maternally toxic doses Rat NOAEL: 300 mg/kg bw/day Rabbit NOAEL: 50 mg/kg bw/day	
Delayed neurotoxicity	No relevant effects, NOAEL: 2000 mg/kg bw/day	
Acceptable Daily Intake (ADI)	0.5 mg/kg bw/day Based on developmental toxicity in rabbits	Safety factor 100
Acceptable Operator Exposure Level (AOEL)	0.1 mg/kg bw/day Based on maternal toxicity in rabbit teratogenicity study	Safety factor 100 Corrected for oral absorption of 20%

was recently highlighted as requiring statistical significance, wherein the confidence interval of a relative risk ratio is bracketed above 1.0, as well as concluding that the association may not be attributable to bias, confounding or sampling error (Woodside and Davis 2013). According to Bradford Hill, should an epidemiology study be considered to demonstrate a "perfectly clear-cut" association between glyphosate exposure and a human health outcome, only then should the Bradford Hill criteria be investigated to determine whether there is causality. To date, no such "perfectly clear-cut" association between glyphosate exposure and any cancer exists. However, investigative toxicology is an important discipline to evaluate chemicals before any human exposure occurs, and these data may inform subsequent considerations of whether associations are attributable to causality. One Bradford Hill criterion in establishing disease causality is plausibility, based on known disease etiologies. In the case of lymphoma, there are numerous etiologies for the numerous and different lymphoma diseases, and as such, each lymphoma type should be investigated for a plausible mechanism to determine whether causality may be attributed an appropriately qualified association. Another Bradford Hill criterion is identification of a biological gradient, or dose-response, which is a key consideration in the following data evaluation.

Chronic toxicity studies

Several one-year chronic studies have been undertaken in dogs and one in rats, in addition to the many chronic/carcinogenicity studies with one-year interim sacrifice groups. Current Test Guidelines (OECD, EPA, EU and JMAFF) for long-term studies clearly state that the highest dose tested should either be at the maximum tolerated dose (MTD), conventionally interpreted as a dose causing non-lethal toxicity, often noted as reduced body weight gain of 10% or more (IUPAC 1997). For test substances with low toxicity, a top dose not exceeding 1000 mg/kg bw/day may apply, except when human exposure indicates the need for a higher dose level to be used (OECD 2012a). All human exposure estimates are well below 1 mg/kg bw/day (see Discussion section), so that 1000 mg/kg bw/day is a practical limit dose for glyphosate in carcinogenicity studies. In the original pre-guideline chronic/carcinogenicity study, rats were dosed well below the MTD (Monsanto 1981), but in many subsequent studies, they were dosed well in excess of today's standard practice of not exceeding the dose limit.

Dog chronic studies

Five one-year oral toxicity studies have been conducted in Beagle dogs (Table 2). Studies in dogs are not designed to detect neoplastic effects; these studies are therefore not discussed in detail. Nonetheless, the histopathological investigations that are part of one-year dog studies according to OECD TG 452 did not identify (pre) neoplastic lesions related to the administration of glyphosate.

Treatment-related effects in dog studies with glyphosate were restricted to non-specific findings like small retardations in body weight gain and soft stools, which are common findings in this test species. The lowest relevant NOAEL (i.e. highest NOAEL below the lowest LOAEL) in dogs on a daily treatment regimen for one year was 500 mg/kg bw/day. These studies demonstrate that glyphosate is of very low toxicity following repeat exposures in dogs.

Rat chronic studies

The chronic toxicity potential of glyphosate acid was assessed in a 12-month feeding study (conducted in 1995 and 1996) in

Table 2. Summary of one-year toxicity studies with glyphosate.

Authors:	Monsanto (1985)
Reliability/Justification	2 Study performed according to GLP and OECD guideline requirements, with the following deviation: MTD not reached by highest dose
Substance:	Glyphosate (96.1% pure)
Species/Strain:	Dog/Beagle, groups of 6 ♂ and 6 ♀
Administration route:	Oral, capsule
Doses:	0, 20, 100, 500 mg/kg bw/day
Duration:	1 year
Findings:	≥ 500 mg/kg bw/day: NOAEL (♂ + ♀) no treatment-related effects
Authors:	**Cheminova (1990)**
Reliability/Justification	1 Study performed according to GLP and OECD guideline requirements, with no deviations.
Substance:	Glyphosate (98.6–99.5% pure)
Species/Strain	Dog/Beagle, groups of 4 ♂ and 4 ♀
Administration route:	Oral, capsule
Doses:	0, 30, 300, 1000 mg/kg bw/day
Duration:	1 year
Findings:	300 mg/kg bw/day: NOAEL (♂ + ♀) 1000 mg/kg bw/day: soft, liquid stools (attributable to capsule administration); equivocal impact on body weight gain
Authors:	**Nufarm (2007)**
Reliability/Justification	2 Study performed according to GLP and OECD guideline requirements, with the following deviation: MTD not reached by highest dose
Substance:	Glyphosate (95.7% pure)
Species/Strain	Dog/Beagle, groups of 4 ♂ and 4 ♀
Administration route:	Oral, capsule
Doses:	0, 30, 125, 500 mg/kg bw/day
Duration:	1 year
Findings:	≥ 500 mg/kg bw/day: NOAEL (♂ + ♀) No treatment-related effects
Authors:	**Arysta Life Sciences (1997c)**
Reliability/Justification	2 Study performed according to GLP and OECD guideline requirements, with the following deviation: MTD not reached by highest dose
Substance:	Glyphosate (94.6% pure)
Species/Strain	Dog/Beagle, groups of 4 ♂ and 4 ♀
Administration route:	Oral, diet
Concentration:	0, 1600, 8000, 50 000 ppm diet (♂ about 34.1, 182, 1203 mg/kg bw/day; ♀ about 37.1, 184, 1259 mg/kg bw/day)
Duration:	1 year
Findings:	182/184 mg/kg bw/day: NOAEL (♂/♀) At high dose: loose stool, non-statistically significant retarded body weight gain, decreased urinary pH, slight and non-statistically significant focal pneumonia (♀), minor clinical chemistry changes of Cl ↑, albumin ↓, P ↓ (♀)
Authors:	**Syngenta (1996a)**
Reliability/Justification	1 Study performed according to GLP and OECD guideline requirements, with no deviations.
Substance:	Glyphosate (95.6% pure)
Species/Strain	Dog/Beagle, groups of 4 ♂ and 4 ♀
Administration route:	Oral, diet
Concentration:	0, 3000, 15 000, 30 000 ppm diet (♂ about 90.9, 440, 907 mg/kg bw/day; ♀ about 92.1, 448, 926 mg/kg bw/day)
Duration:	1 year
Findings:	15 000 ppm diet: NOAEL (♀) ≥ 30 000 ppm diet: NOAEL (♂): No treatment-related effects 30 000 ppm diet: slight body weight reduction (♀)
Authors:	**Syngenta (1996b)**
Reliability/Justification	1 Study performed according to GLP and OECD guideline requirements, with no deviations.
Substance:	Glyphosate (95.6% pure)
Species/Strain	Rat/Wistar Alpk: AP,SD, groups of 24 ♂ and 24 ♀
Administration route:	Oral, diet
Concentration:	0, 2000, 8000, 20 000 ppm diet (♂ about 141, 560, 1409 mg/kg bw/day; ♀ about 167, 671, 1664 mg/kg bw/day)
Duration:	1 year
Findings:	8000 ppm diet: NOAEL (♂+♀) 20 000 ppm diet: parotid salivary glands (focal basophilia of the acinar cells considered non-adverse adaptive response, ♂: 13/24, ♀: 15/24), body weight reduction

24 male and female Wistar rats per group, dosed at 0, 2000, 8000 and 20 000 ppm (Syngenta 1996). The mean achieved dose levels were 0, 141, 560 and 1409 mg/kg bw/day for males, and 0, 167, 671 and 1664 mg/kg bw/day for females. Spastically significant reductions in bodyweight were evident in animals receiving 20 000 ppm glyphosate acid, together with a marginal reduction in bodyweight in rats receiving 8000 ppm, but food consumption relative to controls was lower for these dose groups, suggesting reduced palatability of the diets containing these doses of glyphosate. There were no toxicologically significant or treatment-related effects on hematology, blood and urine clinical chemistry, or organ weights (Table 2).

The treatment-related pathological finding, that is increased incidence of mild focal basophilia, and a hypertrophy of the acinar cells of the parotid salivary gland in both sexes which had received 20 000 ppm glyphosate acid, is considered an adaptive response due to oral irritation from the ingestion of glyphosate, an organic acid, in the diet. This was verified by

mode of action investigations and studies with dietary administration of citric acid, a non-toxic organic acid with irritation properties and pH dilution curve similar to those of glyphosate (Saltmiras et al. 2011), which elicited the same response in the acinar cells of the parotid salivary glands.

In conclusion, the 12-month NOAEL in rats for glyphosate acid, as determined from this study, is 8000 ppm (corresponding to 560 mg/kg bw/day in males and 671 mg/kg bw/day in females). This study does not cover neoplastic endpoints. These were addressed in a subsequent study by the same sponsor (Syngenta 2001). Consistent with the findings observed in dogs, this study demonstrates that glyphosate is of very low toxicological concern following long-term daily exposures.

Similarly, most of the following 2-year rat carcinogenicity studies included additional groups for 1-year interim sacrifice to evaluate chronic toxicity. These studies did not elucidate significant toxicological concerns for chronic dietary exposures to glyphosate in rats in multiple expert reviews by governmental agencies and several technical branches of the World Health Organization including the Joint Meeting on Pesticide Residues Toxicological Evaluations (WHO/FAO 2004a).

Carcinogenicity studies

Chronic/carcinogenicity tests are designed to simulate lifetime exposures to an individual chemical and represent the most robust *in vivo* assay to evaluate the effects of chronic exposure including carcinogenicity. These models are biological systems with natural background variability due to tumor formation as a natural consequence of aging. Glyphosate was found to have no carcinogenic potential, which is reflected in the data showing only background noise of spontaneous tumors across the wide range of doses. Normal biological variability should display various tumor types across all dose groups without an apparent dose-response. The study summaries discuss "select neoplasms", identified by the authors as having an elevated incidence above concurrent controls across one or more dose groups, most of which lacked statistical significance and/or dose-response within an individual study. These tumors are then evaluated in the context of the whole data set, to provide a robust weight of evidence overview for the doses spanning several orders of magnitude. While not all studies have select neoplasms identified in the individual study summary tables, select neoplasms for all studies are reported in Tables 20–23. Summary tables of the select neoplasms footnote the strain tested for each dose, to allow consideration of strain differences in spontaneous tumor susceptibility (Tables 20–23). In addition, complete tumor incidence summary tables have been extracted from the original eight rat (the published rat study, Study 9, is not included) and five mouse study reports or study files, and posted in their original format, as a comprehensive online data supplement to this manuscript.

Rat carcinogenicity

A total of nine chronic/carcinogenicity studies in the rat, including one peer-reviewed published study, were available for review. This duplication of large-scale studies in the same animal model using the same test substance is not consistent with today's broader appreciation for animal welfare and the reduction of unnecessary animal testing. However, these studies offer the opportunity for a critical discussion of findings in individual studies in the context of the larger body of data. Wistar and Sprague Dawley were the strains used for the bioassays in rats. Seven studies were conducted under conditions of GLP, and two studies were not under GLP (Study 1, conducted before the introduction of GLP; Study 9, non-GLP). Most studies in rats were designed as combined chronic toxicity/carcinogenicity studies, with interim sacrifices after 12 months of treatment for the assessment of non-neoplastic chronic toxicity. Statistical methods are noted in the manuscript tables where statistical significance was attained. Statistical differences in neoplasm incidence summary tables are reported in the online data supplements. Chronic endpoints and NOAEL values are captured in each study summary table; however, the following study reviews focus on carcinogenicity.

Study 1 (Monsanto 1981)

An early study into the long-term effects of orally administered glyphosate in the rat was conducted between 1978 and 1980 (Monsanto 1981), prior to the adoption of international test guidelines and GLP standards (Tables 3–6). Nonetheless, the test protocol was broadly compliant with OECD TG 453 (1981). However, an MTD was not reached and the high dose was well below an acceptable dose limit of 1000 mg/kg bw/day. Therefore, this study is rated Klimisch 3 for reliability, and is considered inadequate for carcinogenicity evaluation from a regulatory perspective.

Groups of 50 male and 50 female Sprague Dawley rats were administered glyphosate acid in the diet, at concentrations of 0, 30, 100 and 300 ppm, for up to least 26 months. The mean doses achieved were 0 (control), 3, 10, and 31 mg/kg bw/day for the males, and 0 (control), 3, 11, and 34 mg/kg bw/day for the females. Study results are summarized in Table 3.

In general, the incidences of all neoplasms observed in the treated and control animals were similar, or occurred at low incidence, such that a treatment-related association could not be made. The most common tumors found were common spontaneous neoplasms, as reported in the literature relating to rat (Johnson and Gad 2008), in the pituitary glands of both control and treated animals (Table 4). In the females, mammary gland tumors were the next most common neoplasm across control and dose groups (see data Supplementary Study 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423).

Table 3. Study 1–26-month feeding study of glyphosate in rats (Monsanto 1981).

Study owner:	Monsanto (1981)
Reliability/Justification:	3 Study not performed under GLP. High-dose well below MTD. Does not conform to modern testing standards.
Substance:	Glyphosate (98.7% pure)
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀
Administration route:	Diet
Concentration:	0, 30, 100, 300 ppm diet (♂ about 0, 3, 10, 31 mg/kg bw/day; ♀ about 0, 3, 11, 34 mg/kg bw/day)
Duration:	26 months
Findings:	≥ 300 ppm diet: NOAEL (♂ + ♀) No treatment-related effects
Select neoplasms:	Pituitary adenoma, Testes interstitial cell

Table 4. Study 1 – Pituitary tumor findings.

	Dose group (mg/kg bw/day)							
	Males				Females			
Tumors	0	3.05	10.3	31.49	0	3.37	11.22	34.02
Pituitary tumors	Number of animals/total number examined (% per group)							
Adenomas - B	16/48 (33)	19/49 (39)	20/48 (42)	18/47 (38)	34/48 (70)	29/48 (60)	31/50 (62)	26/49 (53)
Carcinomas - M	3/48 (6)	2/49 (4)	3/48 (6)	1/47 (2)	8/48 (17)	7/48 (14)	5/48 (19)	12/49 (24)
Combined	19/48 (40)	21/49 (43)	23/48 (48)	19/47 (40)	42/48 (88)	36/48 (75)	36/50 (72)	38/49 (78)

B benign, *M* malignant

The incidence of interstitial cell tumors of the testes in male rats in both the scheduled terminal sacrifice animals, as well as for all animals, suggested a possible treatment-related finding, and was presented along with contemporary historical control data for comparison (Tables 5 and 6). It was noted that at 12 months, the incidence of interstitial tumors was near zero; however, in animals aged 24–29 months at necropsy, the incidence increased to approximately 10%. The historical control data for chronic toxicity and carcinogenicity from 5 studies terminated at 24–29 months showed background levels of interstitial cell tumors comparable to those found at the highest dose in the study. Furthermore, the reported incidences in all dose groups reflect the normal range of interstitial cell tumors in rat testes, reported in the Registry of Industrial Toxicology Animal Data (Nolte et al. 2011). The incidence of interstitial cell hyperplasia did not provide evidence of a pre-neoplastic lesion. The investigators noted that at terminal sacrifice, the incidence of interstitial cell tumor was 15.4% (4/26), while the range in control animals from 5 contemporary studies (historical controls) was 6.2% (4/65) to 27.3% (3/11), with an overall mean value of 9.6% (16/166). When all animals on test are included, the incidence for the high-dose males was 12% (6/50), compared to a contemporary historical control range of 3.4% (4/116) to 6.7% (5/75), with a mean of 4.5% (24/535). The concurrent control incidence of interstitial cell tumors (0%) was not representative of the normal background incidence noted in contemporary historical control data. Therefore, the data suggest that the incidence in treated rats is within the normal biological variation observed for interstitial cell tumors at this site in this strain of rat. When evaluated in the context of the full data set for male rats (Table 20), a dose-response is clearly absent for the 25 doses evaluated in rats, ranging from 3 to 1290 mg/kg bw/day, which demonstrates that this tumor is clearly not a consequence of glyphosate exposure.

In conclusion, glyphosate was not considered carcinogenic in Sprague Dawley rats following continuous dietary exposure of upto 300 ppm, corresponding to 31 and 34 mg/kg bw/day in males and females, respectively, which is consistent with evaluations by the US EPA (US EPA 1993), the original Annex I listing in Europe (EC 2002), and WHO/FAO (WHO/FAO 2004a).

Based on the low doses tested in Study 1, Monsanto was obliged to conduct a second chronic/carcinogenicity study in rats (Study 2, discussed below) in accordance with OECD TG 453 (1981), which had been developed and instituted after this initial study was conducted.

Study 2 (Monsanto 1990)

In response to evolving regulatory requirements, this study was conducted in accordance with the contemporary version of OECD TG 453 (Monsanto 1990). The chronic toxicity and carcinogenic potential of glyphosate were assessed in a 24-month feeding study in 50 male and 50 female Sprague Dawley rats, dosed with 0, 2000, 8000 and 20 000 ppm (equivalent to mean achieved dose levels of 0, 89, 362 and 940 mg/kg bw/day for males and 0, 113, 457 and 1183 mg/kg bw/day for females (Table 7). In addition, 10 rats per sex per dose were included for interim sacrifice after 12 months. Observations covered clinical signs, ophthalmic examinations, body weight, food consumption, hematology, clinical chemistry and urinalysis, as well as organ weights, necropsy, and histopathological examination. This study was rated Klimisch 1 for reliability.

Treatment-related findings in this study were significantly reduced body weight in high-dose females, as well as increased liver weight in high-dose males and females, and a slight increase in incidence of cataract lens changes in high-dose males, which was not statistically significant for eye lesions confirmed by histopathology (Table 7). The body weight changes confirm that the MTD was achieved in the highest dose group. Benign thyroid C-cell adenomas were statistically higher than controls in the mid-dose terminally sacrificed males, but when pooled with unscheduled deaths, no statistically significant increase was noted. Benign pancreas islet cell adenomas were not statistically higher for the unscheduled or scheduled deaths, but when combined, were statistically higher than controls in the low and high dose males. In both cases, the benign tumors did not exhibit a dose-response, and did not progress to carcinomas, and thus the US EPA concluded that these tumors were not related to the administration

Table 5. Study 1 - Interstitial cell tumor findings in the testes.

	Dose (mg/kg bw/day)			
Tumors	0	3.05	10.3	31.49
Interstitial cell tumor – B	Number of animals/total number examined (% per group)			
Terminal sacrifice	0/15 (0)	2/26 (7.7)	1/16 (6.3)	4/26 (15.4)
All Animals	0/50 (0)	3/50 (6)	1/50 (2)	6/50 (12)
Interstitial cell hyperplasia	Number of animals (% per group)			
Terminal sacrifice	1/15 (6.7)	1/26 (3.8)	0/16 (0)	0/26 (0)
All Animals	1/50 (2)	1/50 (2)	1/50 (2)	0/50 (0)

B benign, *M* malignant

Table 6. Study 1 – Summary of the contemporary historical control data for interstitial cell tumors in the testes of rats in chronic toxicity studies.

	Study 1	Study 2	Study 3	Study 4	Study 5	
	Number of control animals/total number examined (% per study)					Range
Terminal sacrifice	4/65 (6.2)	3/11 (27.3)	3/26 (11.5)	3/24 (12.5)	3/40 (7.5)	6.2–27.3%
All animals	4/116 (3.4)	5/75 (6.7)	4/113 (3.5)	6/113 (5.3)	5/118 (4.2)	3.4–6.7%

of glyphosate (US EPA 1993). These neoplasms, in addition to skin keratoacanthoma in males, a common rat tumor, were selected for further weight of evidence evaluation (Tables 20 and 21). No evidence of a glyphosate-induced carcinogenic effect was noted in either sex (see data Supplementary Study 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423).

In conclusion, glyphosate was not carcinogenic in Sprague Dawley rats following continuous dietary exposure of up to 20000 ppm for 24 months, corresponding to 940 and 1183 mg/kg bw/day in males and females, respectively, which is consistent with evaluations by the US EPA (US EPA 1993), European Authorities (EC 2002), and WHO/FAO (WHO/FAO 2004a).

Study 3 (Cheminova 1993a)

The chronic toxicity and carcinogenic potential of glyphosate technical acid were assessed in a 104-week feeding study in male and female Sprague Dawley rats (Cheminova 1993a). The study was conducted between 1990 and 1992. Groups of 50 rats per sex received daily dietary doses of 0, 10, 100, 300, or 1000 mg/kg bw/day of glyphosate technical acid for 24 months (Table 8). Five additional groups of 35 rats per sex, receiving daily dietary doses of, 0, 10, 100, 300 or 1000 mg/kg bw/day, were included for interim sacrifice at the 12th month for evaluation of chronic toxicity. The dietary glyphosate levels were adjusted weekly to ensure that animals were receiving the intended dose levels at all times. This study was rated Klimisch 1 for reliability.

At 1000 mg/kg bw/day, female mean liver weights were decreased, while males and females had statistically significant reductions in body weight throughout the study, confirming that the MTD was achieved (Table 8). Neoplasms were noted in control and treated groups, but dose-responses were not evident, and no statistically significant increases versus controls were noted for any tumor type ($p < 0.05$). No treatment-related neoplastic lesions were observed at termination.

Table 7. Study 2 – Two-year feeding study of glyphosate in rats (Monsanto 1990).

Study owner:	Monsanto (1990)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (96.5% pure)			
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀ (10 rats per sex per dose were included for interim sacrifice after 12 months).			
Administration route:	Diet			
Concentration:	0, 2000, 8000, 20 000 ppm diet (♂ about 0, 89, 362, 940 mg/kg bw/day; ♀ about 0, 113, 457, 1183 mg/kg bw/day)			
Duration:	2 years			
Findings:	8000 ppm diet: NOAEL (♂+♀) 20 000 ppm diet: cataracts (♂), > 20% reduced cumulative body weight gain through months 18–20 (♀), 13% increased liver weight (♂). Local effects: inflammation of gastric mucosa			
Select neoplasms:	Pancreatic islet cell adenoma, skin keratoacanthoma (males), thyroid C cell adenoma			
Tumor		Dose (mg/kg bw/day)		
Males	0	89	362	940
Findings for dead and moribund sacrificed animals				
Pancreas: Islet cell adenoma – B	1/34 (3%)	4/28 (14%)	2/33 (6%)	4/32 (13%)
Skin: Keratoacanthoma – B	0/36	1/31 (3%)	2/33 (6%)	1/32 (3%)
Thyroid: C cell adenoma – B	0/36	2/29 (7%)	1/31 (3%)	1/33 (3%)
Thyroid: C cell carcinoma – M	0/36	1/29 (3%)	2/31 (6%)	1/33 (3%)
Findings for animals sacrificed at termination				
Pancreas: Islet cell adenoma – B	0/14	4/19 (21%)	3/17 (6%)	3/17 (6%)
Skin: Keratoacanthoma – B	0/13	2/19 (11%)	2/17 (12%)	2/17 (12%)
Thyroid: C cell adenoma – B	0/14	2/19 (11%)	*7/17 (41%)	4/17 (24%)
Thyroid: C cell carcinoma – M	0/14	0/19	0/17	0/17
Females	0	113	457	1183
Findings for dead and moribund sacrificed animals				
Pancreas: Islet cell adenoma – B	3/28 (11%)	0/28	3/33 (9%)	0/31
Thyroid: C cell adenoma – B	0/28	0/28	1/33 (3%)	2/32 (6%)
Thyroid: C cell carcinoma – M	0/28	0/28	1/33 (3%)	0/32
Findings for animals sacrificed at termination				
Pancreas: Islet cell adenoma – B	2/22 (9%)	1/22 (5%)	1/17 (6%)	0/18
Thyroid: C cell adenoma – B	2/22 (9%)	2/22 (9%)	5/17 (29%)	4/18 (22%)
Thyroid: C cell carcinoma – M	0/22	0/22	0/17	0/18

B benign, *M* malignant

*Statistically higher than controls ($p < 0.05$, Fisher's Exact Test with the Bonferroni Inequality).

Table 8. Study 3 – Two-year feeding study of glyphosate in rats (Cheminova 1993a).

Study owner:	Cheminova (1993a)
Reliability/ Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.
Substance:	Glyphosate (98.7–98.9% pure)
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀ (additional groups of 35 ♂ and 35 ♀per dose were included for 1-year interim sacrifice)
Administration route:	Diet
Achieved dose:	♂+♀: 0, 10, 100, 300, 1000 mg/kg bw/day (weekly adjustment of dietary concentration for the first 13 weeks and 4-weekly thereafter)
Duration:	2 years
Findings:	300 mg/kg bw/day: NOAEL (♂+♀) 1000 mg/kg bw/day: body weights ↓, urinary pH ↓, salivary glands (histopathology, organ weight ↑); evidence of weak liver toxicity (alkaline phosphatase ↑, ♀: organ weight ↓)
Select neoplasms:	No neoplasms from this study were identified for further consideration.

and no select neoplasms were identified in this study for further consideration (see data Supplementary Study 3 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423). Glyphosate was not considered carcinogenic in male and female Sprague Dawley rats following 104 weeks of continuous dietary exposure of up to 1000 mg/kg bw/day, the limit dose, which is consistent with evaluations by the European Authorities (EC 2002, Germany Rapporteur Member State 2015b) and WHO/FAO (WHO/FAO 2004a).

Study 4 (Feinchemie Schwebda 1996)

A 2-year bioassay in the Wistar rat used dietary glyphosate levels of 0, 100, 1000, and 10 000 ppm (Feinchemie Schwebda 1996). Groups of 50 rats per sex were fed for 24 months. The mean achieved dose levels were 0, 7.4, 73.9, and 740.6 mg/kg bw/day (Table 9). This study was rated Klimisch 1 for reliability.

In addition, one vehicle control with ten rats per sex and one high dose (10 000 ppm) group with 20 rats per sex were included for interim sacrifice after one year of treatment, to study non-neoplastic histopathological changes. The mean achieved dose level in the treated group was 764.8 mg/kg bw/day. Observations covered clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy, and histopathological examination.

There were no treatment-related deaths or clinical signs in any of the dose-groups. Moreover, there were no treatment-related effects on body weight gain or food consumption noted. This suggests that the MTD may not have been reached by the applied dosing regimen.

There was some background variation in the incidences of benign tumors (e.g. reduced tumor incidence in low and mid-dose males, increased tumor incidence in middose females), which was considered incidental in absence of a dose-response relationship (see data Supplementary Study 4 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423).

The different liver tumors observed in the dead and moribund sacrificed and terminally sacrificed rats included hepatocellular adenoma, intrahepatic bile duct adenomas, cholangiocarcinoma, hepatocellular carcinoma, histiocytic sarcoma, fibrosarcoma, and lymphosarcoma. Among these, hepatocellular adenomas and carcinomas occurred more frequently, as often observed in aging rats (Thoolen et al. 2010). These tumors appeared to be incidental and not compound-related, as their frequency of occurrence was not dependent on dose. Hepatocellular adenomas and carcinomas were considered select neoplasms (Table 9), based on increased incidence above controls for total animals, albeit non-dose

Table 9. Study 4 – Two-year feeding study of glyphosate in rats (Feinchemie Schwebda 1996).

Study owner:	Feinchemie Schwebda (1996)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (96.0–96.8% pure)			
Species/Strain:	Rat/Wistar, groups of 50 ♂ and 50 ♀			
Administration route:	Diet			
Concentration:	0, 100, 1000, 10 000 ppm diet (♂ about 0, 6.3, 59.4, 595 mg/kg bw/day; ♀ about 0, 8.6, 88.5, 886 mg/kg bw/day)			
Duration:	2 years			
Findings:	10 000 ppm diet: ≥ NOAEL (♂+♀) Only mild effects on clinical chemistry (liver enzymes), without histopathological changes.			
Select neoplasms:	Hepatocellular adenoma, hepatocellular carcinoma			
Tumor		Dose (mg/kg bw/day)		
Males	0	7.4	73.9	741
Findings for dead and moribund sacrificed animals				
Hepatocellular adenoma – B	9/30 (30%)	9/30 (30%)	6/32 (19%)	6/21 (29%)
Hepatocellular carcinoma – M	12/30 (40%)	12/30 (40%)	9/32 (28%)	5/21 (24%)
Findings for animals sacrificed at termination				
Hepatocellular adenoma – B	15/20 (75%)	13/20 (65%)	4/16 (25%)	15/20 (75%)
Hepatocellular carcinoma – M	9/20 (45%)	16/20 (80%)	9/16 (56%)	19/29 (66%)
		Dose (mg/kg bw/day)		
Females	0	7.4	73.9	741
Findings for dead and moribund sacrificed animals				
Hepatocellular adenoma – B	2/26 (8%)	8/23 (3%)	3/17 (18%)	5/29 (17%)
Hepatocellular carcinoma – M	4/26 (15%)	4/23 (17%)	2/17 (12%)	5/29 (17%)
Findings for animals sacrificed at termination				
Hepatocellular adenoma – B	16/24 (67%)	10/25 (40%)	16/32 (50%)	8/21 (38%)
Hepatocellular carcinoma – M	6/24 (25%)	11/25 (44%)	12/32 (38%)	4/21 (19%)

B benign, *M* malignant

responsive, for adenoma in mid-dose females, carcinoma in low- and high-dose males, and carcinoma in low- and mid-dose females. These liver neoplasms are considered in the weight of evidence evaluation (Tables 20 and 21).

The study report concluded that glyphosate technical acid was not carcinogenic in Wistar rats following continuous dietary exposure of up to 595 and 886 mg/kg bw/day in males and females, respectively, for 24 months, which is consistent with evaluations by the European Authorities (EC 2002, Germany Rapporteur Member State 2015b).

Study 5 (Excel 1997)

A 2-year feeding study in the Sprague Dawley rats (Excel 1997) featured dietary concentrations of 0, 3000, 15 000, and 25 000 ppm glyphosate technical acid. Groups of 50 rats per sex were fed for 24 months, and mean dose levels of 0, 150, 780 and 1290 mg/kg bw/day (males) and 0, 210, 1060 and 1740 mg/kg bw/day (females) were achieved (Table 10).

In addition, 20 rats/sex/group were included for interim sacrifice at week-52, to study non-neoplastic histopathological changes with a different high-dose level of 30 000 ppm. The dietary doses correspond to 180, 920 and 1920 mg/kg bw/day (males) and 240, 1130 and 2540 mg/kg bw/day (females), for 3000, 15 000 and 30 000 ppm, respectively. Thus, a limit dose above 1000 mg/kg bw/day was achieved.

The study report notes that glyphosate technical acid was not carcinogenic in Sprague Dawley rats following continuous dietary exposure to up to 1290 mg/kg bw/day, and 1740 mg/kg bw/day for males and females, respectively, for 24 months. However, this study was rated Klimisch 3 for reliability (Germany Rapporteur Member State 2015b), and therefore, is considered unreliable for carcinogenicity evaluation based on lower than expected background tumor incidences (see data Supplementary Study 5 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423). In addition, the test substance was not adequately characterized, and several deviations from the OECD Test Guideline 453 were noted.

Study 6 (Arysta Life Sciences 1997b)

A combined chronic toxicity/carcinogenicity study in Sprague Dawley rats (Arysta Life Sciences 1997b) was conducted between December 1994 and December 1996. The rats were fed 0, 3000, 10 000, and 30 000 ppm glyphosate for two years (equivalent to 0, 104, 354 and 1127 mg/kg bw/day for males and 0, 115, 393 and 1247 mg/kg bw/day for females (Table 11). Thus, a limit dose was achieved, and the MTD was noted at the high dose in males and females with decreased body weight, increased cecum weight, distention of the cecum, loose stool and skin lesions. In addition, 30 rats/sex/group were included for interim sacrifice at 26, 52 and 78 weeks, to study non-neoplastic histopathological changes. Observations covered clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy, and histopathological examination. This study was rated Klimisch 1 for reliability.

Non-statistically significant increases versus controls ($p < 0.05$) were noted for pituitary adenomas, skin keratoacanthoma in high-dose males, and mammary gland fibroadenoma in low and mid-dose females (Table 11). These neoplasms were considered for the weight of evidence evaluation (Tables 20 and 21), and the full tumor summary data are available online (see data Supplementary Study 6 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423). As mentioned under Study 1, pituitary and mammary tumors are common spontaneous neoplasms in aging rats (Johnson and Gad 2008), and skin keratoacanthoma is noted as one of the most common spontaneous benign neoplasms in male Sprague Dawley rats (Chandra et al. 1992). The study report concluded that glyphosate was not carcinogenic in Sprague Dawley rats following continuous dietary exposure to up to 30 000 ppm for 24 months, corresponding to 1127 mg/kg bw/day and 1247 mg/kg bw/day for males and females, respectively, which is consistent with the recent evaluation in Europe under the Annex I Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Table 10. Study 5 – Two-year feeding study of glyphosate in rats (Excel 1997).

Study owner:	Excel (1997)			
Reliability/Justification:	3 Test substance not characterized and other deviations from OECD 453, lower than expected background tumor incidence			
Substance:	Glyphosate (no purity reported)			
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀, additional groups of 20 rats per sex and group were included for interim sacrifice after 52 weeks			
Administration route:	Diet			
Concentration:	2-year group: 0, 3000, 15 000, 25 000 ppm diet (♂ about 0, 150, 780, 1290 mg/kg bw/day; ♀ about 0, 210, 1060, 1740 mg/kg bw/day) 1-year group: 0, 3000, 15 000, 30 000 ppm diet (♂ about 0, 180, 920, 1920 mg/kg bw/day; ♀ about 0, 240, 1130, 2540 mg/kg bw/day)			
Duration:	2 years			
Findings:	≥ 25 000 ppm diet: NOAEL (♂+♀) Only mild toxic effects, such as clinical chemistry of questionable relevance in aged rats, without correlating histopathological organ changes.			
Select neoplasms:	No neoplasms from this study were identified for further consideration. Low background tumor incidence indicates low study reliability with no relevant increases in the incidence of tumors.			
Males		Dose (mg/kg bw/day)		
	0	150	740.6	1290
Mortality	16/50 (32%)	17/50 (34%)	18/50 (36%)	23/50 (46%)
Females		Dose (mg/kg bw/day)		
	0	210	1060	1740
Mortality	19/50 (38%)	20/50 (40%)	20/50 (40%)	25/50 (50%)

Table 11. Study 6 – Two-year feeding study of glyphosate in rats (Arysta Life Sciences 1997b).

Study owner:	Arysta Life Sciences (1997b)
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.
Substance:	Glyphosate (94.6–97.6% pure)
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀; satellite groups of 30 ♂ and 30 ♀for interim investigations
Administration route:	Diet
Concentration:	0, 3000, 10 000, 30 000 ppm diet (♂ about 0, 104, 354, 1127 mg/kg bw/day; ♀ about 0, 115, 393, 1247 mg/kg bw/day)
Duration:	2 years
Findings:	3000 ppm diet: NOAEL (♂+♀) 10 000 ppm diet: cecum weight↑, distension of cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, body weight ↓
Select neoplasms:	Pituitary adenoma, skin keratoacanthoma (males), mammary gland fibroadenoma (females)

Tumor	Dose (mg/kg bw/day)			
Males	0	104	354	1127
Findings for dead and moribund sacrificed animals (Table 25–10)				
Pituitary anterior adenoma – B	22/32 (69%)	21/30 (70%)	*14/32 (44%)	18/21 (86%)
Skin keratoacanthoma – B	2/32 (6%)	1/30 (3%)	0/32	1/21 (5%)
Findings for animals sacrificed at termination (after 104 weeks, Table 25–8)				
Lung adenoma – B	0/18	2/20 (10%)	1/18 (6%)	3/29 (10%)
Pituitary anterior adenoma – B	13/18 (72%)	14/20 (70%)	13/18 (72%)	21/29 (72%)
Pituitary adenoma in intermediate part – B	0/18	1/20 (5%)	0/18	0/29 (0%)
Skin keratoacanthoma – B	1/18 (6%)	2/20 (10%)	0/18	6/29 (21%)

Tumor	Dose (mg/kg bw/day)			
Females	0	115	393	1247
Findings for dead and moribund sacrificed animals				
Pituitary anterior adenoma – B	34/35 (97%)	29/31 (94%)	28/33 (82%)	31/36 (86%)
Thyroid follicular adenoma – B	0/35	2/31 (6%)	0/32	0/36
Mammary gland fibroadenoma – B	13/35 (37%)	14/31 (45%)	12/34 (35%)	20/36 (56%)
Findings for animals sacrificed at termination				
Pituitary anterior adenoma – B	12/15 (80%)	19/19 (100%)	12/16 (75%)	13/14 (93%)
Mammary gland fibroadenoma – B	10/15 (67%)	13/19 (68%)	12/16 (75%)	10/14 (71%)

B benign, *M* malignant
*Statistically lower than controls ($p < 0.05$).

Study 7 (Syngenta 2001)

The same rat model that was used in the previously discussed 12-month chronic rat study (Syngenta 1996b) was also employed in a 2-year feeding study (Syngenta 2001). A group of 52 male and 52 female Wistar rats received 0, 2000, 6000 or 20 000 ppm via feed (Table 12). The mean achieved dose levels were 0, 121, 361 and 1214 mg/kg bw/day for males, and 0, 145, 437 and 1498 mg/kg bw/day for females. Thus, a limit dose was achieved. In addition, three satellite groups with 12 rats per sex each were included for interim sacrifice after 12 months of treatment, to investigate potential non-neoplastic histopathological changes. Observations covered clinical signs, body weight, food consumption, hematology, clinical chemistry, and urinalysis, as well as organ weights, necropsy, and histopathological examination. This study was rated Klimisch 1 for reliability.

Treatment-related findings in this study were found in the liver and kidney, and were confined to animals (predominantly males) fed 20 000 ppm glyphosate acid. There were a number of changes in males and females fed 20 000 ppm glyphosate acid, notably renal papillary necrosis, prostatitis, periodontal inflammation, urinary acidosis, and hematuria, which may be attributed to the acidity of the test substance. Slight increases in proliferative cholangitis and hepatitis were noted in males at 20 000 ppm. Despite the findings at 20 000 ppm, survival was better in males fed 20 000 ppm than in the controls and lower dose groups. This improved survival was associated with a decreased severity of renal glomerular nephropathy and a 5% reduction in body weight (see data Supplementary Study 7 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423, for neoplastic and non-neoplastic findings).

A small increase in the incidence of hepatocellular adenoma was observed in males fed 20 000 ppm glyphosate acid. While not statistically significant using the Fisher's exact test, the difference was statistically significant for total male rats using the Peto Test for trend. However, there was no evidence of pre-neoplastic foci, no evidence of progression to adenocarcinomas, and no dose-response. In addition, the incidence was within the laboratory's historical control range for tumors of this type in the liver (Table 12). Therefore, the increased incidence was considered not to be related to treatment, yet these were considered select neoplasms (Table 12) and evaluated in context of the complete data set (Tables 20 and 21).

The study report concluded that glyphosate acid was not carcinogenic in the Wistar rats following continuous dietary exposure to up to 20 000 ppm for 24 months, at 1214 and 1498 mg/kg bw/day in males and females, respectively, which is consistent with the WHO/FAO review (WHO/FAO 2004a) and the recent evaluation in Europe under the Annex I Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Study 8 (Nufarm 2009b)

The most recent study in this series of regulatory studies investigating the potential carcinogenicity of glyphosate in rats was conducted from September 2005 through March 2008 (Nufarm 2009b). The study was conducted by feeding dietary concentrations of 0, 1500, 5000 and 15 000 ppm glyphosate to groups of 51 Wistar rats per sex. To ensure that a received limit dose of 1000 mg/kg bw/day overall was achieved, the highest dose level was progressively increased to 24 000 ppm.

Table 12. Study 7 – Two-year feeding study of glyphosate in rats (Syngenta 2001).

Study owner:	Syngenta (2001)			
Reliability/Justification	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (97.6% pure)			
Species/Strain	Rat/Wistar Alpk: AP,SD. groups of 52 ♂ and 52 ♀ (additional 12 animals per sex and dose for 1-year interim sacrifice)			
Administration route:	Diet			
Concentration:	0, 2000. 6000. 20 000 ppm diet (♂ about 0. 121. 361. 1214 mg/kg bw/day; ♀ about 0. 145, 437, 1498 mg/kg bw/day)			
Duration:	2 years			
Findings:	6000 ppm diet: NOAEL (♂+♀)			
	20 000 ppm diet: Kidney and liver findings. Increased survival due to reduction in CPN, prostatitis, periodontal inflammation			
Select neoplasms:	Hepatocellular adenoma (males), not a statistically significant increase for the high dose using the Fisher's exact test, but statistically significant using Peto trend analysis			
		Dose (mg/kg bw/day)		
Males	0	121	361	1214
Liver				
Hepatocyte fat vacuolation	6	7	11	11
Hepatitis	3	4	2	5
Kidney				
		Dose (mg/kg bw/day)		
Females	0	145	437	1498
Liver				
Hepatocyte fat vacuolation	7	5	6	6
Hepatitis	6	5	4	4
Tumors:		Dose (mg/kg bw/day)		
Males	0	121	361	1214
Findings for dead and moribund sacrificed animals				
*Hepatocellular adenoma – B	0/37	2/36 (6%)	0/35	3/26 (12%)
Hepatocellular carcinoma – M	0/37	0/36	0/35	0/26
Findings for animals sacrificed at termination				
*Hepatocellular adenoma – B	0/16	0/17	0/18	2/26 (8%)
Hepatocellular carcinoma – M	0/16	0/17	0/18	0/26

B benign, *M* malignant
*Historical Control Range: 0–11.5% total males with hepatocellular adenoma, 26 studies, 1984–2003

Mean dose levels of 86/105, 285/349, and 1077/1382 mg glyphosate/kg bw/day (males/females) were achieved (Table 13). This study was rated Klimisch 1 for reliability.

Non-neoplastic findings included transient liver enzyme activity for mid-dose males and high-dose males and females, and equivocal nephrocalcinosis depositions at the high-dose. Histopathology noted a statistically significant increase in adipose infiltration of the bone marrow in high-dose males compared to controls, suggestive of myeloid hypoplasia, which may be considered a stress response (Everds et al. 2013).

Skin keratoacanthoma in males and mammary gland adenocarcinoma in females (Table 13) were considered for evaluation in the context of the weight of evidence for rat tumor incidence (Tables 20 and 21), wherein dose-

Table 13. Study 8 – Two-year feeding study of glyphosate in rats (Nufarm 2009b).

Study owner:	Nufarm (2009a)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations			
Substance:	Glyphosate (95.7% pure)			
Species/Strain:	Rat/Wistar, groups of 51 ♂ and 51 ♀			
Administration route:	Diet			
Concentration:	0, 3000. 10 000. 15 000 ppm diet. the top dose was progressively increased to reach 24 000 ppm diet by Week-40 (♂ about 0, 84, 285. 1077 mg/kg bw/day; ♀ about 0, 105. 349, 1382 mg/kg bw/day)			
Duration:	2 years			
Findings:	≥ 1077/1382 mg/kg bw/day: NOAEL (♂/♀)			
	Transient liver enzyme activity for mid-dose males and high-dose males and females; equivocal nephrocalcinosis depositions at the high-dose males and females; increased adipose infiltration of the bone marrow in high-dose males			
Select neoplasms:	Skin keratoacanthoma (males), mammary gland adenocarcinoma			
Tumor			Dose (mg/kg bw/day)	
Males	0	84	285	1077
Findings for all animals				
Skin keratoacanthoma – B	2/51 (4%)	3/51 (6%)	0/51	6/51 (12%)
			Dose (mg/kg bw/day)	
Females	0	105	349	1382
Findings for all animals				
Mammary gland adenocarcinoma – M	2/51 (4%)	3/51 (6%)	1/51 (2%)	6/51 (12%)

B benign. *M* malignant

responses were not evident. Tumor incidence summary data have been tabulated (see data Supplementary Study 8 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423). Microscopic evaluation of tissues did not reveal any indications of neoplastic lesions caused by glyphosate treatment. The study report concluded that glyphosate acid was not carcinogenic in Wistar rats following continuous dietary exposure to up to 24 000 ppm for 24 months, at 1077 and 1382 mg/kg bw/day in males and females, respectively, which is consistent with the recent evaluation in Europe under the Annex I Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Study 9 Publication (Chruscielska et al. 2000a)

A two-year combined chronic toxicity and carcinogenicity study in Wistar rats was published by academic researchers from Warsaw, Poland. The study was conducted as a drinking-water study in Wistar-RIZ rats according to OECD TG 453. The test material was a 13.85% aqueous formulation of glyphosate as its ammonium salt (equivalent to 12.6% glyphosate acid). However, the ammonium salt of glyphosate tested is not commercially available, and the concentration of active ingredient suggests that a glyphosate-formulated product was tested; this is supported by a concurrent genotoxicity publication by the same lead author (Chruscielska et al. 2000b), previously reviewed by Kier and Kirkland (Kier and Kirkland 2013), in which a glyphosate formulation, Perzocyd, was tested. Deficiencies noted with respect to OECD TG 453 include insufficient dosing to elicit toxic effects, inadequate test material characterization, no reporting of water/feed consumption, body weights and diet composition, and no individual animal data. Although the manuscript reporting deficiencies may have been included in the study, they were not reported in the manuscript, and could warrant a Klimisch reliability score of 4 (not assignable), but the low doses employed in this study justify a Klimisch reliability score of 3.

The test material was administered in water at glyphosate salt concentrations of 0, 300, 900, and 2700 mg/L. Each dose group consisted of 85 animals per sex. Ten animals per sex and dose were sacrificed after 6, 12, and 18 months of exposure, for evaluation of general toxicity. The remaining 55 animals per sex and dose were scheduled for sacrifice after 2 years of exposure.

Water consumption was claimed to have been measured, but these data have not been reported. To estimate the glyphosate doses received via drinking water, the assumed default water consumptions were 50 and 57 mL/kg bw/day by male and female rats, respectively (Gold et al. 1984). Using these standard figures and the glyphosate content of the tested formulation (12.6%), daily doses are estimated at 0, 1.9, 5.7, and 17 mg of glyphosate/kg bw/day for males and 0, 2.2, 6.5, and 19 mg of glyphosate/kg bw/day for females. As this study appears to have tested a formulated product, data were not included in the weight of evidence review (Tables 20 and 21), but given the very low glyphosate doses and reported low tumor incidence, these were of no consequence to the overall data review.

Exposure to glyphosate ammonium salt had no effect on body weight, appearance and behavior, and hematological parameters, which is consistent with glyphosate chronic toxicity data regulatory reviews. Even though there seems to be a trend towards higher 2-year mortality in treated females (Table 14), this difference had no statistical significance according to the authors. There were sporadic alterations of clinical-chemical and urinalysis parameters, but not in a consistent fashion over time and without dose-dependence. These alterations were not interpreted as treatment-related. There was no effect of glyphosate on the incidence of neoplastic lesions (Table 14). Thus, the NOAEL for chronic toxicity and carcinogenicity in this study was greater than or equal to 17 and 19 mg glyphosate/kg bw/day, in males and females, respectively.

Due to the lack of systemic effects in the highest dose group, the MTD was not reached by this study. Judging from other rat studies reviewed here, the MTD is likely to be greater than 1000 mg/kg bw/day. Thus, the top glyphosate dose of an estimated 19 mg/kg bw/day in this study is too low to satisfy regulatory validity criteria for a carcinogenicity study.

Mouse carcinogenicity

There are a total of five carcinogenicity studies with glyphosate in mice, that have been submitted to support glyphosate Annex I renewal in the European Union. All but the oldest study (Study 10) were considered reliable without restriction, and were performed under conditions of GLP following OECD TGs. Most studies were conducted in the CD-1 strain. Each study was sponsored by a different manufacturer. In each case, technical grade glyphosate was administered via diet for at least 18 months. Select neoplasms, mostly lymphoreticular, liver and lung, are summarized for all mouse chronic studies in Tables 22 and 23. These neoplasms are widely recognized as occurring spontaneously in aging mice (Gad et al. 2008, Son and Gopinath 2004). Lymphomas have been recognized for many years as one of the most common, if not the most common category of spontaneous neoplastic lesions in aging mice (Brayton et al. 2012, Gad et al. 2008, Son and Gopinath 2004). The subclassification of malignant lymphomas is not a typical diagnostic feature in rodent studies, likely due to either expense and/or feasibility. It is, however, important to recognize that lymphomas are not a single type of neoplasm, rather they are a grouping of different neoplasms arising from different pathogeneses, and should be considered as different diseases (Bradley et al. 2012). As is the case for NHL in humans, these different immune system neoplasms are clustered together based on manifestation in lymphocytes, despite their very different etiologies; for example, the most common subset of NHL lymphomas clustered together as "diffuse large B cell lymphomas", have for many years been considered multiple clinical-pathologic entities (Armitage 1997), and therefore may be considered attributable to different modes of action. Chronic endpoints and NOAEL values are captured in each study summary table; however, the following study reviews focus on carcinogenicity.

Study 10 (Monsanto 1983)

The first chronic-carcinogenicity mouse study with glyphosate was conducted between March 1980 and March 1982 (Monsanto 1983), prior to the institution of GLP (Table 15). The study design was essentially in compliance with OECD TG 451 for carcinogenicity studies, adopted in 1981, when

Table 14. Publication, Study 9 – Two-year drinking water study in rats with 13.85% glyphosate ammonium salt (Chruscielska et al. 2000a).

Authors:	Chruscielska et al. (2000a)
Reliability/Justification:	3 Study not performed according to GLP, but according to OECD TG 453, with the following deficiencies: Reporting deficits (water and feed consumption, body weights, diet composition, individual animal data, substance composition, purity, and stability) Highest dose did not elicit toxicity.
Substance:	Ammonium salt of glyphosate, 13.85% solution
Species/Strain:	Rat/Wistar -RIZ outbred, 85 ♂ and 85 ♀ per dose group. 10 ♂ and 10 ♀each were sacrificed after 6, 12, and 18 months of exposure.
Administration route:	Drinking water
Concentration:	0, 300, 900, and 2700 mg/L Estimated glyphosate intake: ♂: 0, 1.9, 5.7, and 17 mg/kg bw/day. ♀: 0, 2.2, 6.5, and 19 mg/kg bw/day, based on assumed water consumptions of 50/57 mL/kg bw/day (♂/♀), (Gold, et al. 1984)
Duration:	2 years
Findings:	17/19 mg glyphosate/kg bw/day: NOAEL (♂/♀) No treatment-related effects
Tumors reported for 85 rats/sex/dose:	No increase in the incidence of tumors attributable to glyphosate administration

	Estimated dose (mg/kg bw/day)							
	0		1.9/2.2		5.7/6.5		17/19	
	♂	♀	♂	♀	♂	♀	♂	♀
Two-year mortality	42%	38%	42%	45%	54%	53%	44%	60%
Lungs								
Lymphoma	2	–	2	–	1	–	3	1
Histiocytoma	–	–	–	–	–	–	–	1
Adenocarcinoma	1	–	–	–	–	–	–	–
Histiocytoma, malignant	–	1	–	–	1	–	–	–
Spleen, leukemia	0	–	2	–	0	–	1	–
Kidneys, Fibrous histiocytoma	–	–	–	–	–	–	1	–
Pituitary gland								
Adenoma	4	10	4	6	2	8	0	3
Adenoma, malignant (assumed to be carcinoma)	0	1	0	3	1	2	1	5
Carcinoma	0	–	0	–	1	–	0	–
Thyroid								
Adenoma	1	1	1	2	0	0	3	3
Carcinoma	0	–	1	–	0	–	0	–
Uterus, cervix carcinoma	–	0	–	0	–	0	–	1
Uterus, body, histiocytoma	–	3	–	1	–	0	–	1
Mammary gland								
Fibroma	–	0	–	0	–	0	–	0
Fibroadenoma	–	3	–	2	–	3	–	3
Adrenal medulla, adenoma	1	2	2	2	1	2	0	2
Thymus, lymphoma	0		0		0		1	
Testis, Leydigoma	–		3		6		1	
Subcutaneous tissue								
Fibroma	0		1		1		3	
Lipoma	–	–	–	–	–	–	–	1
Cystadenoma	–	1	–	–	–	–	–	–
Lymph nodes								
Lymphoma	0		0		0		1	
Lymphoma, malignant	–	1	–	–	–	–	–	–
Skin, carcinoma	2	–	–	–	–	–	–	–
Prostate, adenoma	1	–	–	–	–	–	–	–

the study was already ongoing. Groups of 50 male and female CD-1 mice received glyphosate at dietary levels of 1000, 5000, and 30 000 ppm, over a period of nearly two years. The mean achieved doses were 157/190, 814/955, and 4841/5874 mg/kg bw/day in males and females, respectively, exceeding the limit dose. Based on this study predating both GLP and OECD TG 451, a reliability score of Klimisch 2 has been assigned.

In addition to post-mortem pathological examinations after terminal sacrifice, hematological investigations were performed on 10 mice per sex and dose at months 12 and 18, and on 12 male animals/group, as well as all surviving females at scheduled termination.

Two non-neoplastic histological changes affecting the liver and urinary bladder were assumed to be treatment-related. There was a higher incidence of centrilobular hepatocyte hypertrophy in high-dose males, and a more frequent occurrence of slight-to-mild bladder epithelial hyperplasia in the mid and high dose; however, a clear dose-response was lacking. Tumor incidences, which did not significantly increase with dose, were mostly bronchiolar-alveolar, hepatocellular, or lymphoreticular, all of which are commonly noted spontaneously occurring tumors in aging mice (Table 15). Lymphoreticular tumors combined for males and females totaled 7, 12, 10 and 12 for control, low, mid- and high-dose groups respectively, and were not considered as being related to test substance.

A more frequent occurrence of slight-to-mild bladder epithelial hyperplasia was observed in the mid and high-dose groups; however, clear dose-response was lacking (Table 15) and no urinary bladder neoplasms were noted at these doses (see data Supplementary Study 10 to be found online at http://

Table 15. Study 10 – Two-year feeding study with glyphosate in mice (Monsanto 1983).

Study owner:	Monsanto (1983)			
Reliability/Justification	2 Study was performed prior to institution of GLP and OECD guideline requirements			
Substance:	Glyphosate (99.7% pure)			
Species/Strain:	Mouse/CD-1, groups of 50 ♂ and 50 ♀			
Administration route:	Diet			
Concentration:	0, 1000, 5000, 10 000 ppm diet (♂ about 0, 157, 814, 4841 mg/kg bw/day; ♀ about 0, 190, 955, 5874 mg/kg bw/day)			
Duration:	24 months			
Findings:	1000 ppm diet: NOAEL (♂ + ♀)			
	5000 ppm diet: body weight ↓, histological changes in liver and urinary bladder (slight to mild epithelial hyperplasia in males at mid and high doses)			
Select neoplasms:	Lymphoreticular neoplasms, bronchiolar-alveolar adenocarcinoma			
		Dose (mg/kg bw/day)		
Males	0	157	814	4841
Lymphoreticular system				
Lymphoblastic lymphosarcoma with leukemia – M	1/48 (2%)	4/49 (8%)	3/50 (6%)	2/49 (4%)
Lymphoblastic lymphosarcoma without leukemia – M	0/48	1/49 (2%)	0/50 (0%)	0/49
Composite lymphosarcoma – M	1/48 (2%)	0/49	1/50 (2%)	0/49
Histiocytic sarcoma – M	0/48	1/49 (2%)	0/50	0/49
Total lymphoreticular neoplasms[#]	2/48 (4%)	6/49 (12%)	4/50 (8%)	2/49 (4%)
		Dose (mg/kg bw/day)		
Females	0	190	955	5873
Lymphoreticular system				
Lymphoblastic lymphosarcoma with leukemia – M	1/50 (2%)	4/48 (8%)	5/49 (10%)	1/49 (2%)
Lymphoblastic lymphosarcoma without leukemia – M	0/50 (0%)	1/48 (2%)	0/49 (0%)	3/49 (6%)
Composite lymphosarcoma – M	4/50 (8%)	1/48 (2%)	1/49 (2%)	6/49 (12%)
Histiocytic sarcoma – M	0/50 (0%)	0/48 (0%)	0/49 (0%)	0/49 (0%)
[#] Total lymphoreticular neoplasms	5/50 (10%)	6/48 (13%)	6/49 (12%)	10/49 (20%)

[#]Sum of lymphoblastic lymphosarcoma, composite lymphosarcoma, and histiocytic sarcoma.
M malignant

informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423). Benign renal tubule adenomas were noted in mid- and high-dose males at incidences of 1/50 and 3/50 respectively. These neoplasms were not observed in females, lacked statistical significance, and were considered spontaneous and unrelated to glyphosate administration by the study pathologists; this neoplasm, while not seen in the concurrent control group, had previously been noted in control male CD-1 mice of comparable age by the author of the study. As an additional measure of diligence, a Pathology Working Group was convened, and it concluded that the absence of any pre-neoplastic kidney lesion in all male animals provided sufficient evidence that this finding was spurious and not related to glyphosate administration. This is reflected in the US EPA review of glyphosate (US EPA 1993). This neoplasm was not observed in the other four mouse carcinogenicity studies discussed.

The author of the study also reported a trend towards a non-statistically significant increased occurrence of lymphoreticular neoplasia in treated female mice (Table 15). However, these consisted of three different categories of lymphoreticular neoplasms. Regulatory reviews confirmed that there is no apparent dose-dependence for these endpoints (EC 2002, US EPA 1993, WHO/FAO 2004a). Summary tables of incidence of neoplastic findings are available (see data Supplementary Study 10 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423).

Glyphosate was reported as not carcinogenic in CD-1 mice up to doses well in excess of the limit dose for carcinogenicity testing, which is consistent with evaluations by the US EPA (US EPA 1993), European Commission (EC 2002), recent EU Annex I Renewal evaluation by the Rapporteur (Germany Rapporteur Member State 2015b), and WHO/FAO (WHO/FAO 2004a).

Study 11 (Cheminova 1993b)

Another carcinogenicity bioassay in mice was conducted between December 1989 and December 1991 (Table 16) (Cheminova 1993b). In this assay, 50 male and 50 female CD-1 mice per dose group received glyphosate via their diet over a period of approximately two years. This treatment period is 6 months longer than the 18 months stipulated for mice by OECD TG 451 (1981 version). The dietary levels were adjusted regularly to achieve constant dose levels of 0, 100, 300 and 1000 mg/kg bw/day, achieving the limit dose. This study was rated Klimisch 1 for reliability.

Slight non-statistically significant increases in bronchiolar-alveolar adenomas were noted for all male dose groups above controls in a non-dose-responsive manner. Bronchiolar-alveolar neoplasms are evaluated in the context of the full data set (Tables 22 and 23), demonstrating a lack of dose-response across doses ranging from approximately 15 mg/kg bw/day to 5000 mg/kg bw/day. Although the number of pituitary adenomas were low and considered incidental, they were conservatively included in the select neoplasms, based on being slightly higher in high dose females than concurrent controls (Table 16). The data summary of all histological findings, including tumor incidence, is available (see data Supplementary Study 11 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423).

There were no statistically significant increases in the occurrence of any tumor type in this study. The observed variations did not show a dose relationship, and were within the range of historical control data. Glyphosate was determined to be not carcinogenic to CD-1 mice at up to 1000 mg/kg bw/day, which is consistent with evaluations by the European Commission (EC 2002) and WHO/FAO (WHO/FAO 2004a).

Table 16. Study 11 – Two-year feeding study with glyphosate in mice (Cheminova 1993b).

Study owner:	Cheminova (1993b)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements			
Substance:	Glyphosate (98.6% pure)			
Species/Strain:	Mouse/CD-1, groups of 50 ♂ and 50 ♀			
Administration route:	Diet			
Concentration:	♂+♀: 0, 100, 300, 1000 mg/kg bw/day (regular adjustment of dietary concentration)			
Duration:	24 months			
Findings:	≧ 1000 mg/kg bw/day: NOAEL (♂+♀) no treatment-related effects			
Select neoplasms:	Bronchiolar-alveolar adenoma, bronchiolar-alveolar carcinoma, pituitary adenoma (females)			
		Dose (mg/kg bw/day)		
Males	0	10	300	1000
Bronchiolar-alveolar adenoma – B	9/50 (18%)	15/50 (30%)	11/50 (22%)	13/50 (26%)
Bronchiolar-alveolar carcinoma – M	10/50 (20%)	7/50 (14%)	8/50 (16%)	9/50 (18%)
		Dose (mg/kg bw/day)		
Females	0	100	300	1000
Bronchiolar-alveolar adenoma – B	7/50 (14%)	3/50 (6%)	3/50 (6%)	6/50 (12%)
Bronchiolar-alveolar carcinoma – M	3/50 (6%)	2/50 (4%)	1/50 (2%)	5/50 (10%)
Pituitary adenoma – B	1/41 (2%)	0/32	0/23	3/43 (6%)

B benign, *M* malignant

Study 12 (Arysta Life Sciences 1997a)

An 18-month feeding study in ICR-CD-1 mice, conducted between February 1995 and September 1996, investigated higher doses by admixing 1600, 8000, or 40 000 ppm glyphosate into the diet fed to groups of 50 male and 50 female mice per dose (Arysta Life Sciences 1997a). The calculated test substance intake was 165/153, 838/787, and 4348/4116 mg/kg bw/day (males/females, Table 17), exceeding the limit dose. This study was rated Klimisch 1 for reliability.

Histopathological examinations did not show statistically significant increases for any type of neoplastic lesion in all treatment groups of both sexes (see data Supplementary Study 12 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423). Select neoplasms evaluated across the data set with some non-statistically significant increases above concurrent controls included lymphoma and lung tumors, all of which lacked a clear dose-response. Glyphosate was considered not carcinogenic in CD-1 mice up to doses well in excess of the limit dose for carcinogenicity testing, which is consistent with the recent evaluation in Europe under the Annex I Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Study 13 (Feinchemie Schwebda 2001)

An 18-month feeding study in Swiss albino mice (Feinchemie Schwebda 2001), conducted between December 1997 and June 1999, featured treatment groups, each with 50 animals per sex, receiving 100, 1000, and 10 000 ppm technical grade glyphosate

Table 17. Study 12 – Two-year feeding study with glyphosate in mice (Arysta Life Sciences 1997a).

Study owner:	Arysta Life Sciences (1997b)			
Reliability/ Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (94.6–97.6% pure)			
Species/Strain	Mouse/CD-1, groups of 50 ♂ and 50 ♀			
Administration route:	Diet			
Concentration:	0, 1600, 8000, or 40 000 ppm diet (♂ about 0, 165, 838, 4348 mg/kg bw/day; ♀ about 0, 153, 787, 4116 mg/kg bw/day)			
Duration:	18 months			
Findings:	8000/1600 ppm diet: NOAEL (♂/♀) 8000 ppm diet (♀): retarded growth 40 000 ppm diet: pale-colored skin ♂, loose stool, retarded growth, reduced food consumption and food efficiency, cecum distension and increased absolute and relative cecum weight, without histopathological findings of increased incidence of anal prolapse, consistent with histopathological erosion/ulcer of the anus			
Select neoplasms:	Lung adenoma, lung adenocarcinoma, lymphoma			
		Dose (mg/kg bw/day)		
Males	0	165	838	4348
Lung adenoma – B	8/50 (16%)	14/50 (28%)	13/50 (26%)	11/50 (11%)
Lung adenocarcinoma – M	1/50 (2%)	1/50 (2%)	6/50 (12%)	4/50 (8%)
Lymphoma – M	2/50 (4%)	2/50 (4%)	0/50	6/50 (12%)
		Dose (mg/kg bw/day)		
Females	0	153	787	4116
Lung adenoma – B	8/50 (16%)	5/50 (10%)	12/50 (24%)	5/50 (10%)
Lung adenocarcinoma – M	1/50 (2%)	2/50 (4%)	3/50 (6%)	1/50 (2%)
Lymphoma – M	6/50 (12%)	4/50 (8%)	8/50 (16%)	7/50 (14%)

B benign, *M* malignant

Table 18. Study 13–18-Month feeding study with glyphosate in mice (Feinchemie Schwebda 2001).

Study owner:	Feinchemie Schwebda (2001)
Reliability/Justification	2 Study performed according to GLP and OECD guideline requirements, with no deviations, but possible viral infection may have confounded interpretation of results
Substance:	Glyphosate (> 95% pure)
Species/Strain	Mouse/Swiss albino, groups of 50 ♂ and 50 ♀
Administration route:	Diet
Concentration:	0, 100, 1000, 10 000 ppm diet (♂ about 0, 14.5, 150, 1454 mg/kg bw/day; ♀ about 0, 15.0, 151, 1467 mg/kg bw/day)
Duration:	18 months
Findings:	1000 ppm diet: NOAEL (♂+♀) 10 000 ppm diet (♂+♀): increased mortality
Select neoplasms:	Bronchiolar/alveolar adenoma, lymphoma

	Historical controls		Dose (mg/kg bw/day) 0	14.5	150	1454
Males						
Mortality	§11/50–27/50		†22/50 (6)	20/50 (6)	22/50 (8)	27/50 (8)
Findings for dead and moribund sacrificed animals						
Lymphoma – M	#20/75	26.7% [0–44]	9/22 (41.0%)	*12/20 (60.0%)	*13/22 (59.0%)	13/27 (48.0%)
Findings in animals sacrificed at termination						
Lymphoma – M	26/175	14.9% [8–24]	1/28 (3.6%)	3/30 (10.0%)	3/28 (10.7%)	*6/23 (26.1%)
Total animals						
Lymphoma – M	46/250	18.4% [6–30]	10/50 (20.0%)	15/50 (30.0%)	16/50 (32.0%)	*19/50 (38.0%)

	Historical controls		Dose (mg/kg bw/day) 0	15.0	151	1467
Females						
Mortality	12/50–20/50		16/50 (7)	16/50 (7)	20/50 (2)	20/50 (3)
Findings for dead and moribund sacrificed animals						
Bronchiolar/alveolar adenoma – B	—	—	0/16	0/16	1/20 (5%)	2/20 (10%)
Lymphoma – M	49/77	63.6% [0–100]	9/16 (56.0%)	10/16 (63.0%)	13/20 (65.0%)	12/20 (60.0%)
Findings in animals sacrificed at termination						
Bronchiolar/alveolar adenoma – B			1/34 (3%)	0/0	1/1 (100%)	1/30 (3%)
Lymphoma – M	50/175	28.9% [20–43]	9/34 (26.5%)	10/30 (29.4%)	6/30 (20.0%)	*13/28 (43.3%)
Total animals						
Bronchiolar/alveolar adenoma – B			1/50 (2%)	0/16	2/21 (10%)	3/50 (6%)
Lymphoma – M	99/250	39.6% [14–58]	18/50 (36.0%)	20/50 (40.0%)	19/50 (38.0%)	*25/50 (50.0%)

B benign, *M* malignant.
§Nine studies, performed by the same laboratory in the timeframe encompassing the study summarized here.
†(Number of animals killed in extremis).
#Five studies, conducted in the same laboratory between 1996 and 1999.
*Statistically higher than concurrent controls ($p < 0.05$).

in the diet. Control mice received a plain diet. The calculated test substance intake was 14.5/15.0, 150/151, 1454/1467 mg/kg bw/day (males/females, Table 18), exceeding the limit dose, as reflected in elevated mortality in the high dose groups. This study was rated Klimisch 2 for reliability, based on speculation of a viral infection within the colony, discussed below.

Based on the slightly higher mortality and lower survival rates in the high dose groups, the NOAEL was considered 1000 ppm (151 mg/kg bw/day). There were no treatment-related effects on clinical signs, behavior, eyes, body weight, body weight gain, food consumption, and differential white blood cell counts in both sexes. Gross pathology, organ weight data, and histopathological examination demonstrated no treatment-related effects. An increase in the number of malignant lymphomas, the most common spontaneously occurring tumor category in the mouse, was statistically significant in the high-dose groups compared to controls (Table 18). The Germany Rapporteur Member State concluded that the malignant lymphoma increase in high-dose males was inconclusive but unrelated to treatment in the context of similar higher dosed studies (Germany Rapporteur Member State 2015b), and considered this endpoint irrelevant to carcinogenic risk in humans (Germany Rapporteur Member State 2015a). Whether or not a viral component (Taddesse-Heath et al. 2000) may have contributed to this endpoint, the finding was considered incidental background variation based on historical control data, and in agreement with the study director. As in Study 11, bronchiolar-alveolar adenoma was also considered a select neoplasm for evaluation in the broader data set (Tables 22 and 23), and as previously discussed, demonstrates a lack of dose-response across doses ranging from approximately 15 mg/kg bw/day to 5000 mg/kg bw/day. Summary tables of all histopathological neoplastic findings are available (see data Supplementary Study 13 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423).

Technical grade glyphosate was reported as not carcinogenic in Swiss albino mice, following continuous dietary exposure of up to 1460 mg/kg bw/day (average for both sexes) for 18 months. The NOAEL for general chronic toxicity was 151 mg/kg bw/day for both sexes combined.

Study 14 (Nufarm 2009a)

The most recent mouse carcinogenicity assay was conducted between October 2005 and November 2007 (Nufarm 2009a).

Table 19. Study 14–18-Month feeding study with glyphosate in mice (Nufarm 2009a).

Study owner:	Nufarm (2009b)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations			
Substance:	Glyphosate (94.6–97.6% pure)			
Species/Strain:	mouse/CD-1, groups of 51 ♂ and 51 ♀			
Administration route:	Diet			
Concentration:	0, 500, 1500, and 5000 ppm diet (♂ about 0, 0, 71.4, 234, 810 mg/kg bw/day; ♀ about 0, 97.9, 300, 1081 mg/kg bw/day)			
Duration:	18 months			
Findings:	≥ 5000 ppm diet: NOAEL (♂/♀) No treatment-related effects			
Select neoplasms:	Bronchiolar-alveolar adenoma, Bronchiolar-alveolar adenocarcinoma, hepatocellular adenoma (males), hepatocellular carcinoma (males), lymphoma, pituitary adenoma (females)			
		Dose (mg/kg bw/day)		
Males	0	157	814	4841
Bronchiolar-alveolar adenoma – B	9/51 (18%)	7/51 (14%)	9/51 (18%)	4/51 (8%)
Bronchiolar-alveolar adenocarcinoma – M	5/51 (10%)	5/51 (10%)	7/51 (14%)	11/51 (22%)
Hepatocellular adenoma – B	1/51 (2%)	1/51 (2%)	4/51 (8%)	2/51 (4%)
Hepatocellular carcinoma – M	6/51 (12%)	11/51 (22%)	7/51 (14%)	4/51 (8%)
Lymphoma – M	0/51	1/50 (2%)	2/51 (4%)	5/51 (10%)
		Dose (mg/kg bw/day)		
Females	0	190	955	5873
Bronchiolar-alveolar adenoma – B	2/51 (4%)	4/51 (8%)	2/51 (4%)	2/51 (4%)
Bronchiolar-alveolar adenocarcinoma – M	5/51 (10%)	2/51 (4%)	2/51 (4%)	3/51 (6%)
Lymphoma – M	11/51 (22%)	8/51 (16)	10/51 (20%)	11/51 (22%)
Pituitary adenoma – B	0/51	1/50 (2%)	0/51	2/51 (4%)

B benign, *M* malignant

Groups of 51 CD-1 mice per sex received daily dietary doses of 0, 500, 1500, and 5000 ppm technical grade glyphosate (equivalent to an average intake of 85, 267 and 946 mg/kg bw/day, Table 19). The MTD was apparently not reached in the high-dose group, which is more indicative of low general toxicity of the test substance rather than a flaw in the study design. The NOAEL for chronic toxicity was 810 mg/kg bw/day for male mice and 1081 mg/kg bw/day for female mice, the highest dosage tested. Despite not quite achieving a limit dose in males, this study was arguably rated Klimisch 1 for reliability.

Several increases in common spontaneous mouse neoplasms in male mice were noted. Non-dose-response increases were noted for hepatocellular adenoma and carcinoma in males, and dose-responses were noted for bronchiolar-alveolar adenocarcinoma and malignant lymphoma in males, but not females. Pituitary adenoma incidences were low, and considered incidental in low and high-dose females, although they were slightly higher than controls (Table 19). These neoplasms were all evaluated in context of the broader data set (Tables 22 and 23). The summary of neoplastic findings is available (see data Supplementary Study 14 to be found online at http://informahealthcare.com/doi/abs/10.3109/10408444.2014.1003423).

Glyphosate was considered not carcinogenic in the CD-1 mice, following continuous average dietary exposure for males and females, to quantities up to 945.6 mg/kg bw/day for 18 months, which is consistent with the recent evaluation in Europe under the Annex I Renewal of glyphosate (Germany Rapporteur Member State 2015b).

Discussion

An extraordinarily large volume of animal data has been compiled to evaluate the carcinogenic potential of glyphosate. The expected normal biological variability for spontaneous tumor formation is reflected across this extensive data set (Tables 20–23). However, no specific neoplasm stands out as a consequence of glyphosate exposures. While some individual studies may note an increase in a specific neoplasm at the high dose, the pooled data fail to identify any consistent pattern of neoplasm formation, demonstrating that the effect is not reproducible and not treatment-related. The lack of a dose-response across the several orders of magnitude suggests that no individual tumor of single etiology is attributable to glyphosate administration.

Glyphosate has undergone repeated and extensive review by the United States Environmental Protection Agency (US EPA 1993), the European Union (EC 2002, Germany Rapporteur Member State 2015b) and the World Health Organization/Food and Agriculture Organization of the United Nations (WHO/FAO 2004b, WHO/FAO 2004a). With regard to potential carcinogenic effects of glyphosate, the unanimous outcome of these reviews has been that the data provide sufficient evidence to conclude that glyphosate should not be considered a carcinogen. Genotoxicity studies with glyphosate, conducted under conditions stipulated by internationally accepted testing guidelines and GLP, as reviewed in 2000 (Williams et al. 2000) and recently updated (Kier and Kirkland 2013), indicate that glyphosate clearly does not exhibit the properties of a DNA-reactive genotoxic carcinogen. This lack of mutagenicity rules out an important concern for carcinogenicity.

Mink et al. published a review of the available epidemiological studies that investigated possible associations between glyphosate and cancer diagnosed in humans (Mink et al. 2012). No evidence was found for a statistically significant positive association between cancer and exposure to glyphosate. While one Agricultural Health Study (AHS) publication mentions a "suggested association" between glyphosate use and multiple myeloma (De Roos et al. 2005), a later summary of AHS

Table 20. Summary of select neoplasms in male rats (Studies 1–8).

	Tumor Incidence/number of animals examined, by dose (mg/kg bw/day)												
Select neoplasm	Controls – 0 [% range for studies]	[a]3	[d]7.4	[a]10	[c]10	[a]31	[d]73.9	[h]86	[b]89	[c]100	[f]104	[g]121
Pancreas islet cell adenoma	20/397 [0–14]	5/49	0/30	2/50	1/24	2/50	0/32	1/51	8/57	2/17	1/75	2/64
Pituitary adenoma	153/398 [6–57]	19/49	4/30	20/48	12/24	18/47	3/31	11/51	32/58	8/19	41/75	17/63
Pituitary carcinoma	4/98 [2–6]	2/49	NF	3/48	1/24	1/47	NF	NF	NF	0/19	NF	NF
Testes interstitial cell (Leydig)	14/447 [0–8]	3/50	0/37	1/50	1/25	6/50	2/32	3/51	0/60	0/19	2/75	2/63
Thyroid C cell adenoma	35/391 [4–18]	1/49	0/26	0/49	1/21	2/49	1/29	#1/51	5/58	1/17	10/74	#1/63
Hepatocellular adenoma	30/351 [0–48]	NF	22/50	NF	1/50	NF	10/48	2/51	2/60	1/49	0/75	2/64
Hepatocellular carcinoma	22/384 [0–42]	0/50	28/50	1/50	1/50	2/50	18/48	0/51	2/60	1/49	1/75	NF
Benign keratoacanthoma (skin)	8/250 [2–5]	NF	NF	NF	NF	NF	NF	3/51	3/60	NF	3/75	0/64

	Tumor Incidence/number of animals examined, by dose (mg/kg bw/day)												
Select neoplasm	[c]150	[h]285	[c]300	[f]354	[g]361	[b]362	[d]740.6	[c]780	[b]940	[c]1000	[h]1077	[f]1127	[g]1214	[c]1290
Pancreas islet cell adenoma	NF	2/51	2/21	1/80	0/64	5/60	1/49	NF	7/59	1/49	1/51	1/78	1/64	NF
Pituitary adenoma	NF	10/51	7/21	33/80	18/64	34/58	5/49	NF	32/59	17/50	20/51	42/78	19/63	NF
Pituitary carcinoma	NF	NF	1/21	NF	NF	NF	NF	NF	NF	0/50	NF	NF	NF	NF
Testes interstitial cell (Leydig)	1/49	1/51	0/21	0/80	2/63	3/60	3/50	2/49	2/60	2/50	1/51	2/78	2/64	0/47
Thyroid C cell adenoma	NF	#0/51	2/21	5/79	#1/63	8/58	1/50	NF	7/60	8/49	#3/51	6/78	#0/64	NF
Hepatocellular adenoma	NF	0/51	2/50	2/80	0/64	3/60	21/50	NF	8/60	2/50	1/51	1/78	5/64	NF
Hepatocellular carcinoma	1/49	0/51	0/50	2/80	NF	1/60	24/50	0/49	2/60	0/50	0/51	1/78	NF	0/47
Benign keratoacanthoma (skin)	NF	0/51	NF	0/80	1/64	4/60	NF	NF	5/59	NF	6/51	7/78	1/63	NF

[a]Study 1 (Monsanto) (CD) SD rats, rated unreliable for carcinogenicity evaluation.
[b]Study 2 (Monsanto) (CD) SD rats, including interim sacrifice groups.
[c]Study 3 (Cheminova) SD rats.
[d]Study 4 (Feinchemie Schwebda) Wistar rats.
[e]Study 5 (Excel) SD rats, rated unreliable for carcinogenicity evaluation.
[f]Study 6 (Arysta Life Sciences) Crj:CD SD rats, including interim sacrifice groups.
[g] Study 7 (Syngenta) Alpk:AP$_f$SD Wistar rats, including interim sacrifice groups.
[h] Study 8 (Nufarm) Wistar Han Crl:WI rats.
#Recorded as parafollicular adenoma.
NF not found/not reported

Table 21. Summary of select neoplasms in female rats (Studies 1–8).

	Tumor Incidence/number of animals examined, by dose (mg/kg bw/day)												
Select neoplasm	Controls – 0 [% range for studies]	[a]3	[d]7.4	[c]10	[a]11	[a]34	[d]73.9	[c]100	[h]105	[b]113	[f]115	[g]145
Pancreas islet cell adenoma	11/397 [0–9]	1/50	0/23	2/27	1/50	0/49	0/16	2/29	0/51	1/60	2/79	0/63
Pituitary adenoma	246/397 [14–78]	29/48	13/33	19/28	31/50	26/49	7/23	19/29	23/51	48/60	54/79	44/63
Pituitary carcinoma	16/155 [2–17]	7/48	NF	5/28	5/50	12/49	NF	5/28	NF	0/60	NF	NF
Thyroid C cell adenoma	25/302 [3% – 16%]	3/49	0/24	1/27	6/50	3/47	1/17	1/29	# 1/51	2/60	7/78	# 0/63
Hepatocellular adenoma	22/302 [0–36]	NF	18/48	1/50	NF	NF	19/49	3/50	0/51	2/60	1/79	0/64
Hepatocellular carcinoma	14/210 [0–20]	0/50	15/48	0/50	0/50	2/50	14/49	0/50	0/51	0/60	NF	NF
Mammary gland fibroadenoma	113/384 [6–58]	16/46	NF	12/28	20/48	16/44	NF	17/29	9/51	$24/54	30/79	4/63
Mammary gland adenocarcinoma	40/334 [2–22]	6/46	0/30	NF	5/48	8/44	0/33	NF	3/51	10/54	8/79	0/63

	Tumor Incidence/number of animals examined, by dose (mg/kg bw/day)												
Select neoplasm	[e]210	[c]300	[h]349	[f]393	[g]437	[b]457	[d]740.6	[c]1000	[e]1060	[b]1183	[f]1247	[h]1382	[g]1498	[c]1740
Pancreas islet cell adenoma	NF	2/29	0/51	1/78	1/64	4/60	1/49	1/49	NF	0/59	1/78	0/51	0/64	NF
Pituitary adenoma	NF	25/30	16/51	47/77	46/63	46/60	6/50	34/49	NF	34/59	52/78	32/51	49/64	NF
Pituitary carcinoma	NF	2/30	NF	NF	NF	0/60	NF	7/49	NF	1/59	NF	NF	NF	NF
Thyroid C cell adenoma	NF	2/29	#1/50	8/76	#0/64	6/60	1/47	7/49	NF	6/60	4/78	# 0/51	# 2/64	NF
Hepatocellular adenoma	NF	1/50	1/51	0/78	1/64	6/60	13/50	2/50	NF	1/60	0/78	1/51	0/64	NF
Hepatocellular carcinoma	NF	0/50	1/51	NF	NF	1/60	9/50	0/50	NF	2/60	NF	0/51	NF	NF
Mammary gland fibroadenoma	1/22	19/30	7/51	27/77	6/64	$27/59	NF	29/50	5/22	$28/57	30/78	5/51	5/64	5/50
Mammary gland adenocarcinoma	0/22	NF	1/51	11/77	0/64	¬14/59	0/48	NF	0/22	¬9/57	8/78	6/51	2/64	0/50

[a]Study 1 (Monsanto) (CD) SD rats, rated unreliable for carcinogenicity evaluation.
[b]Study 2 (Monsanto) (CD) SD rats, including interim sacrifice groups.
[c]Study 3 (Cheminova) SD rats.
[d]Study 4 (Feinchemie Schwebda) Wistar rats.
[e]Study 5 (Excel) SD rats, rated unreliable for carcinogenicity evaluation.
[f]Study 6 (Arysta Life Sciences) Crj:CD SD rats, including interim sacrifice groups.
[g]Study 7 (Syngenta) Alpk:AP,SD Wistar rats, including interim sacrifice groups.
[h]Study 8 (Nufarm) Wistar Han Crl:WI rats.
[$]Recorded as adenoma/adenofibroma/fibroma.
¬Recorded as carcinoma/adenocarcinoma.
NF not found/not reported.

Table 22. Summary of select neoplasms in male mice (Studies 10–14).

	Tumor Incidence/number of animals examined, by dose (mg/kg bw/day)							
Select neoplasm	Controls – 0 [% range for studies]	[d]14.5	[c]85	[b]100	[d]150	[a]157	[c]165	[c]267
Bronchiolar-alveolar adenoma	31/249 [10–18]	2/22	[§]7/51	15/50	0/22	9/50	[§]14/50	[§]9/51
Bronchiolar-alveolar adenocarcinoma	10/149 [2–10]	NF	[§]5/51	NF	NF	3/50	[§]1/50	[§]7/51
Bronchiolar-alveolar carcinoma	10/100 [0–20]	0/22	NF	7/50	0/22	NF	NF	NF
Hepatocellular adenoma	27/250 [0–28]	5/25	1/51	12/50	3/28	0/50	15/50	4/51
Hepatocellular carcinoma	15/250 [0–16]	0/25	11/51	5/50	0/28	0/50	1/50	7/51
Malignant lymphoma	16/205 [0–100]	15/50	1/51	2/4	16/50	[#]5/50	2/50	2/51
Myeloid leukemia	3/101 [0–6]	1/50	1/51	NF	1/50	NF	NF	0/51
	Tumor Incidence/number of animals examined, by dose (mg/kg bw/day)							
Select neoplasm	[b]300	[a]814	[c]838	[c]946	[b]1000	[d]1454	[c]4348	[a]4841
Bronchiolar-alveolar adenoma	11/50	9/50	[§]13/50	[§]4/51	13/50	1/50	[§]11/50	9/50
Bronchiolar-alveolar adenocarcinoma	NF	2/50	[§]6/50	[§]11/51	NF	NF	[§]4/50	1/50
Bronchiolar-alveolar carcinoma	8/50	NF	NF	NF	9/50	1/50	NF	NF
Hepatocellular adenoma	11/50	1/50	15/50	2/51	9/50	3/50	7/50	0/50
Hepatocellular carcinoma	6/50	0/50	3/50	4/51	7/50	2/50	1/50	2/50
Malignant lymphoma	1/1	[#]4/50	0/50	5/51	6/8	19/50	6/50	[#]2/50
Myeloid leukemia	NF	NF	NF	0/51	NF	1/50	NF	NF

[a]Study 10 (Monsanto) CD-1 mice.
[b]Study 11 (Cheminova) CD-1 mice.
[c]Study 12 (Arysta Life Science) CD-1 mice.
[d]Study 13 (Feinchemie Schwebda) Swiss albino mice.
[e]Study 14 (Nufarm) CD-1 mice.
[§]Recorded as lung rather than bronchiolar-alveolar.
[#]Recorded as sum of malignant lymphoblastic lymphosarcoma with leukemia, lymphoblastic lymphosarcoma without leukemia and composite lymphosarcoma.
[$]Recorded as lymphoblastic lymphosarcoma with leukemia.
NF not found/not reported.

results note that there were no associations between glyphosate use and a number of cancers, including lymphohematopoietic cancers, leukemia, NHL, and multiple myeloma (Weichenthal et al. 2010). A subsequent reanalysis of AHS data obtained under the Freedom of Information Act notes no suggestion of an association between glyphosate use and multiple myeloma, with a relative risk of 1.1 and 95% and a confidence interval of 0.5–2.9 (Sorahan 2012). A recent review paper (Alavanja et al. 2013) cites another epidemiology study claiming an association between glyphosate use and NHL (Eriksson et al. 2008), but this research is strongly criticized in the recent Reevaluation Assessment Report for glyphosate Annex I Renewal in Europe (Germany Rapporteur Member State 2015b), highlighting potential referral bias, selection bias, uncontrolled confounding, limited data usage contrary to claims of including all new cases (living cases only, rather than living

Table 23. Summary of select neoplasms in female mice (Studies 10–14).

	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)							
Select neoplasm	Controls – 0 [% range for studies]	[d]15.0	[e]85	[b]100	[d]151	[c]153	[a]190	[c]267
Bronchiolar-alveolar adenoma	28/250 [2–20]	0/16	[§]4/51	3/49	2/21	[§]5/50	9/50	[§]2/51
Bronchiolar-alveolar adenocarcinoma	2/99 [2]	NF	[§]2/51	NF	NF	[§]2/50	3/50	[§]2/51
Bronchiolar-alveolar carcinoma	9/151 [2–10]	0/16	NF	2/49	0/20	NF	NF	NF
Malignant lymphoma	54/215 [10–100]	20/50	8/51	12/15	19/50	4/50	[#]6/50	10/51
Myeloid leukemia	2/156 [0–4]	1/50	0/51	NF	2/50	0/50	NF	1/51
Pituitary adenoma	1/232 [0–2]	0/16	1/51	0/32	0/17	1/50	0/21	0/51
	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)							
Select neoplasm	[b]300	[c]787	[c]946	[a]955	[b]1000	[d]1467	[c]4116	[a]5874
Bronchiolar-alveolar adenoma	3/50	[§]12/50	[§]2/51	10/49	6/50	3/50	[§]5/50	1/50
Bronchiolar-alveolar adenocarcinoma	NF	[§]3/50	[§]3/51	4/49	NF	NF	[§]1/50	4/50
Bronchiolar-alveolar carcinoma	1/50	NF	NF	NF	5/50	0/50	NF	NF
Malignant lymphoma	9/12	8/50	11/51	[#]6/50	13/14	25/50	7/50	[#]10/50
Myeloid leukemia	NF	0/50	0/51	NF	NF	1/50	1/50	NF
Pituitary adenoma	0/23	0/50	2/51	0/44	[~]3/50	1/48	0/50	0/37

[a]Study 10 (Monsanto) CD-1 mice.
[b]Study 11 (Cheminova) CD-1 mice.
[c]Study 12 (Arysta Life Science) CD-1 mice.
[d]Study 13 (Feinchemie Schwebda) Swiss albino mice.
[e]Study 14 (Nufarm) CD-1 mice.
[§]Recorded as lung rather than bronchiolar-alveolar.
[#]Recorded as sum of lymphoblastic lymphosarcoma with leukemia, lymphoblastic lymphosarcoma without leukemia and composite lymphosarcoma.
[~]2 animals in anterior lobe, 1 animal in intermediate lobe.
NF not found/not reported.

plus dead), and questionable definition/interpretation of dose-response. It is important to note that the Eriksson et al. study did detect statistically significant positive associations for small lymphocytic lymphoma/chronic lymphocytic leukemia and "unspecified NHL", while the following lymphomas were not statistically significantly associated with glyphosate use: B-cell lymphomas, grade I–III follicular lymphoma, diffuse large B-cell lymphoma, other specified B-cell lymphomas, unspecified B cell lymphomas, and T-cell lymphomas (Eriksson et al. 2008). As previously discussed, statistically significant associations need to be evaluated further for study bias, confounders and sampling error, before expending resources and energy on further evaluation of potential causality.

Epidemiological investigations face the difficulty of reliably determining the magnitude of exposure to the chemical in question, while ruling out confounders like co-exposure to other chemicals, and environmental and lifestyle factors. In contrast, carcinogenicity studies in experimental animals, when conducted according to appropriate testing guidelines, are designed in a fashion that allows a direct association between observed effects and substance exposure, yet the relevance of observed findings to humans is an important consideration. This manuscript collectively presents the scientific community with carcinogenicity results from a remarkably large body of data from fourteen long-term carcinogenicity studies on glyphosate.

Glyphosate is of very low acute toxicity with an oral LD_{50} in the rat in excess of 5000 mg/kg of body weight.. The sub-chronic NOAEL is 400 mg/kg bw/day, and is based on effects that do not impair long-term survival (WHO/FAO 2004b, WHO/FAO 2004a). This allows administration of very high glyphosate doses to rodents for a prolonged time. Dietary levels of up to 30 000 and 40 000 milligrams of glyphosate per kilogram of diet have been administered to rats and mice, respectively, in chronic feeding studies covering their expected lifespan without apparent effects on longevity.

One of the most critical aspects of designing a carcinogenicity study is the choice of dose levels, especially the top dose, at either the limit dose or MTD. The relevant OECD TGs 451 and 453 for carcinogenicity studies propose a body weight depression of approximately 10% as evidence for systemic toxicity. This is equivalent to the concept of the MTD, which is discussed in a supporting OECD guidance document (OECD 2012b). For chemicals which are well tolerated by the experimental animal, where no dose-limiting toxicity is observed, the respective OECD guidance suggests 1000 mg/kg bw/day as the highest dose level (OECD 2012a). Many of the carcinogenicity studies performed in rats and mice with glyphosate have been conducted with the high dose group receiving levels of glyphosate at, or in excess of the limit dose because of its very low toxicity following repeat exposure. Following this extensive testing, even at very high exposure levels, there was no evidence of a carcinogenic effect related to glyphosate treatment. The select neoplasms highlighted in Tables 20–23 show normal biological background levels of spontaneous neoplasms, with lack of dose-response across the data sets. The combined studies clearly indicate that glyphosate's carcinogenic potential is extremely low or non-existent in animal models up to very high doses.

By way of comparison, the worst-case calculated human dietary exposure to glyphosate, the Theoretical Maximum Daily Intake (TMDI) is 0.14 mg/kg bw/day (EFSA 2012). Systemic exposure of operators, as assessed for the EU reapproval of glyphosate, is predicted to be between 0.0034 (German BBA model, tractor-mounted ground-boom sprayer) and 0.226 mg/kg bw/day (UK POEM, hand-held-spraying to low targets, data not shown). The model estimates are supported by human biomonitoring data in farmers showing systemic exposures of 0.004 and 0.0001 mg/kg/day for worst-case and mean acute doses, respectively (Acquavella et al. 2004). The high doses in chronic rodent studies at which no evidence of carcinogenicity is demonstrated are at least hundreds of thousands fold greater than peak human systemic exposure levels. Clearly, there is no scientific basis for concern of carcinogenic risk to humans resulting from glyphosate exposure.

With over 40 years of scientific research on glyphosate, no compelling evidence exists for a mechanism for glyphosate to cause cancer. Mammalian metabolism does not activate glyphosate to a toxic metabolite (Anadon et al. 2009, WHO/FAO 2004a). The lack of glyphosate DNA reactivity supports the

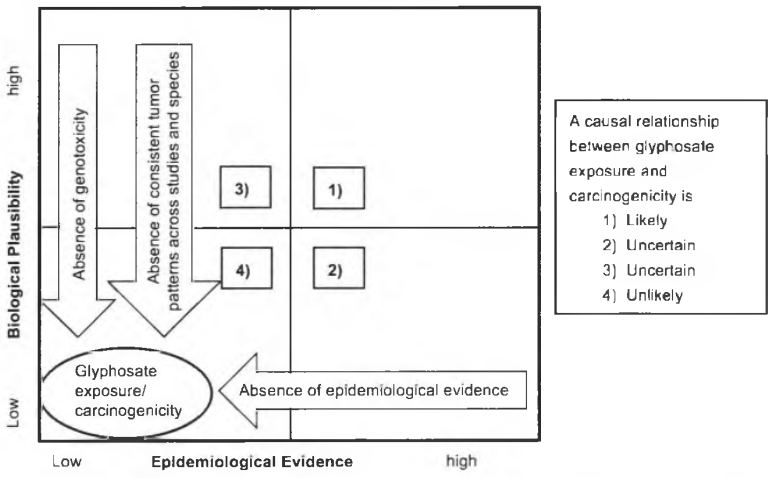


Figure 2. Likelihood of glyphosate carcinogenicity based on experimental and epidemiological data; a causal inference grid as proposed by Adami et al. (2011) to utilize both toxicological and epidemiological data.

lack of potential for an initiation event for carcinogenesis (Kier and Kirkland 2013). Clearly, there is a lack of potential for glyphosate to induce hormonal oncogenesis, based on both the tumor incidence data presented and the unequivocal evidence that glyphosate is not an endocrine disruptor (Bailey et al. 2013, Levine et al. 2012, Saltmiras and Tobia 2012, Webb et al. 2013, Williams et al. 2012).

The absence of test substance-related neoplastic findings in a total of 14 rodent cancer bioassays with glyphosate is in stark contrast to the recent dramatic media reports, internet postings, and YouTube videos of rat tumors, hypothesized to be caused by treatment with maize containing glyphosate residue or drinking water spiked with a glyphosate formulation (Seralini et al. 2014). Such reports, under the scrutiny of the global scientific community, demand greater data transparency and accountability within the peer review process.

The absence of a glyphosate-related mechanism for carcinogenesis, the huge volume of genotoxicity data studies indicating no likely mutagenic or DNA-reactive potential (Kier and Kirkland 2013), combined with the lack of epidemiological evidence for glyphosate-induced cancer (Mink et al. 2012), and the lack of carcinogenicity in multiple rodent carcinogenicity assays, are depicted in a causal inference grid in Figure 2, as put forth by Adami et al. (Adami et al. 2011). The overwhelming weight of the available evidence, demonstrating a lack of both biological plausibility and epidemiological effects, draws a compelling conclusion that glyphosate's carcinogenic potential is extremely low or non-existent.

Acknowledgements

Special thanks go to Elizabeth Webb, Monsanto Toxicologist, for her detailed attention to document and data table formatting and as the reference library curator. Quality control and review of data transcription were valued services provided by Carrie Leigh Logan and Aparna Desai Nemali, Monsanto Quality Assurance Specialists.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. Volker Mostert was an employee of the consulting group, Dr. Knoell Consult GmbH, involved in the preparation of the recent glyphosate Annex I Renewal dossier for the Glyphosate Task Force (GTF; a consortium of European glyphosate registrants http://www.glyphosatetaskforce.org/). Helmut Greim was funded as an independent consultant for his expert contributions to this manuscript. David Saltmiras and Christian Strupp are employed by member companies of the GTF, Monsanto and ADAMA Agriculture B.V. (formerly Feinchemie Schwebda GmbH) respectively. David Saltmiras is also Chair of the Toxicology Technical Working Group of the GTF. Christian Strupp is an expert member of the Toxicology Technical Working Group of the GTF. Monsanto Company was the original producer and marketer of glyphosate formulations. The authors had sole responsibility for the writing and content of the paper and the interpretations and opinions expressed in the paper are those of the authors and may not necessarily be those of the member companies of the Glyphosate Task Force.

References

Acquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, Chapman P, Bleeke M. (2004). Glyphosate biomonitoring for farmers and their families: Results from the farm family exposure study. Environ Health Perspect, 112, 321–6.

Adami HO, Berry SC, Breckenridge CB, Smith LL, Swenberg JA, Trichopoulos D, et al. (2011). Toxicology and epidemiology: improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference. Toxicol Sci, 122, 223–34.

Alavanja MC, Ross MK, Bonner MR (2013). Increased cancer burden among pesticide applicators and others due to pesticide exposure. CA Cancer J Clin, 63, 120–42.

Anadon A, Martinez-Larranaga MR, Martinez MA, Castellano VJ, Martinez M, Martin MT, et al. (2009). Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats. Toxicol Lett, 190, 91–5.

Antoniou M, Habib M, Howard C, Jennings R, Leifert C, Nodari R, et al. (2012). Teratogenic effects of glyphosate-based herbicides: divergence of regulatory decisions from scientific evidence. J Environ Anal Toxicol, S4, 006.

Aris A, Leblanc S. (2011). Maternal and fetal exposure to pesticides associated to genetically modified foods in Eastern Townships of Quebec, Canada. Reprod Toxicol, 31, 528–33.

Aris A, Paris K. (2010). [Hypothetical link between endometriosis and xenobiotics-associated genetically modified food]. Gynecol Obstet Fertil, 38, 747–53.

Armitage JO. (1997). The changing classification of non-Hodgkin's lymphomas. CA Cancer J Clin, 47, 323–5.

Arysta Life Sciences. (1997a). HR-001: 18-Month Oral Oncogenicity Study in Mice. Tokyo, Japan: The Institute of Environmental Toxicology.

Arysta Life Sciences. (1997b). HR-001: 24-Month Oral Chronic Toxicity and Oncogenicity Study in Rats. Kodaira-shi, Tokyo, Japan: The Institute of Environmental Toxicology.

Arysta Life Sciences. (1997c). HR-001: 12-Month Oral Chronic Toxicity Study in Dogs. IET 94-0157

Bailey J, Hauswirth J, Stump D. (2013). No evidence of endocrine disruption by glyphosate in male and female pubertal assays (Conference Abstract PS 1937). The Toxicologist (supplement to Toxicological Sciences), 132, 412.

Barale-Thomas E. (2013). The SFPT feels compelled to point out weaknesses in the paper by Seralini et al. (2012). Food Chem Toxicol, 53, 473–4.

Benachour N, Seralini GE. (2009). Glyphosate formulations induce apoptosis and necrosis in human umbilical, embryonic, and placental cells. Chem Res Toxicol, 22, 97–105.

Berry C. (2013). Adverse effects in a feeding study of a GM derived corn in rats. Food Chem Toxicol, 53, 445–6.

Berry CL. (2010). Relativism, regulation and the dangers of indifferent science: the Sir Roy Cameron lecture of the Royal College of Pathologists. Toxicology, 267, 7–13.

Bradford Hill A. (1965). The environment and disease: association or causation? Proc R Soc Med, 58, 295–300.

Bradley A, Mukaratirwa S, Petersen-Jones M. (2012). Incidences and range of spontaneous findings in the lymphoid and haemopoietic system of control Charles River CD-1 mice (Crl: CD-1(ICR) BR) used in chronic toxicity studies. Toxicol Pathol, 40, 375–81.

Brayton CF, Treuting PM, Ward JM. (2012). Pathobiology of aging mice and GEM: background strains and experimental design. Vet Pathol, 49, 85–105.

Brock WJ. (2014). Strengthening the peer review process for the International Journal of Toxicology. Int J Toxicol, 33, 351–2.

Chandra M, Riley MG, Johnson DE. (1992). Spontaneous neoplasms in aged Sprague-Dawley rats. Arch Toxicol, 66, 496–502.

Cheminova. (1990). Glyphosate: 52 Week Oral Toxicity Study in Dogs. Inveresk Research International Report No.: 7502. Cheminova report No.: 52 GLY.

Cheminova. (1993a). Glyphosate – 104 Week Combined Chronic Feeding/Oncogenicity Study in Rats with 52 Week Interim Kill (Results After 104 Weeks). Tranent, UK: Inveresk Research International, Ltd.

Cheminova. (1993b). Glyphosate: 104 week dietary carcinogenicity study in mice. Tranent, UK: Inveresk Research International, Ltd.

Chruscielska K, Brzezinski J, Kita K, Kalhorn D, Kita I, Graffstein B, et al. (2000a). Glyphosate – evaluation of chronic activity and possible

far-reaching effects. Part 1. Studies on chronic toxicity. Pestycydy (Warsaw), 3–4, 11–20.

Chruscielska K, Graffstein B, Szarapinska-Kwaszewska J, Brzezinski J, Kalhorn D. (2000b). Glyphosate: Evaluation of chronic activity and possible far-reaching effects. Part 2. Studies on mutagenic activity. Pestycydy (Warsaw) 3–4, 21–5.

De Roos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, et al. (2005). Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect, 113, 49–54. doi 10.1289/ehp.7340.

de Souza L, Oda LM. (2013). Letter to the editor. Food Chem Toxicol, 53, 440.

EC. (2002). Review report for the active substance glyphosate. European Commission., Directorate F – Food Safety: plant health, animal health and welfare, international questions, E1-Plant health.

EFSA. (2012). Reasoned Opinion – Modification of the existing MRL for glyphosate in lentils. EFSA J, 10, 2250.

Eriksson M, Hardell L, Carlberg M, Akerman M. (2008). Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer, 123, 1657–63.

EU. (2008). Council Regulation (EC) No 440/2008. Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri = OJ:L:2008:142:0001:0739:en:PDF. Accessed on November 13, 2012.

Everds NE, Snyder PW, Bailey KL, Bolon B, Creasy DM, Foley GL, et al. (2013). Interpreting stress responses during routine toxicity studies: a review of the biology, impact, and assessment. Toxicol Pathol, 41, 560–614.

Excel. (1997). Combined Chronic Toxicity/Carcinogenicity Study of Glyphosate Technical in Sprague Dawley Rats. Pune, India: Indian Institute of Toxicology.

Feinchemie Schwebda. (1996). Combined Chronic Toxicity and Carcinogenicity Study with Glyphosate Technical in Wistar Rats. Bangalore, India: Rallis India, Ltd.

Feinchemie Schwebda. (2001). Carcinogenicity Study with Glyphosate Technical in Swiss Albino Mice. Bangalore, India: Rallis India. Ltd.

Gad SC, Frith CH, Goodman DG, Boysen BG. (2008). Chapter 2. The Mouse. In: Gad, SC, Ed. Animal Models in Toxicology, Second Edition. Informa Health Care USA, Inc. ISBN-13: 978-0-8247-5407-5. ISBN-10: 0-8247-5407-7.

Gasnier C, Benachour N, Clair E, Travert C, Langlois F, Laurant C, et al. (2010). Dig1 protects against cell death provoked by glyphosate-based herbicides in human liver cell lines. J Occup Med Toxicol, 5, 29.

Germany Rapporteur Member State. (2015a). Glyphosate Renewal Assessment Report. Volume 1. Report and Proposed Decision. Revised 29th. January 2015.

Germany Rapporteur Member State. (2015b). Glyphosate Renewal Assessment Report, Volume 3, Annex B.6.1 Toxicology and Metabolism. Revised 29th. January 2015.

Germany Rapporteur Member State. (2015c). List of Endpoints, Active Substance Glyphosate. Report and Proposed Decision. Revised 29th. January 2015.

Gold LS, Sawyer CB, Magaw R, Backman GM, de Veciana M, Levinson R, et al. (1984). A carcinogenic potency database of the standardized results of animal bioassays. Environ Health Perspect, 58, 9–319.

Grunewald W, Bury J. (2013). Comment on "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize" by Seralini et al. Food Chem Toxicol, 53, 447–8.

Hammond B, Goldstein DA, Saltmiras D. (2013). Response to original research article, in press, corrected proof, "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize". Food Chem Toxicol, 53, 459–64.

Hayes AW. (2014). Reply to letter to the editor: Editor in Chief of *Food and Chemical Toxicology* answers questions on retraction. Food Chem Toxicol, 65, 394–5.

IUPAC. (1997). Compendium of Chemical Terminology, 2nd ed. (the "Gold Book"). Compiled by A. D. McNaught and A. Wilkinson. Blackwell Scientific Publications, Oxford (1997). XML on-line corrected version: http://goldbook.iupac.org (2006-) created by M. Nic, J. Jirat, B. Kosata; updates compiled by A. Jenkins. ISBN 0-9678550-9-8. doi:10.1351/goldbook. (http://goldbook.iupac.org/M03771.html).

JMAFF. (2000). Data Requirements for Supporting Registration of Pesticides. Appendix. Section 2-1-15. Available at: http://www.acis.famic.go.jp/eng/shinsei/8147annex.pdf. Accessed on March 8, 2013.

Johnson MD, Gad SC. (2008). Chapter 3. The Rat. In: Gad, SC, Ed. Animal Models in Toxicology, Second Edition. Informa Health Care USA, Inc. ISBN-13: 978-0-8247-5407-5. ISBN-10: 0-8247-5407-7.

Kier LD, Kirkland DJ. (2013). Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol, 43, 283–315.

Klimisch HJ, Andreae M, Tillmann U. (1997). A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol, 25, 1–5.

Langridge P. (2013). Problems lie at several levels and bring into serious question the quality and standard of the editorial processes in your journal. Food Chem Toxicol, 53, 441.

Le Tien D, Le Huy H. (2013). Comments on "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize". Food Chem Toxicol, 53, 443–4.

Levine S, Saltmiras D, Webb E, Holmes C, Mortensen S, Honegger J, Bailey J. (2012). Tier 1 EDSP Assays and Regulatory Safety Studies Provide a Weight of Evidence that Glyphosate is Not an Endocrine Disruptor (Conference Abstract 529). Abstract Book for SETAC North America 33rd Annual Meeting. Long Beach, California. November 11–15, 2012.

Mink PJ, Mandel JS, Sceurman BK, Lundin JI. (2012). Epidemiologic studies of glyphosate and cancer: a review. Regul Toxicol Pharmacol, 63, 440–52.

Monsanto. (1981). A Lifetime Feeding Study of Glyphosate (ROUNDUP Technical) in Rats. East Millstone, New Jersey, USA: Bio/dynamics Inc.

Monsanto. (1983). A Chronic Feeding Study of Glyphosate (Roundup® Technical) in Mice. East Millstone, New Jersey, USA: Bio/dynamics, Inc.

Monsanto. (1985). Twelve-month Study of Glyphosate administered by Gelatin Capsule to Beagle Dogs. Monsanto report ML-83-137.

Monsanto. (1990). Chronic Study of Glyphosate Administered in Feed to Albino Rats. St. Louis, MO, USA: Monsanto Agricultural Company.

Nolte T, Rittinghausen S, Kellner R, Karbe E, Kittel B, Rinke M, Deschl U. (2011). RITA–Registry of Industrial Toxicology Animal data: the application of historical control data for Leydig cell tumors in rats. Exp Toxicol Pathol, 63, 645–56.

Nufarm. (2007). Glyphosate technical: 52-week Toxicity Study by Oral Route (Capsule) in Beagle Dogs. Study No. 29647 TCC.

Nufarm. (2009a). Glyphosate Technical: Dietary Carcinogenicity Study in the Mouse. Derbyshire, UK: Harlan Laboratories Ltd.

Nufarm. (2009b). Glyphosate Technical: Dietary Combined Chronic Toxicity/Carcinogenicity in the Rat. Shardlow, Derbyshire, UK: Harlan Laboratories Ltd.

OECD. (2012a). Guidance Document 116 on the Conduct and Design of Chronic Toxicity and Carcinogenicity Studies, Supporting Test Guidelines 451, 452 and 453, 2nd Edition. Available at: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote = ENV/JM/MONO(2011)47&doclanguage = en. Accessed on 20th. January 2015.

OECD. (2012b). OECD Guidelines for the Testing of Chemicals, Section 4 - Health Effects. Available at: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788. Accessed on 20th, January 2015.

Ollivier L. (2013). A comment on "Seralini, G.-E., et al., Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Food Chem. Toxicol. (2012)". Food Chem Toxicol, 53, 458.

Paganelli A, Gnazzo V, Acosta H, Lopez SL, Carrasco AE. (2010). Glyphosate-based herbicides produce teratogenic effects on vertebrates by impairing retinoic acid signaling. Chem Res Toxicol, 23, 1586–95.

Panchin AY. (2013). Toxicity of Roundup-tolerant genetically modified maize is not supported by statistical tests. Food Chem Toxicol, 53, 475.

Romano MA, Romano RM, Santos LD, Wisniewski P, Campos DA, de Souza PB, et al. (2012). Glyphosate impairs male offspring reproductive development by disrupting gonadotropin expression. Arch Toxicol, 86, 663–73.

Romano RM, Romano MA, Bernardi MM, Furtado PV, Oliveira CA. (2010). Prepubertal exposure to commercial formulation of the herbicide glyphosate alters testosterone levels and testicular morphology. Arch Toxicol, 84, 309–17.

Saltmiras D, Remick A, Haas M. (2011). Repeat dietary administration of an organic acid causes salivary gland alterations. Toxicol Lett, 205S, S233.

Saltmiras D, Tobia A. (2012). No evidence of endocrine disruption by glyphosate in Hershberger and Uterotrophic assays (Conference Abstract PS 2198). The Toxicologist (supplement to Toxicological Sciences), 126, 474.

Sanders D, Kamoun S, Williams B, Festing M. (2013). Re: Seralini, G.-E., et al. Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Food Chem. Toxicol. (2012). Food Chem Toxicol, 53, 450–3.

Schmitz P, Harvert H. (2012). Die ökonomische Bedeutung des Wirkstoffes Glyphosat fur den Ackerbau in Deutschland [Agro-Economic Analysis of the use of Glyphosate in Germany]. J Kulturpflanzen, 64, 150–62.

Schorsch F. (2013). Serious inadequacies regarding the pathology data presented in the paper by Seralini et al. (2012). Food Chem Toxicol, 53, 465–6.

Seralini GE, Clair E, Mesnage R, Gress S, Defarge N, Malatesta M, et al. (2014). Republished study: long-term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize. Environ Sci Eur [Online], 26, 14.

Son WC, Gopinath C. (2004). Early occurrence of spontaneous tumors in CD-1 mice and Sprague-Dawley rats. Toxicol Pathol, 32, 371–4.

Sorahan T. (2012). Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study data. Abstract P27-02. Toxicol Lett, 211S, S127.

Syngenta. (1996a). Glyphosate Acid: 1 Year Dietary Toxicity Study in Dogs. Alderley Park, Macclesfield, Cheshire, UK: Central Toxicology Laboratory.

Syngenta. (1996b). Glyphosate Acid: One Year Dietary Toxicity Study in Rats. CTL/P/5143.

Syngenta. (2001). Glyphosate Acid: Two Year Dietary Toxicity and Oncogenicity Study in Rats. Central Toxicology Laboratory, Alderley Park Macclesfield, Cheshire, UK: Syngenta.

Taddesse-Heath L, Chattopadhyay SK, Dillehay DL, Lander MR, Nagashfar Z, Morse HC, III, Hartley JW. (2000). Lymphomas and high-level expression of murine leukemia viruses in CFW mice. J Virol, 74, 6832–7.

Tester M. (2013). It does not become the quality of a journal such as Food and Chemical Toxicology to publish such poor work. Food Chem Toxicol, 53, 457.

Thoolen B, Maronpot RR, Harada T, Nyska A, Rousseaux C, Nolte T, et al. (2010). Proliferative and nonproliferative lesions of the rat and mouse hepatobiliary system. Toxicol Pathol, 38, 5S–81S.

Trewavas A. (2013). Science requires the dispassionate presentation of information. Food Chem Toxicol, 53, 449.

Tribe D. (2013). My comments about the paper do not adequately describe the serious failures that have occurred in the peer review process at FCT. Food Chem Toxicol, 53, 467–72.

US EPA. (1993). Reregistration eligibility decision (RED): glyphosate. United States Environmental Protection Agency, Office of Prevention, Pesticides, and Toxic Substances. Washington, DC, USA.

US EPA. (2012). OCSPP Harmonized Test Guidelines - Series 870 - Health Effects Test Guidelines. Available at: http://www.epa.gov/ocspp/pubs/frs/publications/Test_Guidelines/series870.htm. Accessed on November 13, 2012.

Webb E, Saltmiras D, Levine S. (2013). Endocrine Disruptor Screening Program (EDSP) Tier 1 In Vitro Assays Indicate Glyphosate Does Not Interact with Estrogen and Androgen Receptor Nor Inhibit Steroidogenesis (Poster abstract P500. American College of Toxicology 33rd Annual Meeting, November 4–7, 2012). Int J Toxicol, 32, 77.

Weichenthal S, Moase C, Chan P. (2010). A review of pesticide exposure and cancer incidence in the Agricultural Health Study cohort. Environ Health Perspect, 118, 1117–25.

WHO/FAO. (2004a). Pesticides residues in food – 2004. Part II Toxicological Evaluations. Joint meeting of the FAO Panel of Experts on pesticide residues in food and the environment and the WHO Core Assessment Group (JMPR). World Health Organization/Food and Agriculture Organization of the United Nations, Rome, Italy. http://www.inchem.org/documents/jmpr/jmpmono/v2004pr01.pdf. Accessed on 20th, January 2015.

WHO/FAO. (2004b). Pesticides residues in food – 2004. Report of the joint meeting of the FAO Panel of Experts on pesticide residues in food and the environment and the WHO Core Assessment Group on Pesticide Residues (JMPR). World Health Organization/Food and Agriculture Organization of the United Nations, Rome, Italy. http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Reports_1991-2006/report2004jmpr.pdf. Accessed on 20th, January 2015.

Williams AL, Watson RE, DeSesso JM. (2012). Developmental and reproductive outcomes in humans and animals after glyphosate exposure: a critical analysis. J Toxicol Environ Health B Crit Rev, 15, 39–96.

Williams GM, Kroes R, Munro IC. (2000). Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol, 31, 117–65.

Woodside FC, Davis AG. (2013). The Bradford Hill Criteria: The Forgotten Predicate. Thomas Jefferson Law Rev, 35, 103–25.

Supplementary material available online

Data Supplementary Study 1–14.

Critical Reviews in Toxicology

http://informahealthcare.com/txc
ISSN: 1040-8444 (print), 1547-6898 (electronic)

Crit Rev Toxicol, 2015; 45(3): 209–218
© 2015 Informa Healthcare USA, Inc. DOI: 10.3109/10408444.2015.1010194

informa
healthcare

REVIEW ARTICLE

Review of genotoxicity biomonitoring studies of glyphosate-based formulations

Larry D. Kier

Private Consultant, Buena Vista, CO, USA

Abstract

Human and environmental genotoxicity biomonitoring studies involving exposure to glyphosate-based formulations (GBFs) were reviewed to complement an earlier review of experimental genotoxicity studies of glyphosate and GBFs. The environmental and most of the human biomonitoring studies were not informative because there was either a very low frequency of GBF exposure or exposure to a large number of pesticides without analysis of specific pesticide effects. One pesticide sprayer biomonitoring study indicated there was not a statistically significant relationship between frequency of GBF exposure reported for the last spraying season and oxidative DNA damage. There were three studies of human populations in regions of GBF aerial spraying. One study found increases for the cytokinesis-block micronucleus endpoint but these increases did not show statistically significant associations with self-reported spray exposure and were not consistent with application rates. A second study found increases for the blood cell comet endpoint at high exposures causing toxicity. However, a follow-up to this study 2 years after spraying did not indicate chromosomal effects. The results of the biomonitoring studies do not contradict an earlier conclusion derived from experimental genotoxicity studies that typical GBFs do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

Abbreviations: BC, blood cells; BM, blood monocyte cells; BNMN, binucleated cells with micronuclei; CBMN, cytokinesis-block micronucleus; CA, chromosomal aberrations; GBF, glyphosate-based formulation; MN, micronucleus; MOMN, mononuclear cells with micronuclei; SCE, sister chromatid exchange; 8-OHdG, 8-hydroxydeoxyguanosine

Keywords

biomonitoring, formulation, genotoxicity, glyphosate, mutagenicity

History

Received 7 January 2015
Revised 17 January 2015
Accepted 18 January 2015
Published online 16 February 2015

Table of Contents

Introduction

Glyphosate is the active ingredient of very extensively used herbicide formulations and, accordingly, glyphosate and glyphosate-based formulations (GBFs) have been extensively studied for their toxic properties. One of these toxic properties is genotoxicity and there has been a recent extensive review of glyphosate and GBF experimental genotoxicity studies (Kier and Kirkland 2013). This review concluded that there was a strong weight of evidence that glyphosate and GBFs are predominantly negative in well-conducted core bacterial reversion and *in vivo* mammalian micronucleus and chromosomal aberration assays. Although some positive results for glyphosate and GBFs were reported in DNA damage assays and for the micronucleus endpoint for GBFs in non-mammalian studies, the positive results were associated with high dose levels and/or toxic effects. The preponderance of negative results in core assays supports the conclusion that reports of DNA damage or non-mammalian micronucleus effects are likely to be secondary to cytotoxicity rather than indicative of DNA-reactive mechanisms. This conclusion is consistent with and supported by a recent review of 14 experimental rodent carcinogenicity studies of glyphosate that indicated a weight of evidence that there was no carcinogenic effect related to glyphosate treatment (Greim et al. 2015).

The earlier Kier and Kirkland (2013) review focused on experimental studies and did not consider reports of human

Address for Correspondence: Larry D. Kier, Private Consultant, 16428 CR 356-8, Buena Vista, CO 81211 USA. Tel: +(719) 395-1993. E-mail: foreman48@hotmail.com

or environmental biomonitoring studies where there was GBF exposure. This review complements the earlier review by identifying and considering a number of human and environmental biomonitoring studies where exposure to GBFs was indicated and one or more genotoxicity endpoints were employed. Such studies can provide perspective on potential for effects on humans or other organisms with actual environmental or occupational exposures. However, they are also much more complicated to interpret and derive definitive conclusions from than experimental studies because of confounding exposures to other agents, complexity of applying methodology to subject populations and limits on availability of endpoints and sample sizes.

Identification of published studies

The published studies for review consideration were identified by literature searches for published reports containing references to glyphosate or GBFs (e.g., Roundup™ formulation) that also contained searchable terms which indicated that human or environmental genotoxicity studies were performed (e.g., alkaline single cell gel electrophoresis (comet) or micronucleus endpoints). Emphasis was placed on publications in peer-reviewed journals. Abstracts or other sources with incomplete information were not considered. Reviews without original data were not considered for evaluation; however, these reviews were examined to determine if there were any cited publications that had not been detected in the literature searches.

General methodology

Populations

Table 1 summarizes the identified genotoxicity biomonitoring studies involving GBF exposure. Most of these studies are cross-sectional studies in which genotoxicity biomarkers in an exposed population were compared to an unexposed referent population. A few studies are longitudinal studies where sampling was made before and after exposures (Lebailly et al. 2003, Bolognesi et al. 2009). For cross-sectional studies, a suitable sample size and a carefully matched referent population are important (Albertini et al. 2000, Collins et al. 2014). Although sample size should ideally be defined in reference to a pre-determined desired sensitivity, this does not appear to have been rigorously considered in the identified studies. A few of the studies had quite small (e.g., < 25) exposed and referent population sizes (e.g., Gregio D'Arce and Colus 2000, Vlastos et al. 2006, Paz-y-Mino et al. 2007, Bortoli et al. 2009).

Careful matching of exposed and referent populations for cross-sectional studies requires consideration of the specific endpoint and confounding factors that might affect the endpoint. Recommendations of major endpoint specific factors include gender and age for the CBMN endpoint (Battershill et al. 2008, Fenech et al. 2011), age for the buccal micronucleus (MN) endpoint (Bonassi et al. 2011), and gender, age and smoking status for the comet endpoint in blood cells (Collins et al. 2014). For genotoxicity endpoints, a large number of other factors may also be considered as possible confounding variables such as diet (Bonassi et al. 2011, Fenech et al. 2011, Collins et al. 2014), sleep (Kahan et al. 2010, Tenorio et al. 2013), disease status (Albertini et al. 2000, Battershill et al. 2008, Fenech et al. 2011), and seasonal variation (Albertini et al. 2000, Moller 2005, Verschaeve et al. 2007).

Many of the human biomonitoring studies had similar gender, age and usually smoking and alcohol consumption distributions for their exposed and referent populations. Although many of the studies indicated that information on lifestyle or other factors was collected (e.g., medical history and treatments, X-ray exposures and diet), most of the studies did not present comprehensive detailed data on these confounding factors. Some of the studies had moderate to fairly large differences in gender distribution (Bolognesi et al. 2002, 2004, Pastor et al. 2003, Simoniello et al. 2008, Benedetti et al. 2013, Koureas et al. 2014). One factor recommended for recording of the blood cell comet endpoint in human biomonitoring studies is exercise (Collins et al. 2014); however, the cross-sectional studies employing the comet endpoint did not appear to explicitly consider this as a confounding variable.

Exposures

Human exposures were usually characterized by self-reporting of the types of pesticides used as determined by survey of the exposed population or by more general use information. Additionally, the use of personal protective equipment may have been indicated. In most cases pesticides were characterized only by the active ingredient and not as a specific formulation. In some cases the extent of individual pesticide use was described as a frequency of use and/or amount of use but in most cases there were exposures to multiple pesticides. There are only a few biomonitoring studies where some assessment of the specific effects of exposures to GBFs can be inferred from the circumstances or exposure data presented. The identified studies only rarely attempted to estimate actual amount of exposure to specific pesticides or to evaluate exposure by chemical monitoring. No cases of chemical monitoring of exposure to glyphosate or GBFs were encountered in the genotoxicity biomonitoring studies. Uncertainty in extent and amount of exposure and dose is a major limitation in interpretation of the genotoxicity biomonitoring studies of pesticide exposure.

Endpoints

The most common endpoints employed in the biomonitoring studies were the CBMN assay on cultured lymphocytes (six human studies), the micronucleus assay on buccal cells (six human studies) and the comet assay on blood cells (five human studies and one environmental study). Other endpoints included measurement of sister chromatid exchange (SCE) in cultured lymphocytes (three human studies), chromosomal aberration in cultured lymphocytes (three human studies), erythrocyte micronucleus assays (two environmental studies), and bacterial reversion (Ames test strains) on urine (one human study). Two human studies measured DNA alterations (bulky adducts and oxidative DNA damage).

The CBMN assays generally used similar standardized methodologies for culture, including addition of cytochalasin B at 44 h after phytohemagglutinin stimulation. The studies used whole blood rather than isolated leukocytes for culture and scored 1000 or 2000 binucleated cells per subject for micronuclei. Referent population frequencies of binucleated cells with micronuclei (BNMN) ranged from about 1.8 to 9 per 1000 which seems reasonably close to a mean of 6.5 per

Table 1. Studies of human and environmental populations with reported GBF exposure.

Exposed population[a]	Endpoint[b]	Pesticide/GBF exposures	Exposed group result[c]	References
Human studies				
Agricultural workers (20); R (16)	Lymphocyte CA[NC]	19 pesticides reported used Including GBF	No statistically significant increase in CA	Gregio D'Arce and Colus (2000)
Greenhouse farmers (104); R (44)	Lymphocyte SCE[NC]	9 pesticides or pesticide classes reported as used. GBF used by 99/104 farmers	Statistically significant increases in SCE/ chromosome and high SCE frequency cells	Shaham et al. (2001)
Floriculturists (107); R (61)	Lymphocyte CBMN	> 30 pesticides reported used. GBF use reported in 57/107 workers	Statistically significant increase in BNMN	Bolognesi et al. (2002)
Hungarian agricultural workers (84); R (65)	Lymphocyte CBMN Buccal MN	14 pesticides reported used. GBF use frequency reported as 16.1%	No statistically significant increases in BNMN or buccal cell MN frequencies	Pastor et al. (2003)
Fruit growers (12 in one season for urine and comet; 17 in second season for urine only) ; NR	BM comet[NC] Ames test on urine	Samples collected before and after captan spraying. GBF use reported in 2/29 growers 1 day before captan spraying and in 1/19 grower on the day of captan spraying	No statistically significant effects on comet % DNA damage or tail moment; correlation between predicted captan exposure and response In Salmonella strain TA102	Lebailly et al. (2003)
Floriculturists (51); R (24)	Lymphocyte CBMN	25 pesticides reported used. GBF use reported in 21/51 workers with average of 106.5 kg/year applied	No statistically significant increase in BNMN	Bolognesi et al. (2004)
Workers exposed to pesticides (33); R (33)	Lymphocyte SCE Lymphocyte CBMN Lymphocyte CA	> 30 pesticides reported used including GBF	Statistically significant increases in BNMN and SCE but not CA	Costa et al. (2006)
Farmers (11); R (11)	Lymphocyte CBMN[NC]	17 pesticides reported used. GBF use reported in 3/11 farmers	Statistically significant increase in MN frequency but not in frequency of BNMN; statistically significant increases in small MN	Vlastos et al. (2006)
Fruit farmers (29); NR	BC DNA adducts (^{32}P-postlabelling)	GBF use reported in 1 of 29 fruit farmers. Sampling on morning of and morning after spraying	No statistically significant effects comparing relative adduct levels at different sampling times	Andre et al. (2007)
Individuals at or near GBF acrial spraying (24); R (21)	BC comet[NC]	GBF aerially sprayed within 3 km. Blood samples collected two weeks to two months after spraying	Statistically significant increase in comet tail length and appearance of high damage comets	Paz-y-Mino et al. (2007)
Workers exposed to pesticides (54); R (30)	BC comet	13 pesticides reported used including GBF	Statistically significant increase in damaged cells	Simoniello et al. (2008)
Humans in 3 areas where GBF was sprayed (60, 64 and 28); R (region of no pesticide exposure. 60).	Lymphocyte CBMN	Samples collected before, within 5 days and 4 months after GBF spraying in 3 regions Pesticide use reported by 76.6%, 61.7%and 28.6% of subjects in GBF sprayed regions	Statistically significant increase in BNMN sampled within 5 days of GBF spraying in 3 regions; statistically significant decrease In 4 month sample compared to < 5 day sample in 1 region.	Bolognesi et al. (2009)
Agricultural workers (29); R (37)	Buccal MN	10 pesticides reported used including GBF	Statistically significant increase in MN cell frequency	Bortoli et al. (2009)
Agricultural workers (70); R (70)	Lymphocyte SCE Buccal MN	25 pesticides reported used including GBF	Statistically significant increases in SCE/ metaphase and MN cell frequency	Martinez-Valenzuela et al. (2009)
Subjects in areas with GBF aerial spraying up to 2 years previously (92); R (90)	Lymphocyte CA[NC]	Aerial GBF spraying for illicit crop control up to two years before sampling	Normal karyotypes and percentage of chromosomal fragility within normal parameters	Paz-y-Mino et al. (2011)
Agricultural workers (81); R (46)	BC comet Buccal MN[NC]	25 pesticides reported used including GBF	Statistically significant increases in damaged comets and MN cell frequency	Benedetti et al. (2013)

(*Continued*)

Table 1. (*Continued*)

Exposed population[a]	Endpoint[b]	Pesticide/GBF exposures	Exposed group result[c]	References
Children living in areas of pesticide application (125); R (125)	Buccal MN^{NC}	>30 pesticides reported used including GBF	Statistically significant increase in MN cell frequency	Gomez-Arroyo et al. (2013)
Agricultural workers (41); R (32)	BC comet^{NC} Buccal MN^{NC}	Exposure of up to 7 different pesticides with 56.7% of workers exposed to a single pesticide (fenpropathrin, carbofuran or GBF)	Statistically significant increase in MN cell frequency and in comet endpoints (%DNA in tail and tail moment)	Khayat et al. (2013)
Pesticide sprayers (80); R (206)	BC 8-OHdG	>30 pesticides used including GBF	Statistically significant increases in 8-OHdG; no statistically significant increase with frequency of GBF applications in last spraying season	Koureas et al. (2014)
Environmental Studies				
Meadow voles living on golf courses (22 in 2001, comet only; 61 in 2002, comet and MN); R (0 in 2001; 8 in 2002)	BC comet^{NC} Erythrocyte MN^{NC}	Numerous pesticides reported used including GBF	Comet tail length and moment statistically correlated with total pesticide exposure in 2001 but not 2002; no statistically significant pesticide effects on polychromatic erythrocyte MN frequencies	Knopper et al. (2005)
Fish from dams (various species; 3 per species)	Erythrocyte MN	Wide GBF use reported in adjacent lands along with other pesticides	Higher MN frequencies than normal or expected from other reports but no negative concurrent controls used	Salvagni et al. (2011)

[a]Description of exposed population with number of exposed individuals in (). R with () indicates number of individuals in non-exposed referent population. NR indicates no concurrent referent population studied.
[b]Genotoxicity endpoint(s) measured. See abbreviations for endpoint abbreviations. ^{NC} after SCE, CBMN or comet endpoints indicates that slides were not indicated as coded before scoring.
[c]Results reported for exposed group compared to referent group.

thousand with an inter-quartile range of 3–12 per thousand observed for a large number of normal subjects from many laboratories (Fenech et al. 2011).

The buccal micronucleus (buccal MN) assays generally followed recommendations for number of cells scored with 1000–3000 cells scored per subject. There is a recommendation for the use of DNA-specific staining for this assay such as Feulgen-Fast Green (Thomas et al. 2009). Two of the laboratories used relatively non-specific Giemsa staining (Benedetti et al. 2013, Bortoli et al. 2009). The mean frequencies of micronucleated cells in referent populations ranged from about 0.37 per thousand to 1.78 per thousand. This range seems reasonably close to a mean of 0.74 micronucleated cells per thousand for a large number of healthy subjects not knowingly exposed to genotoxic substances or radiation (Bonassi et al. 2011). The study with the highest mean frequency of micronucleated cells in a referent population (1.78 per thousand) employed the relatively non-specific Giemsa stain (Bortoli et al. 2009).

The comet studies generally used similar standard methodology for cell lysis, alkaline treatment, and staining of DNA. One study used isolated leukocytes (Lebailly et al. 2003) but the other studies used whole blood. It should be noted that whole blood contains a high percentage of short-lived neutrophils and thus may be more suitable for recent exposures to genotoxic agents (Collins et al. 2014). Recent guidance for comet assay methodology suggests that the most useful comet measurement is the percentage of DNA in the comet tail (Anderson et al. 2013, Azqueta and Collins 2013, Collins et al. 2014). Only one of the six comet studies reported measurement of percentage of DNA in the comet tail (Khayat et al. 2013).

Most of the endpoints employed in the biomonitoring studies involve visual scoring for endpoints or visual selection of comets for image analysis. There are consistent and numerous recommendations that slides for scoring for these endpoints should be coded so that the scorer is not aware of the treatment conditions, individual or groups to which the slides belong (e.g., OECD 479, 1986, OECD 474, 1997, Albertini et al. 2000, Tice et al. 2000, Hartmann et al. 2003, Fenech 2007, Thomas et al. 2009, OECD 475, 2014, OECD 489, 2014). However, a number of the biomonitoring studies for these endpoints, as indicated in Table 1, did not include an explicit statement in the methodology that slides were coded for analysis. It is possible that the methodology used actually did involve coding of slides but that this was not mentioned in the publication. If this is the case then clear indication of coding slides for analysis should be encouraged in the methodology sections of such publications. Alternately, it is possible that coding was not used and that the scorers may have been aware of the groups to which the slides belonged. This would be a significant deviation from recommended practice and coding of slides and reporting this in the methodology should be encouraged for all biomonitoring study endpoints where visual scoring or selection of objects is involved.

Results for human biomonitoring studies

Studies with low GBF exposure incidence

Table 2 summarizes conclusions about the studies relevant to GBF effects. For some of the human biomonitoring studies, the indicated frequency or incidence of pesticide exposure to GBF in the pesticide exposed population was very low (Pastor et al. 2003, Lebailly et al. 2003, Vlastos et al. 2006, Andre et al. 2007). The incidence of GBF exposure reported for these studies was too low to allow any reasonable conclusions about any relationships between GBF exposure and genotoxicity endpoint effects or lack of effects.

Studies with exposure to multiple pesticides

A number of human monitoring studies in Table 1 and as summarized in Table 2 indicated exposure to a list of multiple pesticides including GBF but did not indicate the frequency or extent of exposure to any specific pesticides (Gregio D'Arce and Colus 2000, Costa et al. 2006, Simoniello et al. 2008, Bortoli et al. 2009, Martinez-Valenzuela et al. 2009, Benedetti et al. 2013, Gomez-Arroyo et al. 2013). One of the studies did not find statistically significant increases for the lymphocyte CA endpoint in agricultural workers (Gregio D'Arce and Colus 2000). The other six studies reported statistically significant increases for genotoxic endpoints for pesticide exposed populations compared to referent populations. An interesting observation of the Costa et al. (2006) study is that two endpoints (lymphocyte CBMN and SCE) had statistically significant increases in the exposed population but the chromosomal aberration endpoint did not. This suggests the possibility of different sensitivity to genotoxic effects of the endpoints which could possibly reflect different

Table 2. Summary GBF exposure conclusions from human genotoxicity biomonitoring studies.

Study reference	GBF conclusions and comments[a]
Reported low GBF exposure incidence	
Pastor et al. (2003)	Not informative because of low reported incidence of GBF exposure
Lebailly et al. (2003)	Not informative because of low reported incidence of GBF exposure. Longitudinal study focusing on captan exposure
Vlastos et al. (2006)	Not informative because of low reported incidence of GBF exposure
Andre et al. (2007)	Not informative because of low reported incidence of GBF exposure. Longitudinal study with no referent population
Multiple pesticide exposures and unknown extent of GBF exposure	
Gregio D'Arce and Colus (2000)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure. Negative result for CA endpoint indicates no positive effects from GBF exposure but extent of GBF exposure is not known
Costa et al. (2006)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure. Negative results for CA endpoint indicates no positive effects from GBF exposure but extent of GBF exposure is not known
Simoniello et al. (2008)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Bortoli et al. (2009)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Martinez-Valenzuela et al. (2009)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Benedetti et al. (2013)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Gomez-Arroyo et al. (2013)	Not informative because of exposures to multiple pesticides and unknown extent of GBF exposure
Multiple pesticide exposures and reported significant extent of GBF exposure	
Shaham et al. (2001)	Not informative because significant exposures to multiple pesticides were reported including GBF. Positive SCE effects not ascribed to GBF exposure
Bolognesi et al. (2002)	Not informative because significant exposures to multiple pesticides were reported including GBF. Positive CBMN effects not ascribed to GBF exposure
Khayat et al. (2013)	Not informative because significant exposures to multiple pesticides were reported including GBF. Positive buccal MN and BC comet effects not ascribed to GBF exposure. Use of only one pesticide (including GBF) reported for a large proportion of the population but no separate endpoint analysis of single pesticide exposure indicated
Informative for GBF exposure effects	
Bolognesi et al. (2004)	Some limited evidence for lack of effects of GBF exposure on lymphocyte CBMN endpoint. No statistically significant increases in BNMN frequency of exposed population with significant proportion (21/51) reporting exposure to GBF. Difference in gender distribution between exposed and referent populations. Small sample size of population exposed to GBF
Paz-y-Mino et al. (2007)	Evidence for BC comet effects for population in region of GBF aerial spraying. Small exposed and referent populations with differences in gender distribution. Samples collected and processed at different times after spraying. No indication of coding of slides for scoring. Significant clinical signs of toxicity and much higher than normal rates of application reported for exposed population. Comet effects may be secondary to toxicity
Bolognesi et al. (2009)	Inconclusive for lymphocyte CBMN effects for populations in regions of aerial GBF spraying. Statistically significant increases in BNMN frequencies were observed immediately after GBF spraying but statistically significant correlations were not observed with self-reported exposure to spray and results were not consistent with GBF application rates
Paz-y-Mino et al. (2011)	Some evidence of lack of chromosomal effects in a population exposed earlier to GBF aerial spraying. Publication indicates no chromosomal effects but contains no details on methodology or detailed chromosomal aberration data
Koureas et al. (2014)	Some evidence of lack of oxidative DNA damage from GBF exposure. Univariate analysis indicated lack of statistically significant correlation between reported GBF exposure frequency and 8-OHdG in blood DNA. Exposures are reported from last spraying season and relationship between exposure and sampling is not clear

[a]See abbreviations for endpoint abbreviations.

mechanisms and sensitivities to those mechanisms. Some support for this possibility is also provided by the negative lymphocyte CA result of Gregio D'Arce and Colus (2000), but this study did not measure other endpoints. None of these studies presented any detailed information on individual pesticide exposure or ascribed observed genotoxic effects to any specific pesticide. The fact that there were exposures to multiple pesticides, ranging from 10 to more than 30, in these studies and an unknown extent or frequency of exposure to GBFs does not allow any conclusions about genotoxic biomarker effects or lack of effects related to GBF exposure. It should be noted that positive results in genotoxicity biomonitoring studies involving multiple pesticide exposures have been frequently observed regardless of whether these exposures included GBF (Bolognesi et al. 2003, Bull et al. 2006).

Another set of human biomonitoring studies involved exposures to multiple pesticides but indicated frequency of exposure to specific pesticides that included a significant proportion of the exposed population using GBF (Shaham et al. 2001, Bolognesi et al. 2002, 2004, Khayat et al. 2013). One of these studies reported no statistically significant increase in BNMN frequency compared to a referent population for the CBMN endpoint in a population of 51 floriculturists of whom 21 reported GBF use (Bolognesi et al. 2004). Although the authors suggested trends for an increase in BNMN frequency with pesticide use and exposure time and a trend toward higher proportion of centromere-containing MN with pesticide exposure and in a subgroup using benzimidazolic compounds, the statistically negative result for BNMN frequency might be taken as some evidence indicating lack of detectable effect for this endpoint in the appreciable portion of floriculturists exposed to GBF.

Three other studies with multi-pesticide exposure including significant frequency of GBF use in the exposed populations reported positive genotoxic effects for the lymphocyte SCE endpoint (Shaham et al. 2001), the CBMN endpoint (Bolognesi et al. 2002), and the blood cell comet and buccal MN endpoints (Khayat et al. 2013). Two of these studies presented data on frequency of pesticide or pesticide class use and for both of these studies most participants used multiple pesticides and GBF use, while frequent, was not dominant compared to numerous other pesticides (Shaham et al. 2001, Bolognesi et al. 2002). Neither of these studies analyzed or attributed genotoxicity marker effects to specific pesticides and, given the multiplicity of pesticide exposures, there is no basis to conclude that GBF exposure was responsible for the effects observed. The Khayat et al. (2013) study reported that an appreciable percentage (56.7%) of the exposed population were exposed to only one pesticide and the single pesticide exposures were to GBF, fenpropathrin, or carbofuran. How many workers were exposed to each pesticide was not indicated. It should be noted that the Khayat et al. (2013) data table reporting multiplicity of pesticide exposures appeared to only present data for 30 workers but there were 41 workers in the exposed population. Despite the apparent occurrence of single pesticide exposures in a large portion of the exposed group, the study did not indicate a pesticide-specific analysis of genotoxic marker effects. In the absence of such analysis the genotoxic marker effects observed cannot be attributed to any specific pesticide, including GBF.

Studies assessing GBF exposure effects

As indicated in Tables 1 and 2, there were four studies where specific information on GBF exposure effects was presented. Three published studies focused on populations believed to be exposed to GBFs by their presence at or near aerial GBF spraying operations (Paz-y-Mino et al. 2007, 2011, Bolognesi et al. 2009).

One of these studies reported induction of blood cell comet effects on a Northern Ecuadorian population living within 3 km of areas sprayed with GBF for illicit crop eradication (Paz-y-Mino et al. 2007). The sprayed material was reported to be Roundup Ultra, a GBF containing 43.9% glyphosate, polyethoxylated tallowamine surfactant, and a proprietary component, Cosmoflux 411F. The populations studied were relatively small (24 exposed individuals and 21 non-exposed individuals) and the referent population had a higher proportion of males (4/21 vs. 1/24 in the exposed group). Blood sampling was reported to have been at 2 weeks to 2 months after spray exposure and samples were indicated to have been processed immediately. Specific methods for collection, storage, and transport of blood samples were not described for either the exposed population or referent group but it was noted that referent group samples were not processed concomitantly with the exposed group samples. Time between collection and assay and storage conditions and variation in sampling time between exposed and referent sample collection have been cited as potentially important variables for human biomonitoring studies using the comet endpoint (Collins et al. 2014). Inclusion of reference standards is advised when samples are processed at different times (Azqueta and Collins 2013) but this was not indicated in Paz-y-Mino et al. (2007) publication. The Paz-y-Mino publication also did not indicate that slides were coded for scoring for comet effects. As noted above there are numerous recommendations for coding of slides scored in the comet assay unless the scoring is fully automated (Tice et al. 2000, Hartmann et al. 2003, Collins et al. 2014, OECD 489, 2014).

The Paz-y-Mino et al. (2007) study reported increases in damaged cell categories and statistically significant increases in DNA migration (tail length) in the presumably exposed population. Interpretation of the results of this study should consider numerous reported signs of toxicity in the exposed population and the reported application rate of 23.4 liters/ha which was stated to be more than 20 times the maximum recommended application rate. Some of the reported exposed group health effects described by Paz-y-Mino et al. (2007) appear to be consistent with severe exposures noted in clinical reports of acute poisoning incidents (often self-administered) with GBFs and other pesticide formulations rather than typical bystander exposures (Menkes et al. 1991). Given the considerably favorable general toxicology profile of glyphosate as reported by the WHO/FAO Joint Meeting on Pesticide Residues (WHO/FAO 2004) and in Williams et al. (2000), factors related to either high surfactant exposure, unusual GBF components in this formulation or other undocumented variables appear to be confounding factors in this study. It is possible that the reported comet effects, if indeed resultant from GBF exposure, could well have been secondary to the clinical toxicity reported in this study population.

Subsequent to the original Paz-y-Mino et al. (2007) study, a baseline study was conducted on residents on the northeastern Ecuadorian border near where there had been aerial applications of GBF (Paz-y-Mino et al. 2011). Apparently, samples were collected about 2 years after the last aerial spraying. The exposed population used for genomic and chromosome analysis (92 individuals) and the referent sample population (90 individuals) were much larger than those of the previous Paz-y-Mino et al. (2007) study and the proportion of males in the exposed population was much higher. Publication details on sample collection, storage, transportation, and methodology for chromosomal aberration analysis are very limited and typical data for the chromosomal aberration endpoint were not presented. Thus, there is some uncertainty that the endpoint used was the typical chromosomal aberration endpoint. Nevertheless, the publication indicated that none of the exposed population had any type of chromosomal alteration and the percentage of chromosomal fragility was within normal parameters.

Another publication (Bolognesi et al. 2009) reported results for a lymphocyte CBMN study of individuals in three areas of Columbia treated with GBF by aerial spraying for illicit crop eradication (Putumayo and Nariño regions) or sugar cane maturation (Valle del Cauca region). Other populations were from an area using manual eradication for illicit crops and pesticides including GBF for agriculture (Boyaca region) and a region where agricultural practices do not include pesticide application (Santa Marta region). Although the title of the publication contains the term "agricultural workers", it appears that only some of the total population studied had agriculture as an occupation. The percent of subjects listing agriculture as an occupation varied from 7.1% in Valle del Cauca to 60% or more in Putumayo and Nariño. Although percentage of subjects reporting current use of pesticides is reported for the various regions and there was a reference to higher prevalence of use of genotoxic pesticides in Putumayo and Nariño no detailed information on the pesticides used or frequency of use was presented in the publication.

The human lymphocyte culture and scoring methodology employed in the Bolognesi et al. (2009) study appear to be generally consistent with commonly used and recommended practices for this assay. There is a question as to how long the blood samples used in the study were stored prior to initiating cultures. The publication only indicated that blood samples were kept at room temperature and cultures were initiated at a central laboratory within 24 h of collection. There may have been differences in the time between sampling and culture initiation for different sets of samples. Also, the populations in the aerially sprayed regions had a second sampling within 5 days after the first sampling and this second sampling time was not used for the other regions. It appears that collection and processing of samples may have occurred for different times for the aerially sprayed regions and the other regions.

The publication reported a small statistically significant increase in the frequency of BNMN in samples collected from people living in three regions within 5 days after spraying of GBFs compared with values for samples collected just before spraying. The publication also indicated a statistically significant increase of micronucleated mononuclear cells (MOMN) in the immediate post-spraying samples for two regions (Nariño and Valle del Cauca). In the samples taken 4 months after spraying, a statistically significant decrease in BNMN frequency compared to immediate post-spraying frequency was observed for one of the spraying regions (Nariño) but the other sprayed regions did not exhibit a statistically significant difference in BNMN frequency between the immediate post-spraying and 4-month samples.

Although the increases in BNMN frequencies in the post-spraying samples of the three regions suggest an effect from GBF exposure, more detailed consideration of exposure factors raises significant questions about this conclusion. The populations in each of the sprayed regions self-reported exposure to the spray (e.g., being in sprayed fields after spraying or observing spray drops in the air or on skin). For all three sprayed regions, there was no statistically significant difference in BNMN frequency between those self-reporting spraying exposure and those self-reporting no spraying exposure. The largest percentage post-spraying increase in BNMN frequency was reported for Valle del Cauca but only 1 of 26 people from this population self-reported spray exposure. Also, it was noted that GBF spraying in Valle del Cauca was at a rate significantly lower (1 kg acid equivalents glyphosate/ha) than that in Nariño and Putumayo (3.69 kg acid equivalents glyphosate/ha). The lack of clear correlation between self-reported exposure and BNMN increases after regional GBF spraying led to some caution in interpretation by the authors. The Bolognesi et al. (2009) publication suggested that results indicated low genotoxic risk from the GBF aerial spraying for illicit crop eradication. Another possible conclusion that appears to be supported by the self-reported exposure information is that this study does not clearly demonstrate an association between GBF exposure and CBMN endpoint effects.

Koureas et al. (2014) published a study examining effects of pesticide exposure on a measure of oxidative DNA damage, 8-hydroxydeoxyguanosine (8-OHdG) in blood DNA, which addressed whether GBF exposure appeared to affect this endpoint. The publication indicated that the exposed population had recently applied pesticides with no longer than 7 days between the last application and sampling. Several of the analyses were based on self-reported frequency of exposure to specific pesticides during the last spraying season and the timing relationship between specific pesticide applications and blood sampling is not clear. Statistically significant increases in 8-OHdG DNA levels were observed in blood samples collected from pesticide applicators compared to a non-exposed referent population. A univariate analysis was conducted to determine if specific high/low pesticide exposure classifications based on seasonal application frequencies were statistically associated with increased 8-OHdG levels in blood DNA. This analysis found statistically significant associations with 8-OHdG levels for herbicide exposure frequency and specifically for glufosinate herbicide exposure. Other statistically significant specific pesticide frequency exposure correlations were observed for neonicotinoids. A statistically significant exposure frequency correlation was not observed for GBF exposure. While certainly of limited power, this analysis provides some evidence that GBF exposures in pesticide applicators were not associated with oxidative DNA damage.

The human genotoxicity biomonitoring studies that specifically address GBF effects appear to have some evidence for

lack of persistent genotoxic effects, especially under normal conditions of exposure. One study suggests lack of DNA oxidation effects with GBF application and a study employing CBMN does not show statistically significant effects correlating with self-reported exposure to GBF spraying. One study reported effects on the blood cell comet endpoint following exposures to very high levels of GBF spraying which apparently were sufficient to elicit significant clinical signs of toxicity. However, a subsequent study conducted 2 years after GBF spraying using much larger populations did not detect chromosomal alterations or an increase in chromosomal fragility indicating that the comet effects did not appear to be manifested as persistent genotoxic effects. It should be noted that there is growing appreciation that comet endpoint effects in biomonitoring studies may result from indirect (i.e., non DNA-reactive) mechanisms such as inhibition of DNA repair, perturbation of cytokinesis, and oxidative stress (Collins et al. 2014). It seems very likely that the observed blood cell comet effects, if indeed associated with GBF exposure, were secondary to toxicity from very high GBF exposures and that these effects do not indicate DNA-reactive genotoxicity or a genotoxic risk from normal GBF exposures.

Results for environmental biomonitoring studies

There are two publications related to environmental biomonitoring for genotoxic endpoints. One study using blood cell comet and erythrocyte MN endpoints was conducted on samples from meadow voles living on or near golf courses where pesticides had been applied (Knopper et al. 2005). Different comet sample processing methodology (use or non-use of dimethylsulfoxide in lysis buffer) was used for the two different seasons and statistically significant differences in the average comet tail moment between the two seasons were ascribed to this different methodology. Although some suggestions of effects were reported, GBF was only one of a number of applied pesticides and the effects observed were considered by the authors as possibly attributable to exposure to Daconil® fungicide.

A second publication reported results for the erythrocyte MN assay applied to fish collected from several dams in Brazil (Salvagni et al. 2011). GBF was one of a number of pesticides reported to be used in the area of the dams. This study reported what were considered to be high numbers of micronuclei in cells but there were no concurrent negative controls. In the absence of these controls, the results might not be interpreted as conclusively indicating effects of pesticide exposure.

Conclusions

Two environmental genotoxicity biomonitoring studies conducted on a mammalian species and fish species were not informative about possible environmental genotoxic effects of GBFs. Both studies involved exposures or potential exposures to multiple pesticides without characterizing the relative extent of GBF exposure.

There have been a fairly large number of human genotoxicity biomonitoring studies where some exposure to GBFs was reported. Several of these studies were not informative about effects of GBF exposure because there was exposure to multiple pesticides and reported GBF exposure frequencies were low or very low. Another set of human biomonitoring studies were also not informative about possible genotoxic effects of GBF exposure because these studies listed exposure to large numbers of pesticides (10 to more than 30) in the exposed population without indicating the frequency or extent of exposure to any of the pesticides. Although positive genotoxic endpoint effects were observed in most of these studies no conclusions can be made regarding which pesticide exposures were responsible for the effects.

A third set of human genotoxicity biomonitoring studies involved exposures to multiple pesticides but did indicate significant frequency of GBF exposure in the populations. One of these studies did not find statistically significant effects for the lymphocyte CBMN endpoint in the exposed population compared to a referent population. This study offers some limited evidence for lack of significant, detectable effects on this endpoint for human exposure to any of the pesticides with significant exposure frequencies, including GBF, but the population sizes exposed were low. Three other studies reported positive genotoxic endpoint effects but the exposure data and endpoint data presented did not permit attribution of these effects to any specific pesticide exposure.

Finally, there are data from four human genotoxicity biomonitoring studies that provide information on GBF exposure effects. A study of oxidative effects on blood DNA indicated that observed increases in oxidative DNA damage did not statistically correlate with last season frequency of GBF application. These results provide limited evidence for this indirect genotoxic mechanism not operating at a significant level in humans using GBFs. Three studies involved measurement of genotoxic endpoints in human populations living in regions where GBFs were applied by aerial spraying. One study used a longitudinal design involving populations in regions of aerial GBF applications where samples were taken before, within 5 days and 4 months after GBF spraying. Statistically significant post-spraying increases for the CBMN endpoint were observed in these populations. However, the increases were not significantly correlated with self-reported exposure to the sprays or with the spraying application rate. Application of well-respected criteria for relating epidemiology cause and effect (Bradford-Hill 1965) to these results does not permit a conclusion that the observed effects were clearly related to GBF spray exposure. Two other studies were made of humans in GBF aerial spraying regions. A cross-sectional study found increases for the blood cell comet endpoint in the exposed population compared to a referent population. The exposures in this study appeared to be very excessive in terms of GBF application rate and significant signs of toxicity were observed in the exposed population. It seems possible that effects for this endpoint, if induced by GBF spraying exposure, may well have been indirect mechanism effects secondary to toxicity. A follow-up study of larger sample size from the sprayed regions conducted 2 years after spraying did not indicate any effects on chromosomal alteration or fragility endpoints. These latter results suggest that no persistent genotoxic effects were induced in the sprayed population and are consistent with the possibility that earlier reported comet effects may well have been secondary to toxic effects rather than resulting from a DNA-reactive mechanism.

The overall conclusion from the human biomonitoring studies is that none of the reported positive results for

studies involving exposure to multiple pesticides present evidence specifically relating GBF exposure to these results. There is some limited evidence for lack of oxidative DNA damage from normal human GBF exposure. The studies of populations in regions where GBF spraying occurred do not provide clear evidence correlating exposure to chromosomal effects such as aberrations or induction of micronuclei. The single study result of DNA damage comet effects in a population presumably exposed to GBF aerial spraying might well have been due to abnormally high toxic exposures to the GBFs rather than a DNA-reactive mechanism and does not indicate genotoxic risk to humans under normal exposure conditions.

An earlier review of a very extensive number of experimental genotoxicity studies of glyphosate and GBFs concluded that there is a convincing weight of evidence supporting the lack of genotoxic potential for both glyphosate and typical GBFs in core gene mutation and chromosomal effect endpoints and that observations of DNA damage effects were likely to be secondary to toxicity (Kier and Kirkland 2013). This earlier review concludes that the lack of genotoxic hazard potential evidenced by core gene mutation and chromosomal effect studies, coupled with the very low human and environmental species systemic exposure potential, indicate that glyphosate and typical GBFs present negligible genotoxicity risk. A subsequent review of experimental rodent carcinogenicity studies did not indicate that glyphosate was associated with carcinogenicity (Greim et al. 2015) which supports the conclusion that glyphosate does not have DNA-reactive genotoxic properties. A review of human and environment genotoxicity biomonitoring studies does not indicate any significant evidence to contradict these conclusions.

Acknowledgements

The author extends a note of appreciation to the three anonymous reviewers, selected by the Editor, whose comments were helpful in improving the scientific content and clarity of the manuscript.

Declaration of interest

Larry Kier is a paid consultant of the Monsanto Company for the preparation of this review. Larry Kier is also a past employee of Monsanto Company. Monsanto Company was the original producer and marketer of glyphosate formulations. The author has not participated in any legal or regulatory proceedings in the past 5 years concerning the class of compounds that is the subject of this review that has drawn on material presented in the review paper. The author had sole responsibility for the writing and content of the paper and the interpretations and opinions expressed in the paper are those of the author and may not necessarily be those of Monsanto Company.

References

Albertini RJ, Anderson D, Douglas GR, Hagmar L, Hemminki K, Merlo F, et al. (2000). IPCS guidelines for the monitoring of genotoxic effects of carcinogens in humans. International programme on chemical safety. Mutat Res, 463, 111–117.

Anderson D, Dhawan A, Laubenthal J. (2013). The comet assay in human biomonitoring. Methods Mol Biol, 1044, 347–362.

Andre V, Le Goff J, Pottier D, Lebailly P, Peluso M, Munnia A, Gauduchon P. (2007). Evaluation of bulky DNA adduct levels after pesticide use: Comparison between open-field farmers and fruit growers. Toxicol Env Chem, 89, 125–139.

Azqueta A, Collins AR. (2013). The essential comet assay: a comprehensive guide to measuring DNA damage and repair. Arch Toxicol, 87, 949–968.

Battershill JM, Burnett K, Bull S. (2008). Factors affecting the incidence of genotoxicity biomarkers in peripheral blood lymphocytes: impact on design of biomonitoring studies. Mutagenesis, 23, 423–437.

Benedetti D, Nunes E, Sarmento M, Porto C, Dos Santos CE, Dias JF, da Silva J. (2013). Genetic damage in soybean workers exposed to pesticides: evaluation with the comet and buccal micronucleus cytome assays. Mutat Res, 752, 28–33.

Bolognesi C, Perrone E, Landini E. (2002). Micronucleus monitoring of a floriculturist population from western Liguria, Italy. Mutagenesis, 17, 391–397.

Bolognesi C. (2003). Genotoxicity of pesticides: a review of human biomonitoring studies. Mutat Res, 543, 251–272.

Bolognesi C, Landini E, Perrone E, Roggieri P. (2004). Cytogenetic biomonitoring of a floriculturist population in Italy: micronucleus analysis by fluorescence in situ hybridization (FISH) with an all-chromosome centromeric probe. Mutat Res, 557, 109–117.

Bolognesi C, Carrasquilla G, Volpi S, Solomon KR, Marshall EJ. (2009). Biomonitoring of genotoxic risk in agricultural workers from five colombian regions: association to occupational exposure to glyphosate. J Toxicol Environ Health A, 72, 986–997.

Bonassi S, Coskun E, Ceppi M, Lando C, Bolognesi C, Burgaz S, et al. (2011). The HUman MicroNucleus project on eXfoLiated buccal cells (HUMN(XL)): the role of life-style, host factors, occupational exposures, health status, and assay protocol. Mutat Res, 728, 88–97.

Bortoli GM, Azevedo MB, Silva LB. (2009). Cytogenetic biomonitoring of Brazilian workers exposed to pesticides: micronucleus analysis in buccal epithelial cells of soybean growers. Mutat Res, 675, 1–4.

Bradford-Hill A. (1965). The Environment and Disease: Association or Causation? Proc R Soc Med, 58, 295–300.

Bull S, Fletcher K, Boobis AR, Battershill JM. (2006). Evidence for genotoxicity of pesticides in pesticide applicators: a review. Mutagenesis, 21, 93–103.

Collins A, Koppen G, Valdiglesias V, Dusinska M, Kruszewski M, Moller P, et al. (2014). The comet assay as a tool for human biomonitoring studies: the ComNet project. Mutat Res Rev Mutat Res, 759, 27–39.

Costa C, Teixeira JP, Silva S, Roma-Torres J, Coelho P, Gaspar J, et al. (2006). Cytogenetic and molecular biomonitoring of a Portuguese population exposed to pesticides. Mutagenesis, 21, 343–350.

Fenech M. (2007). Cytokinesis-block micronucleus cytome assay. Nat Protoc, 2, 1084–1104.

Fenech M, Holland N, Zeiger E, Chang WP, Burgaz S, Thomas P, et al. (2011). The HUMN and HUMNxL international collaboration projects on human micronucleus assays in lymphocytes and buccal cells–past, present and future. Mutagenesis, 26, 239–245.

Gomez-Arroyo S, Martinez-Valenzuela C, Calvo-Gonzalez S, Villalobos-Pietrini R, Waliszewski S, Calderon-Segura ME, et al. (2013). Assessing the genotoxic risk for Mexican children who are in residential proximity to agricultural areas with intense aerial pesticide applications. Rev Int Contam Ambie, 29: 217–225.

Greim H, Mostert V, Strupp C, Saltmiras, D. (2015) Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies. Crit Rev Toxicol, 45, 185–208.

Gregio D'Arce LP, Colus IM. (2000). Cytogenetic and molecular biomonitoring of agricultural workers exposed to pesticides in Brazil. Teratog Carcinog Mutagen, 20, 161–170.

Hartmann A, Agurell E, Beevers C, Brendler-Schwaab S, Burlinson B, Clay P, et al. (2003). Recommendations for conducting the in vivo alkaline Comet assay. 4th International Comet Assay Workshop. Mutagenesis, 18, 45–51.

Kahan V, Ribeiro DA, Andersen ML, Alvarenga TA, Tufik S. (2010). Sleep loss induces differential response related to genotoxicity in multiple organs of three different mice strains. Basic Clin Pharmacol Toxicol, 107, 598–602.

Khayat CB, Costa EO, Goncalves MW, da Cruz c Cunha DM, da Cruz AS, de Araujo Melo CO, et al. (2013). Assessment of DNA damage in Brazilian workers occupationally exposed to pesticides: a study from Central Brazil. Environ Sci Pollut Res Int, 20, 7334–7340.

Kier LD, Kirkland DJ. (2013). Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol, 43, 283–315.

Knopper LD, Mineau P, McNamee JP, Lean DR. (2005). Use of comet and micronucleus assays to measure genotoxicity in meadow voles (Microtus pennsylvanicus) living in golf course ecosystems exposed to pesticides. Ecotoxicology, 14, 323–335.

Koureas M, Tsezou A, Tsakalof A, Orfanidou T, Hadjichristodoulou C. (2014). Increased levels of oxidative DNA damage in pesticide sprayers in Thessaly Region (Greece). Implications of pesticide exposure. Sci Total Environ, 496, 358–364.

Lebailly P, Devaux A, Pottier D, De Meo M, Andre V, Baldi I, et al. (2003). Urine mutagenicity and lymphocyte DNA damage in fruit growers occupationally exposed to the fungicide captan. Occup Environ Med, 60, 910–917.

Martinez-Valenzuela C, Gomez-Arroyo S, Villalobos-Pietrini R, Waliszewski S, Calderon-Segura ME, Felix-Gastelum R, Alvarez-Torres A. (2009). Genotoxic biomonitoring of agricultural workers exposed to pesticides in the north of Sinaloa State, Mexico. Environ Int, 35, 1155–1159.

Menkes DB, Temple WA, Edwards IR. (1991). Intentional self-poisoning with glyphosate-containing herbicides. Hum Exp Toxicol, 10, 103–107.

Moller P. (2005). Genotoxicity of environmental agents assessed by the alkaline comet assay. Basic Clin Pharmacol Toxicol, 96, 1–42.

OECD 474. (1997). Mammalian Erythrocyte Micronucleus Test. OECD Guideline for the Testing of Chemicals. Available from: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788. [last accessed on 30 Dec 2014.]

OECD 475. (2014). Mammalian Bone Marrow Chromosome Aberration Test. OECD Guideline for the Testing of Chemicals. Available from: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788. [last accessed on 30 Dec 2014.]

OECD 479. (1986). Genetic Toxicology: In Vitro Sister Chromatid Exchange Assay in Mammalian Cells. OECD Guideline for the Testing of Chemicals. Available from: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788. [last accessed on 30 Dec 2014.]

OECD 489 (2014). In Vivo Mammalian Alkaline Comet Assay. OECD Guideline for the Testing of Chemicals. Available from: http://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788. [last accessed on 30 Dec 2014.]

Pastor S, Creus A, Parron T, Cebulska-Wasilewska A, Siffel C, Piperakis S, Marcos R. (2003). Biomonitoring of four European populations occupationally exposed to pesticides: use of micronuclei as biomarkers. Mutagenesis, 18, 249–258.

Paz-y-Mino C, Sanchez ME, Arevalo M, Muñoz MJ, Witte T, De-la-Carrera GO, Leone PE. (2007). Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate. Genet Molec Biol, 30, 456–460.

Paz-y-Mino C, Munoz MJ, Maldonado A, Valladares C, Cumbal N, Herrera C, et al. (2011). Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border. Rev Environ Health, 26, 45–51.

Salvagni J, Ternus, RZ, Fuentefria, AM. (2011). Assessment of the genotoxic impact of pesticides on farming communities in the countryside of Santa Catarina State, Brazil. Genet Mol Biol, 34, 122–126.

Shaham J, Kaufman Z, Gurvich R, Levi Z. (2001). Frequency of sister-chromatid exchange among greenhouse farmers exposed to pesticides. Mutat Res, 491, 71–80.

Simoniello MF, Kleinsorge EC, Scagnetti JA, Grigolato RA, Poletta GL, Carballo MA. (2008). DNA damage in workers occupationally exposed to pesticide mixtures. J Appl Toxicol, 28, 957–965.

Tenorio NM, Ribeiro DA, Alvarenga TA, Fracalossi AC, Carlin V, Hirotsu C, et al. (2013). The influence of sleep deprivation and obesity on DNA damage in female Zucker rats. Clinics (Sao Paulo), 68, 385–389.

Thomas P, Holland N, Bolognesi C, Kirsch-Volders M, Bonassi S, Zeiger E, et al. (2009). Buccal micronucleus cytome assay. Nat Protoc, 4, 825–837.

Tice RR, Agurell E, Anderson D, Burlinson B, Hartmann A, Kobayashi H, et al. (2000). Single cell gel/comet assay: guidelines for in vitro and in vivo genetic toxicology testing. Environ Mol Mutagen, 35, 206–221.

Verschaeve L, Koppen G, Gorp UV, Schoeters G, Jacobs G, Zwijzen C. (2007). Seasonal variations in spontaneous levels of DNA damage; implication in the risk assessment of environmental chemicals. J Appl Toxicol, 27, 612–620.

Vlastos D, Stivaktakis P, Matthopoulos DP. (2006). Pesticide exposure and genotoxicity correlations within a Greek farmers' group. Int J Environ Anal Chem, 86, 215–223.

WHO/FAO. (2004). Pesticide residues in food. FAO Plant Production and Protection Paper. Rome, Italy, World Health Organization and Food and Agricultural Organization of the United Nations

Williams GM, Kroes R, Munro IC. (2000). Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol, 31, 117–165.

Critical Reviews in Toxicology

http://informahealthcare.com/txc
ISSN: 1040-8444 (print), 1547-6898 (electronic)

Crit Rev Toxicol, 2013; 43(4): 283–315
 DOI: 10.3109/10408444.2013.770820

informa
healthcare

REVIEW ARTICLE

Review of genotoxicity studies of glyphosate and glyphosate-based formulations

Larry D. Kier[1] and David J. Kirkland[2]

[1]*Private Consultant, Buena Vista, CO, USA and* [2]*Kirkland Consulting, Tadcaster, UK*

Abstract

An earlier review of the toxicity of glyphosate and the original Roundup™-branded formulation concluded that neither glyphosate nor the formulation poses a risk for the production of heritable/somatic mutations in humans. The present review of subsequent genotoxicity publications and regulatory studies of glyphosate and glyphosate-based formulations (GBFs) incorporates all of the findings into a weight of evidence for genotoxicity. An overwhelming preponderance of negative results in well-conducted bacterial reversion and *in vivo* mammalian micronucleus and chromosomal aberration assays indicates that glyphosate and typical GBFs are not genotoxic in these core assays. Negative results for *in vitro* gene mutation and a majority of negative results for chromosomal effect assays in mammalian cells add to the weight of evidence that glyphosate is not typically genotoxic for these endpoints in mammalian systems. Mixed results were observed for micronucleus assays of GBFs in non-mammalian systems. Reports of positive results for DNA damage endpoints indicate that glyphosate and GBFs tend to elicit DNA damage effects at high or toxic dose levels, but the data suggest that this is due to cytotoxicity rather than DNA interaction with GBF activity perhaps associated with the surfactants present in many GBFs. Glyphosate and typical GBFs do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

Keywords

Formulation, genotoxicity, glyphosate, mutagenicity, Roundup™

History

Received 19 December 2012
Revised 23 January 2013
Accepted 24 January 2013
Published online 12 March 2013

Table of Contents

Introduction

Glyphosate is an active ingredient (a.i.) in very widely used herbicide formulations. Accordingly, the toxicity of glyphosate and glyphosate-based formulations (GBFs) has been extensively studied. An earlier extensive review of glyphosate and glyphosate formulation safety and risk assessment included descriptions and analyses of genetic toxicology studies of glyphosate and Roundup™-branded and other

Address for correspondence: Larry D. Kier, Private Consultant, 16428 CR 356-8, Buena Vista, CO 81211, USA. Tel: (719) 395-1993. Email: foreman48@hotmail.com

Abbreviations

a.e., acid equivalents
a.i., active ingredient
CB MN, cytokinesis block micronucleus
GBF, glyphosate-based formulation
i.p., intraperitoneal
MN, micronucleus
MN PCE, micronucleated polychromatic erythrocyte
NCE, normochromatic erythrocyte
PCE, polychromatic erythrocyte
p.o., oral administration
SCE, sister chromatid exchange
SCGE, single cell gel electrophoresis (Comet assay)
OECD, Organization for Economic Co-operation and Development
S9, 9000×g liver homogenate supernatant
UDS, unscheduled DNA synthesis.

glyphosate formulations (Williams et al., 2000). These studies included a wide variety of test systems and endpoints. Subsequent to this review a number of genotoxicity studies of glyphosate and GBFs have been published in the literature. Additionally, there are large number of genetic toxicology studies of glyphosate and GBFs sponsored by companies that were not included in the previous review. The number and diversity of these studies warrant careful examination and integration of their findings with previous results to produce an updated assessment of the overall genotoxicity profile for glyphosate and a genotoxicity profile that is typical of the GBFs.

Identification and analysis of published studies

The published studies for review consideration were identified by literature searches for published reports containing references to glyphosate that also contained searchable terms which indicated that genotoxicity studies were performed. Details of search procedures are provided in the "online supplementary material". Each identified publication was evaluated to verify that it contained original results of one or more experimental genotoxicity studies on glyphosate or GBFs. Monitoring studies are not included in this review. Emphasis was placed on publications in peer-reviewed journals. Abstracts or other sources with incomplete information were not considered. Reviews without original data were not considered for the evaluation; however, these reviews were examined to determine if there were any cited publications that had not been detected in the literature searches.

Each relevant publication was examined using several criteria to characterize the scientific quality of the reported genetic toxicology studies. Useful, objective criteria for this purpose were international guidelines for genetic toxicology studies formulated by expert groups. These include principles for conducting studies, reporting results, and analyzing and interpreting data. Some of the principles of the guidelines are generally applicable to all studies, while others are specific for a particular type of test system and endpoint. Some of the specific types of studies encountered in the review do not yet have international guidelines; however, some of the guideline elements should be generically applicable to these studies. The guidelines for genetic toxicology tests developed for the Organization for Economic Co-operation and Development (OECD) are a pre-eminent source of internationally agreed guidelines. Other international and national guidelines for regulatory genetic toxicology testing are usually concordant with the OECD guidelines. The "online supplementary material" contains a summary table of some key OECD guideline criteria that were found to be relevant to the analysis of the studies considered in this review.

Comparison of the published studies to the criteria in guidelines used for regulatory purposes does not represent an absolute judgment standard but can provide a way for evaluating the quality of the protocols used in various published studies. Some of the criteria are rarely met in scientific publications and should be given little or no weight in evaluating the studies. For example, data for individual cultures and individual animals are not commonly included in publications in scientific journals. These data are presumably collected but are usually summarized as group means with a measure of variance for the treatment and control groups. This is not considered to be a significant omission in a scientific publication. However, other guideline features are more essential as scientific quality standards and should be considered as having greater weight in evaluating a study. For example, there are consistent recommendations that assays involving visual scoring (e.g. chromosomal aberration, micronucleus and sister chromatid exchange (SCE) endpoints) should use slides that are independently coded so that scoring is performed without any knowledge of the treatment or control group being scored. This guidance is good scientific practice and studies that do not explicitly include a description of coding or "blind" scoring in the methodology would appear to have a deficiency either in the methodology, or perhaps a limitation in the description of the methodology used if coding was actually used and either not indicated or was assumed to be indicated by a reference citation. Other examples of guideline features that have clear experimental scientific value are the use of concurrent negative and positive controls and concurrent measurement and reporting of toxicity endpoints in main experiments, especially in *in vitro* mammalian cell assays.

Review and analysis of sponsored regulatory studies

Reports of sponsored genetic toxicology studies were provided by the companies. The studies were sponsored by companies for regulatory purposes and were conducted at in-house or contract toxicology laboratories. For brevity, the industry-sponsored regulatory studies will be subsequently referred to as regulatory studies.

Each study examined was stated to have been conducted in accordance with Good Laboratory Practice (GLP) standards with almost all studies citing the OECD Principles of Good Laboratory Practice (OECD GLP, 1982, 1997). Reports also cited compliance with various national and regional GLP Guidelines (e.g. European Commission GLP Directives 87/18/EEC or 88/320/EEC; U.S. Environmental Protection

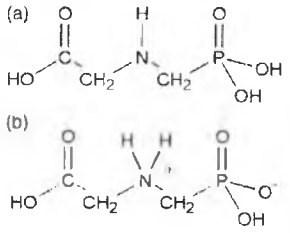


Figure 1. Chemical structure of glyphosate, (N-(phosphonomethyl)glycine, CAS 1071-83-6): (a) neutral form; (b) ionic form.

Agency Good Laboratory Practice Standards, 40 CFR Part 160; Japanese Ministry of Agriculture, Forestry, and Fisheries (MAFF) Good Laboratory Practice Standards, 11 Nousan No. 6283). Variations from GLPs were considered not to have significantly impacted the study results.

Almost all the studies were reported to have been conducted in accordance with the relevant OECD test guidelines applicable at the time of the study. Study reports were examined to determine that the protocols and experimental methods for the report were consistent with the OECD guidelines and any deviations were noted and considered. Report data were examined to confirm the conclusion of the report regarding whether treatment-related activity had been observed.

Glyphosate structure activity analysis

Glyphosate consists of the amino acid glycine joined with a phosphonomethyl group (Figure 1). Glyphosate was evaluated for mutagenic structural alerts using Derek for Windows software (Llhasa Ltd., Leeds, UK, Version 11.0.0, 24 October 2009). No structural alerts were identified for chromosomal damage, genotoxicity, mutagenicity or carcinogenicity. The structural components of the glyphosate molecule are not known to be genotoxic; therefore, the lack of structure activity alerts for glyphosate was expected.

GBF compositions

Glyphosate-based formulations are herbicide formulations which, by definition, contain the a.i. glyphosate typically in a salt form (e.g. isopropylamine or potassium glyphosate), but the % glyphosate may be expressed in acid equivalents (a.e.) as percent weight of glyphosate acid without the counter ion. In addition to the a.i., other compounds are included in the formulation to help achieve or improve the herbicidal activity for the desired application. A very common functional component, especially for terrestrial applications, is a compound (or compounds) with surfactant activity that enables better penetration of the a.i. through leaf surfaces. Because formulation compositions are considered proprietary, their specific compositions are not generally indicated in literature reports and are not publicly available for regulatory studies. GBF test materials are usually identified with names or designations and should include either % a.i. or a.e. detail.

It should be noted that a common problem encountered in the published literature is the use of the terms "glyphosate", "glyphosate salt" or "Roundup" to indicate any kind of GBF that contains additional components such as surfactants. Published results from studies with different formulations have sometimes been incorrectly or inappropriately attributed to the a.i. The original Roundup™-branded formulation (MON 2139), containing 41% isopropylamine glyphosate salt and 15.4% MON 0818 (a polyethoxylated tallowamine based surfactant blend), is no longer sold in many markets. However, other GBFs are sold under the Roundup™ brand name with varying glyphosate forms, concentrations and surfactant systems. Clear identification of the test material is very important in toxicology studies because the toxicity of formulations can be dramatically different from the a.i. The fact that test materials identified as Roundup™-branded formulations may actually have different compositions should be considered when comparing results of different studies, as should the possibility that any observed effects may be due to specific GBF components other than the glyphosate active ingredient.

Gene mutation endpoint

Bacterial reversion assays

Glyphosate and glyphosate salts

As reviewed by Williams et al. (2000), six reports of bacterial reversion assays for glyphosate were all negative. No reports of bacterial reversion assays for glyphosate were encountered in the subsequent literature.

A large number of regulatory bacterial reversion assays have been conducted on technical glyphosate and glyphosate salt solutions. These 18 assays are presented in Table 1. Summary data tables and associated information for the regulatory studies are available in "online supplementary material". Methodology and experimental design for these studies was generally in compliance with OECD Guideline 471 (OECD 471, 1997) for studies conducted in or after 1997. The previous guidelines (OECD 471, 1983, for *Salmonella* strains; OECD 472, 1983, for *Escherichia coli* strains) were used for studies conducted before 1997. All of the assays employed a core battery of *Salmonella typhimurium* test strains (TA98, TA100, TA1535 and TA1537 or TA 97a) and most of the assays employed additional *S. typhimurium* TA102 or *E. coli* WP2-derived strains to detect oxidative and cross-linking effects as recommended in OECD 471 (1997). Limitations for some of the studies included three studies using larger than half-log dose level spacing and some studies did not employ a confirmatory assay. One study used positive controls not requiring exogenous metabolic activation for two strains in the presence of S9 (9000×g liver homogenate supernatant). Although this may be considered as a deficiency, in that the activity of the S9 was not thoroughly checked, it is only in one of the 18 studies. The top concentration employed in the assays ranged from 1000 to 5000 µg/plate with most of the studies using the OECD guideline limit dose of 5000 µg/plate. With only a couple of exceptions, the top dose tested produced the toxicity as evidenced by thinning of the background lawn, reduction in revertants/plate or both.

None of the studies exhibited revertants/plate exceeding threshold criteria for a positive response: greater than three times the control value for strains with low spontaneous

Table 1. Bacterial reversion assays.

Test material/Solvent*	Strains†	S9‡	Treatment¶ Method	Treatment¶ Maximum	Com§	Results‖ Toxicity	Results‖ Mutagenicity	References
Glyphosate and glyphosate salts								
Regulatory studies								
G (98.6%) (W)	0,9,5,7	AR 4% (PI) 6.6% (PR)	PI, PR	2500 µg (−S9) 5000 µg (+S9)	C	T(R)	neg	Jensen (1991a)
G (96.0%) (W)	0,9,5,7,8	AR 10%	PI	1000 µg	>HL, C, P	T(R)	neg#	Suresh (1993a)
G (95.68%) (W)	0,9,5,7,PU	PBR 10%	PR	5000 µg	C	T(R)	neg	Akanuma (1995b)
G (95.6%) (D)	0,9,5,7,PK,PUK	PNR 10%	PI, PR	5000 µg	C	T(R)	neg**	Callander (1996)
G (95.3%) (W)	0,9,5,7,PU	AR 10%	PI	5000 µg	C	T(R)	neg	Thompson (1996)
GK (60%) (W)	0,9,5,7,PK,PUK	PNR 10%	PI, PR	5000 µg	C	T(R)	neg††	Callander (1999)
GI (612.7 g/kg) (W)	0,9,5,7 a	AR 10%†	PI	5000 µg	>HL, S	T(R)	neg‡‡	Ranzani (2000)
G (95.1%) (W)	0,9,5,7,PU	PNR 10%	PI, PR	5000 µg	C	T(R)	neg	Sokolowski (2007a)
G (97.7%) (W)	0,9,5,7,PU	PNR 10%	PI, PR	5000 µg	C	PI,T(BR) PR,T(R)	neg	Sokolowski (2007b)
G (95.0%) (W)	0,9,5,7,PU	PNR 10%	PI, PR	5000 µg	C	PI,T(BR) PR,T(R)	neg	Sokolowski (2007c)
G (980.1 g/kg) (D)	0,9,5,7,2	AR ?%	PI	5000 µg	S	N	neg¶¶	Ribeiro do Val (2007)
G (980.5 g/kg) (D)	0,9,5,7a,2	AR 5%	PI	1000 µg	>HL, S	T(R)	neg§§	Miyaji (2008)
G (98.8 % w/w) (W)	0,9,5,7,2	AR 5%	PI, PR	3160 µg	C	T(BR)	neg‖‖	Flugge (2009a)
G (96.66% w/w) (D)	0,9,5,7,PU	PNR 10%	PI, PR	5000 µg	C	T(R)	neg	Sokolowski (2009a)
G (96.3%) (W)	0,9,5,7,PK,PUK	PNR 10%	PI, PR	5000 µg	C	T(R)	neg	Sokolowski (2009b)
G (96.4%) (W)	0,9,5,7,2	AR 5%	PI, PR	3160 µg	C	T(BR)	neg‖‖	Flugge (2010b)
G (96.0%) (D)	0,9,5,7,PU	PNR 5%	PI, PR	5000 µg	C	T(R)	neg	Schreib (2010)
G (982 g/kg) (D)	0,9,5,7,2	PNR 5%	PI, PR	5000 µg	C	PI,T(BR) PR,T(R)	neg	Wallner (2010)
GBFs								
Literature study								
Perzocyd 10 SL (?)##	0,9,7a,2	AR ?%##	PI	200 µg?##	?##	?##	neg##	Chruscielska et al. (2000)
Regulatory Studies								
MON 78239 (36.6%a.e. GK) (W)	0,9,5,7,PU	AR 10%	PI	3330 µg (−S9)$ 5000 µg (+S9)	C	T(BR)	neg^	Mecchi (2003a)
MON 78634 (65.2%a.e. GA) (W)	0,9,5,7,PU	AR 10%	PI	3330 µg$	C	T(BR)	neg	Mecchi (2003b)
FSG 3090-H1 (360 g/L G) (W)	0,9,5,7,2	AR 5%	PI, PR	316 µg (PI, PR − S9) 100 µg (PR −S9)	C	T(BR)	neg	Uhde (2004)
MON 78910 (30.3%a.e.) (W)	0,9,5,7,PU	AR 10%	PI	3330 µg (−S9) 5000 µg (+S9)	C	T(BR)	neg	Xu (2006)
MON 79672 (68.2%a.e. GA) (D)	0,9,5,7,2	AR? 4%	PI	2000 µg	>HL, S	T(R)	neg	Lope (2008)
MON 79864 (38.7%a.e.) (W)	0,9,5,7,PU	AR 10%	PI	5000 µg	C	T(BR)	neg	Mecchi (2008a)
MON 76313 (30.9%a.e.) (W)	0,9,5,7,PU	AR 10%	PI	5000 µg	C	T(BR)	neg	Mecchi (2008b)
MON 76171 (31.1%a.e.) (W)	0,9,5,7,PU	AR 10%	PI	5000 µg	C	T(BR)	neg	Mecchi (2008c)
Glyphosate liquid formulation (480 g/L GI) (W)	0,9,5,7,2	AR 5%	PI	200 µg	S	N	neg	Camolesi (2009)
MON 76190 (53.2%a.e. GM) (D)	0,9,5,7,2	AR? 4%	PI	2000 µg	>HL, S	T(R)	neg	Catoyra (2009)
MON 79991 (71.6%a.e.) (W)	0,9,5,7,PU	AR 10%	PI	5000 µg	C	T(R)	neg	Mecchi (2009a)
MON 76138 (38.5%a.e.) (W)	0,9,5,7,PU	AR 10%	PI	5000 µg	C	T(BR)	neg	Mecchi (2009b)

(*continued*)

Table 1. Continued

Test material/Solvent*	Strains†	S9‡	Treatment¶		Com§	Results‖		References
			Method	Maximum		Toxicity	Mutagenicity	
MON 77280 (495.29 g/La.e.) (W)	0,9,5,7,2	AR 5%	PI	200 µg	S	N	neg	Camolesi (2010)
TROP M (Glyphosate 480) (48.46% GI) (W)	0,9,5,7,2	AR 5%	PI, PR	1000 µg (PI) 31.6 µg (PR)	C	T(BR)	neg	Flugge (2010a)
Glyphosate 757 g/kg granular form (76.1% GA) (W)	0,9,5,7,2	AR 5%	PI, PR	100 µg (PI) 10 µg (PR)	C	T(BR)	neg	Flugge (2010d)

*Test material and solvent used: G, glyphosate technical (acid); GK potassium salt of glyphosate; GI, isopropylamine salt of glyphosate; GA, monoammonium salt of glyphosate. First entry in () for glyphosate or glyphosate salts indicates purity or concentration. First entry in ( ) for GBFs indicates active ingredient, if available, and ingredient concentration. a.e. after % indicates concentration is in acid equivalents. Second entry in ( ) indicates test material solvent: (W), water; (D), dimethyl sulfoxide.

†Test strains used: 0, TA100; 9, TA98; 5, TA1535; 7, TA1537;7a, TA97a; 2, TA102; 8, TA1538; PU, *E. coli* WP2 (uvrA); PUK, *E. coli* WP2 [pKM101]; PK, *E. coli* WP2 [pKM101].

‡S9 metabolic activation system: AR, Aroclor-induced rat liver; PNR, phenobarbital- and napthoflavone-induced rat liver; PBR, phenobarbital- and benzoflavone-induced rat liver; percentage number indicates percentage of S9 in S9 Mix.

¶Treatment conditions: Method – treatment methodology: PI, plate incorporation; PR, preincubation. Maximum – maximum amount per plate tested. In some cases differences between treatment conditions were used as indicated.

§Comments on assay:. >HL, more than half-log ($\sqrt{10}$) for one or more dose intervals; C, confirmatory experiment reported; S, single experiment reported; P, positive controls that didn't require S9 were used for two strains (TA1535 and TA1537) with S9.

‖Results reported for:

Toxicity: T, toxic effects at maximum concentration or lower; (R), reduced revertants/plate; (B), reduced background lawn; (BR), reduced revertants/plate and background lawn; N, no toxic effects.

Mutagenicity: overall judgment of assay result for test material: neg, negative; individual study increases in revertants/plate or statistical findings are indicated as individual footnotes.

#Statistically significant increase for TA100 (+S9) reported in text but not indicated in data tables. Increases were less than two-fold over control and judged not to indicate a treatment-related effect.

**Statistically significant increases in revertants/plate in one experiment for TA100 +S9, WP2 [pKM101] +S9, TA98 −S9 and WP2 (pKM101) −S9. Increases were less than two-fold, not reproducible in separate experiments and not consistent with a dose–response (e.g. occurring at mid-dose levels). Increases were less than two-fold over control and judged not to indicate a treatment-related effect.

††Statistically significant increases in revertants/plate for several strain/S9 combinations. Increases were all less than two-fold over control values, not reproducible and not consistent with a dose–response and judged not to indicate treatment-related effects.

‡‡Statistically significant increases in revertants/plate for TA98 +S9 and TA100 +S9. Increases were all less than two-fold, not consistent with a dose-response and judged not to indicate treatment- related effects.

¶¶Statistically significant ANOVA with increases for lowest dose levels for TA1537 +S9. Increases were all less and two-fold, not consistent with a dose-response and judged not to indicate treatment- related effects.

§§Statistically significant increases for TA98 + S9 (low to mid doses) and for TA100 +S9 at one dose. Increases were judged not to indicate treatment-related effects because they were less and two-fold and not consistent with a dose–response.

|||Statistical analysis suggested in text but not clearly evident in data tables.

##Not clearly indicated in the publication. Numerical data for revertants/plate not presented but summarized as "–" for the lack of mutagenic activity.

$5000 µg/plate maximum dose level for WP2*uvrA* –S9 and in one experiment for TA98 and TA1535 −S9 (Mecchi, 2003a).

^Several dose levels exceeded control revertants/plate by more than three-fold in one experiment for TA98 −S9 and TA1535 −S9. There was no dose–response and the result was not observed in a second experiment. The result was considered due to a low control values rather than a treatment-related response.

revertants/plate (TA1535 and TA1537) or exceeding two times the control value for the other strains (Kier et al., 1986). Some studies reported statistical effects. However, none of these cases involved as much as two-fold elevations in revertants per plate and the observations were not consistent with biologically plausible dose-responses. In cases with repeated experiments, any increases in revertants/plate were generally not reproducible between experiments. Therefore, none of the statistically significant effects were judged to indicate mutagenic activity of the test material. Thus, all of the 18 bacterial reversion studies were concluded to be negative as judged by the absence of significant, reproducible, dose-related increases in revertants/plate. These studies provide abundant weight of evidence that glyphosate and glyphosate salt solutions are negative in bacterial reversion assays under experimental conditions that generally satisfy the OECD guidelines.

Glyphosate-based formulations

As reviewed by Williams et al. (2000) most bacterial reversion studies (Ames/*Salmonella* test strains) for GBFs were negative. Four studies reported negative results for Roundup™-, Rodeo™- and Direct™-branded GBFs. A reported positive Ames/*Salmonella* result for a Roundup™-branded formulation was not replicated in these studies.

Subsequent to the Williams et al. (2000) review only one published GBF bacterial reversion assay was reviewed (Table 1). This publication reported a negative Ames/*Salmonella* assay result for a GBF of undefined glyphosate composition, Percozyd 10 SL (Chruscielska et al., 2000). Although this result is consistent with the majority of negative Ames/*Salmonella* results for GBFs, the reported study results have significant limitations. One of the recommended test strains, TA1535, was not used and results were only presented as "–" without a presentation of revertants/plate data.

A large number of regulatory bacterial reversion assays have been conducted on GBFs. These are presented in Table 1 with summary data tables in "online supplementary material". Methodology and experimental design for these studies was generally in compliance with the OECD Guideline 471 (OECD 471, 1997) and with other guidelines. However, two of the studies used some dose level spacings that were larger than the recommended maximum half-log spacing and four studies did not employ a confirmatory assay. All of the assays employed a core battery of *S. typhimurium* test strains (TA98, TA100, TA1535 and TA1537) and employed an additional *S. typhimurium* TA102 or *E. coli* WP2-derived strain to detect oxidative and cross-linking DNA effects as recommended in OECD 471 (1997). The top concentration employed in the assays ranged from 100 to 5000 μg/plate for plate incorporation methodology. With only two exceptions the top dose tested produced the toxicity as evidenced by thinning of the background lawn, reduction in revertants/plate or both. For the two exceptions, the toxicity was noted at higher concentrations per plate in rangefinder assays but the toxicity was not noted for the maximum dose selected for the mutagenicity assays.

Only one of the studies exhibited revertants/plate for some strains exceeding up to three-fold of the control value (Mecchi et al., 2003a). However, these increases were not reproducible between experiments and did not exhibit a dose–response pattern. These results were therefore judged to be due to low vehicle control revertants/plate and not to indicate treatment-related mutagenic activity. All of the 15 regulatory bacterial reversion studies of GBFs were concluded to be negative as judged by the absence of significant, reproducible, dose-related increases in revertants/plate. These studies provide abundant weight of evidence that a variety of GBFs are negative in properly conducted bacterial reversion assays.

In vitro mammalian cell assays

Glyphosate and glyphosate salts

As reviewed by Williams et al. (2000), a CHO/HGPRT *in vitro* mammalian cell gene mutation assay was reported negative for glyphosate when tested up to toxic dose levels of 22.5 mg/mL (≈133 mM), i.e. well above the current top limit of 10 mM (appropriate for glyphosate and glyphosate salts), in the presence and absence of mammalian metabolic activation.

Two regulatory mouse lymphoma *tk* locus gene mutation studies were reviewed (Table 2 and "online supplementary material"). One study was conducted according to the 1984 OECD guideline for *in vitro* mammalian gene mutation assays (Jensen, 1991b; OECD 476, 1984). Somewhat fewer cells were exposed (3×10^5 –S9, 1.8×10^5 + S9) than the 10^6 cells recommended in the updated OECD guideline (OECD 476, 1997) but this was not considered as a significant deficiency. Cells were exposed at four concentrations up to 4200 μg/mL with S9 (≈24.8 mM) or 5000 μg/mL without S9 (≈ 29.6 mM). Although no toxic effects (reduction in cloning efficiency) were seen on day 0 or day 2, these dose levels exceed the currently recommended upper dose level of 10 mM (1.69 mg/mL for glyphosate) for relatively non-toxic test materials (OECD 476, 1997). It should be noted that most OECD guidelines for *in vitro* mammalian cell genotoxicity assays specify an upper limit dose for soluble, relatively non-toxic substances of 10 mM or 5 mg/mL, whichever is lower. The lower and appropriate upper limit dose for glyphosate and glyphosate salts is 10 mM. A second study conducted later followed several updated recommendations for *in vitro* mammalian cell gene mutation assays adopted in 1997 (Clay, 1996; OECD 476, 1997). These included the use of at least 10^6 cells in exposed cultures and consideration of test material effects on pH and osmolality. The latter consideration proved to be important because concentrations of 1500 and 2000 μg/mL (≈8.9–11.8 mM) produced large (>1 pH unit) decreases in pH and the maximum dose level employed for mutation measurement (1000 μg/mL, ≈5.9 mM) was appropriate to avoid excessive effects on pH. This dose level did not produce effects on the day 0 cloning efficiency. Although three dose levels were used in the initial experiment, four dose levels (as recommended in OECD 476, 1997) were used in the confirmatory experiment.

Both of the regulatory mouse lymphoma studies were negative for glyphosate when tested up to dose levels that either exceeded the current limit dose or avoided excessive pH effects. These negative results provide important corroboration of a lack of gene mutation activity in the earlier negative CHO/HGPRT study. They also indicate a lack of

Table 2. *In vitro* mammalian cell assays of glyphosate, glyphosate salt solutions and GBFs.

Test material*	Endpt†	Cell type‡	Treatment¶ S9§	Time‖ −S9	Time‖ −S9	Dose levels/ Replicates / Ind. expts. #	Maximum dose**	pH††	Score‡‡	Results Tox¶¶	Results Mutagenicity§§	References
Gene mutation												
Glyphosate and glyphosate salts												
Regulatory studies												
G (98.6%) (M)	TK	ML		4 (48)		4/2/C	5000 µg/mL (≈29.6 mM)	NI	NA	CE−	neg	Jensen (1991b)
			AR 30%		3 (48)	4/2/C	4200 µg/mL (≈24.8 mM)	NI	NA	CE−	neg	
G (95.6% w/w) (D)	TK	ML	PNR 5%	4 (48)	4 (48)	3 and 4/2/C	1000 µg/mL (≈5.9 mM)	pH	NA	RS−	neg	Clay (1996)
Chromosomal aberration or micronucleus												
Glyphosate and glyphosate salts												
Literature studies												
GI (62%) (W)	CB MN	BL	none	24		5/?/C	0.56 mM	NI	1000BN (NC)	CBPI−	neg	Piesova (2004)
	CB MN	BL	none	48		5/?/C	0.56 mM	NI	1000BN (NC)	CBPI−	equiv‖‖	
GI (62%) (W)	CB MN	BL	AR 10%	2 (20?)	2 (20?)	5/?/C	0.56 mM	NI	1000BN (NC)	CBPI−	neg	Piesova (2005)
	CB MN	BL	none	48		5/?/C	0.56 mM	NI	1000BN (NC)	CBPI−	equiv‖‖	
GI (62%) (W)	CA (1)	BL	none	24		6/?/C	1.12 mM	NI	350–900 M (NC)	NI	neg##	Holeckova (2006)
GI (62%) (W)	CA	BL	none	24		6/?/C	1.12 mM	NI	100 M (NC)	MI+	neg	Sivikova & Dianovsky (2006)
G (96%) (M)	CA	HL	none	48		3 (>HL)/?/C	6 mM	pHa	100 M	MI−	neg	Manas et al. (2009)
G (98%) (P)	CB MN	HL		4 (72?) $		5 (>HL)/2/C	580 µg/mL (≈3.43 mM)	pHa	1000BN (NC)	EA+ NE+ NB+ CBPI−	equiv^	Mladinic et al. (2009a)
	CB MN	HL	H 10%		4 (72?) $	5 (>HL)/2/C	580 µg/mL (≈3.43 mM)	pHa	1000BN (NC)	EA+ NE+ NB+ CBPI−	pos	
G (98%) (P)	CB MN	HL		4 (72?) $		5 (>HL)/2/C	580 µg/mL (≈3.43 mM)	pHa	2000BN (NC)	CBPI− NB+	equiv^^	Mladinic et al. (2009b)
			H 10%		4 (72?) $	5 (>HL)/2/C	580 µg/mL (3.43 mM)	pHa	2000BN (NC)	CBPI− NB+	pos	
G (95%) (M)	CB MN	TR146	none	20 min. (48)		3/3/S	20 mg/L (≈0.12 mM)	NI	>3000BN (NC)	AP− NE+ NB+	pos	Koller et al. (2012)
Regulatory studies												
G (95.3% w/w) (M)	CA	CHL	AR 5%	6 (24), 24, 48	6 (24)	3/2/S	1250 µg/mL (≈7.39 mM)	pH	200 M	RG−	neg	Wright (1996)
G (95.6%) (M)	CA	HL	PNR 25%	20	3 (20)	3 (>HL)/2/C	1250 µg/mL (≈7.39 mM)	pH	200 M	MI+(−S9)	neg	Fox (1998)
				44	3 (44)	1/2/S	1250 µg/mL (≈7.39 mM)	pH	200 M	MI−	neg	

(*continued*)

DOI: 10.3109/10408444.2013.770820

Table 2. Continued.

			Treatment¶							Results		
				Time‖								
Test material*	Endpt†	Cell type‡	S9§	−S9	+S9	Dose levels/ Replicates./ Ind. expts. #	Maximum dose**	pH††	Score‡‡	Tox¶¶	Mutagenicity§§	References
G (95.68%) (H,M)	CA	CHL	PBR 30%	6 (24)	6 (24)	3/2/S	1000 µg/mL (≈5.92 mM)	pHn	200 M	MI−	neg	Matsumoto (1995)
				24		3/2/S	500 µg/mL (≈2.96 mM)	pHn	200 M	MI−	neg	
				48		3/2/S	500 µg/mL (≈2.96 mM)	pHn	200 M	MI−	neg	
GBFs												
Literature studies												
herbazed (84% G) (M)	CA	MS	none	24		3 (>HL)/5/S	50 mM$$	NI	500 M	VC−	pos	Amer et al. (2006)
Roundup™ Ultra Max (450 g/L G) (M)	CB MN	TR146	none	20 min (48)		3/3/S	20 mg/L glyphosate (≈0.12 mM)	NI	>3000BN (NC)	AP+ NE+ NB−	pos	Koller et al. (2012)

*Test material and solvent used: G, glyphosate technical (acid); GK, potassium salt of glyphosate; GI, isopropylamine salt of glyphosate; GA, monoammonium salt of glyphosate. First entry in ( ) for glyphosate indicates percent purity or concentration. First entry in ( ) for GBFs indicates active ingredient and ingredient concentration. Second ( ) entry indicates test material solvent: (W) water; (D) dimethyl sulfoxide; (M) culture medium; (H) Hanks balanced salt solution; (P), phosphate buffered saline.

†Assay endpoint: TK, gene mutation at the TK locus; CA, chromosomal aberration; CA (1), chromosomal aberration (FISH analysis of chromosome 1 for acentric fragments); CB MN, cytokinesis block micronucleus

‡ML, L5178Y mouse lymphoma; CHL, Chinese hamster lung; HL, human peripheral blood lymphocytes; BL, bovine peripheral blood lymphocytes; TR146, human buccal epithelial cell line; MS, mouse spleen cells

¶In cases where treatments differ in the presence and absence of exogenous metabolic activation treatment parameters are presented on separate lines.

§Type of S9 used with %S9 homogenate in S9 Mix indicated in ( ): AR, Aroclor-induced rat liver; PNR, phenobarbital/naphthoflavone-induced rat liver; PBR, phenobarbital/5,6-benzoflavone-induced rat liver; H, human liver; ?, S9 not clearly indicated; none, no experiments conducted with exogenous mammalian metabolic activation.

‖Duration of treatment in hours with total time or times to harvest in hours from treatment in ( ) if treatment was not continuous. min indicates minutes of treatment for one study.

#First number: number of analyzable treatment dose levels with (>HL) indicating spacing between one or more treatment levels greater than half-log; second number: number of replicates cultures for each treatment with ? indicating that number of replicates is not clear; third character: C, confirmatory experiments reported for cell lines or multiple donors for lymphocytes; S, no confirmatory experiment reported.

**Maximum dose level tested and scored with calculated mM in ( ) for glyphosate.

††Assessment or consideration of pH effects of test material: NI, no measurement or control of pH reported; pH, large pH effects noted at higher concentrations and maximum set to minimize pH effects; pHn, effects on pH noted but not used to set maximum treatment concentration; pHa, pH adjusted.

‡‡Number of cells or metaphases scored per treatment level/time point for chromosomal aberration and micronucleus assays. M, metaphases; BN, binucleated cells. (NC) indicates that coding of slides for scoring was not explicitly indicated. In some cases coding was not explicitly indicated but may have been implied by a reference citation. NA, not applicable.

¶¶Measurement of cytotoxicity with + indicating effects on endpoint at one or more treatment levels and -indicating no effects on endpoint up to maximum treatment level: CE, cloning efficiency; RS, relative survival; RG, relative growth; MI, mitotic index; CBPI, cytokinesis block proliferation index; EA, early apoptosis; NE, necrosis ; AP, apoptosis; NB, nuclear buds; LDH, LDH release (cell integrity); NR, neutral red (vital stain); VC, viable cell staining; NI, no concurrent cytotoxicity measurement reported.

§§ Evaluation of mutagenicity or chromosomal effects: neg, negative; pos, positive; equiv, equivocal. Evaluation different from publication or report indicated with individual footnote.

‖‖Statistically significant increases observed at a single different dose for each of two donors. Publications indicate dose responses were not observed and effects were weak or minimal with 48 h treatment.

##No positive control reported.

$Lymphocytes apparently treated before exposure to mitogenic stimulus.

^Small increases in MN frequency in binucleate cells observed for a wide range of dose levels (3.5–580 µg/mL) but not statistically significant.

^^No statistically significant increases in MN frequency for any dose level. Statistically significant correlation observed between dose and MN frequency but approximately the same small increase was observed over a very wide range of doses (3.5–580 µg/mL) and this is considered to be questionable as a biologically plausible dose response.

$$Calculated from the stated concentration of 5×10^{-5} M glyphosate/mL.

induction of effects such as large deletions in DNA that may be detected in the autosomal *tk* locus assay (Aaron et al., 1994).

Glyphosate-based formulations

No *in vitro* mammalian cell gene mutation assays of GBFs were observed in the published literature or the regulatory study reports.

Other non-mammalian assays

Glyphosate and glyphosate salts

No gene mutation assays on glyphosate other than bacterial reversion or *in vitro* mammalian test systems were reported in Williams et al. (2000) or as regulatory studies. A positive result for glyphosate was reported in the *Drosophila* wing spot assay which can indicate both gene mutation and mitotic recombination endpoints (Kaya et al., 2000). Small increases in small wing spot frequencies were observed in one of four crosses of larvae treated with up to 10 mM (≈1.69 mg/mL) of glyphosate. Negative or inconclusive results were observed for the other crosses. The lack of a positive response in the balancer–heterozygous cross offspring, which are insensitive to mitotic recombination events, suggests that there is no evidence for effects on gene mutation endpoint events such as intragenic mutations or deletions in this publication.

Glyphosate-based formulations

Williams et al. (2000) described one report of a positive result for a GBF in the *Drosophila* sex-linked recessive lethal assay but this was contradicted by a negative result for the same GBF in this assay reported by another laboratory. Further, the positive study had some features that hampered interpretation, including the lack of concurrent negative controls (Williams et al., 2000). No non-mammalian cell gene mutation assays of GBFs other than bacterial reversion assays were observed in the published literature or the regulatory study reports.

Chromosomal effects endpoints

In vitro mammalian cell assays

Glyphosate and glyphosate salts

Two human and one bovine *in vitro* peripheral lymphocyte chromosomal aberration studies of glyphosate were considered in the earlier review (Williams et al., 2000). One human lymphocyte *in vitro* study had negative results for glyphosate tested up to 0.33 mg/mL and 0.56 mg/mL (≈2–3 mM) in the absence and presence of an exogenous mammalian activation system, respectively. The other two studies with human and bovine lymphocytes and no metabolic activation system reported positive results at concentrations more than two orders of magnitude lower. The reasons for the conflicting results are unclear, but the Williams et al. (2000) review noted several unusual features about the positive studies including an unusual exposure protocol and discordant positive results for another chemical found negative in other laboratories.

Subsequent to the Williams et al. (2000) review, four publications have reported results for glyphosate salt solutions using cytokinesis block micronucleus (CB MN) or chromosomal aberration endpoints with cultured bovine lymphocytes (Table 2). These publications used a test material reported as 62% by weight isopropylamine salt of glyphosate from a Monsanto source. This test material appears to be a manufacturing batch of the isopropylamine salt of glyphosate in water without surfactants, which is not sold as a formulation. In two publications from one laboratory, no statistically significant increases in the frequencies of micronucleated binucleate cells were observed following the treatment with up to 560 μM (≈94.7 μg/mL acid equivalent, a.e.) for 24 h in the absence of S9 (Piesova, 2004) or 2 h in the absence and presence of a mammalian metabolic activation system (Piesova, 2005). These two studies report a statistically significant increase in micronucleus frequency with 48 h of treatment without S9 in one donor at 280 μM (≈47.3 μg/mL a.e.) but not at 560 μM and in a second donor at 560 μM but not 280 μM. The lack of a consistent response pattern between donors suggests that the results after 48 h of treatment are questionable. Two other publications found negative results for the chromosomal aberration endpoint in cultured bovine lymphocytes with what appears to be the same isopropylamine glyphosate salt solution (Holeckova, 2006; Sivikova & Dianovsky, 2006). Both of these studies used a maximum concentration of 1.12 mM (≈0.189 mg/mL a.e.), which was reported to induce a decrease in mitotic index of >50%, and treatments of 24 h without S9. These two studies have several limitations including no use of an exogenous mammalian metabolic activation system. In addition, Holeckova (2006) only examined effects detectable by staining of chromosome 1 and apparently did not use a positive control. These four studies consistently indicated the lack of chromosomal damaging effects in bovine lymphocytes in the absence of metabolic activation following up to 24 h of exposure to 0.56–1.12 mM (≈0.094–0.189 mg/mL a.e.) concentrations of glyphosate isopropylamine salt.

Three publications reported testing of technical glyphosate for micronucleus or chromosomal aberration endpoints in cultured human lymphocytes (Table 2; Manas et al., 2009; Mladinic et al., 2009a,b). The treatment schedule of the Mladinic et al. publications is not clear. Although standard procedures for human lymphocyte assays recommend the treatment of exponentially growing cells at 44–48 h after mitogenic stimulation (OECD 487, 2010), the methodology described in the Mladinic et al. publications suggests that the 4 h treatment took place before mitogen stimulation. The cultures were then centrifuged and washed before mitogen was added. Thus, only non-dividing cells would have been exposed and this is clearly not in accordance with the OECD guideline. It is also unclear how long the cultures were maintained after the treatment. It appears that they may have been cultured for 72 h after the treatment, which suggests that the cells would have passed through the required 1.5–2 cell cycles after reaching the exponential growth (OECD 487, 2010) even though it appears they were not exposed during the exponential growth. Negative or equivocal results for the micronucleus and chromosomal aberration endpoints were observed in the absence of exogenous metabolic activation (S9) in all three publications. The maximum exposure concentration in the absence of S9 was in the range of 3–6 mM (≈0.51–1.01 mg/mL) in these studies.

In contrast to the cultured bovine and human lymphocyte results, Koller et al. (2012) reported positive results for glyphosate in a CB MN assay using cultured human buccal epithelial cells in the absence of S9. Limitations of this study include no explicit indication of coding of slides or control of pH. However, pH effects would probably not have been observed at the concentrations used. Statistically significant effects were observed at treatment levels of 15–20 mg/L (≈0.09–0.12 mM) for 20 minutes. Statistically significant effects on nuclear morphology (nuclear buds and nucleoplasmic bridges) were observed at 10–20 mg/L and statistically significant increases in apoptosis and necrosis were observed at 20 mg/L. The concentrations and exposure times reported as producing effects in this study are substantially lower than the upper dose levels and exposure times used in the previously discussed studies. The results for this discrepancy are not clear, although Koller et al. (2012) suggest that epithelial cells may be more sensitive to the effects of glyphosate than cells of the hematopoietic system such as lymphocytes. It should be noted that negative genotoxicity results have been observed in a number of regulatory *in vitro* mammalian cell genotoxicity studies using cultured cells other than lymphocytes (mouse lymphoma and CHL cells).

Mladinic et al. (2009a,b) reported increases in micronucleated cells using the cytokinesis-block method in cultured human lymphocytes exposed to glyphosate for 4 h in the presence of an exogenous human liver metabolic activation system (S9). As discussed above, the methodology used in these studies is unclear, but it appears that cells were treated before mitogenic stimulation and cultured for 72 h. In both publications, a statistically significant increase in micronuclei was observed with S9 at the highest dose level of glyphosate tested (580 µg/mL, ≈3.4 mM), but how this could be possible when undividing cells were exposed is unclear. Increased proportions of centromere- and DAPI-positive micronuclei were observed for the high-dose with S9 suggesting that the induced micronuclei were derived from chromosome loss rather than chromosomal fragments. This observation is somewhat unusual, because there do not appear to be any known aneuploidy-inducing agents that require metabolic activation (Kirsch-Volders et al., 2003). Statistically significant increases in the frequency of nuclear abnormalities (buds and bridges) and DNA strand breakage were also observed at the highest dose tested in both publications. In parallel experiments cytotoxic effects such as early apoptosis, late apoptosis and necrosis were observed and these effects tended to be enhanced in the presence of S9 (Mladinic et al., 2009a). Also, the negative control levels of such endpoints as necrosis and comet tail moment were significantly increased in the presence of S9 (Mladinic et al., 2009a). It should be noted that glyphosate is mostly excreted unmetabolized *in vivo* in mammals with only very small levels of aminomethylphosphonic acid (AMPA) or an AMPA-related structure observed (Anadon et al., 2009, Brewster et al., 1991). There is also one report that glyphosate is essentially unmetabolized *in vitro* in the presence of a rat liver S9 homogenate (Gohre et al., 1987). It also does not seem likely that human S9, used by Mladinic et al., would be expected to be more active than much more commonly used induced rat liver S9. These observations suggest that the S9 mediated effects reported by Mladinic et al. are not likely to be due to *in vivo* relevant metabolites. Given the unusual methodology in these studies, the chromosomal-damaging effects of glyphosate in the presence of S9 are not convincing, and it is possible that artifacts due to low pH in the presence of S9 (Cifone et al., 1987; Morita et al, 1989; Scott et al., 1991) may be responsible. Such effects would not be relevant to *in vivo* exposures.

Three regulatory *in vitro* mammalian cell chromosomal aberration studies were conducted on technical glyphosate (Table 2 and "online supplementary material"). These studies were conducted in accordance with the 1983 OECD Guideline 473 for the *in vitro* mammalian chromosomal aberration test (OECD 473, 1983). The study protocols employed exposures in both the presence and absence of an exogenous mammalian metabolic activation system. Treatment and harvest times were appropriate to assess cells exposed in different stages of the cell cycle. Treatment times included a shorter treatment with and without S9 and extended treatments without S9. Appropriate media and culture conditions for these assays were confirmed by experimental results for negative and positive control exposures. In these studies slides were coded before the analysis and 200 metaphases per treatment were scored for chromosomal aberrations, as recommended in the updated OECD Guideline 473 (OECD 473, 1997). The maximum dose levels used in two of the studies (1250 µg/mL, ≈7.4 mM; Fox, 1998; Wright, 1996) were set so as to avoid excessive pH shifts as recommended in the updated OECD Guideline 473. The third study (Matsumoto, 1995) used maximum dose levels (500–1000 µg/mL, ≈3–5.9 mM) set by rangefinder results but noted pH-related medium color changes at dose levels of 500 µg/mL and higher.

No induction of chromosomal aberrations was observed in these regulatory studies employing cultured Chinese hamster lung (CHL) cells (two studies) or in two experiments with cultured human lymphocytes from different donors (third study). The two CHL studies also reported negative results for polyploidy induction. Taken together, these three studies provide clear evidence for the lack of *in vitro* mammalian cell clastogenic activity of glyphosate in robust assays for two different mammalian cell types conducted under a variety of exposure conditions in the absence and presence of S9.

The reviewed results for mammalian *in vitro* chromosomal effect assays demonstrate a weight of evidence that technical glyphosate and glyphosate salt concentrates are generally negative for this endpoint in cultured mammalian cells in the absence of an exogenous mammalian metabolic activation system. Three publications from three laboratories and three regulatory studies report negative *in vitro* mammalian cell chromosomal aberration or micronucleus results in the absence of exogenous activation. Two of the CHL regulatory studies also reported negative results for polyploidy induction. Two publications from one laboratory have questionably equivocal results for the micronucleus endpoint in human lymphocytes in the absence of exogenous activation, while two publications from another laboratory reported positive results for bovine lymphocytes only with extended treatment but these results did not exhibit a consistent dose–response between donors. One publication reported positive

results for human epithelial cells in the absence of S9 with a short exposure time. The negative studies were conducted at upper dose levels and with treatment times that were the same or higher than the studies with positive or equivocal results and include different cell types. These results reinforce the Williams et al. (2000) conclusion that positive chromosomal aberration results reported for glyphosate in cultured human lymphocytes in the absence of an exogenous metabolic activation system are not convincing.

Recent reports of positive chromosomal effect results for glyphosate in the presence of an exogenous mammalian activation system in cultured human lymphocytes in one laboratory (Mladinic et al., 2009a,b) were not reproduced in three *in vitro* mammalian cell chromosomal aberration regulatory studies, including a study that employed cultured human lymphocytes. These positive results are also discordant with one previously reviewed result demonstrating a negative result for glyphosate in cultured human lymphocytes with mammalian metabolic activation using the chromosomal aberration endpoint (Williams et al., 2000) and a negative result in the presence of S9 for the micronucleus endpoint in bovine lymphocytes (Piesova, 2005). They are also discordant with negative results for three *in vitro* mammalian cell gene mutation studies that included an exposure to S9. The unusual methodology used for cultured human lymphocytes in the Mladinic et al. studies further complicates the interpretation of results from these studies. Thus, the weight of evidence for the *in vitro* chromosomal effect assays generally indicates a lack of chromosomal effects in either the presence or absence of S9.

Glyphosate-based formulations

No *in vitro* mammalian cell chromosomal aberration assays of GBFs are described in Williams et al. (2000).

Only two publications with data from *in vitro* mammalian cell chromosomal aberration assays of GBFs have been found since the review of Williams et al. (2000). Results are in Table 2. Amer et al. (2006) reported positive *in vitro* chromosomal aberration effects in mouse spleen cells for a test material described as "herbazed" herbicide, which was reported to contain 84% glyphosate and 16% solvent, an unusually high glyphosate concentration for a formulation. The test material is not further characterized in the publication but is considered a GBF in this review. The glyphosate or GBF concentrations to which the cells in the study were exposed are not entirely clear because the most consistent concentration unit used in the report is M glyphosate/ml which is an unusual concentration unit. Assuming this means, moles of glyphosate per mL the maximum exposure would be 5×10^{-5} M glyphosate/mL medium or 50 mM. An upper exposure concentration of 50 mM ($\approx$ 8.45 mg/mL glyphosate) would be well in excess of the limit level of 10 mM or 5 mg/mL currently recommended in the OECD guidelines (OECD 473, 1997). In addition to the uncertainty regarding the concentrations used, there are several other limitations to the reported study including no indication that pH of treatment solutions was controlled, no use of a mammalian metabolic activation system and no reported use of coded slides for scoring. Given these limitations, the uncertainty about the concentrations used and the nature of the test material, these results should not be considered to have significant relevance with respect to typical GBFs.

Another publication reported positive results for Roundup™ UltraMax GBF for the CB MN assay in cultured human buccal epithelial cells (Koller et al., 2012). Limitations in conduct or reporting of this study included no indication that pH of treatment solutions was controlled and no explicitly reported use of coded slides for scoring. As noted earlier, pH effects would not be likely at the low concentrations used. Increased MN frequencies were reported for 20 minute treatments with 10–20 mg/L of glyphosate a.i. ($\approx$0.06–0.12 mM glyphosate). Statistically significant effects on nuclear morphology (nuclear buds and nucleoplasmic bridges) were also observed at 10–20 mg/L and increases in apoptosis and necrosis were observed at 20 mg/L but only the necrosis effect was statistically significant.

There were no regulatory studies of GBFs in *in vitro* mammalian cell chromosomal aberration or micronucleus assays. Thus, there are only the two studies of different GBFs (discussed above) with uncertainties and limitations in this endpoint category. While the published literature reports suggest the possibility of activity of GBFs in *in vitro* chromosomal damage assays, the paucity of studies and their limitations do not permit a generic conclusion regarding this endpoint for *in vitro* mammalian cells for GBFs in general.

In vivo mammalian assays

Micronucleus and chromosomal aberration

Glyphosate and glyphosate salts.

The Williams et al. (2000) glyphosate toxicity review presented results from *in vivo* mammalian chromosomal effect assays. Results from several mouse bone marrow erythrocyte studies of glyphosate were negative for micronucleus induction. These included the studies from different laboratories mostly following modern guidelines. The intraperitoneal (i.p.) route was used for most of the negative studies. In addition to i.p. studies, a 13-week mouse feeding study was also negative for the micronucleus endpoint with an estimated maximum daily glyphosate dose of over 11 000 mg/kg body weight/day. There was one published report of a weak positive mouse bone marrow micronucleus response observed for glyphosate. This study, which employed a smaller number of animals per group than other negative studies, clearly conflicted with the numerous other negative studies, not only in terms of increased micronucleus frequencies but also the finding of altered polychromatic erythrocyte to normochromatic erythrocyte (PCE/NCE) ratios. The overall weight of evidence from the earlier reviewed studies was that glyphosate and glyphosate formulations were negative in the mouse bone marrow erythrocyte micronucleus assay. The earlier review also noted a negative mouse dominant lethal result for glyphosate administered by gavage at a maximum dose level of 2000 mg/kg body weight.

As indicated in Table 3, two publications reported results for glyphosate in the mouse bone marrow erythrocyte micronucleus assay. It should be noted that there are some fairly

consistent limitations in the reported conduct of these studies compared to the OECD guidelines. In these studies, concurrent indications of the toxicity other than PCE/NCE ratio effects on the bone marrow and mortality are not reported, coding of slides for scoring is not explicitly reported and fewer than the currently recommended number of 2000 PCEs or erythrocytes per animal were scored. As noted earlier, failure to explicitly report coding of slides in the methodology may reflect either failure to code slides or failure to explicitly indicate this in the methodology description in the publication.

Negative results were reported in one study which used a dose of 300 mg/kg body weight of glyphosate administered once i.p. with sacrifices at 24, 48 and 74 h after dosing (Chruscielska et al., 2000). This study had some limitations including the use of only one dose level (several dose levels should be used except when there is no toxicity up to the limit dose), and no explicit reported coding of slides for scoring and scoring of only 1000 PCEs per animal. A second publication reported positive results for glyphosate administered at 50, 100 and 200 mg/kg body weight via two i.p. injections 24 h apart, with sacrifice at 24 h after the second dose (Manas et al., 2009). A statistically significant increase in micronucleated erythrocytes was observed in the high-dose group in this study. A particular concern with this second publication is that "erythrocytes" rather than polychromatic erythrocytes were indicated as scored for micronuclei. This does not appear to be a case of using "erythrocytes" to mean polychromatic erythrocytes because the term "polychromatic erythrocytes" is used elsewhere in the publication describing measurements of PCE/NCE ratios. Scoring of all erythrocytes instead of immature polychromatic erythrocytes for micronuclei would be inappropriate in an assay with the stated treatment and harvest times because of the transient nature of micronucleated PCEs in bone marrow (OECD 474, 1997). PCEs containing micronuclei would not have reached maturity in such a short time, so micronuclei in matured erythrocytes could not have been induced by the chemical treatment.

There is no definitive explanation for the discrepancy between the two publications. Although one study used a single dose with multiple harvest times and the second used two doses and a single harvest time, both are acceptable protocols and would not be expected to lead to such discordant results (OECD 474, 1997). The negative result reported for the 13-week feeding study in the earlier review (Williams et al., 2000) confirms that positive results are not simply due to the repeated dosing. The reported negative result (Chruscielska et al., 2000) seems to be in accordance with a majority of earlier reviewed mouse bone marrow micronucleus studies of glyphosate using similar doses and the i.p. or feeding routes (Williams et al., 2000). Also, the apparent scoring of micronuclei in erythrocytes at such an early time point raises questions regarding the reported positive study.

A large number of regulatory rodent bone marrow assays were conducted on technical glyphosate or glyphosate salt solutions (Table 3 and "online supplementary material"). Most of these were mouse bone marrow erythrocyte micronucleus studies, but there is also one rat bone marrow erythrocyte micronucleus assay and one mouse bone marrow chromosomal aberration study. Most of the rodent bone marrow erythrocyte micronucleus studies were reported to be conducted in accordance with the OECD Guideline 474 (1983) for studies conducted prior to 1997 and the OECD Guideline 474 (1997) for studies conducted after 1997. The mouse bone marrow chromosomal aberration study was reported as conducted according to the OECD Guideline 475 (OECD 475, 1984). Protocol features for the micronucleus studies included single dosing with harvest at 24 and 48 h after the treatment (also 72 h in one study) or two treatments 24 h apart with a single harvest at 24 h after the last treatment. These treatment and harvest time alternatives are both considered acceptable in the most recent guideline (OECD 474, 1997) for bone marrow erythrocyte studies. For the bone marrow chromosomal aberration study, the use of a single 24 h sampling time after two treatments separated by 24 h deviates from an earlier recommendation to have 6 h and 24 h sampling times with multiple dosing (OECD 475, 1984), but differs slightly from more recent recommendations to sample approximately 1.5 cell cycles (usually around 12–18 h) after two daily doses (OECD 475, 1997). Some studies used only males when there was no evident difference in toxicity to both sexes, which is acceptable under the most recent guideline (OECD 474, 1997). Three treatment groups were generally used but some studies only used a single high-dose group when a limit dose had little or no toxicity as accepted in OECD 474 (1997). In most studies, 2000 PCEs per animal were scored as recommended in the most recent guideline (OECD 474, 1997). The earlier guideline had recommended scoring 1000 PCEs per animal (OECD 474, 1983). In the mouse bone marrow chromosomal aberration study, 50 metaphases per animal were scored, which is lower than the currently recommended 100 metaphases per animal (OECD 475, 1997).

Eleven mouse and one rat bone marrow erythrocyte micronucleus regulatory studies for technical glyphosate or glyphosate salt solutions were conducted. The upper dose levels for orally administered glyphosate were, with one exception, the earlier suggested limit dose of 5000 mg/kg body weight or the more recently recommended limit dose of 2000 mg/kg body weight. In these studies little or no toxicity was observed at the limit dose. One study (Zoriki Hosomi, 2007) observed considerable toxicity and lethality at an oral dose of 50 mg/kg body weight and employed a lower maximum dose level for the main study (30 mg/kg body weight). The reason for the higher reported toxicity in this study compared to other glyphosate studies is not apparent. Studies of glyphosate employing the intraperitoneal route generally employed lower maximum dose levels (62.5 to 3024 mg/kg body weight) and the maximum dose levels were set by observations of toxicity and lethality in rangefinder studies.

Micronucleated PCE frequency results for the maximum dose levels of the regulatory rodent bone marrow micronucleus studies of glyphosate and glyphosate salts are presented in Table 4. For eight of the 12 regulatory bone marrow erythrocyte micronucleus studies there were no statistically significant increases in micronucleated PCEs observed for any of the glyphosate treated groups. Three studies had small statistically significant increases in micronucleated PCE frequency that were judged not to be treatment related because the frequencies were well within historical

Table 3. *In vivo* mammalian chromosomal effect studies.

Test material*	Endpt†	Strain/Species	Treatment‡ Veh	Rte	No/Sex	Grps	Schedule	Maximum dose	Scoring¶	Results§ Tox	Mutagenicity	References
Glyphosate and glyphosate salts												
Literature MN studies												
G	BM MN	C3H mice	W	i.p.	6M	1	S (24, 48C, 72)	300	1000P (NC)	M−, R−	neg	Chruscielska et al. (2000)
G (96%)	BM MN	BalbC mice	S?	i.p.	5M 5F	3	T (24)	200	1000E(NC)	M−, C−, R−	pos‖	Manas et al. (2009)
Regulatory MN studies												
G (98.6%)	BM MN	NMRI SPF mice	0.5% CMC	p.o.	5M 5F	1	S (24, 48C, 72)	5000	2000P *N	M−, R−	neg	Jensen (1991c)
G (96.8%)	BM MN	Swiss mice	PO	p.o.	5M 5F	3 (>HL)	T (24)	5000	≈2000E (NC) ≈1000P	M−, C−, R−	inc#	Suresh (1993b)
G (95.6% w/w)	BM MN	CD-1 mice	PS	p.o.	5M 5F	1	S (24, 48)	5000	2000P	M−, C−, R−	neg	Fox & Mackay (1996)
GK (59.3%)	BM MN	CD-1 mice	W	p.o.	5M	1	S (24, 48)	2000	2000P	M−, C−, R−	neg**	Jones (1999)
G (954.9 g/kg)	BM MN	Swiss albino mice	W	i.p.	5M 5F	3	T (24)	562.5	1000P 1000N	M−, R−	neg	Marques (1999)
GI (612.7 g/kg)	BM MN	Swiss albino mice	W	i.p.	5M††5F††	3	T (24)	3024	1000P *N	M+, R−	neg	Gava (2000)
G (97.73%)	BM MN	NMRI mice	PEG 400	p.o.	5M 5F	3	S (24, 48 H)	2000	2000P	M−, C−, R−	neg	Honarvar (2005)
G (95.7% w/w)	BM MN	Crl:CD-1®(ICR) BR mice	PBS	i.p.	7M	3	S (24, 48 CH)	600	2000P	M−, C−, R−	neg‡‡	Durward (2006)
G (980.1 g/kg)	BM MN	Swiss mice	W	p.o.	6M	3	T (24)	30	3000P	M−, R−	neg¶¶	Zoriki Hosomi (2007)
G (99.1% w/w)	BM MN	NMRI mice	0.5% CMC	p.o.	5M	3 (24 h)	S (24, 48 CH)	2000	2000P	M−, C−, R−	neg	Honarvar (2008)
G (980.0 g/kg)	BM MN	Swiss albino mice	CO	i.p.	5M 5F	3	T (24)	62.5	2000P *N	M−, R−	neg	Costa (2008)
G (98.8% w/w)	BM MN	Crl(CD)(SD) rats	0.8% HPMC	p.o.	5M 5F	3	S (24, 48 CH)	2000	2000P	M−, C−, R−	neg	Flugge (2009b)
Regulatory CA study												
G (96.8%)	BM CA	Swiss albino mice	PO	p.o.	5M 5F	1	T (24)	5000	50M	M−, C+, MI−	neg	Suresh (1994)
GBFs												
Published studies												
Perzocyd 10 SL	BM MN	C3H mice	W	i.p	6M	1	S (24, 48C, 72)	90	1000P (NC)	M−, R−	neg	Chruscielska et al. (2000)
Roundup™ 69	BM MN	mice	NI	i.p.	6M	3	T (25)	200	1000P (NC) 1000N	M−, R−	neg	Coutinho do Nascimento & Grisolia (2000)
Roundup (480 g/L GI)	BM MN	Swiss mice	W?	i.p.	8M 8F	3	T (24)	200	2000E(P) NC	M−, R−	neg	Grisolia (2002)
Roundup (480 g/L GI)	BM CA	New Zealand white rabbits	W	d.w.	5M	2§§	60 days	750 ppm	50M (NC)	M	pos	Helal & Moussa (2005)
Herbazed (84% G)	BM CA	Swiss mice	NI	i.p.	5M	1	1, 3, 5d (24)	50 gly?	100M (NC)	M−	inc‖‖	Amer et al. (2006)
Herbazed (84% G)	SC CA	Swiss mice	NI	i.p.	5M	1	1, 3, 5d (24)	50 gly?	100M (NC)	M−	pos	
Herbazed (84% G)	BM CA	Swiss mice	NI	p.o.	5M	2	1, 7, 14, 21d (24)	100 gly?	100M (NC)	M−	pos	
Herbazed (84% G)	SC CA	Swiss mice	NI	p.o.	5M	2	1, 7, 14, 21d (24)	100 gly?	100M (NC)	M−	pos	
Roundup	BM CA	C57BL mice	W	p.o.	8M	1	S (6, 24, 48, 72, 96, 120)	1080	50M	M−	neg	Dimitrov et al. (2006)

(*continued*)

DOI: 10.3109/10408444.2013.770820

Table 3. Continued.

Test material*	Endpt†	Strain/Species	Treatment‡ Veh	Rte	No/Sex	Grps	Schedule	Maximum dose	Scoring¶	Results§ Tox	Mutagenicity	References
	BM MN	C57BL mice	W	p.o.	8M	1	S (24, 48, 72, 96, 120)	1080	500P	M−, R−	neg	Dimitrov et al. (2006)
Roundup (41% GI)	BM CA	Swiss mice	DMSO	i.p.	5M	2	S (24, 48, 72)	50 gly?	75M (NC)	M−, MI+	pos	Prasad et al. (2009)
	BM MN	Swiss mice	DMSO	i.p.	5M	2	S (24, 48, 72)	50 gly?	2000(P) (NC)	M−, MI+	pos	
Regulatory studies												
MON 78239 (36.6%a.e. GK)	BM MN	Crl:CD 1®(ICR) BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M−, C−, R−	neg##	Erexson (2003a)
MON 78634 (65.2%a.e.)	BM MN	Crl:CD-1®(ICR) BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M−, C−, R−	neg	Erexson (2003b)
MON 78910 (30.3%a.e.)	BM MN	CD-1® (ICR)BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M−, C−, R−	neg	Erexson (2006)
MON 79864 (38.7%a.e.)	BM MN	Hsd:ICR(CD-1 mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M−, C+, P−	neg##	Xu (2008a)
MON 76171 (31.1%a.e.)	BM MN	CD-1®(ICR)BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M−, C−, R−	neg	Xu (2008b)
MON 79991 (71.6%a.e.)	BM MN	CD-1®(ICR)BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M−, C−, R+?	neg	Xu (2009a)
MON 76138 (38.5%a.e.)	BM MN	CD-1®(ICR)BR mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M−, C−, R−	neg	Xu (2009b)
MON 76313 (30.9%a.e.)	BM MN	Hsd:ICR(CD-1) mice	W	p.o.	5M	3	S (24, 48CH)	2000	2000P	M−, C−, R−	neg	Xu (2009c)
A17035A (280.7 g/L G)	BM MN	Swiss mice	W	p.o.	6M	1	T (24)	2000	3000P	M , C , R	neg	Negro Silva (2009)
TROP M (483.6 g/l GI)	BM MN	NMRI mice	.8% CMC	p.o.	5M 5F	3	S (24, 48CH)	2000	2000P	M−, C−, R−	neg	Flugge (2010c)
Glyphosate 757 g/kg formulation (69.1%a.e. G)	BM MN	Crl(CD)(SD) rat	0.8% HPMC	p.o.	5M 5F	3	S (24, 48CH)	2000	2000P	M−, C−, R−	neg	Flugge (2010e)
Glyphosate SL (499.35 g/L G)	BM MN	Swiss mice	W	p.o.	6M	1	T (24)	2000	3000P	M−, C−, R−	neg	Negro Silva (2011)

*G, glyphosate technical acid; GK, potassium glyphosate salt. GI, isopropylamine glyphosate salt; ( ) indicates purity or concentration for glyphosate or glyphosate salts or a.i. content for GBFs. Concentration in acid equivalents indicated as a.e.

†Endpoint: BM MN , bone marrow erythrocyte micronucleus; BM CA, bone marrow chromosomal aberration; SC CA, spermatocyte chromosomal aberration.

‡Treatment:

Veh – Vehicle used: W, water; S, saline; PO, peanut oil; PS, physiological saline; PEG 400; polyethylene glycol; PBS, phospate buffered saline; CO, corn oil; HMC, DMSO, dimethylsulfoxide; CMC, carboxymethylcellulose; HPMC, hydroxypropylmethylcellulose; NI, not indicated.

Rte – Route of administration: p.o. oral (gavage); i.p., intraperitoneal injection; d.w., drinking water.

No/Sex – Number of males (M) and females (F) scored for each glyphosate or GBF treatment group.

Grps – Number of glyphosate or GBF dose level treatments scored for micronuclei or chromosomal aberrations. >HL indicates spacing between one or more treatment groups greater than half-$\sqrt{10}$.

Schedule – Treatment schedule for glyphosate treatments: S, single treatment; T, two treatments 24 h apart; d, consecutive days of treatment with a separate group for each number of days. Numbers in parentheses are harvest times in hours after treatment or last treatment with a separate group for each harvest time. Treatment or harvest conditions used specifically for other groups are indicated as C, vehicle control, H, high-dose.

Maximum dose – Maximum glyphosate or GBF treatment dose level in mg/kg body weight except for ppm which indicates amount in drinking water. gly for GBFs indicates that dose units were reported as mg/kg body weight of glyphosate.

¶Number indicates cells or metaphases scored per animal for P (PCEs), N (NCEs), E (erythrocytes), M (metaphases). *N, variable NCEs scored for micronuclei while scoring the indicated number of PCEs. E(P) indicates number of erythrocytes scored with results for PCEs reported separately. NC, coding of slides for scoring not explicitly indicated in report or publication. In some cases coding was not explicitly indicated but may have been implied by a reference citation.

§Results:

Tox – Measures of toxicity reported: M, mortality; C, clinical signs; R, PCE/NCE ratio; MI, mitotic index. A "+" after the measure indicates treatment-related effects. A "–" after the measure indicates no treatment-related effects; +? Indicates a decrease in (R) but control (R) value for the corresponding time point was unusually high. No mortality (MI-) was assumed unless mortality was indicated.

Mut – Overall evaluation of study results as negative (neg), positive (pos) or or inconclusive (inc) for treatment-related effects. Individual footnotes used to indicate statistically significant effects or difference from conclusion of publication or report authors.

‖Statistically significant increase reported for micronucleated erythrocytes. Results not reported for micronucleated PCEs.

#Statistically significant increase in MN erythrocytes for high-dose females. Control MN PCE frequencies were unusually high and historical control data not presented.

**Statistically significant increase in MN PCE frequency at 24 h only, within historical control, not judged to be treatment related.

††Only four males and four females scored for high-dose group.

‡‡Statistically significant increase in MN PCE frequency only for 24 h high-dose, within historical control, not judged to be treatment related.

¶¶Statistically significant increase for high-dose MN PCE frequency, within historical control, not judged to be treatment related.

§§Two groups treated with same level of Roundup GBF but one group also treated with vitamin E.

|||Increases in abnormal metaphases not statistically significant excluding gaps from aberrant cells. Authors conclude positive result based on statistically significant increases in abnormal metaphases including gaps.

##Statistically significant increase for high-dose at 48 h, within historical control, but judged to be due to a low control group value and not treatment-related.

DOI: 10.3109/10408444.2013.770820

Table 4. High-dose and control MN PCE frequencies for regulatory glyphosate and glyphosate salt studies.

					Micronucleated PCE per 1000 PCE mean ± std. dev.		
Test material†	Sex	Dose (mg/kg bw)	Route	Harvest (h)	Control	High-dose	References
G	M	5000	p.o.	24		1.7 ± 0.6	Jensen (1991c)
				48	1.5 ± 0.7	1.1 ± 0.4	
				72		0.9 ± 0.7	
	F	5000		24		1.5 ± 0.7	
				48	1.2 ± 0.3	1.7 ± 0.8	
				72		0.8 ± 0.6	
G	M	5000	p.o.	24	6.7 ± 5.5	8.8 ± 1.8	Suresh (1993b)
	F	5000		24	4.9 ± 2.7	10.4 ± 4.9*	
G	M	5000	p.o.	24	1.6 ± 0.8	2.1 ± 1.6	Fox & Mackay (1996)
				48	1.7 ± 1.3	2.1 ± 1.9	
	F	5000		24	1.4 ± 0.7	2.1 ± 2.5	
				48	0.7 ± 0.6	0.8 ± 0.8	
GK	M	2000	p.o.	24	0.2 ± 0.4	0.9 ± 0.4*	Jones (1999)
				48	0.8 ± 1.0	0.9 ± 1.0	
G	M	562.5	i.p.	24	0.4 ± 0.5	0.4 ± 0.9	Marques (1999)
	F	562.5		24	0.8 ± 0.8	0.6 ± 0.5	
GI	M	3024	i.p.	24	0.6 ± 0.5	0.7 ± 1.0	Gava (2000)
	F	3024			0.4 ± 0.5	0.7 ± 1.0	
G	M	2000	p.o.	24	0.9 ± 0.6	0.9 ± 0.7	Honarvar (2005)
	F	2000		24	0.7 ± 0.8	0.6 ± 0.7	
	M	2000		48		1.5 ± 1.0	
	F	2000		48		1.1 ± 0.9	
G	M	600	i.p.	24	0.6 ± 0.6	1.9 ± 0.7*	Durward (2006)
				48	1.0 ± 1.2	0.9 ± 1.1	
G	M	30	p.o.	24	0.6 ± 0.3	1.4 ± 0.4*	Zoriki Hosomi (2007)
G	M	2000	p.o.	24	0.7 ± 0.7	0.7 ± 0.4	Honarvar (2008)
		2000		48	0.7 ± 0.6	0.8 ± 0.6	
G	M	62.5	i.p.	24	0.0 ± 0.0	0.3 ± 0.7	Costa (2008)
	F	62.5		24	0.0 ± 0.0	0.0 ± 0.0	
G	M (rat)	2000	p.o.	24	0.8 ± 0.6	0.6 ± 0.4	Flugge (2009b)
				48	1.0 ± 0.9	0.8 ± 0.4	
	F (rat)	2000		24	0.9 ± 0.2	0.4 ± 0.4	
				48	1.1 ± 0.7	0.4 ± 0.4	

*Statistically significant increase over control value.
†G, glyphosate technical acid; GK, potassium salt of glyphosate; GI, isopropylamine salt of glyphosate.

control values (Durward, 2006; Jones, 1999; Zoriki-Hosomi, 2007).

A statistically significant increase in the micronucleated polychromatic erythrocyte (MN PCE) frequency was observed for females, but not for males, treated with 5000 mg/kg in the study of Suresh (1993b). This increase was only about two-fold over the concurrent control and no increase was observed for frequencies of micronucleated normochromatic erythrocytes for this group, although at such an early sampling time this would not be expected. Historical control data were not presented. Suresh (1993b) employed a high level of glyphosate treatment, 5000 mg/kg body weight, which is well above the currently recommended limit dose of 2000 mg/kg body weight (OECD 474, 1997) as well as an unusual use of groundnut oil as a vehicle for a water soluble test material. The negative control MN PCE frequencies in this study (4.9 and 6.7 MN per 1000 PCEs for females and males, respectively) exceeded control MN PCE frequencies commonly observed in mice (Salamone & Mavournin, 1994). The recommendation by Salamone & Mavournin (1994) is that MN PCE frequencies above 5/1000 MN PCE should be questioned and in most cases confirmed. Two other bone marrow erythrocyte studies which employed 5000 mg/kg body weight treatment did not observe any statistically significant increases in MN PCE frequency (Fox & MacKay, 1996; Jensen, 1991c). A mouse bone marrow chromosomal aberration study conducted in the same laboratory using the same vehicle and a 5000 mg/kg body weight dose level (Suresh, 1994) was negative. These observations provide a strong weight of evidence that the statistically significant increase observed in Suresh (1993b) is not evidence of a treatment-related effect.

The results presented in Table 3 clearly indicate a very strong overall weight of evidence that glyphosate or glyphosate salt solutions do not induce micronucleated PCEs in rodent bone marrow erythrocyte micronucleus assays conducted with maximum dose levels which are appropriate either because of toxic effects or are recommended limit doses for relatively non-toxic compounds. Statistically significant increases in MN PCE frequency in isolated studies were not reproducible in a number of other studies. Furthermore, these studies include several examples of negative results for i.p. administration at maximum doses that exceed those employed by Manas et al. (2009). It should also be noted that the i.p. route of administration is not relevant to human exposure. In combination with the results presented in Williams et al. (2000), there is overall a strong weight of evidence that technical glyphosate and glyphosate

salt solutions are not genotoxic in *in vivo* mammalian micronucleus assays at high dose levels.

Glyphosate-based formulations.

The Williams et al. (2000) glyphosate toxicity review presented results from several mouse bone marrow erythrocyte micronucleus studies of GBFs (e.g. Roundup™, Rodeo™ and Direct™-branded formulations) that were mostly negative for micronucleus induction. The i.p. route was used for most of the negative studies and maximum doses for many of the studies were toxic or appropriately close to LD_{50} values. There was one published report of a weak positive mouse bone marrow micronucleus response observed for a Roundup™-branded GBF. This study, which employed a smaller number of animals per group than other negative studies, was clearly aberrant from the numerous other negative studies not only in micronucleated cell frequency finding but also the finding of altered polychromatic erythrocyte to normochromatic erythrocyte (PCE/NCE) ratios. The overall weight of evidence from the earlier reviewed studies was that GBFs were negative in the mouse bone marrow erythrocyte micronucleus assay.

As indicated in Table 3, seven publications reported results for GBFs in *in vivo* mammalian micronucleus or chromosomal aberration assays. It should be noted that there are some fairly consistent limitations in the reported conduct of these studies compared to the OECD guidelines. In most studies, concurrent indications of toxicity other than effects on bone marrow are not reported, coding of slides for scoring is not explicitly indicated and, in many studies, fewer than the currently recommended number of 2000 polychromatic erythrocytes or 100 metaphases per animal were scored.

Three publications report negative results for Roundup™-branded GBFs in mouse chromosomal aberration or micronucleus assays. In two of these publications, negative results in mouse bone marrow erythrocyte micronucleus assays were reported for different Roundup™-branded GBFs administered at 200 mg/kg body weight twice 24 h apart by the i.p. route (Coutinho do Nascimento & Grisolia, 2000; Grisolia, 2002). The third publication reported negative results in mouse bone marrow studies for both the chromosomal aberration and erythrocyte micronucleus endpoints using a single oral dose of 1080 mg/kg body weight of a Roundup™-branded GBF (Dimitrov et al., 2006).

In contrast, one publication reported positive results for a Roundup™-branded GBF in mouse bone marrow for the chromosomal aberration and erythrocyte micronucleus endpoints using a single maximum dose of 50 mg glyphosate/kg body weight i.p. (Prasad et al., 2009). Both the positive results and the magnitude of the increases in frequencies of chromosomal aberrations and micronuclei reported in this study are remarkably discordant with other reported results for Roundup™-branded and other GBFs in mouse bone marrow chromosomal aberration and micronucleus studies in a number of laboratories and publications (Table 3 and Williams et al., 2000). The reasons for this discordance are not clear. One unusual feature of the Prasad et al. (2009) study is that the Roundup™-branded GBF was administered in dimethylsulfoxide (DMSO) vehicle. This is an unusual vehicle to use in *in vivo* genotoxicity studies, particularly using the i.p. route and for a test material which is water soluble. A published toxicity study has reported that use of a DMSO/olive oil vehicle by the i.p. route dramatically enhanced the toxicity of glyphosate formulation or the formulation components without glyphosate compared to saline vehicle (Heydens et al., 2008). The enhanced toxicity observed with this vehicle was not observed when the oral route was used. DMSO has also been shown to enhance the toxicity of other hydrocarbons when administered via the i.p. route (Kocsis et al., 1968). These observations suggest that use of DMSO as a vehicle for administration of chemicals or formulations by the i.p. route might produce unusual toxic effects that are not relevant to normally encountered exposures. Furthermore, the i.p. route is considered by many regulatory agencies to be an unphysiological route and is not recommended for the safety evaluation of chemicals. Regardless of the reasons for the discordant positive results, it is clear that a large preponderance of evidence indicates that Roundup™-branded GBFs are typically negative in mouse bone marrow chromosomal aberration and erythrocyte endpoints.

One publication reported positive results for bone marrow chromosomal aberration in rabbits administered Roundup™-branded GBF in drinking water at 750 ppm for 60 days (Helal & Moussa, 2005). This study is unique in terms of species and route of administration. The publication does not report water intake in the test and control groups. Given the potential for water palatability issues with a formulated product, this is a significant shortcoming, as any effects noted might be attributable to dehydration (Saunders, 2005). This study had further limitations including the use of only a single dose level and not explicitly indicating the coding of slides for scoring. This study did not include a positive control for chromosomal aberration effects. Examination of the chromosomal aberration scoring results showed that, for the treated group, large increases were observed for gaps and "centromeric attenuation" that were included in the summation and evaluation of structural chromosomal aberration effects. Ordinarily gaps are scored but are not included in the total aberration frequency, and centromeric attenuation is not included in conventional identification of structural aberrations (OECD 475, 1997; Savage, 1976). These unusual scoring and interpretive features raise significant questions about using this study to make conclusions about clastogenicity of the GBF tested.

Two other publications report *in vivo* mammalian chromosomal aberration or micronucleus results for non-Roundup™-branded GBFs. In one of these, an uncharacterized GBF, Percozyd 10 L, was reported to be negative in a mouse bone marrow erythrocyte micronucleus assay (Chruscielska et al., 2000). The maximum dose level tested, 90 mg/kg i.p., was reported to be 70% of the i.p. LD_{50} as determined experimentally by the authors, and so may have exceeded the maximum tolerated dose. This study had several limitations including use of less than three dose levels and no explicit reported coding of slides for scoring.

In an other study, positive results were reported for another uncharacterized GBF, herbazed, in mouse bone marrow and spermatocyte chromosomal aberration studies (Amer et al., 2006) using oral and i.p. routes and treatments from 1 to up to

5 d (i.p.) or 21 d (oral). Although i.p. exposures of 1, 3 and 5 d produced statistically significant increases in bone marrow abnormal metaphase frequency when gaps were included, the increases were not significant excluding the gaps and the OECD 475 (1997) recommends not including gaps in total aberration frequency. Statistically significant positive results were observed after multiple i.p. exposures (3–5 d bone marrow only including gaps; 5 d for spermatocytes) and after extended oral treatments (14–21 d, bone marrow; 7–21 d spermatocytes). Although not a genotoxic endpoint *per se*, it should be noted that statistically significant increases in frequency of sperm with abnormal morphology were observed in mice treated with 100 and 200 mg/kg body weight glyphosate p.o. for 5 d. The fact that positive results were not observed in an erythrocyte micronucleus test of mice treated with glyphosate up to 50 000 ppm in feed for 13 weeks (Williams et al., 2000) indicates that, by contrast, extended glyphosate treatment by the oral route does not induce detectable chromosomal effects. This treatment was longer and up to much higher glyphosate exposures than those used for the Amer et al. (2006) studies. Thus, it appears likely that these effects were due to some component(s) of the specific herbazed GBF tested rather than glyphosate. It is noteworthy that the Amer et al. (2006) publication is unique in reporting positive responses for such a large number of endpoints for a single test material.

A total of 12 mouse bone marrow erythrocyte micronucleus regulatory studies of GBFs were available (Table 3 and "online supplementary material"). These studies were designed to be in compliance with the OECD 474 (1997) guidance for rodent erythrocyte micronucleus assays. The treatment regimen was either a single oral dose with harvests at 24 and 48 h after dosing or two oral doses 24 h apart with a single sacrifice at 24 h after the last dose. Either of these treatment regimens is acceptable under the most recent OECD guideline for this assay (OECD 474, 1997). Many of the studies used only males but reported no significant differences in gender response in preliminary toxicity studies. All of these studies employed a maximum dose of 2000 mg/kg body weight and most of the studies also used lower doses. This is consistent with a limit dose recommendation of 2000 mg/kg body weight in the OECD guideline. The upper dose level was not reported to induce mortality in any of the studies but in a few studies clinical signs were observed in high-dose animals. No toxic effects on bone marrow were generally observed in these studies as judged by PCE/NCE ratios. A decrease in PCE/NCE for 48 h high-dose animals was observed in one study (Xu, 2009a) but this may not have been treatment-related because the control PCE/NCE ratio was unusually high.

Ten of the studies did not exhibit a statistically significant increase in MN PCE for any treatment group. Two studies had statistically significant increases in MN PCE frequency at the 48 h time point but the MN PCE frequencies were within historical control levels and judged in each case to be due to a statistical anomaly from a low vehicle control MN PCE frequency and is not treatment-related (Erexson, 2003a; Xu, 2008a). Thus, none of these 12 studies indicated treatment-related increases in MN PCE frequencies and all studies were considered negative for this endpoint.

In summary, in addition to the *in vivo* rodent bone marrow chromosomal effect studies presented in Williams et al. (2000), a majority (three of four) of the rodent bone marrow studies in the subsequent published literature are negative for Roundup™-branded formulations at maximum dose levels that significantly exceed the maximum dose level of the study reporting positive results. One noteworthy feature of the positive study is the use of a DMSO vehicle which is unusual, if not inappropriate, for a water soluble test material. A rabbit drinking water study found positive effects for a Roundup™-branded GBF; however, this study had a large number of limitations including not presenting information on palatability and no positive control. Publication reports for other GBFs included a negative study for Perzocyd 10 SL and positive chromosomal aberration results for both bone marrow and spermatocytes for a herbazed GBF using extended oral and i.p. treatments. A very large number of well-conducted regulatory mouse bone marrow micronucleus studies indicated that a variety of GBFs are negative in this assay system up to the limit dose of 2000 mg/kg body weight. While the possibility that GBFs with different compositions might have different properties cannot be excluded, the overall data certainly indicate that a typical GBF is negative for the induction of chromosomal damage *in vivo*.

Rodent dominant lethal

The Williams et al. (2000) review notes a negative result in a mouse dominant lethal assay of glyphosate using a maximum treatment level of 2000 mg/kg body weight administered by gavage.

No rodent dominant lethal assays of glyphosate or GBFs were encountered in the subsequent literature.

One regulatory rat dominant lethal study was available (Suresh, 1992; "online supplementary material"). This study was reported to be conducted in accordance with the OECD 478 (1984). In this study, groups of 30 male Wistar rats were given a single oral administration of glyphosate (suspension in groundnut oil vehicle) at dose levels of 200, 1000 and 5000 mg/kg body weight. Control groups received vehicle only or ethyl methane sulfonate as a positive control. Each week for 10 consecutive weeks males were mated 1:1 to separate groups of untreated virgin females. Each week's paired females were removed after co-housing for 6 d and were sacrificed on the 16th day after pairing and reproductive parameters were measured (pregnancy status, corpora lutea, early and late resorptions, and live implants). One unusual aspect of this study is that mean body weights of all treatment groups were initially statistically higher than the control group mean body weight and this pattern persisted throughout the study. The following effects were observed in the first group of week 1 females mated to high-dose males: reductions in pregnancy rate, decreases in live implants and increases in pre- and post-implantation loss. There were also increases in embryonic resorptions ("small moles") in week 1 females mated to mid-dose males. These effects were attributed to significant acute toxic effects of glyphosate (not dominant lethal effects) exhibited after the treatment in week 1 as evidenced by body weight loss in the mid and high-dose males and clinical signs. Although some

Table 5. Blood erythrocyte micronucleus assays in non-mammalian systems.

Test system	Test material	Maximum dose*	Result	Comment†	Reference
Oreochromis niloticus (fish)	Roundup 69	170 mg/kg i.p. (maximum tolerated)	Equivocal‡		Coutinho do Nascimento & Grisolia (2000)
T. rendalli (fish)	Roundup™ formulation	170 mg/kg (abdominal injection)	Positive		Grisolia (2002)
Carassius auratus (fish)	Roundup™ formulation	15 ppm glyphosate in water (2, 4 and 6 d)	Positive		Cavas & Konen (2007)
Prochilodus lineatus (fish)	Roundup™ formulation	10 mg/L in water (6, 24 and 96 h)	Negative	NC	Cavalcante et al. (2008)
Caiman eggs/hatchlings	Roundup® Full II formulation	1750 µg/egg	Positive		Poletta et al. (2009)
Caiman eggs/hatchlings	Roundup® Full II formulation	Nest sprayed 3% (3 L/100 L water/ha)	Positive		Poletta et al. (2011)
O. cordobae (amphibian) *R. arenarum* (amphibian)	Roundup formulation	100 mg a.i./L 800 mg a.i./L	Equivocal¶ Equivocal§		Bosch et al. (2011)
Corydoras paleatus (fish)	Roundup® formulation	6.67 µg/L in water (3.2 µg/L a.e.) (3, 6 and 9 d)	Negative	PC, NC	de Castilhos Ghisi & Cestari (2012)

*a.e., concentration in glyphosate acid equivalents.; a.i. concentration of active ingredient.
†PC, no concurrent positive control; NC, independent coding of slides for scoring not explicitly indicated for visually scored slides. In some cases coding may have been implied by reference citation.
‡Statistically significant increase in micronucleated erythrocyte frequency only at mid-dose level.
¶Increase in micronucleated erythrocyte frequency not statistically significant for single group surviving treatment; authors appear to conclude increase may have been treatment-related.
§Authors appear to conclude increases in micronucleated erythrocytes were treatment-related. No statistically significant differences were observed among the experimental groups by the analysis of variance. A statistically significant positive correlation between concentration and micronucleated erythrocyte frequency but this analysis apparently omitted the high-dose group.

statistically significant findings in post-implantation loss were sporadically observed in subsequent weeks these were not considered to be treatment-related because they were not consistent with a biologically plausible dose-response or a biologically plausible time course (see post-implantation loss data table in "online supplementary material"). This conclusion was also indicated in an EU monograph report (BBA, 1998–2000). This study appears to be in accordance with the study noted in Williams et al. (2000) indicating that glyphosate is not active as a rodent germ cell mutagen.

Non-mammalian assays

Glyphosate and glyphosate salts

The Williams et al. (2000) review reported negative results for isopropylamine salt of glyphosate in an onion root tip chromosomal aberration assay.

One subsequent published study reported a weak positive result for technical glyphosate in a *Drosophila* wing spot assay (Kaya et al., 2000). Statistically significant positive increases were found only in one of four crosses for small twin spots and not for the two other wing spot categories (large wing spots and twin wing spots). As discussed above, only negative or inconclusive results were observed for crosses that were not subjected to mitotic recombination effects. If the result was actually treatment-related it would only indicate an increase in recombination events and not in somatic mutations.

Glyphosate-based formulations

The Williams et al. (2000) review reported a positive result for a Roundup™-branded GBF for chromosomal aberrations in an onion root tip assay and it was noted that this may have been caused by toxic effects of the GBF surfactant.

Negative results were observed in subsequently published *in vitro* assays for the chromosomal aberration and micronucleus endpoints in *Crepis capillaris* root meristems exposed to a Roundup™-branded GBF at concentrations up to 0.5% a.i. (Dimitrov et al., 2006).

Subsequent to the earlier review a number of publications have reported discordant results for blood erythrocyte micronucleus assays conducted on GBFs in several non-mammalian fish, reptile and amphibian species (Table 5). One publication reported what might arguably be considered as equivocal results for the erythrocyte micronucleus test in *Oreochromis niloticus* (Nile tilapia), administered a test material described as Roundup™ 69 GBF at an upper dose of 170 mg/kg i.p. (Coutinho do Nascimento & Grisolia, 2000). Although there was a statistically significant increase in micronucleated erythrocyte frequency at the mid-dose level, a significant increase was not observed at the high-dose level and considerable variability in frequencies in different groups was noted. Negative results were reported in another fish species (*Prochilodus lineatus*) exposed to 10 mg/L Roundup™-branded GBF for 6, 24 and 96 h (Cavalcante et al., 2008). This concentration was reported to be 75% of a 96-h LC_{50}. Negative results were also reported for the micronucleus endpoint in the fish *Corydoras paleatus* exposed to 6.7 µg/L Roundup™-branded GBF (calculated 3.2 µg/L glyphosate) for 3, 6 and 9 days (de Castilhos Ghisi & Cestari, 2012). Positive results were reported for the erythrocyte micronucleus assay conducted in the fish *T. rendalli* exposed to up to 170 mg/kg body weight i.p. of another Roundup™-branded GBF (Grisolia, 2002). Examination of the micronucleus frequencies in this publication indicated that

the negative control micronucleus frequency was considerably lower than the frequencies for all but one of 21 treatment groups for seven different test materials. This suggests an unusually low control frequency and at least one treatment group had statistically significant increases in MN frequencies for each of the seven test materials. In the absence of historical negative control data and few publications from which to estimate negative control ranges, the possibility that the apparently significant increases were due to a low negative control value that should be considered for this publication. Another publication reported positive erythrocyte micronucleus results in goldfish (*Carassius auratus*) exposed to 5 to 15 ppm glyphosate concentration of a Roundup™-branded GBF for 2 to 6 d (Cavas & Konen, 2007).

The reasons for the discordant results are not clear for the fish erythrocyte micronucleus assays of Roundup™-branded GBFs. Although different species and GBFs were used in different studies there were pairs of studies with positive and negative or equivocal results that used similar treatment conditions (e.g. 170 mg/kg i.p. or 10–15 mg/L in water).

An amphibian erythrocyte micronucleus study reported questionable effects of a Roundup™-branded GBF (Bosch et al., 2011). For one species (*O. cordobae*), toxicity and lethality were observed at exposures to concentrations of 200–800 mg/L a.i. (glyphosate active ingredient) of Roundup™-branded GBF. The surviving 100 mg/L a.i. treatment group had an increase in micronucleated erythrocyte frequency after 5 d but the increase was not statistically significant. A second species (*R. arenarum*) tolerated exposure up to 800 mg/L a.i. Roundup™-branded GBF. No statistically significant differences were found in the experimental groups by the analysis of variance. Although a statistically significant correlation between dose and micronucleated erythrocyte frequency was observed at day 2 of the treatment this analysis apparently omitted the high-dose group which had a mean micronucleus frequency comparable to negative control values. The downturn in dose-response and apparent omission of the high-dose from the statistical analysis is peculiar, because significant toxicity was not reported in this species at the 2-day sampling time. The results reported in this publication do not clearly support a conclusion of a micronucleus effect of a GBF in these species.

Results for an unusual test system of exposed caiman eggs are reported in two publications. In one study, eggs were topically exposed in a laboratory setting to Roundup™ Full II GBF, and erythrocyte micronucleus formation was measured in hatchlings (Poletta et al., 2009). The tested GBF was reported to contain the potassium salt of glyphosate. Statistically significant increases in micronucleated erythrocytes were observed in hatchlings from eggs treated with 500–1750 µg/egg. This system is quite unusual in the species tested and even more so in using an egg application with measurement of effects in hatchlings. Although there is some experience with a hen's egg erythrocyte micronucleus assay using *in ovo* exposure, the erythrocytes were evaluated in embryos only a few days after the treatment (Wolf et al., 2008). In the caiman egg assay reported by Poletta et al. (2009), there was presumably a single topical exposure followed by an egg incubation period of about 10 weeks before hatching. It is difficult to envisage that genotoxic events *in ovo* could produce elevated micronucleated erythrocyte frequencies detectable after 10 weeks, given the number of cell divisions occurring in development of a hatchling, and dilution of any micronucleated cells in a larger population as a result of this.

A second publication by Poletta et al. (2011) described two field experiments evaluating caiman hatched from eggs in artificial nests that were sprayed with Roundup™ Full II GBF. Increases in micronucleated erythrocyte frequency in hatchlings were reported for both experiments. Additional measurements of growth in one experiment showed small but statistically significant differences in total length and snout-vent length in 3-month-old, but not 12-month-old, animals. Alanine aminotransferase and creatine kinase enzyme levels in serum of 3-month-old animals were significantly elevated (>two-fold control values). Alterations in these parameters suggest that the treated groups have some persistent biological differences or toxic effects either as a result of the treatment or some other factor. It is certainly possible that the micronucleus effects in both publications are associated with these persistent biological differences or toxic effects rather than from genotoxic effects induced in the embryos.

There were no regulatory reports of non-mammalian chromosomal effect assays.

In summary, the above *in vivo* micronucleus assays in non-mammalian systems have given discordant results for reasons that cannot be precisely defined. Typically these results would be given lower weight than mammalian systems in terms of prediction of mammalian effects, especially since there is very little experience with these systems in comparison with *in vivo* mammalian chromosomal effect assays, such as the rat or mouse bone marrow chromosomal aberration or erythrocyte micronucleus assays.

DNA damage

In vitro mammalian cell assays

Glyphosate and glyphosate salts

Some positive results for glyphosate for induction of SCE were reported in cultured human and bovine lymphocytes in the earlier review (Williams et al., 2000). These results tended to be weak, inconsistent and with limited evidence for dose–response. A number of limitations were observed for these studies such as the failure to control pH and abnormally low control values. Negative results were reported for technical glyphosate in a *B. subtilis* DNA damage assay and a rat primary hepatocyte unscheduled DNA synthesis (UDS) assay.

Subsequent to the review there is one publication of a positive *in vitro* SCE result in cultured bovine lymphocytes (Table 6; Sivikova & Dianovsky, 2006). It is noteworthy that negative effects for the chromosomal aberration endpoint were reported in this publication.

Positive results for technical glyphosate have been reported for the comet (alkaline single cell gel electrophoresis, alkaline SCGE) endpoint in *in vitro* mammalian cell assays in four publications subsequent to the Williams et al. (2000) review (Table 6). Some general protocol concerns for these studies are

Table 6. DNA damage assays of glyphosate, glyphosate salts and GBFs in *in vitro* and *in vivo* mammalian systems.

Endpoint	Test system	Test material	Maximum dose	Result	Comment*	References
***In vitro* studies glyphosate and glyphosate salts**						
Literature studies						
Comet	GM38 human fibroblasts	glyphosate (technical)	6.5 mM	Positive	MA, PH, NC	Monroy et al. (2005)
	HT1080 human fibrosarcoma	glyphosate (technical)	6.5 mM	Positive	MA, PH, NC	Monroy et al. (2005)
SCE	bovine lymphocytes	glyphosate (62% Isopropylamine salt)	1.12 mM (toxic)	Positive (−S9) Equivocal (+S9)	PH, NC	Sivikova & Dianovsky (2006)
Comet	Hep-2 cells	glyphosate (analytical, 96%)	7.5 mM (limited by toxicity)	Positive	MA, PH?, NC	Manas et al. (2009)
Comet	Human lymphocytes	Glyphosate (technical, 98%)	580 µg/mL (toxic) ≈3.43 mM)	Positive (−S9) Positive (+S9)	NC	Mladinic et al. (2009a)
Comet	TR146 human buccal epithelial	Glyphosate (95%)	2000 mg/L ≈11.8 mM)	Positive	MA, PH, NC	Koller et al. (2012)
Regulatory study						
UDS	Primary rat hepatocyte	Glyphosate (>98%)	111.69 mM	Negative	PH	Rossberger (1994)
***In vitro* studies GBF**						
Literature studies						
SCE	mouse spleen cells	herbazed formulation (84% glyphosate)	50 mM glyphosate‡	Positive	MA, PH, TO, NC	Amer et al. (2006)
Comet	TR146 human buccal epithelial	Roundup™ Ultra Max	200 mg/L glyphosate (≈1.18 mM)	Positive	MA, PH, NC	Koller et al. (2012)
***In vivo* studies GBF**						
Literature studies						
Bone marrow SCE	Mouse	herbazed formulation (84% glyphosate)	200 mg/kg p.o. glyphosate	Positive	NC	Amer et al. (2006)

*MA, Mammalian metabolic activation system not used; PH, no indication of pH or osmolality control; TO, no concurrent measurement of toxicity reported or toxicity not observed for highest dose level; NC, independent coding of slides for scoring not explicitly indicated.
‡Calculated from the stated concentration of 5×10^{-5} M glyphosate/mL.

failure to explicitly indicate the assessment or control of pH or to explicitly indicate the coding of slides for scoring. It is possible that these may be deficiencies or limitations in reporting rather than conduct. Positive Comet results were observed for two mammalian cell lines exposed to glyphosate for 4 h at concentrations of 4.0–6.5 mM (≈0.68–1.10 mg/mL, GM38 cells) and 4.75–6.5 mM (≈0.80–1.10 mg/mL, HT1080 cells) (Monroy et al., 2005). These concentrations are close to the upper limit dose of 10 mM (appropriate for glyphosate) generally recommended for *in vitro* mammalian cell assays in the current OECD guidelines. Positive Comet results were also reported in Hep-2 cells exposed for 4 h to 3.0–7.5 mM (≈0.51–1.27 mg/mL) glyphosate (Manas et al., 2009). This publication reported negative results for the chromosomal aberration endpoint in cultured human lymphocytes exposed to up to 6 mM (≈1.01 mg/mL) glyphosate for 48 h and it should be noted that pH control of the culture medium was reported for the chromosomal aberration endpoint. Positive Comet results have also been reported for cultured human lymphocytes exposed to glyphosate at concentrations of up to 580 μg/mL (≈3.4 mM) for 4 h (Mladinic et al., 2009a). Effects were observed both in the presence and absence of S9. A modification of the Comet assay by employing a human 8-hydroxyguanine DNA-glycosylase (hOGG1) to detect an oxidative damage indicated only statistically significant effects on comet tail length for 580 μg/mL with S9. Measurements of total antioxidant capacity and thiobarbituric acid reactive substances showed statistically significant increases at 580 μg/mL in the presence or absence of S9. Interpretation of the significance of metabolic activation effects is complicated by the observation that several of the endpoints (e.g., comet tail intensity and nuclear abnormalities) tended to show increases in the presence of S9 in negative controls or at the very lowest concentrations of glyphosate (0.5–3.5 μg/mL, ≈2.9–20.7 μM). A reasonable summation of the results in this publication is that comet effects and other effects such as nuclear abnormalities, early apoptosis, necrosis and oxidative damage were consistently observed at 580 μg/mL. Positive Comet effects were also reported in a human epithelial cell line at dose levels up to 2000 mg/L (≈11.8 mM) (Koller et al., 2012). An unusual feature of these results is that statistically significant increases in comet tail intensity were reported as low at 20 mg/L (0.118 mM) with not much dose-response between 40 and 2000 mg/L. These dose levels of glyphosate were observed to produce little or no effects on a cellular integrity marker but statistically significant effects on necrosis and apoptosis markers were observed at 20 mg/L in parallel experiments.

One regulatory study of technical glyphosate was reported for a primary rat hepatocyte UDS assay (Rossberger, 1994; Table 6 and "online supplementary material"). In this study, cultures of hepatocytes were exposed to glyphosate concentrations of 0.02–48.98 mM (≈0.34–8.28 mg/mL) and 0.14–111.69 mM (≈0.19–18.88 mg/mL) for 18 h in two experiments. Radio-labeled and halogen-substituted nucleosides were used to enable replicative and unscheduled DNA synthesis to be identified by density-gradient centrifugation and radioactivity counting. No effects on an unscheduled DNA synthesis were observed in this study in two separate experiments. Measurements of replicative DNA synthesis indicated that cytotoxic concentrations were tested and the maximum concentrations were in any case much higher than recommended for other *in vitro* mammalian cell assays (10 mM for glyphosate). This study is limited by the use of only single cultures per experimental point, although there were two separate experiments. The relatively narrow distribution of repair synthesis values with no dose-response in glyphosate-treated cultures, and the clear increases in repair induced by the positive control, suggest that this study provides reasonable evidence for a lack of induced-DNA repair following the exposure of rat primary hepatocytes to very high concentrations of glyphosate.

Overall there are a number of *in vitro* mammalian cell studies in which glyphosate has been reported to produce positive responses in SCE or Comet assays. Most of these positive responses have occurred at high exposures to glyphosate in the millimolar range. Although lower than the limit dose of 10 mM (appropriate for glyphosate) recommended for several *in vitro* mammalian cell culture assays (OECD 473, 1997, OECD 476, 1997, OECD 487, 2010), there have been some suggestions that lower dose levels may be more appropriate, particularly because of concerns about relevance of positive *in vitro* findings observed at higher dose levels (ICHS2(R1), 2011; Morita et al., 2012; Parry et al., 2010). In addition, many of the studies have functional limitations such as the lack of pH control and no explicit statement regarding the coding of slides for visual scoring.

Concerns over the possibility of effects induced by toxicity have led to several suggestions for experimental and interpretive criteria to distinguish between genotoxic DNA-reactive mechanisms for induction of comet effects and cytotoxic or apoptotic mechanisms. One recommendation for the *in vitro* Comet assay is to limit the toxicity to no more than a 30% reduction in viability compared to controls (Henderson et al., 1998; Storer et al., 1996; Tice et al., 2000). Importantly, dye exclusion measurements of cell membrane integrity, such as those reported in some of the above publications, may significantly underestimate cytotoxicity that could lead to comet effects (Storer et al., 1996). Other recommendations include conducting neutral diffusion experiments to determine if apoptotic processes might be responsible for comet effects (Tice et al., 2000).

In contrast to the SCE and comet endpoints, two independent studies of technical glyphosate in the primary rat hepatocyte UDS assay have both been negative. These results provide evidence that this endpoint is not affected by glyphosate at high concentrations in cell lines with endogenous mammalian metabolic activation capability.

Glyphosate-based formulations

Some positive results for glyphosate or GBFs in the SCE endpoint were reported in cultured human and bovine lymphocytes in the earlier review (Williams et al., 2000). These results tended to be weak, inconsistent and with limited evidence for dose–response.

Subsequent publications of DNA damage assays of GBFs in *in vitro* mammalian cell assays are presented in Table 6. Positive SCE results were observed for the uncharacterized herbazed GBF in mouse spleen cells (Amer et al., 2006). Limitations of this study are in common to those described

above (see the section "*In vitro* mammalian cell assays") for the chromosomal aberration endpoint portion of the study. The magnitudes of the increases in SCE/cell were less than two-fold of the control value which may not be considered biologically significant. Given these limitations, and the fact that the mechanism(s) by which SCE are induced is not understood, these positive findings should be viewed with caution. Koller et al. (2012) reported positive Comet results for human epithelial cells exposed to Roundup™ UltraMax formulation. Statistically significant effects on comet tail intensity were observed from exposure to 20–200 mg/L of glyphosate (≈0.12–1.18 mM) for 20 min.

There were no regulatory DNA damage studies of GBFs in *in vitro* mammalian systems. The Amer et al. (2006) report of a positive result for an uncharacterized GBF in the SCE endpoint agrees with other positive findings for this GBF in this publication but because of the discussed limitations does not add significantly to an evaluation of general genotoxic properties for GBFs. Similarly, the single observation of comet effects for a different GBF in an *in vitro* cellular assay is of limited value for assessing general GBF properties.

In vivo mammalian assays

Glyphosate and glyphosate salts

In the earlier review (Williams et al., 2000), positive results for DNA strand breakage were reported in kidney and liver tissue of mice treated by the i.p. route with glyphosate. The earlier review also noted reports of the absence of DNA adducts in mice treated by the i.p. route with the isopropylamine salt of glyphosate and a possible increase in 8-hydroxydeoxyguanosine (8-OHdG) in DNA of mice treated with technical glyphosate.

No new *in vivo* mammalian studies of DNA damage or DNA-reactivity of glyphosate were encountered in publications since 2000 and there were no regulatory studies of this category.

Glyphosate-based formulations

In the earlier review of Williams et al. (2000), positive results for DNA adducts (^{32}P-postlabeling) and DNA strand breakage were reported for mice treated by the i.p. route with Roundup™ GBF. For a number of reasons these observations were not considered to be clear evidence for DNA-reactive genotoxicity of the Roundup™ GBF.

Only one *in vivo* mammalian DNA damage study of a GBF has since been reported. This publication indicated an increase in SCE frequency in bone marrow cells of mice treated with uncharacterized herbazed GBF (Table 6; Amer et al., 2006). Statistically significant positive effects were only observed at the highest dose level tested (200 mg/kg body weight glyphosate administered p.o.) and were less than two-fold of the control value. As noted above, since the mechanism(s) by which SCEs are induced is not understood, this report for one GBF does not add significantly to an evaluation of general genotoxic potential for GBFs.

In a follow-up to ^{32}P-postlabeling, DNA strand breakage and 8-OHdG studies cited in Williams et al. (2000). Heydens et al. (2008) reported on studies in mice to further investigate toxic effects and 8-OHdG levels associated with the routes, vehicles and dose levels of the earlier studies. The Heydens et al. (2008) publication reported significant GBF-induced liver and kidney toxicity for high i.p. doses but no liver or kidney toxicity for comparable oral doses. Statistically significant increases in 8-OHdG were not observed in the latter study under the same conditions as employed by the earlier study. The DMSO/olive oil vehicle dramatically enhanced the toxicity of GBF administered by the i.p. route and the toxicity was also observed for formulation components without glyphosate. These results indicated that the effects reported in the earlier studies were associated with high liver and kidney toxicity that was primarily due to the non-glyphosate components of the formulation when administered at very high doses via the i.p. route of exposure. The toxicity enhancement by the unusual DMSO/olive oil dosing vehicle further calls into question whether the ^{32}P-postlabeling finding represented effects associated with unusual toxicity rather than being indicative of adducts formed from glyphosate or glyphosate formulation components.

Non-mammalian assays

Glyphosate and glyphosate salts

The Williams et al. (2000) review noted a negative result for glyphosate in the *B. subtilis* H17/M45 *rec* bacterial differential killing assay.

As presented in Table 7, two subsequent publications reported positive Comet results for glyphosate on Tradescantia flowers and nuclei (Alvarez-Moya et al., 2011) and negative Comet results for oyster sperm cells exposed to glyphosate (Akcha et al., 2012). The latter study employed a very low maximum exposure of 5 µg/L (≈0.03 µM).

There was one regulatory study of technical glyphosate (95.68%) in the *B. subtilis* H17/M45 differential DNA damage (*rec*) assay (Table 7 and "online supplementary material"; Akanuma, 1995a). This study employed multiple levels of glyphosate on paper disks (up to 240 µg/disk) and measured zones of inhibition. No differential toxicity was observed indicating a lack of genotoxicity in this assay system. This result is in agreement with the earlier reported negative result for this assay by Williams et al. (2000).

Glyphosate-based formulations

In the earlier review of Williams et al. (2000), positive results were reported for DNA strand breakage in mouse tissues and for the comet endpoint in tadpoles of the frog *Rana catesbiana* exposed to a GBF.

There have been several subsequent publications of results for GBFs in a variety of non-mammalian DNA damage assay systems (Table 7). Two published DNA damage assays *in vitro* reported a positive result for a GBF in the *E. coli* SOS DNA damage test (Raipulis, 2009) and a negative Comet result for oyster sperm cells exposed to a very low (5 µg/L glyphosate, ≈0.03 µM glyphosate) concentration of a Roundup™-branded GBF (Akcha et al., 2012).

Several recent publications report Comet results for GBFs in aquatic species and a reptile (Table 7). Negative Comet

Table 7. DNA damage assays of glyphosate, glyphosate and GBF's in non-mammalian systems.

Endpoint	Test system	Test material	Maximum dose	Result	Comment†	References
***In vitro* studies glyphosate and glyphosate salts**						
Literature studies						
Comet	Tradescantia flowers and nuclei	Glyphosate (technical, 96%)	0.7 mM	Positive	NC	Alvarez-Moya et al. (2011)
Comet	Oyster sperm	Glyphosate	5 µg/L (≈0.03 µM)	Negative	NC	Akcha et al. (2012)
Regulatory study						
Rec assay	*B. subtilis*	Glyphosate 95.68%)	240 µg/disk	Negative		Akanuma (1995a)
***In vitro* studies GBF's**						
Literature studies						
SOS*	*E. coli*	Roundup™ BIO formulation	0.25 µg/sample	Positive		Raipulis (2009)
Sperm Comet	Oyster	Roundup Express®	5 µg/L glyphosate (≈0.03 uM)	Negative	NC	Akcha et al. (2012)
***In vivo* studies GBF's**						
Literature studies						
Comet	Freshwater mussel larvae	Roundup™ formulation	5 mg/L glyphosate	Negative	NC	Conners & Black (2004)
Erythrocyte Comet	*Carassius auratus* (fish)	Roundup™ formulation	15 ppm glyphosate in water (2, 4 and 6 d)	Positive		Cavas & Konen (2007)
Erythrocyte and gill cell Comet	*Prochilodus lineatus* (fish)	Roundup™ formulation	10 mg/L in water (6, 24 and 96 h)	Positive		Cavalcante et al. (2008)
Erythrocyte Comet	Caiman eggs /hatchlings	Roundup® Full II formulation	1750 µg/egg	Positive		Poletta et al. (2009)
Erythrocyte Comet	*Anguilla anguilla* (eel)	Roundup™ formulation	116 µg/L (1 and 3 d)	Positive	NC	Guilherme et al. (2010)
Erythrocyte Comet	Caiman eggs /hatchlings	Roundup® Full II formulation	Nest sprayed 3% (3 L/100 L water/ha)	Positive		Poletta et al. (2011)
Liver and gill cell Comet	*Anguilla anguilla* (eel)	Roundup® Ultra	116 µg/L (1 and 3 d)	Positive	NC	Guilherme et al. (2012)
Erythocyte Comet	*Corydoras paleatus* (fish)	Roundup™ formulation	6.67 µg/L (3, 6 and 9 d)	Positive	NC	de Castilhos Ghisi & Cestari (2012)

*SOS response DNA damage assay.
†NC, independent coding of slides for scoring not indicated for visually scored slides. In some cases, coding may have been implied by reference citation.

results were reported in cells of freshwater mussel larvae exposed to a Roundup™-branded GBF at 5 mg/L (glyphosate a.i.) in water for 24 h (Conners & Black, 2004). This concentration was reported to be one-half of a no observable effect concentration and the 24-h LC_{50} for this GBF was reported to be 18.3 mg/L in parallel experiments. Four publications reported positive Comet results in aquatic vertebrates exposed to Roundup™-branded GBFs in water. These publications have a common feature that Comet results were reported as categories of visually damaged cells. In one publication, increases in nuclei exhibiting comet visual damage effects were observed in erythrocytes and gill cells of the tropical fish *Prochilodus lineatus* exposed to 10 mg/L of a Roundup™-branded GBF in water (Cavalcante et al., 2008). Measurement of erythrocyte micronucleus frequency and nuclear abnormalities did not show statistically significant increases in these endpoints. A second publication reported positive Comet results in erythrocytes of the goldfish, *Carassius auratus*, exposed to up to 15 ppm glyphosate concentration of a Roundup™-branded GBF for 2, 4 or 6 d (Cavas & Konen, 2007). Positive comet results were also reported in erythrocytes and liver and gill cells of the European eel, *Anguilla anguilla*, exposed to 0.058 and 0.116 µg/mL of a Roundup™-branded GBF in water for 1 or 3 d (Guilherme et al., 2010; Guilherme et al., 2012). Positive comet effects were also observed in liver and blood cells isolated from the fish species *Corydoras paleatus* exposed to 0.067 µg/mL of Roundup™-branded GBF for 3, 6 or 9 days (de Castilhos Ghisi & Cestari, 2012). No toxicity data other than the absence of mortality were presented but results were negative for the piscine micronucleus endpoint in this study. Two publications previously discussed reported positive erythrocyte Comet results in caiman hatchlings from eggs exposed to Roundup™ Full II GBF (Poletta et al., 2009; Poletta et al., 2011).

Significance of DNA damage endpoint results

DNA damage endpoints such as SCE or comets are generally regarded as supplementary to the gene mutation and chromosomal damage endpoint categories. They are considered indirect measures of genotoxicity. As mentioned above, the precise mechanism(s) behind SCE induction are not understood. DNA damage as measured by Comet assays does not provide information on the consequences of that damage (e.g. repair, mutation or cell death) and such endpoints, therefore do not directly measure effects on heritable mutations or events closely associated with chromosomal mutations. It is widely recognized that *in vitro* DNA damage endpoints such as the SCE or Comet assay can be induced by cytotoxicity and cell death processes rather than from DNA-reactive mechanisms, as discussed below.

There are numerous examples of SCE positive responses which are unique compared to other genotoxic endpoints, are not concordant with carcinogenicity, or which are induced by oxidant stress (Benigni, 1989; Bradley et al., 1979; Decuyper-Debergh et al., 1989; Djelic et al., 2006; Eckl et al., 1993; Speit, 1986; Tayama and Nakagawa, 1994; Zeiger et al., 1990). These examples indicate that the SCE endpoint, particularly in *in vitro* assays, should not be assumed to indicate DNA-reactive genotoxicity or to have the same weight as genotoxicity assays using other endpoints such as gene mutation or chromosomal effects.

Similarly, there are abundant data supporting the concept that induction of DNA strand breakage or comet effects can be secondary to necrotic or apoptotic processes that do not involve DNA reactivity (Amin et al., 2000; Burlinson et al., 2007; Henderson et al., 1998; Kiffe et al., 2003; Storer et al., 1996; Tice et al., 2000). Several clear specific examples exist of *in vitro* induction of comet effects in mammalian cells by conditions which do not appear to be relevant to genotoxic potential at lower doses or which occur by mechanisms that do not involve direct interaction with DNA. These include the induction of comet effects by apoptosis inducers which inhibit topoisomerases (Boos & Stopper, 2000; Gieseler et al., 1999); cytokine treatment of cultured cells (Delaney et al., 1997); sodium dodecyl sulfate and potassium cyanide (Henderson et al., 1998); colchicine, dl-menthol and sodium acetate (Kiffe et al., 2003); luteolin (Michels et al., 2005); gossypol (Quintana et al., 2000), carbon tetrachloride (Sasaki et al., 1998) and vitamin C (Anderson et al., 1994). Further examples of induction of comet effects of questionable genotoxic biological significance include dietary flavonoids quercetin, myricetin and silymarin (Duthie et al., 1997); hemoglobin (Glei et al., 2006); olive oil extracts (Nousis et al., 2005) and capsaicin (Richeux et al., 1999).

The observation of effects of sodium dodecyl sulfate is particularly interesting because it suggests responses to surfactants, which are typically components of GBFs. As a more specific example, polyoxyethylenealkalylmine (POEA), a surfactant component of some GBFs, has been shown to elicit cytotoxic effects such as perturbation of the mitochondrial membrane and disruption of mitochondrial membrane potential in cultured mammalian cells (Levine et al., 2007). Surfactant effects provide a very plausible mechanism for observations of GBFs inducing DNA damage responses. Such responses would be expected to be associated with cytotoxic exposures and to exhibit a threshold.

Some data suggest better concordance of the Comet assay with other genotoxic endpoints or carcinogenicity in *in vivo* mammalian studies (Brendler-Schwaab et al., 2005; Hartmann et al., 2004; Kirkland & Speit, 2008). However, there are examples of *in vivo* studies of comet effects with questionable significance for genotoxicity because of negative results for other *in vivo* genotoxic endpoints or carcinogenicity assays, or which appear to be due to toxicity. Some examples of non-concordance between comet effects and carcinogenicity include thiabendazole, saccharine, tartrazine and ortho-phenylphenol (Brendler-Schwaab et al., 2005). Discordance between carcinogenicity species specificity and *in vivo* Comet assay results has also been observed (Sekihashi et al., 2002), as well as other positive results for non-carcinogens (Kirkland & Speit, 2008). Another example of questionable *in vivo* genotoxic significance is positive comet effects produced in lymphocytes of exercising humans that were not accompanied by micronucleus induction (Hartmann et al., 1998).

In the context of unique results for DNA damage systems, there are several specific examples of published studies considered in this review containing reported positive results

for DNA damage in contrast to negative or equivocal results for chromosomal effect endpoints for glyphosate and glyphosate salts in mammalian cells in the absence of S9 (Manas et al., 2009; Mladinic et al., 2009a; Sivikova & Dianovsky, 2006) and GBFs in fish species (Cavalcante et al., 2008; de Castilhos Ghisi & Cestari, 2012).

Concurrent assessment of cytotoxicity is recommended in *in vitro* and particularly in *in vivo* studies to assist in the interpretation of positive results. The reported "gold standard" for cytotoxicity in *in vivo* studies is the histopathological evaluation of the tissues or cells being evaluated (Burlinson et al., 2007). Other measures for evaluating cytotoxicity include neutral pH SCGE to detect double strand breaks associated with apoptosis or necrosis and measurement of "hedgehogs" which are nuclei in which almost all of the DNA is in the tail (Tice et al., 2000). The latter are thought to represent dead or dying cells severely damaged by cytotoxicity. While "hedgehogs" are usually not included in tabulation of comet effects, they may be used as an additional measure of toxic effects (Smith et al., 2008).

As noted earlier in the section "*In vitro* mammalian cell assays", several Comet studies of glyphosate and GBFs did not employ concurrent measures of cytotoxic effects that were optimally suitable for the interpretation of a relationship between comet DNA damage and cytotoxicity. Examination of different markers of toxicity in some studies indicated the possibility of association with some markers but not others. The development and routine use of cytotoxicity measurements with maximum relevance to comet effect mechanisms would greatly improve the ability to interpret the significance of this endpoint in both *in vitro* and *in vivo* mammalian systems.

Genotoxicity weight of evidence conclusions

The earlier review of Williams et al. (2000) applied a weight of evidence analysis to the available genotoxicity data. Various weighted components included assay system validation, test system species, relevance of the endpoint to heritable mutation, reproducibility and consistency of effects and dose-response, and relationship of effects to toxicity (Williams et al., 2000). The conclusion of that analysis was that glyphosate and Roundup™-branded GBFs were not mutagenic or genotoxic as a consequence of direct chemical reaction with DNA. This was supported by a strong preponderance of results indicating no effects in *in vivo* mammalian assays for chromosomal effects and consistently negative results in gene mutation assays. Although some DNA damage responses were noted, these were judged likely to be secondary to toxicity rather than DNA reactivity.

Since this earlier review, several genotoxicity studies of glyphosate, glyphosate salt solutions and GBFs have been published. Additionally, a large number of unpublished regulatory studies of glyphosate and GBFs were available for this review. A weight of evidence approach was applied to these data that considers the same factors used by Williams et al. (2000) and which are consistent with recommendations for weight of evidence evaluations for genotoxicity data (EFSA, 2011; ICH S2(R1), 2011; UK COM, 2011; U.S. EPA, 1986; U.S. FDA, 2006). Additional considerations include the robustness of the experimental protocols and more recent elaborated considerations relevant to whether genotoxic effects result from direct interaction with DNA or are secondary to other processes such as cytotoxicity (Kirkland et al., 2007; Thybaud et al., 2007).

In terms of composition, the genotoxicity studies of both glyphosate and glyphosate salts can reasonably be considered together to provide an overall evaluation for the glyphosate molecule. This is especially useful when numerous consistent results are observed for a particular endpoint. The fact that glyphosate is present in all GBFs should be considered in evaluating the genotoxicity of GBFs. It is unlikely that glyphosate or glyphosate salts would contribute novel genotoxic activity (i.e. different from when tested alone) as part of a GBF. Analysis of a weight of evidence of genotoxicity of GBFs should consider the fact that different formulations have different compositions. The weight of evidence, therefore, can allow some conclusions about genotoxicity typical of GBFs but the possibility always exists that individual components could lead to different toxic and genotoxic properties.

Apart from genotoxicity, the data indicate that GBFs are more toxic to the genotoxicity test systems than glyphosate or glyphosate salts, which is consistent with findings in aquatic systems (Folmar et al., 1979; Perkins et al., 2000; Tsui & Chu, 2003). In many cases a reasonable explanation for this difference is that surfactants in GBFs contribute more to toxicity than glyphosate or glyphosate salts *per se*.

Gene mutation is one of the two primary endpoints with direct relevance to heritable mutation and is considered to be one of the key drivers in the carcinogenic process. A large number of regulatory bacterial reverse gene mutation studies provide a very consistent pattern that glyphosate, glyphosate salts and numerous GBFs are negative in well-conducted GLP regulatory assays.

Additionally, there are two regulatory *in vitro* mammalian cell gene mutation (mouse lymphoma *tk* locus) studies which gave negative results for glyphosate. As noted earlier, these mouse lymphoma *tk* locus studies detect large deletions as well as gene mutational events that are also detected in the CHO/HGPRT locus assay. The earlier reported negative CHO/HGRPT result (Williams et al., 2000) and these negative *tk* mutation results support the conclusion that glyphosate and glyphosate salts do not induce gene mutations in mammalian cells.

The second primary endpoint with direct relevance to heritable mutation and the carcinogenic process is chromosomal effects, such as the induction of chromosomal aberrations or micronuclei in cultured mammalian cells. The earlier review (Williams et al., 2000) noted mixed results for three *in vitro* chromosomal aberration assays for glyphosate, but concluded that the most reliable result was the negative assay. No *in vitro* mammalian cell chromosomal aberration reports were noted for GBFs in the Williams et al. review.

A number of *in vitro* chromosomal aberration and micronucleus assay results for glyphosate or glyphosate salts have been subsequently published using bovine or human lymphocytes. Some technical limitations of these assays were discussed earlier and should be considered in the weight attributed to these studies. Both positive and negative results

were reported in these assays. In the absence of exogenous metabolic activation, the majority of studies were negative up to high (mM) dose levels that were toxic or close to toxic levels measured in parallel experiments. Two publications from a laboratory reported an increase in micronucleus frequencies for glyphosate in human lymphocytes in the presence of S9 mix but these studies have several limitations discussed earlier that complicate the interpretation of these effects.

A recent publication reported positive CB MN results for glyphosate in cultured human epithelial cells in the absence of metabolic activation at very low dose levels. The dose levels and exposure time reported as producing effects were much lower than dose levels and exposure times of many published and regulatory *in vitro* mammalian cell genotoxicity studies using different cell types that did not produce either genotoxic or toxic effects. Thus, the results of this study, especially the quantitative aspects, are quite unusual.

Three regulatory chromosomal aberration studies, which used upper dose levels of an estimated 3 mM to around 7 mM, gave negative results in both the presence and absence of S9. These results therefore agree with the majority of negative published data in the absence of S9 and support a weight of evidence that glyphosate is not active in *in vitro* mammalian cell gene mutation or chromosomal aberration assays in the presence of S9.

Overall, the weight of evidence indicates that glyphosate and glyphosate salts do not typically induce chromosomal effects *in vitro* in mammalian cells.

Two publications subsequent to the Williams et al. (2000) review reported positive results for chromosomal aberrations with two different GBFs in two different assay systems. The paucity of studies and study limitations discussed earlier precludes any general conclusion for GBFs for this endpoint. However, as discussed above, the weight of evidence is that glyphosate or glyphosate salts are not clastogenic in mammalian cells, so any positive results with GBFs do not appear to be due to glyphosate.

In vivo mammalian chromosomal effect studies are a particularly important class of studies because they are the pre-eminent core assays for *in vivo* mammalian genotoxicity. The Williams et al. (2000) review noted a predominance of negative results for glyphosate in these types of assays with only one study exhibiting a weak positive result.

Two subsequently published studies of glyphosate or glyphosate salt solutions in mouse bone marrow micronucleus assays gave discordant results with one study reporting positive results. However, eight out of 12 regulatory bone marrow micronucleus studies (seven mouse and one rat study) of glyphosate or glyphosate salts did not yield any statistically significant increases in the frequencies of micronucleated PCEs. Three other studies did give statistical increases in MN PCE frequency for high dose levels but these were judged not to be treatment-related because they were clearly within the historical negative control range. A fourth study exhibited a statistically significant increase in MN PCE only in females. This study had high vehicle control MN PCE frequencies and no historical control data were presented. In addition to the micronucleus results, a mouse bone marrow chromosomal aberration study was also negative. There did not appear to be any data to suggest that, in the minority of studies that exhibited some statistical increases in MN PCE frequencies, the effects might be due to factors such as gender, route of exposure or dose level. The clearly negative results from the vast majority of studies, including a large number of robust regulatory studies conducted in accordance with good laboratory practices, indicate that, on weight of evidence, glyphosate and glyphosate salts are not genotoxic in rodent bone marrow micronucleus or chromosomal aberration studies.

A preponderance (4/5) of mouse bone marrow micronucleus assays on GBFs were indicated as negative in the earlier Williams et al. (2000) review. Mixed results were observed in subsequent published rodent bone marrow micronucleus or chromosomal aberration studies with a majority (4/6) being negative including 3/4 studies of Roundup™-branded GBFs. One rabbit drinking water study of a Roundup™-branded GBF was positive but there were some significant limitations of this study, and this is an unusual test model with little or no background data. Another GBF study reported positive results in spermatocytes with extended oral or i.p. treatments. No clear explanation exists for the discordant published mouse bone marrow results such as unique routes or dramatically different maximum dose levels.

The majority of regulatory rodent bone marrow micronucleus studies (11 mouse and one rat study) of various GBFs gave clearly negative results and the two that had statistical increases were also considered negative because the increases were well within historical control values.

The large number of negative regulatory studies, in combination with a majority of negative published studies, indicate that GBFs are generally negative for this important *in vivo* endpoint. The preponderance of negative results for GBFs is also consistent with a weight of evidence that glyphosate or glyphosate salt solutions are negative for chromosomal effects and suggests that formulation surfactant components are also negative for chromosomal effects *in vivo*.

The micronucleus test detects aneugenic as well as clastogenic (chromosomal breakage) events. The negative results for the large number of *in vivo* rodent micronucleus studies therefore support the conclusion that glyphosate, glyphosate salts and GBFs do not induce aneuploidy.

In addition to the rodent bone marrow studies, one regulatory rat dominant lethal study of glyphosate, albeit with some limitations, appears to confirm the earlier negative result for this type of assay, and reinforces the conclusion that glyphosate is not genotoxic for mammalian germ cells.

Although generally consistent negative results were observed for rodent micronucleus or chromosomal aberration assays of GBFs, discordant results were observed in *in vivo* erythrocyte micronucleus studies of fish, amphibians and reptiles. In addition to some technical limitations there is considerably less experience with these assay systems, and consequently these should have less influence in evaluating overall weight of evidence for chromosomal effects.

In general, induction of DNA damage is considered supplementary to induction of gene mutations and chromosomal effects because it does not directly measure heritable events or effects closely associated with heritable events. Regulatory genotoxicity testing focuses on gene mutation and

chromosomal effects for initial *in vitro* core testing (Cimino, 2006; Eastmond et al., 2009; EFSA, 2011; ICHS2(R1), 2011; UK COM, 2011).

The Williams et al. (2000) review noted negative DNA damage results for technical glyphosate in the *B. subtilis rec* assay and the primary hepatocyte UDS assay, but noted positive or equivocal results for SCE assays *in vitro* in human or bovine lymphocytes. The negative results for the *B. subtilis rec* and primary hepatocyte UDS assays have been confirmed in subsequent regulatory studies. The UDS result provides information on the lack of *in vitro* genotoxic activity when mammalian metabolic activation other than S9 is employed.

Subsequent literature publications indicated several positive responses for *in vitro* mammalian DNA damage endpoint assays of glyphosate or glyphosate salts. These include an SCE response in bovine lymphocytes and four positive Comet results in cultured mammalian cell lines or human lymphocytes. The positive Comet results were observed in the absence of mammalian metabolic activation and generally at concentrations in the mM range but one publication found positive results at much lower dose levels in human epithelial cells. As noted earlier, observations of differential responses in Comet and chromosomal aberration assays for some of these studies provide some support for the conclusion that the SCE or Comet responses observed may not be predictive of effects on other more relevant endpoints.

The Williams et al. (2000) review noted some equivocal or positive Roundup™-branded GBF results for the SCE endpoint in human lymphocytes and reports of DNA strand breakage in mouse tissues and induction of comets in tadpoles. An observation of mouse liver DNA adducts for a GBF were considered to be of questionable significance. Subsequent literature results for DNA damage in mammalian systems included induction of SCE in cultured mammalian cells and in mouse bone marrow for the uncharacterized herbazed formulation and induction of comets in cultured mammalian cells with a Roundup™ UltraMax formulation. There were a number of Comet assay reports for GBFs in a variety of aquatic organisms with a preponderance of positive results.

The fact that DNA damage is usually only seen at high, toxic concentrations *in vitro* (e.g. in the 1–10 mM concentration range) or *in vivo* where tissue damage might be induced, suggests that cytotoxic effects rather than DNA interaction may be responsible for the DNA damage reported for glyphosate, glyphosate salts and GBFs. In many Comet assay publications parallel data on toxic effects most directly relevant to comet mechanisms are lacking, and, in addition, many of the positive DNA damage results have been observed for GBFs in non-standard test systems. It is hoped that clarification of the mechanism and significance of comet effects can be improved by the more routine use of relevant markers such as quantitation of double-strand breaks and hedgehogs and histopathology, as appropriate, for *in vivo* studies. Studies with protocols for specifically identifying surfactant effects would also be useful in clarifying the significance of DNA damage effects of GBFs. However, it seems reasonably clear that GBFs are more toxic than the a.i. and a reasonable conclusion is that consistency of observations of DNA damage, particularly comets, with GBFs might be secondary to the toxicity of GBF surfactants.

As discussed extensively in the section "DNA damage" there are both general and specific reasons to consider DNA damage assays as subordinate in a weight of evidence for genotoxic risk, especially when they may arise from mechanisms secondary to toxicity. Whatever the precise causes of these DNA damage effects, they do not translate into gene mutations or chromosomal damage as demonstrated by the large preponderance of negative results for glyphosate, glyphosate salts and GBFs in well-conducted bacterial reversion and *in vivo* rodent bone marrow micronucleus assays.

In addition to considering the results relevant to genotoxicity hazard assessment, an important additional perspective on risk can be provided by comparing levels used in experimental studies with expected human levels. For example, estimated margins of exposure between the *in vivo* genotoxicity test systems (e.g. 1000 mg/kg body weight exposure) and calculated systemic doses from an exposure study of farmers (Acquavella et al., 2004; 0.004 mg/kg maximum systemic exposure; 0.0001 mg/kg geometric mean systemic exposure) are in the range of 250 000 for maximum systemic exposure and 10 million for geometric mean systemic exposure. The margins of exposure compared to *in vitro* mammalian cell exposures are also quite large. Assuming uniform distribution, the estimated systemic concentration of glyphosate from the Acquavella et al. (2004) farmer biomonitoring study would be of the order of 24 nM for the maximum and 0.59 nM for the geometric mean exposure. A typical maximum *in vitro* mammalian exposure of 5 mM represents margins of exposure of 208 000 for the maximum farmer systemic exposure and 8.5 million for the geometric mean farmer systemic exposure. Similarly, exposure levels evaluated in several published DNA damage and micronucleus assays in non-mammalian species were conducted at much higher glyphosate concentrations than anticipated under typical environmental conditions. Relevant environmental concentrations representing biologically available glyphosate are not equivalent to application rates. Sorption to soil and sediment occurs following glyphosate applications, significantly diminishing or eliminating glyphosate and POEA surfactant bioavailability to environmental species (Giesy, 2000).

This evaluation of the large volume of genotoxicity data available presents a convincing weight of evidence supporting the lack of genotoxic potential for both glyphosate and typical GBFs in core gene mutation and chromosomal effect endpoints. Given this conclusion, and for other reasons discussed, the observation of DNA damage effects seems likely to be secondary to cytotoxic effects. The lack of genotoxic hazard potential evidenced by core gene mutation and chromosomal effect studies, coupled with the very low human and environmental species systemic exposure potential discussed above, indicate that glyphosate and typical GBFs present negligible genotoxicity risk.

Acknowledgements

The authors would like to thank the following individuals for their contributions to this work by providing regulatory studies and their thoughtful review of the

manuscript: David Saltmiras (Monsanto Company), Christian Strupp (Feinchemie Schwebda GmbH), Terri Spanogle (Cheminova A/S), Jürgen Wenzel (HELM AG), Andrew Bond (Nufarm Limited), Sylvain Gautier (Arysta LifeScience Corporation), Simon Hill (Syngenta AG), Ganesh Shetgaonkar and B.M. Ravikumar (Excel Crop Care Ltd.). We would also like to acknowledge David Saltmiras for his invaluable service in providing coordination with individual companies and the Glyphosate Task Force.

Declaration of interest

Larry Kier and David Kirkland were paid consultants of the Glyphosate Task Force for the preparation of this review. The Glyphosate Task Force is a consortium of 25 European glyphosate registrants, listed on http://www.glyphosatetask-force.org/. Larry Kier is also a past employee of Monsanto Company. Monsanto Company was the original producer and marketer of glyphosate formulations. The authors had sole responsibility for the writing and content of the paper and the interpretations and opinions expressed in the paper are those of the authors and may not necessarily be those of the member companies of the Glyphosate Task Force.

References

Aaron CS, Bolcsfoldi G, Glatt HR, et al. (1994). Mammalian cell gene mutation assays working group report. Mutat Res, 312, 235–9.

Acquavella JF, Alexander BH, Mandel JS, et al. (2004). Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. Environ Health Persp, 112, 321–6.

Akanuma M. (1995a). HR-001: DNA Repair Test (Rec-Assay). Unpublished Regulatory Study. Report Identification Number: IET 94-0141.

Akanuma M. (1995b). HR-001 reverse mutation test. Unpublished Regulatory Study. Report Identification Number: IET 94-0142.

Akcha F, Spagnol C, Rouxel J. (2012). Genotoxicity of diuron and glyphosate in oyster spermatozoa and embryos. Aquat Toxicol, 106–107, 104–13.

Alvarez-Moya C, Silva MR, Arambula AMV, et al. (2011). Evaluation of genetic damage induced by glyphosate isopropylamine salt using Tradescantia bioassays. Genet Mol Biol, 34, 127–30.

Amer SM, Aly FAE, Farghaly AA, Ibrahim AAE. (2006). In vitro and in vivo evaluation of the genotoxicity of the herbicide glyphosate in mice. Bull Nat Res Centre (Egypt), 31, 427–46.

Amin F, Bowen ID, Szegedi Z, et al. (2000). Apoptotic and non-apoptotic modes of programmed cell death in MCF-7 human breast carcinoma cells. Cell Biol Int, 24, 253–60.

Anadon A, Martinez-Larranaga MR, Martinez MA, et al. (2009). Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats. Toxicol Lett, 190, 91–5.

Anderson D, Yu TW, Phillips BJ, Schmezer P. (1994). The effect of various antioxidants and other modifying agents on oxygen-radical-generated DNA damage in human lymphocytes in the COMET assay. Mutat Res, 307, 261–71.

BBA (Federal Biological Center for Agriculture and Forestry – Germany). (1998–2000). Monograph on the active substance glyphosate and its IPA-, Na- and NH4-salts. Annex to the European Commission report for the active substance glyphosate.

Benigni R. (1989). Analysis of the National Toxicology Program data on in vitro genetic toxicity tests using multivariate statistical methods. Mutagenesis, 4, 412–19.

Boos G, Stopper H. (2000). Genotoxicity of several clinically used topoisomerase II inhibitors. Toxicol Lett, 116, 7–16.

Bosch B, Manas F, Gorla N, Aiassa D. (2011). Micronucleus test in post metamorphic *Odontophrynus cordobae* and *Rhinella arenarum* (Amphibia: Anura) for environmental monitoring. J Tox Env Health Sci, 3, 155–63.

Bradley MO, Hsu IC, Harris CC. (1979). Relationship between sister chromatid exchange and mutagenicity, toxicity and DNA damage. Nature, 282, 318–20.

Brendler-Schwaab S, Hartmann A, Pfuhler S, Speit G. (2005). The in vivo comet assay: use and status in genotoxicity testing. Mutagenesis, 20, 245–54.

Brewster DW, Warren J, Hopkins 2nd WE. (1991). Metabolism of glyphosate in Sprague–Dawley rats: tissue distribution, identification, and quantitation of glyphosate-derived materials following a single oral dose. Fundam Appl Toxicol, 17, 43–51.

Burlinson B, Tice RR, Speit G, et al. (2007). Fourth International Workshop on Genotoxicity Testing: Results of the in vivo comet assay workgroup. Mutat Res, 627, 31–5.

Callander RD. (1996). Glyphosate acid: an evaluation of mutagenic potential using *S. Typhimurium* and *E. Coli*. Unpublished Regulatory Study. Report Identification Number: CTL/P/4874.

Callander RD. (1999). Potassium salt of glyphosate: bacterial mutation assay in *S. Typhimurium* and *E. Coli*. Unpublished Regulatory Study. Report Identification Number: CTL/P/6184.

Camolesi MR. (2009). [Glyphosate 480 g/l liquid formulation] Bacterial Reverse Mutation Test (Ames Test). Unpublished Regulatory Study. Report Identification Number: RL8563/2008 6.0AM-B.

Camolesi MR. (2010). MON 77280 Bacterial Reverse Mutation Test (Ames Test). Unpublished Regulatory Study. Report Identification Number: XX-2010-501.

Catoyra JM. (2009). [Reverse Mutation Assay of Roundup Full II M in *Salmonella typhimurium*]. Unpublished Regulatory Study. Report Identification Number: Study Number XX-2011-0622.

Cavalcante DG, Martinez CB, Sofia SH. (2008). Genotoxic effects of Roundup on the fish Prochilodus lineatus. Mutat Res, 655, 41–6.

Cavas T, Konen S. (2007). Detection of cytogenetic and DNA damage in peripheral erythrocytes of goldfish (*Carassius auratus*) exposed to a glyphosate formulation using the micronucleus test and the comet assay. Mutagenesis, 22, 263–8.

Chruscielska K, Graffstein B, Szarapinska-Kwaszewska J, et al. (2000). Glyphosate evaluation of chronic activity and possible far-reaching effects. Part 2. Studies on mutagenic activity. Pestcydy, 2000, 21–5.

Cifone MA, Myhr B, Eiche A, Bolcsfoldi G. (1987). Effect of pH shifts on the mutant frequency at the thymidine kinase locus in mouse lymphoma L5178Y TK+/− cells. Mutat Res, 189, 39–46.

Cimino MC. (2006). Comparative overview of current international strategies and guidelines for genetic toxicology testing for regulatory purposes. Environ Mol Mutagen, 47, 362–90.

Clay P. (1996). Glyphosate acid: L5178Y TK+/− mouse lymphoma gene mutation assay. Unpublished Regulatory Study. Report Identification Number: CTL/P/4991.

Conners DE, Black MC. (2004). Evaluation of lethality and genotoxicity in the freshwater mussel *Utterbackia imbecillis* (Bivalvia: Unionidae) exposed singly and in combination to chemicals used in lawn care. Arch Environ Contam Toxicol, 46, 362–71.

Costa KC. (2008). Evaluation of the mutagenic potential of GLYPHOSATE TECHNICAL by micronucleus assay in mice. Unpublished Regulatory Study. Report Identification Number: 3996.402.395.07.

Coutinho do Nascimento A, Grisolia C. (2000). Comparative analysis between micronuclei tests in mice and in peripheral erythrocytes of *Oreochromis niloticus* in evaluation of mutagenic potential of the agrotoxins deltamethrin, dicofol, glyphosate, and imazapyr. Pesticides: R Ecotoxicol E Meio Ambiente, Curitiba, 10, 41–8.

de Castilhos Ghisi N, Cestari, MM. (2012). Genotoxic effects of the herbicide Roundup® in the fish *Corydoras paleatus* (Jenyns 1842) after short-term, environmentally low concentration exposure. Environ Monit Assess. doi: 10.1007/s10661-012-2783-x.

Decuyper-Debergh D, Piette J, Laurent C, van de Vorst A. (1989). Cytotoxic and genotoxic effects of extracellular generated singlet oxygen in human lymphocytes in vitro. Mutat Res, 225, 11–14.

Delaney CA, Pavlovic D, Hoorens A, et al. (1997). Cytokines induce deoxyribonucleic acid strand breaks and apoptosis in human pancreatic islet cells. Endocrinology, 138, 2610–14.

Dimitrov BD, Gadeva PG, Benova DK, Bineva MV. (2006). Comparative genotoxicity of the herbicides Roundup, Stomp and Reglone in plant and mammalian test systems. Mutagenesis, 21, 375–82.

Djelic N, Spremo-Potparevic B, Bajic V, Djelic D. (2006). Sister chromatid exchange and micronuclei in human peripheral blood lymphocytes treated with thyroxine in vitro. Mutat Res, 604, 1–7.

Durward R. (2006). Glyphosate technical: micronucleus test in the mouse. Unpublished Regulatory Study. Report Identification Number: 2060/014.

Duthie SJ, Johnson W, Dobson VL. (1997). The effect of dietary flavonoids on DNA damage (strand breaks and oxidised pyrimidines) and growth in human cells. Mutat Res, 390, 141–51.

Eastmond DA, Hartwig A, Anderson D, et al. (2009). Mutagenicity testing for chemical risk assessment: update of the WHO/IPCS Harmonized Scheme. Mutagenesis, 24, 341–9.

Eckl PM, Ortner A, Esterbauer H. (1993). Genotoxic properties of 4-hydroxyalkenals and analogous aldehydes. Mutat Res, 290, 183–92.

EFSA. (2011). Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment. EFSA Scientific Committee. EFSA J, 9, 2379.

Erexson GL. (2003a). In vivo mouse micronucleus assay with MON 78239. Unpublished Regulatory Study. Report Identification Number: CV-2002-187.

Erexson GL. (2003b). In vivo mouse micronucleus assay with Mon 78634. Unpublished Regulatory Study. Report Identification Number: CV-2002-189.

Erexson GL. (2006). In vivo mouse bone marrow micronucleus assay. Unpublished Regulatory Study. Report Identification Number: CV-2005-120.

Flugge C. (2009a). Mutagenicity study of glyphosate TC in the *Salmonella Typhimurium* reverse mutation assay (in vitro). Unpublished Regulatory Study. Report Identification Number: 23916.

Flugge C. (2009b). Micronucleus test of glyphosate TC in bone marrow cells of the CD rat by oral administration. Unpublished Regulatory Study. Report Identification Number: 23917.

Flugge C. (2010a). Mutagenicity study of trop M (glyphosate 480) in the *Salmonella Typhimurium* reverse mutation assay (in vitro). Unpublished Regulatory Study. Report Identification Number: 24753.

Flugge C. (2010b). Mutagenicity study of glyphosate TC in the *Salmonella Typhimurium* reverse mutation assay (in vitro). Unpublished Regulatory Study. Report Identification Number: 24880.

Flugge C. (2010c). Micronucleus test of trop M (glyphosate 480) in bone marrow cells of the NMRI mouse by oral administration. Unpublished Regulatory Study. Report Identification Number: 24754.

Flugge C. (2010d). Mutagenicity study of [glyphosate 757 g/kg granular formulation] in the *Salmonella Typhimurium* reverse mutation assay (in vitro). Unpublished Regulatory Study. Report Identification Number: 25631.

Flugge C. (2010e). Micronucleus test of [glyphosate 757 g/kg granular formulation] in bone marrow cells of the CD rat by oral administration. Unpublished Regulatory Study. Report Identification Number: 25632.

Folmar L, Sanders H, Julin A. (1979). Toxicity of the herbicide glyphosate and several of its formulations to fish and aquatic invertebrates. Arch Environ Contam Toxicol, 8, 269–78.

Fox V. (1998). Glyphosate acid: in vitro cytogenetic assay in human lymphocytes. Unpublished Regulatory Study. Report Identification Number: CTL/P/6050.

Fox V, Mackay JM. (1996). Glyphosate acid: mouse bone marrow micronucleus test. Unpublished Regulatory Study. Report Identification Number: SM0796.

Gava MA. (2000). Evaluation of the mutagenic potential of the test substance GLIFOSTO IPA TECNICO NUFARM by micronucleus assay in mice. Unpublished Regulatory Study. Report Identification Number: RF-G12.022/00.

Gieseler F, Bauer E, Nuessler V, et al. (1999). Molecular effects of topoisomerase II inhibitors in AML cell lines: correlation of apoptosis with topoisomerase II activity but not with DNA damage. Leukemia, 13, 1859–63.

Giesy JP, Dobson S, Solomon KR. (2000). Ecotoxicological risk assessment for Roundup® Herbicide. Rev Environ Contam Toxicol, 167, 35–120.

Glei M, Klenow S, Sauer J, et al. (2006). Hemoglobin and hemin induce DNA damage in human colon tumor cells HT29 clone 19A and in primary human colonocytes. Mutat Res, 594, 162–71.

Gohre K, Casida JE, Ruzo LO. (1987). N-Oxidation and cleavage of the amino acid derived herbicide glyphosate and anilino acid of the insecticide fluvalinate. J Agric Food Chem, 35, 386–92.

Grisolia CK. (2002). A comparison between mouse and fish micronucleus test using cyclophosphamide, mitomycin C and various pesticides. Mutat Res, 518, 145–50.

Guilherme S, Gaivao I, Santos MA, Pacheco M. (2010). European eel (*Anguilla anguilla*) genotoxic and pro-oxidant responses following short-term exposure to Roundup – a glyphosate-based herbicide. Mutagenesis, 25, 523–30.

Guilherme S, Gaivao I, Santos MA, Pacheco M. (2012). DNA damage in fish (*Anguilla anguilla*) exposed to a glyphosate-based herbicide – elucidation of organ-specificity and the role of oxidative stress. Mutat Res, 743, 1–9.

Hartmann A, Pfuhler S, Dennog C, et al. (1998). Exercise-induced DNA effects in human leukocytes are not accompanied by increased formation of 8-hydroxy-2'-deoxyguanosine or induction of micronuclei. Free Radic Biol Med, 24, 245–51.

Hartmann A, Schumacher M, Plappert-Helbig U, et al. (2004). Use of the alkaline in vivo Comet assay for mechanistic genotoxicity investigations. Mutagenesis, 19, 51–9.

Helal A, Moussa H. (2005). Chromosomal aberrations induced by glyphosate isopropylamine herbicide and trials for diminuting its toxicity using some chemical inactivators and antioxidant. Vet Med J Giza, 53, 169–87.

Henderson L, Wolfreys A, Fedyk J, et al. (1998). The ability of the Comet assay to discriminate between genotoxins and cytotoxins. Mutagenesis, 13, 89–94.

Heydens WF, Healy CE, Hotz KJ, et al. (2008). Genotoxic potential of glyphosate formulations: mode-of-action investigations. J Agric Food Chem, 56, 1517–23.

Holeckova B. (2006). Evaluation of the in vitro effect of glyphosate-based herbicide on boving lymphocytes using chromosome painting. Bull Vet Inst Pulawy, 50, 533–6.

Honarvar N. (2005). Micronucleus assay in bone marrow cells of the mouse with glyphosate technical. Unpublished Regulatory Study. Report Identification Number: 872000.

Honarvar N. (2008). Glyphosate technical – micronucleus assay in bone marrow cells of the mouse. Unpublished Regulatory Study. Report Identification Number: 1158500.

ICH S2(R1). (2011). Guidance on genotoxicitytesting and data interpretation for pharmaceuticals intended for human use. International Conferenece on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S2_R1/Step4/S2R1_Step4.pdf [last accessed 27 Aug 2012].

Jensen JC. (1991a). Mutagenicity test: Ames *Salmonella* assay with glyphosate, batch 206-JaK-25-1. Unpublished Regulatory Study. Report Identification Number: 12323.

Jensen JC. (1991b). Mutagenicity test: in vitro mammalian cell gene mutation test with glyphosate, batch 206-JaK-25-1. Unpublished Regulatory Study. Report Identification Number: 12325.

Jensen JC. (1991c). Mutagenicity test: micronucleus test with glyphosate, batch 206-JaK-25-1. Unpublished Regulatory Study. Report Identification Number: 12324.

Jones E. (1999). Potassium salt of glyphosate: mouse bone marrow micronucleus test. Unpublished Regulatory Study. Report Identification Number: CTL/P/6242.

Kaya B, Creus A, Yanikoglu A, et al. (2000). Use of the *Drosophila* wing spot test in the genotoxicity testing of different herbicides. Environ Mol Mutagen, 36, 40–6.

Kier LD, Brusick DJ, Auletta AE, et al. (1986). The *Salmonella typhimurium*/mammalian microsomal assay. A report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutation Res, 168, 69–240.

Kiffe M, Christen P, Arni P. (2003). Characterization of cytotoxic and genotoxic effects of different compounds in CHO K5 cells with the comet assay (single-cell gel electrophoresis assay). Mutat Res, 537, 151–68.

Kirkland DJ, Aardema M, Banduhn N, et al. (2007). In vitro approaches to develop weight of evidence (WoE) and mode of action (MoA) discussions with positive in vitro genotoxicity results. Mutagenesis, 22, 161–75.

Kirkland D, Speit G. (2008). Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens III. Appropriate follow-up testing in vivo. Mutat Res, 654, 114–32.

Kirsch-Volders M, Sofuni T, Aardema M, et al. (2003). Report from the *in vitro* micronucleus assay working group. Mutation Res, 540, 153–63.

Kocsis JJ, Harkaway S, Santoyo MC, Snyder R. (1968). Dimethyl sulfoxide: interactions with aromatic hydrocarbons. Science, 160, 427–8.

Koller VJ, Furhacker M, Nersesyan A, et al. (2012). Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells. Arch Toxicol, 86, 805–13.

Levine SL, Han Z, Liu J, et al. (2007). Disrupting mitochondrial function with surfactants inhibits MA-10 Leydig cell steroidogenesis. Cell Biol Toxicol, 23, 385–400.

Lope N. (2008). Reverse mutation assay of Roundup Ultramax (MON 79672) in *Salmonella typhimurium*. Unpublished Regulatory Study. Report Identification Number: XX-2011-0621.

Manas F, Peralta L, Raviolo J, et al. (2009). Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests. Environ Toxicol Phar, 28, 37–41.

Marques MFC. (1999). A micronucleus study in mice for glifosate tecnico nufarm. Unpublished Regulatory Study. Report Identification Number: RF-G12.79/99.

Matsumoto K. (1995). HR-001: in vitro cytogenetics test. Unpublished Regulatory Study. Report Identification Number: IET 94-0143.

Mecchi MS. (2003a). *Salmonella–Escherichia Coli*/mammalian–microsome reverse mutation assay with a confirmatory assay. Unpublished Regulatory Study. Report Identification Number: CV-2002-186.

Mecchi MS. (2003b). *Salmonella–Escherichia Coli*/mammalian–microsome reverse mutation assay with a confirmatory assay. Unpublished Regulatory Study. Report Identification Number: CV-2002-188.

Mecchi MS. (2008a). Bacterial reverse mutation assay with a confirmatory assay. Unpublished Regulatory Study. Report Identification Number: CV-08-030.

Mecchi MS. (2008b). Bacterial reverse mutation assay with a confirmatory assay. Unpublished Regulatory Study. Report Identification Number: CV-08-242.

Mecchi MS. (2008c). *Salmonella–Escherichia Coli*/mammalian–microsome reverse mutation asay with a confirmatory assay with MON 76171. Unpublished Regulatory Study. Report Identification Number: CV-2007-102.

Mecchi MS. (2009a). *Salmonella–Escherichia coli*/mammalian–microsome reverse mutation assay with a confirmatory assay. Unpublished Regulatory Study. Report Identification Number: CV-2007-082.

Mecchi MS. (2009b). *Salmonella–Escherichia coli*/mammalian–microsome reverse mutation assay with a confirmatory assay with MON 76138. Unpublished Regulatory Study. Report Identification Number: CV-2007-094.

Michels G, Watjen W, Niering P, et al. (2005). Pro-apoptotic effects of the flavonoid luteolin in rat H4IIE cells. Toxicology, 206, 337–48.

Miyaji CK. (2008). Evaluation of the mutagenic potential of the test substance glyphosate technical by reverse mutation assay in *Salmonella Typhimurium* (Ames test). Unpublished Regulatory Study. Report Identification Number: 3996.401.392.07.

Mladinic M, Berend S, Vrdoljak AL, et al. (2009a). Evaluation of genome damage and its relation to oxidative stress induced by glyphosate in human lymphocytes in vitro. Environ Mol Mutagen, 50, 800–7.

Mladinic M, Perkovic P, Zeljezic D. (2009b). Characterization of chromatin instabilities induced by glyphosate, terbuthylazine and carbofuran using cytome FISH assay. Toxicol Lett, 189, 130–7.

Monroy CM, Cortes AC, Sicard DM, de Restrepo HG. (2005). Cytotoxicity and genotoxicity of human cells exposed in vitro to glyphosate. Biomedica, 25, 335–45.

Morita T, Watanabe Y, Takeda K, Okumura K. (1989). Effects of pH in the in vitro chromosomal aberration test. Mutat Res, 225, 55–60.

Morita T, Honma M, Morikawa K. (2012). Effect of reducing the top concentration used in the in vitro chromosomal aberration test in CHL cells on the evaluation of industricl chemical genotoxicity. Mutat Res, 741, 52–6.

Negro Silva LF. (2009). A17035A – mammalian erythrocyte micronucleus test. Unpublished Regulatory Study. Report Identification Number: RL7459/2008 – 14.0MN-B.

Negro Silva LF. (2011). Glyphosate SL (A13013Z) – mammalian erythrocyte micronucleus test. Unpublished Regulatory Study. Report Identification Number: RL69575MN-B.

Nousis, L, Doulias PT, Aligiannis N, et al (2005). DNA protecting and genotoxic effects of olive oil related components in cells exposed to hydrogen peroxide. Free Rad Res, 39, 987–95.

OECD 471. (1983). Genetic toxicology: *Salmonella typhimurium* reverse mutation assay. OECD Guidelines for Testing of Chemicals. Available from: http://www.oecd.org/env/chemicalsafetyandbiosafety/testingofchemicals/45125466.pdf [last accessed 27 Aug 2012].

OECD 471. (1997). Bacterial reverse mutation test. OECD guideline for testing of chemicals. Available from: http://www.oecd.org/chemicalsafety/assessmentofchemicals/1948418.pdf [last accessed 27 Aug 2012].

OECD 472. (1983). Genetic toxicology: *Escherichia coli* reverse mutation assay. Guideline for testing of chemicals. Available from: http://www.oecd.org/env/chemicalsafetyandbiosafety/testingofchemicals/45125467.pdf [last accessed 27 Aug 2012].

OECD 473. (1983). Genetic toxicology: in vitro mammalian cytogenetic test. OECD guideline for the testing of chemicals. Available from: http://www.oecd.org/env/ehs/testing/45125550.pdf [last accessed 27 Aug 2012].

OECD 473. (1997). In vitro mammalian chromosome aberration test. OECD guideline for the testing of chemicals. Available from: http://www.oecd-ilibrary.org/environment/test-no-473-in-vitro-mammalian-chromosome-aberration-test_9789264071261-en [last accessed 27 Aug 2012].

OECD 474. (1983). Genetic toxicology: micronucleus test. OECD guideline for testing of chemicals. Available from: http://www.oecd.org/env/ehs/testing/45125573.pdf [last accessed 27 Aug 2012].

OECD 474. (1997). Mammalian erythrocyte micronucleus test. OECD guideline for the testing of chemicals. Available from: http://www.oecd.org/chemicalsafety/assessmentofchemicals/1948442.pdf [last accessed 27 Aug 2012].

OECD 475. (1984). Genetic toxicology: in vivo mammalian bone marrow cytogenetic test – chromosomal analysis. OECD guideline for testing of chemicals. Available from: http://www.oecd.org/env/ehs/testing/45125582.pdf [last accessed 27 Aug 2012].

OECD 475. (1997). Mammalian bone marrow chromosome aberration test. OECD guideline for the testing of chemicals. Available from: http://www.oecd.org/chemicalsafety/assessmentofchemicals/1948450.pdf [last accessed 27 Aug 2012].

OECD 476. (1984). Genetic toxicology: in vitro mammalian cell gene mutation tests. OECD guideline for testing of chemicals. Available from: http://www.oecd.org/chemicalsafety/testing/45125600.pdf [last accessed 27 Aug 2012].

OECD 476. (1997). In vitro mammalian cell gene mutation test. OECD guideline for the testing of chemicals. Available from: http://www.oecd.org/chemicalsafety/assessmentofchemicals/1948426.pdf [last accessed 27 Aug 2012].

OECD 478. (1984). Genetic toxicology: rodent dominant lethal test. oecd guideline for testing of chemicals. Available from: http://www.oecd.org/env/chemicalsafetyandbiosafety/testingofchemicals/45125644.pdf [last accessed 27 Aug 2012].

OECD 487. (2010). In vitro mammalian cell micronucleus test. OECD guideline for the testing of chemicals. Available from: http://www.oecd-ilibrary.org/environment/test-no-487-in-vitro-mammalian-cell-micronucleus-test_9789264091016-en [last accessed 27 Aug 2012].

OECD GLP. (1982). Good laboratory practice in the testing of chemicals. OECD monograph No. 45. OECD, Paris. ISBN 92-64-12367-9.

OECD GLP. (1997). OECD principles on good laboratory practice (as revised in 1997). OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring Number 1. Available deom: http://www.oecd.org/chemicalsafety/testing/oecdseriesonprinciplesofgoodlaboratorypracticeglpandcompliancemonitoring.htm [last accessed 11 Jan 2013].

Parry JM, Parry E, Phrakonkham P, Corvi R. (2010). Analysis of published data for top concentration considerations in mammalian cell genotoxicity testing. Mutagenesis, 25, 531–8.

Perkins PJ, Boermans HJ, Stephenson GR. (2000). Toxicity of glyphosate and triclopyr using the frog embryo teratogenesis assay – Xenopus. Environ Toxicol Chem, 19, 940–5.

Piesova E. (2004). The influence of different treatment length on the induction of micronuclei in bovine lymphocytes after exposure to glyphosate. Folia Vet Lat, 48, 130–4.

Piesova E. (2005). The effect of glyphosate on the frequency of micronuclei in bovine lymphocytes in vitro. Acta Veterinaria, 55, 101–9.

Poletta GL, Larriera A, Kleinsorge E, Mudry MD. (2009). Genotoxicity of the herbicide formulation Roundup (glyphosate) in broad-snouted caiman (*Caiman latirostris*) evidenced by the Comet assay and the micronucleus test. Mutat Res, 672, 95–102.

Poletta GL, Kleinsorge E, Paonessa A, et al. (2011). Genetic, enzymatic and developmental alterations observed in *Caiman latirostris* exposed in ovo to pesticide formulations and mixtures in an experiment simulating environmental exposure. Ecotox Environ Safe, 74, 852–9.

Prasad S, Srivastava S, Singh M, Shukla Y. (2009). Clastogenic effects of glyphosate in bone marrow cells of swiss albino mice. J Toxicol [Online]: Article ID: 308985. Available from: http://www.hindawi.com/journals/jt/2009/308985/ [last accessed 27 Aug 2012].

Quintana PJ, de Peyster A, Klatzke S, Park HJ. (2000). Gossypol-induced DNA breaks in rat lymphocytes are secondary to cytotoxicity. Toxicol Lett, 117, 85–94.

Raipulis JTM, Balode M. (2009). Toxicity and genotoxicity testing of Roundup. Proc Latvian Acad Sci SectB, 63, 29–32.

Ranzani MRTC. (2000). Evaluation of the mutagenic potential of the test substance Glifosato IPA Tecnico Nufarm. Unpublished Regulatory Study. Report Identification Number: Study No. RF-G11.040/00.

Richeux F, Cascante M, Ennamany R, et al. (1999). Cytotoxicity and genotoxicity of capsaicin in human neuroblastoma cells SHSY-5Y. Arch Toxicol, 73, 403–9.

Ribeiro do Val R. (2007). Bacterial reverse mutation test (Ames test) for [glyphosate technical]. Unpublished Regulatory Study. Report Identification Number: RL3393/2007 - 2.0AM-B.

Rossberger S. (1994). DNA repair test with primary rat hepatocytes. Unpublished Regulatory Study. Report Identification Number: 931564.

Salamone MF, Mavournin KH. (1994). Bone marrow micronucleus assay: a review of the mouse stocks used and their published mean spontaneous micronucleus frequencies. Environ Mol Mutagen, 23, 239–73.

Sasaki YF, Saga A, Akasaka M, et al. (1998). Detection of in vivo genotoxicity of haloalkanes and haloalkenes carcinogenic to rodents by the alkaline single cell gel electrophoresis (comet) assay in multiple mouse organs. Mutat Res, 419, 13–20.

Saunders RA, Davies RR. (2005). Notes on rabbit internal medicine. Oxford: Blackwell Publishing.

Savage JR. (1976). Classification and relationships of induced chromosomal structual changes. J Med Genet, 13, 103–22.

Schreib G. (2010). Reverse mutation assay using bacteria (*Salmonella Typhimurium* and *Escherichia Coli*) with glyphosate technical. Unpublished Regulatory Study. Report Identification Number: 102025.

Scott D, Galloway SM, Marshall RR, et al. (1991). Genotoxicity under extreme culture conditions. International Commission for Protection Against Environmental Mutagens and Carcinogens. A report from ICPEMC Task Group 9. Mutat Res, 257, 147–205.

Sekihashi K, Yamamoto A, Matsumura Y, et al. (2002). Comparative investigation of multiple organs of mice and rats in the comet assay. Mutat Res, 517, 53–75.

Sivikova K, Dianovsky J. (2006). Cytogenetic effect of technical glyphosate on cultivated bovine peripheral lymphocytes. Int J Hyg Environ Health, 209, 15–20.

Smith CC, Adkins DJ, Martin EA, O'Donovan MR (2008). Recommendations for design of the rat comet assay. Mutagenesis, 23, 233–40.

Sokolowski A. (2007a). *Salmonella Typhimurium* and *Escherichia Coli* reverse mutation assay with glyphosate technical. Unpublished Regulatory Study. Report Identification Number: 1061401.

Sokolowski A. (2007b). *Salmonella Typhimurium* and *Escherichia coli* reverse mutation assay with glyphosate technical. Unpublished Regulatory Study. Report Identification Number: 1061402.

Sokolowski A. (2007c). *Salmonella Typhimurium* and *Escherichia Coli* reverse mutation assay glyphosate technical. Unpublished Regulatory Study. Report Identification Number: 1061403.

Sokolowski A. (2009a). *Salmonella Typhimurium* and *Escherichia Coli* reverse mutation assay with glyphosate technical. Unpublished Regulatory Study. Report Identification Number: 1236400.

Sokolowski A. (2009b). Glyphosate technical *Salmonella Typhimurium* and *Escherichia Coli* reverse mutation assay. Unpublished Regulatory Study. Report Identification Number: 1264500.

Speit G. (1986). The relationship between the induction of SCEs and mutations in Chinese hamster cells. I. Experiments with hydrogen peroxide and caffeine. Mutat Res, 174, 21–6.

Storer RD, McKelvey TW, Kraynak AR, et al. (1996). Revalidation of the in vitro alkaline elution/rat hepatocyte assay for DNA damage: improved criteria for assessment of cytotoxicity and genotoxicity and results for 81 compounds. Mutat Res, 368, 59–101.

Suresh TP (1992). Dominant lethal test in Wistar rats. Unpublished Regulatory Study. Report Identification Number TOXI:888-DLT.

Suresh TP. (1993a). Mutagenicity – *Salmonella Typhimurium* reverse mutation assay (Ames test). Unpublished Regulatory Study. Report Identification Number: TOXI: 887-MUT.AMES.

Suresh TP. (1993b). Mutagenicity–micronucleus test in Swiss albino mice. Unpublished Regulatory Study. Report Identification Number: TOXI: 889-MUT.MN.

Suresh TP. (1994). Genetic toxicology – in vivo mammalian bone marrow cytogenetic test – chromosomal analysis. Unpublished Regulatory Study. Report Identification Number: TOXI:890-MUT-CH.AB.

Tayama S, Nakagawa Y. (1994). Effect of scavengers of active oxygen species on cell damage caused in CHO-K1 cells by phenylhydroquinone, an o-phenylphenol metabolite. Mutat Res, 324, 121–31.

Thompson PW. (1996). Technical glyphosate reverse mutation assay (Ames test) using *Salmonella Typhimurium* and *Escherichia Coli*. Unpublished Regulatory Study. Report Identification Number: SPL Proj. No. 434/014.

Tice RR, Agurell E, Anderson D, et al. (2000). Single cell gel/comet assay: guidelines for in vitro and in vivo genetic toxicology testing. Environ Mol Mutagen, 35, 206–21.

Thybaud V, Aardema M, Clements J, et al. (2007). Strategy for genotoxicity testing: hazard identification and risk assessment in relation to in vitro testing. Mutat Res, 627, 41–58.

Tsui MT, Chu LM. (2003). Aquatic toxicity of glyphosate-based formulations: comparison between different organisms and the effects of environmental factors. Chemosphere, 52, 1189–97.

Uhde H. (2004). Mutagenicity study of FSG 03090 H-1 in the *Salmonella Typhimurium* reverse mutaiton assay (in vitro). Unpublished Regulatory Study. Report Identification Number: 18487/04.

UK COM (2011). Guidance on a strategy for genotoxicity testing of chemical substances. UK Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment. Available from: http://www.iacom.org.uk/guidstate/documents/COMGuidance FINAL2.pdf/ [last accessed 17 Sep 2012].

U.S. EPA. (1986). Guidelines for mutagenicity risk assessment. Fed. Register 51. 34006-34012. Available from: http://www.epa.gov/raf/publications/guidelines-mutagenicityl-risk-assessment.htm [last accessed 1 Jan 2013].

U.S. FDA (2006). Guidance for industry and review staff: recommended approaches to integration of genetic toxicology study results. Center for Drug Evaluation and Research. U.S. Food and Drug Administration. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079257.pdf [last accessed 11 Jan 2013].

Wallner B. (2010). Reverse mutation assay using bacteria (*Salmonella Typhimurium*) with glyphosate TC. Unpublished Regulatory Study. Report Identification Number: 101268.

Williams GM, Kroes R, Munro IC. (2000). Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol, 31, 117–65.

Wolf T, Niehaus-Rolf C, Banduhn N, et al. (2008). The hen's egg test for micronucleus induction (HET-MN): novel analyses with a series of well-characterized substances support the further evaluation of the test system. Mutat Res, 650, 150–64.

Wright NP. (1996). Technical glyphosate: chromosome aberration test in CHL cells in vitro. Unpublished Regulatory Study. Report Identification Number: 434/015.

Xu Y. (2006). *Salmonella–Escherichia Coli*/mammalian–microsome reverse mutation assay with a confirmatory assay with MON 78910. Unpublished Regulatory Study. Report Identification Number: CV-2005-119.

Xu Y. (2008a). In vivo mouse bone marrow micronucleus assay. Unpublished Regulatory Study. Report Identification Number: CV-08-031.

Xu Y. (2008b). In vivo mouse bone marrow micronucleus assay with MON 76171. Unpublished Regulatory Study. Report Identification Number: CV-2007-103.

Xu Y. (2009a). In vivo mouse bone marrow micronucleus assay with MON 79991. Unpublished Regulatory Study. Report Identification Number: CV-2007-083.

Xu Y. (2009b). In vivo mouse bone marrow micronucleus assay with MON 76138. Unpublished Regulatory Study. Report Identification Number: CV-2007-095.

Xu Y. (2009c). In vivo mouse bone marrow micronucleus assay. Unpublished Regulatory Study. Report Identification Number: CV-08-243.

Zeiger E, Haseman JK, Shelby MD, et al. (1990). Evaluation of four in vitro genetic toxicity tests for predicting rodent carcinogenicity: confirmation of earlier results with 41 additional chemicals. Environ Mol Mutagen, 16, 1–14.

Zoriki Hosomi R. (2007). Mammalian erythrocyte micronucleus test for [glyphosate technical]. Unpublished Regulatory Study. Report Identification Number: 3393/2007-3.0MN.

CRITICAL REVIEWS IN TOXICOLOGY, 2016
VOL. 46, NO. S1, 1–2
http://dx.doi.org/10.1080/10408444.2016.1234117

Taylor & Francis
Taylor & Francis Group

FOREWORD

Evaluating the potential carcinogenic hazard of glyphosate

Critical Reviews in Toxicology (*CRT*) has been a leader for more than four decades in publishing scientific reviews evaluating the health hazards of exposure to chemicals that are widely used around the globe. These reviews have been internationally recognized for their comprehensive coverage of contemporary topics ranging from novel testing and assessment strategies to the characterization of the potential hazards associated with chemicals. The reviews evaluating potential chemical hazards and risk typically cover and integrate evidence from multiple avenues of investigation, including molecular and cellular research, animal investigations and epidemiological studies. From its first issue in 1971 to the present, *CRT* has a well-earned reputation for scientific rigor and thoroughness of its external peer review.

This Special Issue of *CRT* contains five papers each addressing aspects of the evaluation of the potential carcinogenic hazard of glyphosate, a chemical discovered by a scientist at Monsanto Company in 1970. Glyphosate was rapidly commercialized and initially marketed in 1974 as Roundup. Since going off patent in 2000, glyphosate has been produced and marketed by a growing number of companies. It is one of the most widely used agricultural chemicals in the world and has been of great benefit in weed control and enhanced productivity of a number of crops.

Monsanto conducted the first safety evaluations on glyphosate prior to marketing of products containing the chemical. These in-house evaluations were followed by review and approval for marketing by the U.S. Environmental Protection Agency and then other government agencies around the world. Scientific information available on the potential health hazards of glyphosate continues to increase and is now voluminous.

The International Agency for Research on Cancer (IARC) announced in 2014 that it was going to review glyphosate along with four pesticides for their potential carcinogenic hazard. Four review papers, commissioned by Monsanto Company, addressing various aspects of the toxicity of glyphosate and glyphosate-based formulations, were submitted to Critical Reviews in Toxicology, subjected to rigorous external review, revised and published in *CRT* prior to the IARC meeting (Kimmel et al. 2013; Kier & Kirkland 2013; Kier 2015; Greim et al. 2015). Those papers were frequently accessed on-line and, most importantly, copies were provided to IARC prior to the meeting of the IARC review panel in Lyon, France in March 2015.

The IARC Panel classified glyphosate in Category 2a, probably carcinogenic to humans. At the conclusion of the review, IARC released a press announcement reporting key results of the review; this was followed by publication of a summary paper (Guyton et al. 2015) and publication of a monograph (IARC 2015). The conclusions of the IARC Panel were a surprise to many scientists who had followed the literature on the potential health hazards of glyphosate over many decades. This was especially the case because the IARC classification of glyphosate as probably carcinogenic to humans ran counter to the conclusions of a number of previous carcinogenic hazard assessments conducted by multiple government agencies around the world.

Following the IARC carcinogenic hazard classification of glyphosate, the Monsanto Company engaged Intertek, a scientific and regulatory consulting firm, to convene an independent scientific panel to evaluate and synthesize the scientific evidence of the potential carcinogenic hazard of glyphosate. The activities and conclusions of the independent panel are reported in the five papers in this special issue. Each of the five papers was rigorously reviewed by 5–10 independent reviewers selected by the *CRT* Editor and anonymous to the authors. A total of 27 different reviewers participated with several of the individuals reviewing all five papers. The authors of each paper were provided the review comments on their paper and asked to make appropriate revisions. The final papers, published here, represented the work product of the authors. Each paper includes an Acknowledgements section and an extensive Declaration of Interest section.

In order to facilitate the broadest possible readership, Intertek requested that these five papers be published in a sponsored Open Access Supplement Issue in the 2016 volume of *Critical Reviews in Toxicology*. Negotiations for such sponsored supplements are customarily conducted between the sponsor and publisher, separate from the review process, thereby maintaining the journal's editorial independence. The Editor-in-Chief was not party to these negotiations.

It is anticipated that scientific discussions concerning the science of the potential carcinogenic hazards of glyphosate and its use will continue for some time along with related discussions of how this science informs policy decisions on the regulation of glyphosate-containing products. The contents of these five papers, the extensive listing of references in each paper and the Supplemental Material (available online for several of the papers), will contribute to and facilitate continued scientific discussions and policy decisions on this widely used chemical.

Acknowledgments

The Editor gratefully acknowledges the extensive review comments offered by the 27 external reviewers. Those comments enhanced the quality and completeness of the five papers.

Declaration of interest

Roger O. McClellan, the Editor-in-Chief of *Critical Reviews in Toxicology* (*CRT*), since 1987, currently serves as an independent advisor to private and public entities on environmental and occupational health issues. Early in his career, his research focused on the health effects of radiation and internally-deposited radionuclides as an employee of General Electric Company and the U.S. Atomic Energy Commission (AEC). Later he provided leadership for the Lovelace Inhalation Toxicology Research Institute's extensive research program on airborne radionuclides and other toxicants with primary financial support from the AEC and the U.S. Department of Energy. From 1988 to 1999, he was the President and Chief Executive Officer of the Chemical Industry Institute of Toxicology (CIIT), a not-for-profit research institute whose extensive research program, focusing on mechanisms of action of chemicals, was supported by dues payments from member companies. The Monsanto Company was a founding member of the CIIT. The CIIT did not conduct any research on glyphosate. McClellan, during his career, has served on over 100 major advisory committees for private firms, academic institutions and U.S. government and international agencies, including IARC. None of these advisory assignments has directly involved review of the health hazards of glyphosate. McClellan, in his role as Editor-in-Chief of *CRT*, selected the 27 individuals who reviewed the five papers published in this Special Supplement. The reviewers represented a cross-section of scientists from around the globe employed by academic, government and private entities or working as sole proprietors. The review comments they provided were considered to represent their independent professional views.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

References

Greim H, Saltmiras D, Mostert V, Strupp C. 2015. Evaluation of carcinogenic potential of the herbicide, glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity studies. Crit Rev Tox. 45:185–208.

Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Scoccianti C, Mattock H, Straif K. 2015. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate. Lancet Oncol. 16:490–491.

IARC. 2015. International agency for research on cancer monographs. Evaluation of five organophosphate insecticides and herbicides. Vol. 112. Geneva, Switzerland: WHO.

Kier LD. 2015. Review of genotoxicity biomonitoring studies of glyphosate-based formulations. Crit Rev Toxicol. 45:209–218.

Kier LD, Kirkland DJ. 2013. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol. 43:283–315.

Kimmel GL, Kimmel CA, Williams AC, DeSesso JM. 2013. Evaluation of developmental toxicity studies of glyphosate with attention to cardiovascular development. Crit Rev Toxicol. 43:79–95.

Roger O. McClellan
Editor-in-Chief, Critical Reviews in Toxicology and Advisor, Toxicology and Human Health Risk Analysis, Albuquerque, NM, USA
roger.o.mcclellan@att.net

CRITICAL REVIEWS IN TOXICOLOGY, 2016
VOL. 46, NO. S1, 3–20
http://dx.doi.org/10.1080/10408444.2016.1214677

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS

A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment

Gary M. Williams[a], Marilyn Aardema[b], John Acquavella[c], Sir Colin Berry[d], David Brusick[e], Michele M. Burns[f], Joao Lauro Viana de Camargo[g], David Garabrant[h], Helmut A. Greim[i], Larry D. Kier[j], David J. Kirkland[k], Gary Marsh[l], Keith R. Solomon[m], Tom Sorahan[n], Ashley Roberts[o] and Douglas L. Weed[p]

[a]Department of Pathology, New York Medical College, Valhalla, NY, USA; [b]Marilyn Aardema Consulting, LLC, Fairfield, OH, USA; [c]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; [d]Department of Pathology, Queen Mary, University of London, London, UK; [e]Toxicology Consultant, Bumpass, VA, USA; [f]Boston Children's Hospital, Boston, MA, USA; [g]Department of Pathology, Botucatu Medical School, São Paulo State University, UNESP, São Paulo, Brazil; [h]Department of Occupational Medicine and Epidemiology, EpidStat Institute, University of Michigan, Ann Arbor, MI, USA; [i]Department of Toxicology and Environmental Hygiene, Technical University of Munich, Munich, Germany; [j]Private Consultant, Buena Vista, CO, USA; [k]Kirkland Consulting, Tadcaster, UK; [l]Department of Biostatistics, Center for Occupational Biostatistics & Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA; [m]Centre for Toxicology, University of Guelph, Guelph, ON, Canada; [n]Department of Occupational Epidemiology, University of Birmingham, Birmingham, UK; [o]Intertek Regulatory & Scientific Consultancy, Mississauga, ON, Canada; [p]DLW Consulting Services, LLC, University of New Mexico School of Medicine, Albuquerque, NM, USA

ABSTRACT

The International Agency for Research on Cancer (IARC) published a monograph in 2015 concluding that glyphosate is "probably carcinogenic to humans" (Group 2A) based on limited evidence in humans and sufficient evidence in experimental animals. It was also concluded that there was strong evidence of genotoxicity and oxidative stress. Four Expert Panels have been convened for the purpose of conducting a detailed critique of the evidence in light of IARC's assessment and to review all relevant information pertaining to glyphosate exposure, animal carcinogenicity, genotoxicity, and epidemiologic studies. Two of the Panels (animal bioassay and genetic toxicology) also provided a critique of the IARC position with respect to conclusions made in these areas. The incidences of neoplasms in the animal bioassays were found not to be associated with glyphosate exposure on the basis that they lacked statistical strength, were inconsistent across studies, lacked dose-response relationships, were not associated with preneoplasia, and/or were not plausible from a mechanistic perspective. The overall weight of evidence from the genetic toxicology data supports a conclusion that glyphosate (including GBFs and AMPA) does not pose a genotoxic hazard and therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen. The assessment of the epidemiological data found that the data do not support a causal relationship between glyphosate exposure and non-Hodgkin's lymphoma while the data were judged to be too sparse to assess a potential relationship between glyphosate exposure and multiple myeloma. As a result, following the review of the totality of the evidence, the Panels concluded that the data do not support IARC's conclusion that glyphosate is a "probable human carcinogen" and, consistent with previous regulatory assessments, further concluded that glyphosate is unlikely to pose a carcinogenic risk to humans.

ARTICLE HISTORY
Received 8 April 2016
Revised 20 June 2016
Accepted 15 July 2016

KEYWORDS
Glyphosate; aminomethylphosphoric acid; Roundup; herbicide; cancer; genotoxicity

Table of contents

CONTACT Gary M. Williams gary_williams@nymc.edu Department of Pathology, New York Medical College, BSB413, Valhalla, NY 10595, USA

Introduction

Background on glyphosate

Glyphosate, or N-(phosphonomethyl)glycine (CAS# 1071-83-6), is a widely used broad-spectrum, nonselective post-emergent herbicide that has been in use since 1974. Glyphosate effectively suppresses the growth of many species of trees, grasses, and weeds. Glyphosate works by interfering with the synthesis of the aromatic amino acids phenylalanine, tyrosine, and tryptophan, through the inhibition of the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). Inhibition of the synthesis of these amino acids stops growth of plants such as weeds. Importantly, EPSPS is not present in mammals, which obtain their essential aromatic amino acids from the diet.

A wide variety of new uses have been developed for glyphosate in agricultural, industrial, and home & garden applications. Glyphosate accounts for approximately 25% of the global herbicide market (http://www.glyphosate.eu). Glyphosate is currently marketed under numerous trade names by more than 50 companies in several hundreds of crop protection products around the world. More than 160 countries have approved uses of glyphosate-based herbicide products (http://www.monsanto.com). To further enhance the effectiveness of glyphosate in agriculture, a number of genetically modified crop varieties have been developed which are tolerant to glyphosate (i.e. allows for application after emergence of the crops). In addition, given its effectiveness and broad-spectrum activity, glyphosate is also used worldwide for forestry, rights of way, landscape, and household control of weeds.

Glyphosate is a relatively simple molecule which consists of the amino acid glycine and a phosphonomethyl moiety (Figure 1). As such, glyphosate has no structural alerts for chromosomal damage, genotoxicity, mutagenicity, or carcinogenicity when analyzed by DEREK (Deductive Estimation of Risk from Existing Knowledge) (Kier & Kirkland 2013). It is a polar molecule that is incompletely (15–36%) absorbed orally, undergoes very little biotransformation, and is rapidly excreted unmetabolized (Williams et al. 2000). A molecule with these characteristics would be expected to exhibit, if any, only a low order of toxicity. The results from toxicity studies and regulatory risk assessments have been consistent with that expectation (JMPR 1987, 2006; US EPA 1993; WHO 1994; Williams et al. 2000; European Commission 2002; EFSA 2015).

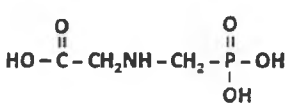


Figure 1. Structure of glyphosate.

Previous assessments of the carcinogenicity of glyphosate

The safety, including the potential carcinogenicity, of glyphosate has been reviewed by scientists and regulatory authorities worldwide, including the US Environmental Protection Agency (US EPA), the European Commission, and the Canadian Pest Management Regulatory Agency (Health and Welfare Canada 1991; US EPA 1993, 2013; WHO 1994; Williams et al. 2000; European Commission 2002; Kier & Kirkland 2013; EFSA 2015; Health Canada 2015; JMPR 2016). The conclusion of all these reviews is that proper use of glyphosate and glyphosate-based formulations (GBFs) does not pose a genotoxic or carcinogenic hazard/risk to humans.

The first assessment of glyphosate's carcinogenic potential was undertaken by the US EPA in 1985. This review was done by a US EPA panel that then was called the Toxicology Branch Ad Hoc Committee, which comprised members of the Toxicology Branch of the Hazard Evaluation Division. At that time, two chronic animal bioassays were available: a combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats and a carcinogenicity study in CD-1 mice. The Agency concluded that the data did not demonstrate a carcinogenic response in rats. However, the US EPA also concluded that the dose levels used in that study were inadequate for assessing glyphosate's carcinogenic potential in this species. The US EPA concluded that there was limited evidence of an increased incidence of renal tubule adenomas in male mice at the high-dose level (4841 mg/kg/day), a dose that greatly exceeds the limit dose level (1000 mg/kg/day) for carcinogenicity testing with pesticides (OECD 2009). Based on this information, the Agency initially classified glyphosate as a Group C (Possibly Carcinogenic to Humans: Agents with limited animal evidence and little or no human data) carcinogen (see US EPA 1991a).

The kidney slides from the mouse study were subsequently reexamined by a consulting pathologist (Dr. Marvin Kuschner M.D., Dean, School of Medicine, State University of New York at Stony Brook), and three other scientists (Dr. Robert A. Squire, Robert A. Squire Associates Inc., Ruxton Maryland; Dr. Klaus L. Stemmer M.D., Kettering Laboratory, University of Cincinnati Medical Center; Dr. Robert E. Olson, M.D., Ph.D., Professor of Medicine and Pharmacological Sciences, State University of New York at Stony Brook) also reviewed the slides and/or the chronic toxicity data. All these scientists concluded that there was no relationship to treatment (US EPA, 1986a). In addition, a Pathology Working Group (PWG), consisting of 5 pathologists (Dr. RM Sauer, Dr. MR Anver, Dr. JD Strandberg, Dr. JM Ward, and Dr. DG Goodman), was also assembled and they issued the following conclusion: "This PWG firmly believes and unanimously concurs with the original pathologist and reviewing pathologist that the incidences of renal tubular cell neoplasms in this study are not compound related" (US EPA 1986a).

All available information was presented to an US EPA FIFRA Science Advisory Panel (SAP) in February 1986. The SAP determined that the carcinogenic potential of glyphosate could not be determined from the existing data and proposed that a chronic rat and/or mouse study be conducted

in order to clarify these unresolved questions; the panel also proposed that glyphosate be categorized as Group D or having "inadequate animal evidence of oncogenicity" (US EPA 1986b).

After considering the SAP's conclusions and recommendations, the US EPA requested that a new 2-year rat oncogenicity study be conducted. In 1991, after the new rat study was completed, the US EPA re-convened its Carcinogenicity Peer Review Committee to review the results of this study as well as all of the relevant scientific data on glyphosate (US EPA 1991a). The Committee concluded that glyphosate should be classified in Group E (evidence of non-carcinogenicity) based upon the lack of a carcinogenic response in two animal species. Subsequent reevaluations by US EPA (1993, 2012, 2013) have re-affirmed the Agency's earlier conclusion.

After Monsanto had marketed glyphosate-based herbicide products for a number of years, other companies entered the glyphosate market; as a result, some of them generated substantial, or even complete, additional toxicology databases. The first additional databases that became available were generated by Cheminova and Syngenta in the mid- to late 1990s timeframe. Additional data packages were subsequently generated by other companies (e.g. Arysta, Excel, Feinchemie, Nufarm) and became available in the mid- and late 2000s timeframe.

In addition to new studies conducted to meet regulatory guidelines and support various re-registration processes globally, new epidemiology and genotoxicity studies (testing glyphosate and glyphosate-based herbicide formulations) began to appear in the scientific literature in the late 1990s and early 2000s. One of the first epidemiological investigations of interest involving glyphosate published in the scientific literature was that of Hardell and Eriksson (1999), and other epidemiology studies were periodically published after 2000 up until the present. Genetic toxicology studies of glyphosate and GBFs began to appear in the literature in increasing numbers throughout the 1990s and were reviewed by Williams et al. (2000). The occurrence of such studies has increased during the 2001–2015 timeframe: approximately 125 such genotoxicity studies were reviewed by Kier and Kirkland (2013), and an additional 40 genotoxicity biomonitoring studies of GBFs were reviewed by Kier (2015).

As glyphosate underwent reregistration processes by major national regulatory authorities and additional reviews by other health agencies after 2000, these evaluations included more and more of the new toxicology, genotoxicity, and epidemiology information generated after the initial Monsanto animal bioassay studies. For example, a 2004 Joint Meeting of the FAO Panel of Experts on Pesticide Residues (JMPR) in Food and the Environment and the WHO Core Assessment Group concluded that there was an absence of carcinogenic potential in animals and a lack of genotoxicity in standard tests; thus, "the Meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans" (JMPR 2006). The Australian Pesticides and Veterinary Medicines Authority (APVMA) evaluated the active ingredient and concluded that the evidence shows that glyphosate is not genotoxic or carcinogenic (APVMA 2013). The US EPA conducted a comprehensive Human Health Risk Assessment in 2012 (US EPA 2012). The Agency noted that "no evidence of carcinogenicity was found in mice or rats," and US EPA concluded that "glyphosate does not pose a cancer risk to humans" (US EPA 2013). Health Canada's Pesticide Management Regulatory Agency (PMRA) completed a comprehensive review of glyphosate as part of the reregistration process in that country. PMRA concluded that "the overall weight of evidence indicates that glyphosate is unlikely to pose a human cancer risk" (Health Canada 2015). The complete genotoxicity, carcinogenicity, and human epidemiology databases were evaluated by the German Federal Institute for Risk Assessment (BfR) for the European Commission on the Annex 1 renewal of glyphosate. The BfR concluded that glyphosate is unlikely to pose a carcinogenic risk to humans (Markard 2014). This conclusion was supported by the peer review evaluation conducted by the European Food Safety Authority (EFSA) both before and after a mandate from the European Commission to consider the findings from IARC regarding glyphosate's carcinogenic potential (EFSA 2015). Most recently, JMPR (2016) reviewed the data and concluded that: "glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet."

IARC assessment of the carcinogenicity of glyphosate

The International Agency for Research on Cancer (IARC) in 2015 undertook an evaluation of the oncogenic potential of glyphosate as part of its Monograph Programme. Glyphosate, along with four other pesticides (the insecticides diazinon, malathion, parathion, and tetrachlorvinphos), was considered by an IARC Working Group, which met in March 2015 at IARC in Lyon, France. A brief summary of IARC's conclusions was initially published in The Lancet Oncology on 20 March 2015 (Guyton et al. 2015), and the full IARC Monograph (Volume 112) was published online on 29 July 2015 (IARC 2015). IARC concluded that glyphosate is "probably carcinogenic to humans (Group 2A)" based on *limited evidence* in humans and *sufficient evidence* in experimental animals; it was also concluded that there was strong evidence of genotoxicity and oxidative stress (IARC 2015).

Expert Panel critique of the IARC assessment and review of relevant data

Since the IARC conclusions were found to be in such stark contrast to those from all other assessments of carcinogenic potential, it was decided that a thorough review should be conducted by scientists in the area of cancer risk assessment, critiquing IARC's processes where appropriate. Toward that end, Intertek Scientific & Regulatory Consultancy (Intertek, Mississauga, Ontario, Canada)[4] was commissioned by the Monsanto Company to assemble panels of scientific experts in the four areas considered by IARC: exposure; epidemiology; cancer in experimental animals; mechanistic and other relevant data (focused on genotoxicity and oxidative stress).

Fifteen scientific experts were selected on the basis of their expertise and standing within the international scientific community (i.e. publication history, participation in scientific

Table 1. Composition of the four Expert Panels.

Expert panel group*	Name of participating scientist	Affiliation of scientist
Human exposures	Keith R. Solomon	Centre for Toxicology, University of Guelph, Guelph, ON Canada
Carcinogenicity bioassays	Gary M. Williams	Professor of Pathology, New York Medical College, Valhalla, NY
	Sir Colin Berry	Emeritus Professor of Pathology, Queen Mary, University of London, London, UK
	Michele M. Burns	Boston Children's Hospital, Boston, MA, USA
	Joao Lauro Viana de Camargo	Professor of Pathology, Botucatu Medical School, São Paulo State Univ, UNESP, SP, Brazil
	Helmut A. Greim	Emeritus Professor of Toxicology and Environmental Hygiene, Technical University of Munich, Germany
Genotoxicity	David Brusick	Toxicology Consultant, Bumpass, VA, USA
	Marilyn Aardema	Marilyn Aardema Consulting, LLC, Fairfield, OH, USA
	Larry D. Kier	Private Consultant, Buena Vista, CO USA
	David J. Kirkland	Kirkland Consulting, Tadcaster, UK
	Gary M. Williams	Professor of Pathology, New York Medical College, Valhalla, NY
Epidemiology	John Acquavella	Professor, Department of Clinical Epidemiology, Aarhus University, Denmark
	David Garabrant	EpidStat Institute; Emeritus Professor of Occupational Medicine and Epidemiology, University of Michigan
	Gary Marsh	Professor of Biostatistics, Director and Founder, Center for Occupational Biostatistics & Epidemiology, University of Pittsburgh, Graduate School of Public Health, Pittsburgh, PA, USA
	Tom Sorahan	Professor of Occupational Epidemiology, University of Birmingham, Birmingham, UK
	Douglas L. Weed	DLW Consulting Services, LLC; Adjunct Professor, University of New Mexico School of Medicine, Albuquerque, NM, USA

*Ashley Roberts of Intertek Scientific & Regulatory Consultancy served as facilitator for each of the four panels.

and regulatory committees, and familiarity with regulatory authorities) and recruited by Intertek to participate on these Expert Panels. Panelists were recruited and assigned to one of the four areas considered by IARC (noted above) based on their areas of expertise; two panelists participated in two areas. A sixteenth scientific expert from Intertek participated on the Expert Panels and served as the overall organizer and facilitator for the panel meetings. A listing of the experts, their affiliations, and the specific "Panel" on which they served is presented in Table 1.

Prior to the meeting, all key studies/publications cited by IARC were made available to the panelists for their review; panelists were told to request any additional information they felt was necessary for them to conduct a thorough evaluation. The epidemiology panel conducted its own independent literature search. The scientists were asked to closely examine the studies/data that IARC used to come to their conclusions; panelists were also advised to examine any additional information needed to come to an overall conclusion in their respective areas.

Based on the scope of the information to be evaluated, it was decided that the panels would meet over a 2-day period to discuss all relevant information and make appropriate conclusions regarding the carcinogenic potential of glyphosate. As needed, the expert scientists held pre-meeting phone conferences and communicated *via* email to establish and plan how they would prepare for and conduct their review at the Expert Panels review meeting. Since the amount, nature, and quality of the data used by IARC varied considerably across the four areas, the evaluation approaches used by the expert panelists in their specialist areas varied somewhat as well. The Expert Panels Meeting was held on 27–28 August 2015 at Intertek in Mississauga, Canada. On the first day of the meeting, the discussions focused on the exposure and human epidemiology data. The second day of the meeting began with a summation of epidemiology and exposure discussions/conclusions and then focused on the animal bioassay and genotoxicity/oxidative stress data. After the Expert Panels met, the reports for the four individual areas were developed by designated scientists; the content of these reports was finalized through additional phone conferences and email communications as necessary with the other panel members. As indicated previously, due to the large amount of data and information evaluated by the individual panels and the subsequent length of the individual reports, it was decided to prepare four separate specialist manuscripts covering the methodologies applied and their respective outcomes and conclusions. This report presents a summary of the deliberations, and conclusions reached, by the Expert Panels in the four areas of research. Prior to publishing the Expert Panels findings, they were presented at the Society for Risk Analysis Annual Meeting at Arlington, Virginia on 7 December 2015.

As a preface to the remainder of the document, the process by which IARC identifies and reviews data must be compared with that employed by the Expert Panel(s). IARC only reviews data included in: "reports that have been published or accepted for publication in the openly available scientific literature" or "data from governmental reports that are publicly available" (IARC 2006). In addition, IARC reviews and assesses these data in the context of hazard (i.e. inherent carcinogenic potential) not risk (i.e. the likelihood of carcinogenic effects at exposure levels humans may encounter). As a result, the conclusion of IARC is often solely associated with hazard. In contrast to IARC, toxicology, mechanism, and exposure Expert Panels evaluated all of the available scientific data, including the results of a number of unpublished reports, some of which have been submitted to and reviewed by regulatory authorities. These reports document GLP- and OECD/FDA Redbook guideline compliant studies, conducted to assess the genotoxic and carcinogenic potential of glyphosate. In essence, these studies provide the highest quality of documentation and verification; hence, a balanced assessment requires the inclusion of such studies in the review process. The third panel (epidemiology) took an approach consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (Moher et al. 2009), standard approaches to critically evaluating epidemiologic studies (Aschengrau & Seage

2003a,b; Sanderson et al. 2007) and well-recognized interpretative methods – e.g. the criteria-based methods of causal inference (Hill 1965, 1971) – sometimes referred to as "weight of evidence" (WoE) methods (Weed 2005). In addition to the identification of hazard potential, the Expert Panels assessed exposure data to provide a perspective from which to comment on potential risk. In the absence of carcinogenic hazard, however, no risk is present regardless of exposure. The conclusions reached by the Expert Panels and IARC clearly differ. However, in the opinion of the Expert Panel(s) this is not due to differences in process (hazard versus risk assessment), but rather the result of the exclusion from the IARC review process of key data (animal bioassay and genotoxicity) or differences in the interpretation of the data that was assessed particularly in regard to the animal bioassay results. Given these differences, even without the data IARC did not include, there is no support for IARC's conclusion that glyphosate is "probably carcinogenic to humans." This critique is presented and discussed in the context of the Expert Panels' assessment of the totality of the data.

Exposures to glyphosate

Unpublished reports of studies on exposure to glyphosate in applicators were provided by Monsanto Company which covered uses in agriculture and forestry (see Solomon 2016 for additional details and bibliography). Other data on exposures were obtained from the open literature as a result of searches in PubMed®, references in reviews, and Google Scholar®. These papers and reports were grouped into sources of exposures and the data analyzed as described below.

Only one paper reported concentrations of glyphosate in air. In a study conducted in Iowa, Mississippi, and Indiana in 2007 and 2008, concentrations of glyphosate and its major environmental degradate, aminomethylphosphonic acid (AMPA), were measured in air and precipitation (Chang et al. 2011). For estimation of human exposure, it was assumed that there was 100% absorption of glyphosate from the air into the body of a 70 kg human breathing 8 m^3 air (half a day for an adult) (US EPA 2009). Also, surface water measurements of glyphosate as part of the National Water-Quality Assessment (NAWQA) program (USGS 2015) since 2002 were downloaded from the NAWQA data warehouse and then sorted by concentration. All values measured across the US between 2002 and 2014 were pooled for the analysis. Where concentrations were less than the level of detection (0.02 µg glyphosate acid equivalents (a.e.)/L), these values were substituted with a dummy value of "zero." Although chlorine and ozone are highly effective in removing glyphosate and AMPA during purification of drinking water (Jönsson et al. 2013), it was assumed that treatment did not remove any glyphosate. The estimated concentrations are thus a worst-case.

Studies documenting exposures through food and to "bystanders" (persons who are located within or directly adjacent to areas where pesticides are applied but who are not actively involved in the process) were reviewed and data extracted (Acquavella et al. 2004; Curwin et al. 2007; Mesnage et al. 2012; Hoppe 2013; Honeycutt & Rowlands 2014; Niemann et al. 2015). For those measurements, publications that provided actual systemic dose calculations were used rather than estimates calculated from default exposure factors (e.g. body weight (bw), water consumption, breathing rate, etc.). Where dietary exposures were calculated the urinary concentration was used to calculate the systemic dose on the assumption of 2 L of urine per day and a 60 kg person (Niemann et al. 2015). In 2013, the JMPR reviewed dietary exposures to glyphosate (glyphosate, N-acetyl glyphosate, AMPA, and N-acetyl AMPA) and calculated the international estimated daily intakes (IEDI) of glyphosate for 13 regional food diets (JMPR 2014). These IEDIs were based on estimated mean residues from supervised trials under normal or good agricultural practice. The US EPA has calculated exposures to glyphosate using the Dietary Exposure Evaluation Model (DEEM, ver 7.81), based on tolerance levels for all commodities and modeled estimates of exposures from food and drinking water for the overall US population (US EPA 2012). For studies using dosimetry, the normalization to systemic dose was conducted using the following assumptions: 70 kg adult, 2.1 m^2 surface area for a 70 kg male (US EPA 2009), 10% penetration through clothing if not actually measured, 1% dermal penetration. The estimated systemic doses were ranked from smallest to largest and a cumulative frequency distribution derived. These values were plotted on a log-probability scale. The median (50th centile) and 90th centile values were calculated from the raw data using the Excel function <=percentile>.

Where an applicator makes a single application, the systemic dose of glyphosate can be estimated from the total amount of glyphosate excreted in the urine over the 4 or 5 days following and including the day of application (Acquavella et al. 2004). If applications are conducted every day, the amount excreted each day provides a time-weighted average for daily exposures. Because glyphosate is applied infrequently in normal agricultural practice, the assumption of a single initial exposure is considered appropriate for risk assessment purposes.

Exposures via air

Based on the above assumptions, inhaling glyphosate in air at the maximum measured concentration would result in an exposure of 1.04×10^{-6} mg/kg body mass (bm)/day. This is about five orders of magnitude less than the systemic ADI proposed by EFSA (2015).

Exposures via water

The concentrations of glyphosate measured in US surface waters ranged from 0.02 to 73 µg/L. The 90th centile value was 0.79 µg/L (see Solomon (2016) for details of the calculations), more than four orders of magnitude less than the EFSA ADI.

Exposures from food and in bystanders

Estimates of glyphosate exposures to bystanders and the general public have been reported by various investigators

(Curwin et al. 2007; Mesnage et al. 2012; Hoppe 2013; Honeycutt & Rowlands 2014; Krüger et al. 2014; Markard 2014). In these studies, the range for estimates of systemic doses was 0.000022–0.00063 mg/kg/day. These values are all less than the ADI suggested by EFSA.

Exposure of applicators

The 90th centile in the dosimetry studies was 0.021 mg/kg/day; about five-times less than the systemic EFSA ADI. The range of values for the systemic doses determined by biomonitoring was smaller than for the passive dosimeters. The 90th centile was 0.0014 mg/kg b.m./day; about 70-times less than the systemic EFSA ADI.

In summary, there is a robust dataset on glyphosate exposures to humans. Even when using worst-case assumptions, systemic exposures to applicators, bystanders, and the general public are very small. Based on current RfDs and ADIs and measured exposures, there is an extremely large margin of safety from exposure to glyphosate *via* normal uses.

Epidemiological data

The epidemiology Expert Panel conducted a systematic review of the published glyphosate literature for the two cancers that were the focus of IARC's epidemiology review: non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) (see Acquavella et al. (2016) for additional details). Initially, an exhaustive search of the medical literature was performed to identify all epidemiological studies that examined the relationships between reported use of glyphosate and NHL or MM. This resulted in seven unique studies for NHL and four studies for MM after removal of duplicates and focusing on the most recent findings for study populations that were the subject of more than one publication. The relevant studies are listed in Table 2. Each study was then reviewed individually according to key validity considerations specified *a priori* and the results for NHL and MM were separately and systematically evaluated according to widely used criteria for judging causal associations from epidemiologic studies (Hill 1965).

Data abstracted from each study included: first author, year of publication, outcome (NHL, MM), study design, study size, statistical methods, results (measure of relative risk [RR] with accompanying 95% confidence interval [95% CI]), exposure-response findings, and variables controlled in the analyses. Each study was evaluated for key features that relate to study validity, most importantly: recall bias, proxy respondents, selection bias, adequate statistical control for confounding factors, and evaluation of dose response (Table 3).

Of the seven NHL studies, only one study – the Agricultural Health Study (AHS) cohort study (de Roos et al. 2005) – was devoid of major concerns about recall bias and selection bias by virtue of the design (prospective versus retrospective), was controlled comprehensively for confounding factors, and extensively considered RR by frequency and duration of glyphosate use. This study of more than 50 000 licensed pesticide farmers and applicators collected information about pesticide use before follow-up for health outcomes, had only first-hand respondents reporting about pesticide use (viz. no proxy respondents), had minimal potential for selection bias, and included statistical analyses that controlled confounding factors by myriad personal characteristics and non-glyphosate occupational exposures. In addition, de Roos et al. (2005) were the only investigators who conducted exposure-response analyses while controlling extensively for confounding exposures. In contrast, the NHL case–control studies had major validity concerns including the strong potential for recall bias, selection bias (either appreciably lesser participation for controls than cases or selecting controls that clearly did not reflect the population that gave rise to the cases [e.g. hospitals controls from rheumatology and orthopedic departments]), proxy respondents, and uncontrolled confounding factors in the statistical analyses. Indeed, in many of the case–control studies virtually every pesticide exposure studied was associated with increased risk for NHL (or MM) – a clear indication of widespread systematic bias.

With these considerations in mind, for NHL, the results of the de Roos et al. (2005) cohort study were considered the only reliable epidemiologic findings. As de Roos et al. (2005)

Table 2. Relevant studies for glyphosate review: non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

First author (year)	Study location(s)	Study design	More recent analysis	Outcome
Cantor et al. (1992)	Iowa + Minnesota	Case–control	de Roos et al. (2003)	NHL
Nordstrom et al. (1998)	Sweden	Case–control	Hardell et al. (2002)	HCL
Hardell and Eriksson (1999)	Sweden	Case–Control	Hardell et al. (2002)	NHL excluding HCL
McDuffie et al. (2001)	Canada	Case–control	n/a	NHL
Hardell et al. (2002)	Sweden	Case–control (pooled)	n/a	NHL + HCL
de Roos et al. (2003)	Nebraska,Iowa/Minnesota,Kansas	Case–control (pooled)	n/a	NHL
de Roos et al. (2005)	Iowa, North Carolina	Cohort	n/a	NHL, MM
Eriksson et al. (2008)	Sweden	Case–control	n/a	NHL
Orsi et al. (2009)	France	Case–control	n/a	NHL, MM
Hohenadel et al. (2011)	Canada	Case–control	Extension of McDuffie et al. (2001)	NHL
Cocco et al. (2013)	Czech, France, Germany, Ireland, Italy, Spain	Case–control	n/a	B-cell lymphoma
Brown et al. (1993)	Iowa	Case–control	n/a	MM
Landgren et al. (2009)	Iowa North Carolina Minnesota	Prevalence, Case–control	n/a	MGUS
Pahwa et al. (2012)	Canada	Case–control	Kachuri et al. (2013)	MM
Kachuri et al. (2013)	Canada	Case–control	n/a	MM
Sorahan (2015)	Iowa, North Carolina	Cohort	Reanalysis of de Roos et al. (2005)	MM

n/a: not available.

Table 3. Key validity considerations in glyphosate epidemiological studies.

First author (year)	Study design	Outcome	Recall bias	Selection bias	Proxy respondents	Adequate control for confounding	Exposure-response and trend test
de Roos et al. (2005)	Cohort	NHL, MM	No	Unlikely	No	Yes	Yes, yes
McDuffie et al. (2001)	Case–control	NHL	Likely	Likely	21% cases 15% controls	No	Yes, no trend test
Hardell et al. (2002)	Case–control	NHL, HCL	Likely	Unlikely	43% NHL cases and controls, 0% for HCL	No	No
de Roos et al. (2003)	Case–control	NHL	Likely	Likely	31% for cases; 40% for controls	Yes	No
Eriksson et al. (2008)	Case–control	NHL	Likely	Unlikely	No	No	Yes, no trend test
Orsi et al. (2009)	Case–control	NHL, MM	Likely	Likely	No	No	No
Cocco et al. (2013)	Case–control	NHL	Likely	Likely	No	No	No
Brown et al. (1993)	Case–control	MM	Likely	Unlikely	42% for cases; 30% for controls	No	No
Kachuri et al. (2013)	Case–control	MM	Likely	Likely	Excluded in analysis	No	Yes, no trend test

NHL: non-Hodgkin's lymphoma; MM: multiple myeloma.
Whether recall bias, exposure misclassification, or selection bias was classified as likely or unlikely was based on a consensus after an in person discussion of each study by the authors.

concluded "... the available data provided evidence of no association between glyphosate exposure and NHL incidence." Results from this study were the basis for the Panel's conclusion of no epidemiologic support for a causal relationship between reported glyphosate use and NHL.

The glyphosate literature for MM is appreciably sparser than the literature for NHL, both in terms of the number of available studies (one cohort and three case–control studies) and the number of cases in those studies with reported glyphosate use. The three case–control studies had important validity concerns, as noted for the NHL case–control studies, and were unable to adjust analyses comprehensively for confounding factors due to the very small number of exposed cases. The AHS cohort study (de Roos et al. 2005 and re-analyzed by Sorahan 2015) found that glyphosate users had about the same rate of MM as non-users adjusting for confounding factors, but had too few exposed cases to conduct informative exposure response analyses.

In summary, the epidemiology Expert Panel concluded that the glyphosate epidemiologic literature does not indicate a causal relationship between glyphosate exposure and NHL. For MM, the evidence was considered too sparse to judge a relationship between MM and reported glyphosate use. The panel's conclusion for NHL differed from that of the IARC working group primarily because the null findings from the AHS (cohort) study were the only epidemiologic findings considered likely to be valid.

Cancer bioassays

The carcinogenicity Expert Panel reviewed all listed cancer bioassays reviewed by Greim et al. (2015) and IARC (2015). The recommended method for evaluating the results of an extensive database of toxicology and carcinogenicity bioassays, as exist for glyphosate, involves the application of a WoE approach (US EPA 1986c; ECHA 2010). Methods for evaluating the results of an extensive database of toxicology and carcinogenicity bioassays, as exist for glyphosate, have evolved from the application of WoE approaches (US EPA, 2005; Suter and Cormier, 2011) to approaches built on the systematic and rigorous methods of systematic evidence-based reviews (James et al. 2015). These approaches recommend that all reliable information be evaluated. Transparent descriptions of studies to be included and excluded are a key component of this approach. In any review, if certain studies are judged to be unreliable and thus not included, the reasons for this should be provided. The carcinogenicity Expert Panel reviewed the incidences of the tumors in the various studies with respect to dose-response, rate of occurrence relative to known spontaneous rates in control animals, and on the basis of biological plausibility. Additional details of the Expert Panel's considerations and conclusions are presented in Williams et al. (2016).

In contrast to the results of past reviews (see Table 4), IARC (2015) concluded that there is *sufficient evidence in experimental animals* for the carcinogenicity of glyphosate, based on the following:

a. A significant positive trend in the incidence ($p = .037$) of renal tubule carcinomas and of adenomas and carcinomas ($p = .034$) in male CD-1 mice of one study only. This is a rare tumor type.
b. In a second feeding study in the same strain of mice, a significant positive trend in the incidence ($p < .001$) of hemangiosarcomas occurred in males.
c. In two dietary studies in SD rats, a significant positive trend ($p < .05$) in the incidence of pancreatic islet cell adenomas occurred in males.
d. In a dietary study in SD rats, a significant positive trend ($p = .016$) in the incidence of hepatocellular adenomas occurred in males.
e. In a dietary study in SD rats, a significant positive trend ($p = .031$) in the incidence of thyroid C-cell adenomas occurred in females.

Kidney tubular – cell neoplasia in mice

In regard to the rare renal tubular tumors in male CD-1 mice, the Expert Panel noted that the conclusions of the IARC were based on only one 2-year oral mouse carcinogenicity study, (Monsanto 1983) excluding two additional 18-month oral studies in CD-1 mice (Arysta Life Sciences 1997; Nufarm 2009)

Table 4. Regulatory agency reviews of three studies evaluated by IARC.

		Conclusions of review – tumors related to treatment?		
	Regulatory authorities	Mouse study (Monsanto 1983)	Rat study (Stout & Ruecker 1990)	Mouse study (Cheminova 1993)
2015	WHO/IARC	Yes	Yes	Yes
2016	WHO/JMPR	*	No	*
2016	US EPA Registration Review**	–	–	–
2016	Japan Food Safety Commission ADI Review**	No	No	–
2015	EU Annex I Renewal (BFR)**	No	No	No
2015	Canada PMRA Registration Review**	No	No	No
2013	Australia	No	No	No
2012	US EPA Human Health RA	No	No	–
2005	WHO/Water Sanitation Health	No	No	
2004	WHO/JMPR	–	No	No
2002	EU Annex I	No	No	No
1999	Japan Food Safety Commission	No	No	–
1994	WHO/IPCS	No	No	–
1993	US EPA RED	No	No	–
1991	Canada PMRA	No	No	–
1991	US EPA Cancer Classification	No	No	–
1987	WHO/JMPR	No	–	–

*The meeting could not exclude the possibility that glyphosate is carcinogenic in mice at very high doses.
**Evaluation not completed.

and one 18-month oral study in Swiss Albino mice (Feinchemie Schwebda 2001). All of the studies were considered by authoritative bodies to have met the guidelines for a carcinogenicity bioassay in mice (US EPA 1990; ICH 1997).

In the study conducted by Monsanto (1983) considered by IARC (2015) to show evidence of renal tubular neoplasia associated with glyphosate dosing, male (M) and female (F) CD-1 mice received 0 (M0/F0 mg/kg/day, control), 1000 (157/190, LD), 5000 (814/955, MD), or 30,000 (4841/5874, HD) ppm in the diet. The incidence by dose of renal neoplasms in male mice was as follows: 1/49, 0/49, 1/50, and 3/50. The important non-neoplastic renal findings of hyperplasia were as follows: 3/49, 0/49, 4/50, and 2/50, indicating lack of a dose-response, with the highest incidence in the mid-dose (MD) group, followed by the control group, and the high-dose (HD) group. The low-dose (LD) group had no renal findings. Females had neither neoplasia nor hyperplasia. Absence of hyperplasia indicates that all renal proliferative and neoplastic lesions, which occurred in all experimental groups (including controls) occurred *de novo*, i.e. were spontaneous or background lesions and were not compound related.

Factors to assess whether an association between exposure and an effect (two variables) is causal include strength, consistency, and specificity of the association, the temporal (latency) and dose-response relationships present, plausibility of effect, and coherence of the available data. When applied to the study by Monsanto (1983), several conclusions were drawn, as follows:

1. The association was not strong because the incidence of rare renal neoplasms was not statistically significant in any exposed group when compared to the control group.
2. The association is not consistent, since four out of five mouse studies did not find similar renal neoplasms at similar doses.
3. The association is not specific, since females of this pivotal study, which were exposed to higher levels of glyphosate, did not develop renal neoplasms. Also, there were no renal findings (hyperplasia, neoplasia) in the LD group, whereas the control group had four.
4. The time required between exposure and effect, i.e. the latency time, was not reduced; all tumors were observed only at termination. Also, no mouse with neoplasia had also hyperplasia.
5. The biological gradient of association or the dose-response curve was absent, since the females and the males in the LD group had no neoplasms, whereas there was one in the control group.
6. A plausible explanation for the association was absent, since the mode of action for induction of these renal neoplasms was not established.
7. Coherence of the association was also absent, as female mice and male and female rats did not display kidney effects. Also in the other four mouse carcinogenicity studies (three of which were not considered in the IARC monograph), the mice did not develop similar neoplastic renal lesions.
8. The association does not demonstrate a dose-response pattern (see #5, 6), and furthermore the "in-study" females had neither neoplasms nor any of the other renal lesions, although they were exposed to higher levels of glyphosate.

Consequently, under the conditions of this assessment, the renal neoplastic effects are not plausibly associated with glyphosate exposure. This conclusion is in agreement with that of JMPR (1987, 2006), US EPA (1993), and EFSA (2015).

Hemangiosarcomas in mice

With respect to the common liver hemangiosarcoma in male mice, in the CD-1 mouse study reported by Cheminova (1993) there were no statistically significant increases in the incidence of any tumors when compared with the in-study and historical (for both sexes 2–12%) control groups and no dose response was apparent (Williams et al. 2016). IARC,

based on their own statistical analysis, indicated/reported that there was an increase in the incidence of hemangiosarcoma in males [$p < .001$, Cochran–Armitage trend test] based on the incidence of the HD group (Table 5). In addition, IARC (2015) did not comment on the lack of hemangiosarcomas in females which have received higher doses of glyphosate, and also of renal tumors in this mouse study.

It is clear that the association between glyphosate treatment and hemangiosarcoma in mice is weak since pairwise comparisons are not significant, there is no consistency (some mouse studies show no tumors of this type at all at comparable doses), and a dose response effect is not seen (some HD groups have a lower incidence than lower doses). In addition, the recorded incidences are within the historical control range.

Given the foregoing analysis, the Expert Panel concludes that overall the evidence does not support the conclusion that glyphosate exposure results in increased incidence of hemangiosarcoma in mice.

Pancreatic tumors in rats

In two of the seven carcinogenicity studies in rats that were evaluated by IARC, tumors of islet cells of the pancreas were diagnosed in both males and females. Both studies were made available to IARC by the US EPA (1991a,b,c).

In the first study Sprague-Dawley rats received doses of 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/day) ppm in the diet for 26 months. No pancreatic islet carcinomas were observed. Adenomas were found having a positive trend ($p < .05$) in the study. The level of significance for an increase in common tumors in the trend test should be $p < .005$. The tumor incidences for controls, low, mid, and high doses respectively were: males – 0/50, 5/49 (10%), 2/50 (4%), 2/50 (4%), and females – 2/50 (4%), 1/50 (2%), 1/50 (2%) 0/50. This incidence demonstrates no dose-response pattern, and an absence of pre-neoplastic effects. In addition, in the first study in males, the adenomas did not progress to carcinomas.

In the second study Sprague-Dawley rats received 0, 2000, 8000, and 20,000 ppm glyphosate (96.5% purity) in the diet, fed *ad libitum* for 24 months. In males, the following pancreatic islet cell tumor incidences were observed in the controls and three dose groups (low to high): adenoma: 1/58 (2%), 8/57 (14%), 5/60 (8%), 7/59 (12%); carcinoma: 1/58 (2), 0/57, 0/60, 0/59. Corresponding incidence values in females were: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59, and 0/60, 0/60, 0/60, 0/59. The historical control rates for pancreatic islet cell tumors at the testing laboratory were in the range 1.8–8.5%. The Panel disagrees with the conclusion of IARC that there is a significant positive trend ($p < .05$) in the incidence of pancreatic adenomas in males, since here again the level of significance should be $p < .005$ (US FDA, 2001; Williams et al. 2014). Moreover, there was no progression of adenomas to carcinomas.

Four additional studies in rats, described by Greim et al. (2015) not evaluated by IARC, similarly did not show pancreatic islet cell tumors. Based on this information the Expert Panel concludes that there is no evidence that glyphosate induces islet cell tumors in the pancreas.

Table 5. Tumor incidence/number of animals examined (mg/kg bw/day)*.

	Males				Females			
	0	100	300	1000	0	100	300	1000
Hemangiosarcoma	0/50	0/50	0/50	4/50 (8%)	0/50	2/50 (4%)	0/50	1/50 (2%)

*Taken from Greim et al. (2015).

Table 6. Sprague-Dawley male rats, hepatocellular tumor rates†, and Cochran–Armitage trend and Fisher's exact tests results (p values).

	Dose (ppm)			
Tumors	0	2000	8000	20 000
Carcinomas	3/34	2/45	1/49	2/48†
(%)	(7)	(4)	(2)	(4)
p	.324	.489	.269	.458
Adenomas	2/44	2/45	3/49	7/48‡
(%)	(5)	(4)	(6)	(15)
p	.016*	.683	.551	.101
Adenoma + carcinoma	5/44	4/45	4/49	9/48
(%)	(11)	(9)	(8)	(19)
p	.073	.486	.431	.245
Hyperplasia only	0/44	0/45	1/49¶	0/48
(%)	(0)	(0)	(2)	(0)
p	.462	1.000	.527	1.000

Source: US EPA (1991a,b).
*Number of tumor-bearing animals/number of animals examined, excluding those that died or were sacrificed before week 55.
†First carcinoma observed at week 85 at 20 000 ppm.
‡First adenoma observed at week 88 at 20 000 ppm.
¶First hyperplasia observed at week 89 at 8000 ppm.
Significance of trend denoted at Control. Significance of pair-wise comparison with control denoted at dose level. If then $p < .05$.

Liver tumors in rats

Hepatocellular neoplasms are common for the SD rat (about 5% in males and 3% in female controls) (Williams et al. 2014).

The IARC evaluation indicated that there was "... a significant ($p = .016$) positive trend in the incidences of hepatocellular adenoma in males..." (IARC 2015). This opinion was based on its interpretation of the Stout and Ruecker (1990) study as presented by the US EPA's Peer Review of Glyphosate (US EPA 1991a,b) (see Table 6). The Stout and Ruecker (1990) study has been reviewed twice by the US EPA (1991a,b). The final interpretation of the US EPA Review committee was: "Despite the slight dose-related increase in hepatocellular adenomas in males, this increase was not significant in the pair-wise comparison with controls and was within the historical control range. Furthermore, there was no progression from adenoma to carcinoma and incidences of hyperplasia were not compound-related. Therefore, the slight increased occurrence of hepatocellular adenomas in males is not considered compound-related" (US EPA 1991b). The US EPA ultimately concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) chemical (US EPA 1991a,b).

There are other aspects of the Stout and Ruecker (1990) data that support the conclusion that glyphosate did not exert an oncogenic effect on the liver of SD rats. For example, chemically induced rat hepatocellular carcinogenesis is a multiple stage process characterized by progressive

functional, morphological, and molecular changes that indicate or precede the full establishment of neoplasia, such as enzyme induction, hepatocyte hypertrophy, degeneration and necrosis, hepatocyte proliferation, altered hepatocellular foci, etc. (Williams 1980; Bannasch et al. 2003; Maronpot et al. 2010). Identification and analyses of these liver changes – that span from adaptive to irreversible toxic effects – can help support characterization of key events along the carcinogenesis process and inform the mode of action of the tested chemical (Williams & Iatropoulos 2002; Holsapple et al. 2006; Carmichael et al. 2011). These changes were not apparent in this study.

In the last 30 years, the systemic carcinogenic potential of glyphosate has been assessed in at least eight studies in Sprague-Dawley or Wistar rats, which were not all included within the IARC monograph (Greim et al. 2015); a ninth could not be evaluated because of a high mortality and the low doses used (Chruscielska et al. 2000). Considered jointly, the animals were exposed through the diet to 24 different doses distributed across a wide range (3.0–1290 mg/kg bw/day). In exposed males, the incidences of hepatocellular adenomas across the doses showed no dose-response relationship and varied within the same range as the controls. Similar rates were also seen for hepatocellular carcinomas. These observations confirm that glyphosate is not carcinogenic to the rat liver.

Thyroid tumors in rats

C-cell tumors of the thyroid are a common tumor in the SD rat (Williams et al. 2014).

The incidence of thyroid C-cell adenoma was reported in the Monograph (IARC 2015), to have a significant positive trend ($p = .031$) in females. IARC based their opinion, again, on their interpretation of the Stout and Ruecker's (1990) study and the US EPA's Second Peer Review of Glyphosate (US EPA 1991a). In the Stout and Ruecker's study (1990), no statistically significant difference (group comparison) was reported in the incidence of thyroid C-cell neoplasms, as shown in Table 7. Additionally, the US EPA (1991a) concluded that "the C-cell adenomas in males and females are not considered compound-related." Although the C-cell adenomas were slightly numerically greater in male and female MD and HD groups, there was no dose-related progression to carcinoma and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. However, IARC concluded that "there was a statistically significant positive trend in the incidence of thyroid, C-cell adenomas in females" ($p = .031$ but, because this is a common tumor type, the trend significance value should be $p < .005$ (US FDA 2001; Williams et al. 2014)). Thus, this tumor is not significant.

Table 7. Tumor incidence/number of animals examined (mg/kg bw/day)*.

	Males				Females			
	0	89	362	940	0	113	457	1183
Thyroid C-cell adenoma	2/60	4/58	8/58	7/60	2/60	2/60	6/60	6/60
Thyroid C-cell carcinoma	0/60	2/58	0/58	1/58	0/60	0/60	1/60	0/60

*Stout and Ruecker (1990) (all deaths reported).

Therefore, in one of the two evaluated studies, the significant trend in the incidence of thyroid C-cell adenomas in female rats did not materialize, and there was no progression to carcinomas. The adenomas were within the historical ranges.

Genetic toxicity and oxidative stress data

The genetic toxicology Expert Panel (Brusick et al. 2016) considered published studies reviewed in the IARC monograph and additional published studies identified by literature searches or from review articles, not considered by IARC. These included both genetic toxicology studies and studies of oxidative stress. A large number of core genetic toxicology regulatory studies were also considered by the Expert Panel for which information was available from review publication supplements. These regulatory studies were not considered in the IARC monograph, but the Expert Panel concluded that sufficient test-related information was available to justify including these studies. In addition, some unpublished regulatory studies not reviewed previously were included in the Expert Panel evaluation.

The universally recommended method for evaluating the databases of the type associated with glyphosate (including GBFs and AMPA), involves the application of a WoE approach as discussed recently for genetic toxicology testing (US FDA 2006; Dearfield et al. 2011). One of the most important requirements of a WoE approach is that individual test methods should be assigned a weight that is consistent with their contribution to the overall evidence, and different types of evidence or evidence categories must be weighted before they are combined into a WoE.

The weight of a category of evidence used in the Expert Panel evaluation is based on four considerations: (i) different categories of evidence (i.e. assay types) have different weights, (ii) the aggregate strength (robustness of protocols and reproducibility) and quality of evidence in the category also influence the weight (Klimisch et al. 1997), (iii) the number of items of evidence within a category influences the weight, and (iv) tests with greater potential to extrapolate results to humans carry greater weight. In general, human and *in vivo* mammalian systems have the highest test system weight, with a lower weight applied to *in vitro* mammalian cell systems and *in vivo* non-mammalian systems and lowest weight to *in vitro* non-mammalian systems (with the exception of the well-validated bacterial reverse mutation-[Ames] test using mammalian metabolic activation). Typically, the results of *in vivo* assays supersede the results of *in vitro* assays (EFSA 2011).

In contrast to the standard WoE approach used by the Expert Panel, IARC's process for evaluating/weighting the genotoxicity data for glyphosate, GBF and AMPA was not defined. IARC's process may be inferred by how the data were summarized and described, and indicate a number of differences from current standard procedures for WoE. For instance, it appears that IARC considered *in vitro* studies in human cells as carrying more weight than rodent *in vivo* studies as evidenced by the order of discussion topics in Section 4.2.1, and the inclusion of a separate table for human *in vitro* studies. Further, the IARC conclusion of

strong evidence of genotoxicity was stated as based on "studies in humans *in vitro* and studies in experimental animals." In contrast, the Expert Panel evaluation considered *in vitro* studies using cells of human origin to be weighted as equivalent to any other *in vitro* mammalian cell assay using the same endpoint. IARC also gave weight to publications in which glyphosate or GBFs have been tested for genotoxicity in a variety of nonstandard non-mammalian species (fish, insects). The Expert Panel did not consider data from these non-mammalian systems and nonstandard tests with glyphosate, GBF and AMPA to have weight in the overall genotoxicity evaluation, especially given the large number of standard core studies assessing the more relevant gene mutation and chromosomal effects categories available in mammalian systems. In addition, nonstandard tests lack internationally accepted guidelines for design and conduct, databases that document acceptable negative control data or positive control responses are absent, and validation with respect to concordance with rodent or human carcinogenicity has yet to be completed. OECD guidelines specifically state that use of any nonstandard tests require justification along with stringent validation including establishing adequate historical negative and positive control databases (OECD 2014).

In addition, the IARC review seemed to apply significant weight to "indicator" tests such as DNA damage (comet assay) or sister chromatid exchange (SCE) studies. These tests are identified as indicators because the measured endpoint is reversible and does not always lead to mutation, a key event in cancer development. As stated by OECD (2015), when evaluating potential genotoxicants, more weight should be given to the measurement of permanent DNA changes than to DNA damage events that are reversible. Therefore, the Expert Panel also considered that the data from these "indicator" tests with glyphosate, GBFs and AMPA should not have significant weight in the overall genotoxicity evaluation, especially given the large number of standard core studies in the more relevant gene mutation and chromosomal effects categories available in mammalian systems.

IARC did not consider the chemical structure of glyphosate in its mechanistic section. Many guidelines recommend that the presence of structural alerts be considered in evaluation of or testing for genotoxicity (Cimino 2006; Eastmond et al. 2009; EFSA 2011; ICH 2011). As reported in Kier and Kirkland (2013), analysis of the glyphosate structure by DEREK software identified no structural alerts for chromosomal damage, genotoxicity, mutagenicity, or carcinogenicity. The lack of structural alerts in the glyphosate molecular structure suggests lack of genotoxicity and that genotoxic effects observed might be secondary to toxicity or resulting from mechanisms other than DNA reactivity.

Genetic toxicology tests relied upon by most regulatory bodies to support decisions regarding safety focus on a set of core endpoints that are known to be involved either in direct activation of genes responsible for neoplastic initiation in somatic cells or alteration of the genetic information in germ cells (EFSA 2011; ICH 2011; Kirkland et al. 2011). Therefore, the endpoints given the greatest weight in Table 8 consist of gene mutation and chromosomal aberrations.

An evaluation of the studies in Table 8 according to their relative contributions to a WoE produced the following results:

- Test methods identified as providing low contribution to the WoE (low weight) produced the highest frequency of positive responses, regardless of whether the responses were taken from the results of IARC-evaluated studies alone (8 of 9) or from all studies combined (8 of 11).
- The highest frequencies of positive responses were reported for test endpoints and systems considered most likely to yield false or misleading positive results due to their susceptibility to secondary effects. This relationship was constant regardless of whether the results were taken from IARC-evaluated studies alone or all studies combined.
- The numbers of studies providing strong evidence of relevant genotoxicity (high weight) were in the minority for both the IARC and the Expert Panel's evaluations, with 6 out of 15 studies identified as high weight being positive for the IARC evaluation, and only 8 out of 92 studies identified as high weight being positive for all studies combined.

In summary, the WoE from *in vitro* and *in vivo* mammalian tests for genotoxicity indicates that:

- Glyphosate does not induce gene mutations *in vitro*. There are no *in vitro* mammalian cell gene mutation data for GBFs or AMPA, and no gene mutation data *in vivo*.
- Glyphosate, GBFs, and AMPA are not clastogenic *in vitro*. Glyphosate is also not clastogenic *in vivo*. Some positive *in vivo* chromosomal aberration studies with GBFs are all subject to concerns regarding their reliability or biological relevance.
- There is limited evidence that glyphosate induces micronuclei (MN) *in vitro*. Although this could be a reflection of increased statistical power in the *in vitro* MN studies, the absence of clastogenic effects suggests the possibility of threshold-mediated aneugenic effects. However, there is strong evidence that glyphosate does not induce MN *in vivo*.
- Limited studies and potential technical problems do not present convincing evidence that GBFs or AMPA induce MN *in vitro*. The overwhelming majority of *in vivo* MN studies on GBFs gave negative results, but conflicting and limited data do not allow a conclusion on *in vivo* induction of MN by AMPA.
- There is evidence that glyphosate and GBFs can induce DNA strand breaks *in vitro*, but these are likely to be secondary to toxicity since they did not lead to chromosome breaks. There is limited evidence of transient DNA strand breakage for glyphosate and GBFs *in vivo*, but for glyphosate at least these are not associated with DNA adducts. These results are assigned a lower weight than results from other more relevant endpoints, which were more abundant.
- There is evidence that glyphosate and AMPA do not induce unscheduled DNA synthesis (UDS) in cultured hepatocytes.

Table 8. Summary of the Panel's evaluation of human, non-human mammalian and selected microbial genotoxicity studies from IARC section 4.2.1 and other published sources.

Source	Test category	Endpoint	Weight	Glyphosate (Pos/Neg)	GBFs (Pos/Neg)	AMPA (Pos/Neg)	Total (Pos/Neg)
Kier and Kirkland (2013) and other published studies not included in IARC	Bacterial reverse mutation	Gene mutation	High	0/19	0/20	0/1	0/40
	Mammalian *in vitro*	Gene mutation	Moderate	0/2	ND	ND	0/2
		Chromosomal aberrations	Moderate	1/5	1/0	ND	2/5
		Micronucleus	Moderate	2/0	1/0	ND	3/0
		UDS	Low	0/1	ND	0/1	0/2
		SCE	None	ND	1/0	ND	1/0
	Mammalian *in vivo*	Chromosomal aberrations	High	0/1	2/0	ND	2/1
		Micronucleus	High	0/13	0/17	0/1	0/31
		SCE	None	ND	1/0	ND	1/0
IARC monograph 112	Bacterial reverse mutation	Gene mutation	High	0/1	0/0	ND	0/1
	Mammalian *in vitro*	Gene mutation	Moderate	0/1	ND	ND	0/1
		Chromosomal aberrations	Moderate	1/2	ND	1/0	2/2
		Micronucleus	Moderate	2/0	ND	1/0	3/0
		Comet/DNA breaks	Low	5/0	2/0	1/0	8/0
		UDS	Low	0/1	ND	ND	0/1
		SCE	None	3/0	2/0	ND	5/0
	Mammalian *in vivo*	Chromosomal aberrations	High	0/1	1/1	ND	1/2
		Micronucleus	High	2/1	2/3	1/0	5/4
		Comet/DNA breaks	Moderate	1/0	1/0	ND	2/0
		Dominant lethal	High	0/1	ND	ND	0/1
	Human *in vivo*	Chromosomal aberrations	High	ND	0/1	ND	0/1
		Micronucleus	High	ND	0/3	ND	0/3
	High weight *Combined totals (IARC results only)*			2/37 (2/4)	5/45 (3/5)	½ (1/0)	8/84 (6/9)
	Moderate weight *Combined totals (IARC results only)*			7/10 (4/3)	3/0 (1/0)	2/0 (2/0)	12/10 (7/3)
	Low weight *Combined totals (IARC results only)*			5/2 (5/1)	2/0 (2/0)	1/1 (1/0)	8/3 (8/1)

ND: no data.
All responses based on study critiques and conclusions of Expert Panel members.
Non-mammalian responses from IARC Monograph in this table did not include 4 positive studies measuring DNA strand breaks in bacteria and 1 negative Rec assay in bacteria from Monograph Table 4.6.

Table 9. Summary of studies presented in Kier and Kirkland (2013) and of other publicly available studies not included in the IARC review.

Test category	Endpoint	Glyphosate (Pos/Neg)	GBFs (Pos/Neg)	AMPA (Pos/Neg)	Total (Pos/Neg)
Non-mammalian (bacterial reverse mutation)	Gene mutation	0/19	0/20	0/1	0/40
Mammalian *in vitro*	Gene mutation	0/2	ND	ND	0/2
	Chromosomal aberrations	1/5	1/0	ND	2/5
	Micronucleus	2/0*	1/0	ND	3/0
	UDS	0/1	ND	0/1	0/2
	SCE	ND	1/0	ND	1/0
Mammalian *in vivo*	Chromosomal aberrations	0/1	2/0*	ND	2/1
	Micronucleus	0/13*	0/17	0/1	0/31
	SCE	ND	1/0	ND	1/0
Total		3/41	6/37	0/3	9/81

*Inconclusive studies not included in count. ND: not done.

- Reports of the induction of SCE *in vitro* by glyphosate and GBFs, and one positive report of SCE induction *in vivo* by a GBF, do not contribute to the overall evaluation of genotoxic potential since the mechanism of induction and biological relevance of SCE are unclear.

Although IARC policies prohibited the inclusion of additional data from unpublished studies or governmental reports, it was the Expert Panel's conclusion that the regulatory genetic toxicology studies published in reviews such as Kier and Kirkland (2013) (Table 9) should be included in a WoE assessment. The rationale supporting the inclusion of these additional studies is that the supplementary tables presented in the Kier and Kirkland (2013) paper, contain sufficient detail supporting the reliability of the studies. Failure to evaluate and consider the large number of results included in the publication by Kier and Kirkland (2013), as well as other publicly available studies not reviewed by IARC, results in an inaccurate assessment of glyphosate, GBFs and AMPA's genotoxic hazard/risk potential.

Based on the results of the WoE critique detailed above and the wealth of regulatory studies reviewed by Kier and Kirkland (2013) and Williams et al. (2000), the Panel concluded that the available data do not support IARC's conclusion that there is strong evidence for genotoxicity across the glyphosate or GBFs database. In fact, the Panel's WoE assessment provides strong support for a *lack* of genotoxicity, particularly in the relevant mechanism

Table 10. Comparison of test response profiles from glyphosate, GBFs, and AMPA to the profile characteristics of confirmed genotoxic carcinogens.

Characteristic	Carcinogens with a proven genotoxic mode of action	Glyphosate, GBFs, and AMPA study data
Profile of test responses in genetic assays	Positive effects across multiple key predictive endpoints (i.e. gene mutation, chromosome aberrations, aneuploidy) both *in vitro* and *in vivo*	No valid evidence for gene mutation in any test; no evidence for chromosome aberrations in humans and equivocal findings elsewhere
Structure–activity relationships	Positive for structural alerts associated with genetic activity	No structural alerts for glyphosate or AMPA suggesting genotoxicity
DNA binding	Agent or breakdown product are typically electrophilic and exhibit direct DNA binding	No unequivocal evidence for electrophilic properties or direct DNA binding by glyphosate or AMPA
Consistency	Test results are highly reproducible both *in vitro* and *in vivo*	Conflicting and/or non-reproducible responses in the same test or test category both *in vitro* and *in vivo*
Response kinetics	Responses are dose dependent over a wide range of exposure levels	Many positive responses do not show significant dose-related increases
Susceptibility to confounding factors (e.g. cytotoxicity)	Responses are typically found at nontoxic exposure levels	Positive responses typically associated with evidence of overt toxicity

AMPA: aminomethylphosphonic acid; GBF: glyphosate-based formulation.

categories (mutation, chromosomal effects) associated with carcinogen prediction. As additional support for the Panel's WoE conclusion, Table 10 provides a comparison between a set of characteristics associated with confirmed genotoxic carcinogens (Bolt et al. 2004; Petkov et al. 2015) and the genotoxic activity profiles for glyphosate, AMPA, and GBFs. There is virtually no concordance between the two sets of characteristics.

Beyond the standard genetic toxicity assays, IARC concluded for humans exposed to GBFs that there was positive evidence of DNA breakage as determined using the comet assay (Paz-y-Miño et al. 2007), negative induction of chromosomal aberrations (Paz-y-Miño et al. 2011), and positive induction of MN (Bolognesi et al. 2009). These papers were critically reviewed by the Expert Panel and were found to be deficient as evidence for GBF genetic effects for many reasons (e.g. identification of cells scored for comets, inconsistent observations, uncertainties with respect to "negative controls," lack of statistical significance, and lack of effect relative to self-reported exposure). In addition to questions about the significance of the comet endpoint there is also a lack of scientific consensus regarding the relevance of MN found in exposed humans (Speit 2013; Kirsch-Volders et al. 2014). Importantly, for the Bolognesi study, increases in MN were not significantly correlated with self-reported GBF spray exposure and were not consistent with application rates. The Expert Panel concluded that there was little or no reliable evidence produced in these studies that would support a conclusion that GBFs, at levels experienced across a broad range of end-user exposures, poses any human genotoxic hazard/risk.

With respect to oxidative stress and genotoxic potential of glyphosate and its formulations, it is noted that many more oxidative stress studies are available for GBFs than for glyphosate or AMPA. A higher proportion of the GBF studies show evidence of oxidative stress. This might be consistent with induction of oxidative stress by GBF components such as surfactants. IARC's statement that there is strong evidence supporting oxidative stress from AMPA seems to result from glyphosate and particularly GBF results rather than AMPA results. In fact, oxidative stress studies of AMPA are very limited. The paucity of cited data does not seem to justify a conclusion of strong evidence for oxidative stress induction by AMPA.

One mechanism connecting oxidative stress to induction of carcinogenicity is oxidative damage to DNA and the generation of mutagenic lesions. Most of the endpoints used in oxidative stress studies cited by IARC are indirect response endpoints and the number of studies examining direct oxidative DNA damage are very few and presented mixed results. Further, research on oxidative stress-induced genotoxicity suggests that it is often a secondary response to toxicity and characterized by a threshold (Pratt & Barron 2003). Comparison of GBF oxidative stress study results with predicted human exposure levels of less than 0.064 mg/kg bw/day, suggests that it is improbable that GBFs would induce levels of oxidative stress likely to exceed endogenous detoxication capacities.

The most appropriate conclusion supported by the oxidative stress data is, based on a WoE approach, that there is no strong evidence that glyphosate, GBFs, or AMPA produce oxidative damage to DNA that would lead to induction of endpoints predictive of a genotoxic hazard or act as a mechanism for the induction of cancer in experimental animals or humans.

A thorough WoE review of genotoxicity data does not indicate that glyphosate, GBFs, or AMPA possess the properties of genotoxic hazards or genotoxic mechanisms of carcinogenesis.

Discussion and conclusions

Four Expert Panels conducted detailed reviews of glyphosate exposure, animal carcinogenicity, genotoxicity, and epidemiologic studies. With respect to exposure, even when using a number of worst-case assumptions, systemic doses of glyphosate in human applicators, bystanders, and the general public are very small. Exposures of the general public are three or more orders of magnitude less than the US EPA's RfD (1.75 mg/kg/day) as well the ADIs established by JMPR (1 mg/kg/day) and EFSA (0.5 mg/kg/day). The RfD is the allowable limit of daily exposure derived from toxicity studies, and even in the most exposed applicators (90th centile) the systemic dose was estimated at 20-fold less that the RfD. Exposures to the public are in the range of 0.00001–0.001 mg/kg bw/day while occupational exposures can range up to 0.01 mg/kg

bw/day. Systemic exposures are even lower than the reported ranges since oral and dermal absorption of glyphosate is low.

With respect to the animal cancer bioassay data, the Expert Panel conducted a thorough overall WoE evaluation that considered a much wider range of studies than IARC, all of which met Good Laboratory Practice (GLP) guidelines and were submitted to support glyphosate Annex I renewal in the European Union. These studies provided evidence that neoplasms naturally occurring in rodents are widely represented in non-exposed animals, as well as those exposed to doses well below those that might be expected in regulatory studies. The pattern of occurrence of these tumors was found to be inconsistent across and within species and no "novel" neoplasms appeared; progression of non-neoplastic to neoplastic lesions also was not seen. Further, the comparatively large number of studies performed would be expected to generate several numerical imbalances by chance. In fact, Haseman (1983) has estimated that the overall false positive rate for animal bioassays that tested both sexes in two species, because of multiple comparisons, corresponds to 7–8% significance level for the study as a whole; the US Food and Drug Administration has estimated that the overall rate can approach 10%.

After review of all available glyphosate rodent carcinogenicity data, the Panel concludes:

- The mouse renal neoplastic effects are not associated with glyphosate exposure, because they lack statistical significance, consistency, specificity, a dose-response pattern, plausibility, and coherence;
- The association of hemangiosarcomas in the livers of mice is weak, lacks consistency, and there was no dose-response effect;
- The association of pancreatic islet-cell adenomas in male SD rats is weak, not seen in the majority of rat studies, lacks a dose-response pattern (the highest incidence is in the low dose followed by the high dose), plausibility and pre-neoplastic/malignant effects;
- In one study, the significant positive trend in the incidence of hepatocellular adenomas in male rats did not materialize, no progression to malignancy was evident and no glyphosate-associated pre-neoplastic lesions were present;
- In one study, the significant positive trend in the incidence of thyroid C-cell adenomas in female rats did not materialize, the adenomas were only slightly increased in mid- and high doses, and there was no progression to malignancy.

Overall, extensive reviews of the genotoxicity of glyphosate, AMPA, and GBFs that were available prior to the development of the IARC Glyphosate Monograph all support a conclusion that glyphosate (and related materials) is inherently not genotoxic. Further, evidence indicative of an oxidative stress mechanism of carcinogenicity is largely unconvincing. The Expert Panel concluded that there is no new, valid evidence presented in the IARC Monograph that would provide a basis for altering these conclusions.

Lastly, the Expert Panel's review of the glyphosate epidemiologic literature and the application of commonly applied causal criteria did not indicate a relationship with glyphosate exposure and NHL. In addition, the Panel considered the evidence for MM to be inadequate to judge a relationship with glyphosate. The extremely large margin of safety found in exposure monitoring studies is considered to be supportive of these conclusions.

In summary, the totality of the evidence, especially in light of the extensive testing that glyphosate has received, as judged by the Expert Panels, does not support the conclusion that glyphosate is a "probable human carcinogen" and, consistent with previous regulatory assessments, the Expert Panels conclude that glyphosate is unlikely to pose a carcinogenic risk to humans.

Acknowledgements

The authors gratefully acknowledge the extensive comments received from nine independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the manuscript.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer.

The Expert Panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists were engaged by, and acted as consultants to, Intertek, and were not directly contacted by the Monsanto Company. Funding for this evaluation was provided to Intertek by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorneys reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food, and pharmaceutical industries. While Intertek has not previously worked on glyphosate-related matters for the Monsanto Company, previous employees (Ian Munro, Barry Lynch) of Cantox, have worked in this capacity. These employees of Cantox, and Gary M. Williams, prepared a safety and risk assessment, including the carcinogenicity, of Roundup herbicide (glyphosate), which was published in 2000 (Williams et al. 2000).

Gary M. Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut A. Greim, David J. Kirkland, Keith R. Solomon, and Tom Sorahan have previously served as independent consultants for the Monsanto Company on the European Glyphosate Task Force. John Acquavella and Larry D. Kier have also served as independent consultants and were previously employees of the Monsanto Company. John Acquavella was employed by Monsanto between the years 1989 and 2004 while Larry D. Kier was employed between 1979 and 2000. David Garabrant serves on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate, and has consulted on behalf of Bayer Corp. on litigation matters concerning glyphosate and leukemia. Gary Williams and Tom Sorahan have consulted for Monsanto on litigation matters involving glyphosate. Tom Sorahan has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112, as an Observer for the Monsanto Company. Douglas L. Weed has consulted on litigation matters concerning Monsanto that did not involve glyphosate. Marilyn Aardema, Michele M. Burns, Gary Marsh, and Ashley Roberts have not previously been employed by the

Monsanto Company or previously been involved in any activity involving glyphosate and as such declare no potential conflicts of interest. Furthermore, other than David Garabrandt, Gary Williams and Tom Sorahan, none of the aforementioned authors have been involved in any litigation procedures involving glyphosate.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

References

Acquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, Chapman P, Bleeke M. 2004. Glyphosate for farmers and their families: results from the Farm Family Exposure Study. Environ Health Perspect. 112:321–326.

Acquavella J, Garabrant D, Marsh G, Sorahan T, Weed DL. 2016. Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. Crit Rev Toxicol, in this issue. doi:10.1080/10408444.2016.1214681.

APVMA. 2013. A review of the Earth Open Source (EOS) report "Roundup and birth defects: is the public being kept in the dark?" Prepared by Canberra (Australia): Scitox Assessment Services for Canberra (Australia): Australian Pesticides and Veterinary Medicine Authority (APVMA). Available from: http://archive.apvma.gov.au/news_media/docs/glyphosate_scitox_review_july_2013.pdf.

Arysta Life Sciences. 1997. HR-001: 18-month oral oncogenicity study in mice. Tokyo (Japan): The Institute of Environmental Toxicology. Cited In: Greim et al. 2015 [As: Arysta Life Sciences 1997a].

Aschengrau A, Seage GR. III. 2003a. Bias. In: Essentials of epidemiology in public health. Sudbury (MA): Jones and Bartlett Publishers; p. 251–279.

Aschengrau A, Seage GR. III. 2003b. Guide to the critical review of epidemiologic studies. In: Essentials of epidemiology in public health. Sudbury (MA): Jones and Bartlett Publishers; p. 348–374.

Bannasch P, Haertel T, Su Q. 2003. Significance of hepatic preneoplasia in risk identification and early detection of neoplasia. Toxicol Pathol. 31:134–139.

Bolognesi C, Carrasquilla G, Volpi S, Solomon KR, Marshall EJP. 2009. Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate. J Toxicol Environ Health. A. 72:986–997. Cited In: IARC 2015.

Bolt HM, Foth H, Hengstler JG, Degen GH. 2004. Carcinogenicity categorization of chemicals-new aspects to be considered in a European perspective. Toxicol Lett. 151:29–41.

Brown LM, Burmeister GD, Everett GD, Blair A. 1993. Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes Control. 4:153–156. Cited In: IARC 2015.

Brusick D, Aardema M, Kier L, Kirkland D, Williams G. 2016. Genotoxicity Expert Panel review. Weight-of-evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations and aminomethylphosphonic acid. Crit Rev Toxicol, in this issue. doi:10.1080/10408444.2016.1214680.

Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, Schuman L, Dick FR. 1992. Pesticides and other agricultural risk factors for Non-Hodgkin's Lymphoma among men in Iowa and Minnesota. Cancer Res. 52:2447–2455.

Carmichael N, Bausen M, Boobis AR, Cohen SM, Embry M, Fruijtier-Pölloth C, Greim H, Lewis R, Meek ME, Mellor H, et al. 2011. Using mode of action information to improve regulatory decision-making: an ECETOC/ILSI RF/HESI workshop overview. Crit Rev Toxicol. 41:175–186.

Chang FC, Simcik MF, Capel PD. 2011. Occurrence and fate of the herbicide glyphosate and itsdegradateaminomethylphosphonic acid in the atmosphere. Environ Toxicol Chem. 30:548–555.

Cheminova. 1993. 104 week combined chronic feeding/oncogenicity study in rats with 52 week interim kill (results after 104 weeks) [Unpublished Report] Tranent (Scotland): Inveresk Research International, Ltd. Submitted to WHO by Lemvig (Denmark): Cheminova A/S (Report No. 7867, IRI project No. 438623). Cited In: Greim et al. 2015 [As: Cheminova 1993a]. Cited In: JMPR 2006 [As: Atkinson et al. 1993b].

Chruscielska K, Brzezinski J, Kita K, Kalhorn D, Kita I, Graffstein B, Korzeniowski P. 2000. Glyphosate – evaluation of chronic activity and possible far-reaching effects. Part 1. Studies on chronic toxicity. Pestycydy (Warsaw) (3/4):11–20. Cited In: Greim et al. 2015 [As: Chruscielska et al. 2000a].

Cimino MC. 2006. Comparative overview of current international strategies and guidelines for genetic toxicology testing for regulatory purposes. Environ Mol Mutagen. 47:362–390.

Cocco P, Satta G, Dubois S, Pili C, Pilleri M, Zucca M, 't Mannetje AM, Becker N, Benavente Y, de Sanjose S, et al. 2013. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occup Environ Med. 70:91–98.

Curwin BD, Hein MJ, Sanderson WT, Striley C, Heederik D, Kromhout H, Reynolds SJ, Alavanja MC. 2007. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. Ann Occup Hyg. 51:53–65.

de Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A. 2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med. 60:E11. doi:10.1136/oem.60.9.e11.

de Roos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, Sandler DP, Alavanja MC. 2005. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect. 113:49–54. Cited In: IARC 2015 [As de Roos et al. 2005a].

Dearfield KL, Thybaud V, Cimino MC, Custer L, Czich A, Harvey JS, Hester S, Kim JH, Kirkland D, Levy DD, et al. 2011. Follow-up actions from positive results of in vitro genetic toxicity testing. Environ Mol Mutagen. 52:177–204.

Eastmond DA, Hartwig A, Anderson D, Anwar WA, Cimino MC, Dobrev I, Douglas GR, Nohmi T, Phillips DH, Vickers C. 2009. Mutagenicity testing for chemical risk assessment: update of the WHO/IPCS Harmonized Scheme. Mutagenesis. 24:341–349.

ECHA. 2010. European Chemicals Agency. Practical Guide 2: How to Report Weight of Evidence. 24 March. ECHA-10-B-05-EN. Available from: http://echa.europa.eu/documents/10162/13655/pg_report_weight_of_evidence_en.pdf.

EFSA. 2011. Scientific Opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee) (Question no EFSA-Q-2009-00782, adopted on 13 September 2011 by European Food Safety Authority, 3 October 2012, replaces the earlier version). EFSA J. 9:2379 [69 p.]. doi:10.2903/j.efsa.2011.2379. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/2379.htm.

EFSA. 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate (EFSA-Q-2014-00546, EFSA-Q-2015-00279, approved on 30 October 2015 by European Food Safety Authority). EFSA J. 13:4302. [107 p.]. doi:10.2903/j.efsa.2015.4302. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/4302.

Eriksson M, Hardell L, Carlberg M, Akerman M. 2008. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer. 123:1657–1663. Cited In: IARC 2015.

European Commission. 2002. Review report for the active substance glyphosate. Finalised in the Standing Committee on Plant Health at its meeting on 29 June 2001 in view of the inclusion of glyphosate in Annex I of Directive 91/414/EEC. Brussels (Belgium): European Commission (EC), Health and Consumer Protection Directorate General (6511/VI/99-Final). Available from: http://ec.europa.eu/food/fs/sfp/ph_ps/pro/eva/existing/list1_glyphosate_en.pdf.

Feinchemie Schwebda. 2001. Carcinogenicity study with glyphosate technical in Swiss Albino mice [Unpublished Report]. Bangalore (India): Rallis India, Ltd. Cited In: Greim et al. 2015.

Greim H, Saltmiras D, Mostert V, Strupp C. 2015. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Crit Rev Toxicol. 45:185–208.

Guyton KZ, Loomis D, Grosse Y, El Ghissassi F, Benbrahim-Tallaa L, Guha N, Scoccianti C, Mattock H, Straif K. 2015. Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate International

Agency for Research on Cancer Monograph Working Group, IARC, Lyon, France. Lancet Oncol. 16:490–491.

Hardell L, Eriksson M. 1999. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer. 85:1353–1360.

Hardell L, Eriksson M, Nordstrom M. 2002. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma. 43:1043–1049. Cited In: IARC 2015.

Haseman JK. 1983. A reexamination of false-positive rates for carcinogenesis studies. Fundam Appl Toxicol. 3:334–339.

Health and Welfare Canada. 1991. Preharvest application of glyphosate (Roundup) herbicide. Ottawa (ON): Health and Welfare Canada, Pest Management Regulatory Agency (PMRA), Plant Industry Directorate. Pesticide Information Division (Pesticides Directorate Discussion Document, Vol. 91, Iss. 1, 92 p.

Health Canada. 2015. Proposed re-evaluation decision PRVD2015-01, glyphosate. Ottawa (ON): Health Canada, Pest Management Regulatory Agency (PMRA). Available from: http://www.hc-sc.gc.ca/cps-spc/pest/part/consultations/_prvd2015-01/prvd2015-01-eng.php [Archived June 17, 2015].

Hill AB. 1965. The environment and disease: association or causation. J R Soc Med. 58:295–300.

Hill AB. 1971. Statistical evidence and inference. In: A short textbook of medical statistics. London: Hodder and Stoughton; p. 283–296.

Hohenadel K, Harris SA, McLaughlin JR, Spinelli JJ, Pahwa P, Dosman JA, Demers PA, Blair A. 2011. Exposure to multiple pesticides and risk of non-Hodgkin Lymphoma in men from six Canadian provinces. Int J Environ Res Public Health. 8:2320–2330.

Holsapple MP, Pitot HC, Cohen SM, Boobis AR, Klaunig JE, Pastoor T, Dellarco VL, Dragan YP. 2006. Mode of action in relevance of rodent liver tumors to human cancer risk. Toxicol Sci. 89:51–56.

Honeycutt Z, Rowlands H. 2014. Glyphosate testing report: findings in American mothers' breast milk, urine and water. Moms Across America & Sustainable Pulse, 19 p. Available from: https://d3n8a8pro7vhmx.cloudfront.net/yesmaam/pages/774/attachments/original/1396803706/Glyphosate__Final__in_the_breast_milk_of_American_women_Draft6_.pdf?1396803706.

Hoppe H-W. 2013. Determination of glyphosate residue in human urine samples from 18 European countries. Bremen (Germany): Medical Laboratory Bremen (Report Glyphosate MLHB-2013-06-06), 18 p. Available from: https://www.bund.net/fileadmin/bundnet/pdfs/gentechnik/130612_gentechnik_bund_glyphosat_urin_analyse.pdf.

IARC. 2006. Data for the Monographs. Preamble to the IARC Monographs (amended January 2006). Lyon (France): World Health Organization (WHO), International Agency for Research on Cancer (IARC). Available from: http://monographs.iarc.fr/ENG/Preamble/index.php.

IARC. 2015. Glyphosate. In: Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, tetrachlorvinphos. IARC Working Group, March 3–10, 2015, Lyon (France). Lyon (France): World Health Organization (WHO), International Agency for Research on Cancer (IARC) (IARC Monographs on the Evaluation of Carcinogen Risks to Humans, Vol. 112), p. 1–92. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php.

ICH. 1997. Testing for carcinogenicity of pharmaceuticals: S1B. Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (ICH Harmonised Tripartite Guideline – Current Step 4 version dated 16 July 1997). Available from: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html [Open S1B].

ICH. 2011. Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use: S2(R1). Geneva (Switzerland): International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (ICH Harmonised Tripartite Guideline – Current Step 4 version [Combines S2A & S2B]). Available from: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html.

James RC, Britt JK, Halmes NC, Guzelian PS. 2015. Evidence-based causation in toxicology: a 10-year retrospective. Hum Exp Tox. 34:1245–1252.

JMPR. 1987. Glyphosate. In: Pesticide residues in food – 1986: part II – toxicology. Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment (JMPR) and the WHO Expert Group on Pesticide Residues, September 29–October 8, 1986, Rome. Rome: Food and Agriculture Organization of the United Nations (FAO)/FAO Panel of Experts on Pesticide Residues in Food and the Environment/WHO Expert Group on Pesticide Residues Joint FAO/WHO Meeting on Pesticide Residues (JMPR) (FAO Plant Production and Protection Paper, Vol. 78), p. 63–76. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v86pr08.htm.

JMPR. 2006. Glyphosate. In: Pesticides residues in food – 2004. Evaluations 2004 Part II–Toxicological. Joint Meeting of the FAO Panel of Experts on Pesticide residues in Food and the Environment and the WHO Core Assessment Group (JMPR), Sep 20–29, 2004, Rome. Rome: Food and Agriculture Organization of the United Nations (FAO)/Geneva: World Health Organization (WHO), International Programme on Chemical Safety (IPCS) (WHO/PCS/06.1), p. 95–169. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v2004pr01.pdf.

JMPR. 2014. 5.21. Glyphosate (158) and metabolites. In: Pesticide residues in food 2013. Joint FAO/WHO Meeting on Pesticide Residues and the WHO Core Assessment Group on Pesticide Residues, Geneva,17 to 26 September 2013. Rome: Food and Agriculture Organization of the United Nations/Geneva, World Health Organization (WHO) (FAO Plant Production and Protection Paper No. 219), p. 225–228, 484–486. Available from: http://www.fao.org/publications/card/en/c/299ca869-ae51-5093-8407-9cb30782b9f5/.

JMPR. 2016. Glyphosate (158). In: Pesticide residues in food 2016. Special Session of the Joint FAO/WHO Meeting on Pesticide Residues, Geneva, 9 to 13 May 2016. Rome: Food and Agriculture Organization of the United Nations/Geneva, World Health Organization (WHO) (FAO Plant Production and Protection Paper No. 227), p. 19–28, 45, 72–82. Available from: http://www.fao.org/3/a-i5693e.pdf.

Jonsson J, Camm R, Hall T. 2013. Removal and degradation of glyphosate in water treatment: a review. Aqua. 62:395–408.

Kachuri L, Demers PA, Blair A, Spinelli JJ, Pahwa M, McLaughlin JR, Pahwa P, Dosman JA, Harris SA. 2013. Multiple pesticide exposures and the risk of multiple myeloma in Canadian men. Int J Cancer. 133:1846–1858. Cited In: IARC 2015.

Kier LD. 2015. Review of genotoxicity biomonitoring studies of glyphosate-based formulations. Crit Rev Toxicol. 45:209–918.

Kier LD, Kirkland DJ. 2013. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol. 43:283–315.

Kirkland D, Reeve L, Gatehouse D, Vanparys P. 2011. A core in vitro genotoxicity battery comprising the Ames test plus the in vitro micronucleus test is sufficient to detect rodent carcinogens and in vivo genotoxins. Mutat Res. 721:27–73.

Kirsch-Volders M, Bonassi S, Knasmueller S, Holland N, Bolognesi C, Fenech MF. 2014. Commentary: critical questions, misconceptions and a road map for improving the use of the lymphocyte cytokinesis-block micronucleus assay for in vivo biomonitoring of human exposure to genotoxic chemicals-a HUMN project perspective. Mutat Res Rev Mutat Res. 759:49–58.

Klimisch H-J, Andreae M, Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol. 25:1–5. Cited In: Greim et al. 2015.

Kruger M, Schledorn P, Shrodl W, Wolfgang Hoppe H, Lutz W, Shehata AA. 2014. Detection of glyphosate residues in animals and humans. J Environ Anal Toxicol. 4:210. doi: 10.4172/2161-0525.1000210.

Landgren O, Kyle RA, Hoppin JA, Freeman LEB, Cerhan JR, Katzmann JA, Rajkumar SV, Alavanja MC. 2009. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood. 113:6386–6391.

Markard C. 2014. Ergebnisse der Vorstudie HBM von Glyphosat. Dessau-Roßlau (Germany): Federal Environmental Agency (UBA), Umweltprobenbank des Bundes [Unpublished Report provided to] Berlin (Germany): German Federal Institute for Risk Assessment (BfR).

Maronpot RR, Yoshizawa K, Nyska A, Harada T, Flake G, Mueller G, Singh B, Ward JM. 2010. Hepatic enzyme induction: histopathology. Toxicol Pathol. 38:776–795.

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. 2001. Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev. 10:1155–1163. Cited In: IARC 2015.

Mesnage R, Moesch C, Grand R, Lauthier G, Vendômois J, Gress S, Séralini G. 2012. Glyphosate exposure in a farmer's family. J Environ Protect. 3:1001–1003.

Moher D, Liberati A, Tetzlaff J, Altman DG. 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. Ann Intern Med. 151:264–269, W264.

Monsanto. 1983. A chronic feeding study of glyphosate (Roundup® technical) in mice [Unpublished Report]. East Millstone (NJ): Bio/dynamics Inc. (Project #77-2062, 1981). Cited In: Greim et al. 2015.

Niemann L, Sieke C, Pfeil R, Solecki R. 2015. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. J Verbr Lebensm. 10:3–12.

Nordstrom M, Hardell L, Magnuson A, Hagberg H, Rask-Andersen A. 1998. Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study. Br J Cancer. 77:2048–2052.

Nufarm. 2009. Glyphosate technical: dietary carcinogenicity study in the mouse [Unpublished Report] Derbyshire (UK): Harlan Laboratories Ltd. Cited In: Greim et al. 2015 [As: Nufarm 2009a].

OECD. 2009. Combined chronic toxicity\carcinogenicity studies. In: OECD guidelines for the testing of chemicals. Paris (France): Organisation for Economic Co-operation and Development (OECD) (OECD Guideline No. 453) [Adopted: 7 September 2009]. Available from: http://www.oecd-ilibrary.org/environment/test-no-453-combined-chronic-toxicity-carcinogenicity-studies_9789264071223-en

OECD. 2014. Guidance document for describing non-guideline in vitro test methods. Paris, France: Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides, and Biotechnology. Paris (France): Organisation for Economic Co-operation and Development (OECD), Environment Directorate, Health and Safety Publications (Series on Testing and Assessment no 211; ENV/JM/MONO(2014)35). Available from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2014)35&doclanguage=en.

OECD. 2015. Overview of the set of OECD genetic toxicology test guidelines and updates performed in 2014-2015. Paris (France): Organisation for Economic Co-operation and Development (OECD), Environment Directorate, Health and Safety Publications. Available from: http://www.oecd.org/chemicalsafety/testing/Genetic%20Toxicology%20Guidance%20Document%20Aug%2031%202015.pdf.

Orsi L, Delabre L, Monnereau A, Delval P, Berthou C, Fenaux P, Marit G, Soubeyran P, Huguet F, Milpied N, et al. 2009. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med. 66:291–298. Cited In: IARC 2015.

Pahwa P, Karunanayake CP, Dosman JA, Spinelli JJ, McDuffie HH, McLaughlin JR. 2012. Multiple myeloma and exposure to pesticides: a Canadian case-control study. J Agromedicine. 17:40–50.

Paz-y-Miño C, Muñoz MJ, Maldonado A, Valladares C, Cumbal N, Herrera C, Robles P, Sánchez ME, López-Cortés A. 2011. Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border. Rev Environ Health. 26:45–51. Cited In: IARC 2015.

Paz-y-Miño C, Sánchez ME, Arévalol M, Muñoz MJ, Wittel T, Oleas De-la-Carreral G, Leonel PEil. 2007. Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate. Genet Mol Biol. 30:456–460. Cited In: IARC 2015.

Petkov PI, Patlewicz G, Schultz TW, Honma M, Todorov M, Kotov S, Dimitrov SD, Donner EM, Mekenyan OG. 2015. A feasibility study: can information collected to classify for mutagenicity be informative in predicting carcinogenicity? Regul Toxicol Pharmacol. 72:17–25.

Pratt IS, Barron T. 2003. Regulatory recognition of indirect genotoxicity mechanisms in the European Union. Toxicol Lett. 140/141:53–62.

Sanderson S, Tatt LD, Higgins JPT. 2007. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol. 36:666–676.

Solomon K. 2016. Glyphosate in the general population and in applicators: a critical review of studies on exposures. Crit Rev Toxicol, in this issue. doi:10.1080/10408444.2016.1214678.

Sorahan T. 2015. Multiple myeloma and glyphosate use: a re-analysis of US agricultural health study (AHS) data. Int J Environ Res Public Health. 12:1548–1559.

Speit G. 2013. Does the recommended lymphocyte cytokinesis-block micronucleus assay for human biomonitoring actually detect DNA damage induced by occupational and environmental exposure to genotoxic chemicals? Mutagenesis. 28:375–380.

Stout LD, Ruecker FA. 1990. Chronic study of glyphosate administered in feed to Albino rats [Unpublished Report] St Louis (MO): Monsanto Agricultural Company (No. MSL-10495, job/project No. ML-87-148/EHL 87122). Cited In: JMPR 2006.

Suter GWII, Cormier SM. 2011. Why and how to combine evidence in environmental assessments: weighing evidence and building cases. Sci Total Environ. 409:1406–1417.

US EPA. 1985. Glyphosate; EPA Reg. #: 524-308; mouse oncogenicity study [memo]. Washington (DC): U.S. Environmental Protection Agency (US EPA) (Document No. 004370). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1986a. Glyphosate; EPA Reg. #: 524-308; Roundup; additional histopathological evaluations of kidneys in the chronic feeding study of glyphosate in mice [memo]. Washington (DC): U.S. Environmental Protection Agency (US EPA) (Document No. 005590). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1986b. Transmittal of the final FIFRA Scientific Advisory Panel reports on the February 11–12, 1986 Meeting. Washington (DC): Environmental Protection Agency (US EPA), Office of Pesticides and Toxic Substances. Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1986c. Guidelines for carcinogen risk assessment. Washington (DC): U.S. Environmental Protection Agency (US EPA) (EPA/630/P-03/001FMarch 2005). Available from: http://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

US EPA. 1990. Determination of glyphosate in drinking water by direct-aqueous-injection HPLC, post column derivatization, and fluorescence detection. In: Methods for the determination of organic compound in drinking water – supplement I. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Research and Development (EPA/600/4-90/020). Available from: http://nepis.epa.gov/Exe/ZyPDF.cgi/30000UX8.PDF?Dockey=30000UX8.PDF.

US EPA. 1991a. Second peer review of glyphosate [memo]. Washington (DC): U.S. Environmental Protection Agency (US EPA). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1991b. Glyphosate; 2-year combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats – list a pesticide for reregistration [memo]. Washington (DC): U.S. Environmental Protection Agency (US EPA) (Document No. 008390). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1991c. Peer review on glyphosate [Memo]. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Pesticides, and Toxic Substances. Cited In: IARC 2015 [As: EPA 1991c].

US EPA. 1993. Reregistration Eligibility Decision (RED): glyphosate. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Prevention, Pesticides, and Toxic Substances (EPA 738-R-93-014). Available from: http://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-417300_1-Sep-93.pdf.

US EPA. 2005. Guidelines for Carcinogen Risk Assessment [EPA/630/P-03/001F]. Washington (DC): U.S. Environmental Protection Agency (U.S. EPA), Risk Assessment Forum, National Center for Environmental Assessment (NCEA). Available from: http://www.epa.gov/risk/guidelines-carcinogen-risk-assessment.

US EPA. 2009. Exposure factors handbook: review draft. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Research and

Development, National Center for Environmental Assessment (No. EPA/600/R-09/052A), 1265 p. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid =209866 [Archived].

US EPA. 2012. Glyphosate. section 3 registration concerning the application of glyphosate to carrots, sweet potato, teff, oilseeds (crop group (CG) 20) and to update the CG definitions for bulb vegetable (CG 3-07), fruiting vegetable (CG 8-10), citrus fruit (CG 10-10), pome fruit (CG 11-10), berry (CG 13-07), human health risk assessment. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Chemical Safety and Pollution Prevention (Decision No.: 459870), 28 p.

US EPA. 2013. Glyphosate pesticide tolerances; Final rule (40 CFR Part 180) [EPA-HQ-OPP-2012-0132; FRL-9384-3]. Fed Regist (US). 78:25396-25401. Available from: http://www.regulations.gov/#%21documentDetail;D=EPA-HQ-OPP-2012-0132-0009.

US FDA. 2001. Draft guidance for industry on the statistical aspects of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals; Availability [Docket No. 01N-0006]. Fed Regist (US). 66:23266-23267.

US FDA. 2006. Guidance for industry and review staff: recommended approaches to integration of genetic toxicology study results. Rockville (MD): US Food and Drug Administration (US FDA), Center for Drug Evaluation and Research (CDER). Available from: http://www.fda.gov/downloads/Drugs/ ... /Guidances/ucm079257.pdf.

USGS. 2015. NAWQA Database. Reston (VA): United States Geological Survey (USGS). Available from: http://cida.usgs.gov/nawqa_public/apex/f?p=136:1:0, Accessed September 2 2015.

Weed DL. 2005. Weight of evidence: a review of concept and methods. Risk Anal. 25:1545-1557.

WHO. 1994. Glyphosate. Geneva: World Health Organization (WHO)/International Programme on Chemical Safety (IPCS)/United Nations Environment Program (UNEP) (Environmental Health Criteria, no 159). Available from: http://www.inchem.org/documents/ehc/ehc/ehc159.htm.

Williams GM. 1980. Classification of genotoxic and epigenetic hepatocarcinogens using liver culture assays. Ann NY Acad Sci. 349:273-282.

Williams GM, Iatropoulos MJ. 2002. Alteration of liver cell function and proliferation: differentiation between adaptation and toxicity. Toxicol Pathol. 30:41-53.

Williams GM, Iatropoulos MJ, Enzmann HG, Deschl UF. 2014. Carcinogenicity of chemicals. In: Hayes AW, Kruger CL, editors. Hayes' principles and methods of toxicology. Boca Raton (FL): CRC Press Taylor & Francis Group; p. 1251-1303.

Williams GM, Berry C, Burns M, de Camargo JLV, Greim H. 2016. Glyphosate rodent carcinogenicity bioassay expert panel review. Crit Rev Toxicol, in this issue. doi: 10.1080/10408444.2016.1214679.

Williams GM, Kroes R, Munro IC. 2000. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol. 31:117-165.

CRITICAL REVIEWS IN TOXICOLOGY, 2016
VOL. 46, NO. S1, 21–27
http://dx.doi.org/10.1080/10408444.2016.1214678

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS

Glyphosate in the general population and in applicators: a critical review of studies on exposures

Keith R. Solomon

Centre for Toxicology, University of Guelph, Guelph, ON, Canada

ABSTRACT

The recent classification of glyphosate as a probable human carcinogen by the International Agency for Research on Cancer (IARC) was arrived at without a detailed assessment of exposure. Glyphosate is widely used as an herbicide, which might result in exposures of the general public and applicators. Exposures were estimated from information in the open literature and unpublished reports provided by Monsanto Company. Based on the maximum measured concentration in air, an exposure dose of 1.04×10^{-6} mg/kg body mass (b.m.)/d was estimated. Assuming consumption of surface water without treatment, the 90th centile measured concentration would result in a consumed dose of 2.25×10^{-5} mg/kg b.m./d. Estimates by the Food and Agriculture Organization of the United Nations (FAO) of consumed doses in food provided a median exposure of 0.005 mg/kg b.m./d (range 0.002–0.013). Based on tolerance levels, the conservative estimate by the US Environmental Protection Agency (US EPA) for exposure of the general population *via* food and water was 0.088 mg/kg b.m./d (range 0.058–0.23). For applicators, 90th centiles for systemic exposures based on biomonitoring and dosimetry (normalized for penetration through the skin) were 0.0014 and 0.021 mg/kg b.m./d, respectively. All of these exposures are less than the reference dose and the acceptable daily intakes proposed by several regulatory agencies, thus supporting a conclusion that even for these highly exposed populations the exposures were within regulatory limits.

ARTICLE HISTORY
Received 8 April 2016
Revised 24 May 2016
Accepted 15 July 2016

KEYWORDS
Residues; dietary; surface-water; air; biomonitoring; dosimetry

Table of contents

Introduction

The recent classification of glyphosate as a probable human carcinogen by the International Agency for Research on Cancer (IARC 2015) has generated considerable interest, particularly as the IARC classification was arrived at without a detailed assessment of risk to applicators and the general public. Glyphosate is widely used for control of weeds in agriculture, forestry, and in the management of public and private landscapes. These uses might result in exposures of the general public as well as applicators. Unfortunately, the IARC monograph merely focused on the potential hazards of glyphosate and not on the risks. Exposure is a critical component of risk assessment and, without measured values; it is difficult to provide guidance on the appropriate uses of glyphosate or, for that matter, any pesticide. It is also not possible to properly assess toxicity and hazard data for relevance to humans and the environment. As per their mandate, none of the IARC evaluations characterize exposures analytically or in the context of risk; the monograph on glyphosate (IARC 2015) summarizes several exposure studies from the open literature, but does not use these values to estimate risks. This is different from the approach used by most regulatory agencies such as the US EPA, the Food and Agricultural Agency (FAO) of the United Nations, and the European Food Safety Agency (EFSA) where exposures are compared to Reference Doses (RfDs) or Acceptable Daily Intake (ADIs).

There are several sources of exposure of humans to glyphosate in the environment. These are: air, water, application

CONTACT Keith R. Solomon ksolomon@uoguelph.ca Center for Toxicology, School of Environmental Sciences, University of Guelph, Guelph, ON N1G 2W1, Canada

to crops and target weeds, and food. The following sections are an analysis of exposures of humans to glyphosate from these sources. Data for these exposures were obtained from papers published in the open literature and from unpublished reports provided by the Monsanto Company. These sources of information are listed in the references and summary data are provided in the Supplemental information (SI).

Methods

Unpublished reports of studies on exposure to glyphosate in applicators were provided by the Monsanto Company and covered uses in agriculture and forestry. Other data on exposures were obtained from the open literature as a result of searches in PubMed®, references in reviews, and Google Scholar®. These papers and reports were grouped into sources of exposures and the data analyzed as described below.

Air

Only one paper reported concentrations of glyphosate in air. In a study conducted in Iowa, Mississippi, and Indiana in 2007 and 2008, concentrations of glyphosate and its major environmental degradation, aminomethylphosphonic acid (AMPA) were measured in air and precipitation (Chang et al. 2011). Detections of AMPA were infrequent and the concentrations were small. These are not discussed further. The frequency of detection of glyphosate ranged from 60 to 100% in air and rainwater. Concentrations in air ranged from <0.01 to 9.1 ng/m^3, while those in rain were from <0.1 to 2.5 µg/L. Unless rainwater was collected as drinking water, this would be an incomplete pathway for exposure of humans. Once in contact with soil, exposures would be via surface waters (see below). Concentrations in air were seasonal and the sources were likely associated with application to crops in the growing season. For estimation of human exposure, it was assumed that there was total absorption of glyphosate from the air into the body of a 70 kg human breathing 8 m^3 air (half a day for an adult, US EPA 2009). These values were then used to calculate the systemic dose, based on a worst-case assumption of 100% uptake *via* the respiratory tract.

Water

Glyphosate can enter surface waters through use on aquatic weeds, runoff from sprayed soils, and from drift of spray. Glyphosate is very soluble in water and, although it binds strongly to soils and sediments, small concentrations have been measured on surface waters in the United States. These measurements are part of the US Geological Survey (USGS) National Water-Quality Assessment (NAWQA) program (USGS 2015), which has been in place since the 1980s. Glyphosate was added to the large range of analytes measured in surface water in 2002. These data were downloaded from the NAWQA data warehouse (USGS 2015) and then sorted by concentration. All values measured across the US between 2002 and 2014 were pooled for the analysis. Where concentrations were less than the level of detection (0.02 µg glyphosate acid equivalents (a.e.)/L), these values were substituted with a dummy value of "zero". The values were ranked from the smallest to the largest and a cumulative frequency distribution was derived. These values were processed using the Weibull formula to estimate ranks and plotted on a log-probability scale (Solomon and Takacs 2002). The 90th centile values were calculated from the raw data using the Excel function <=percentile>. Systemic dose was estimated from the assumption of consumption of 2 L of water per day by a 70 kg human with 20% absorption from the gastrointestinal (GI) tract (EFSA 2015). Although chlorine and ozone are highly effective for removing glyphosate and AMPA during purification of drinking water (Jönsson et al. 2013), it was assumed that treatment did not remove any glyphosate. The estimated concentrations are thus a worst-case.

Food and bystanders

Several studies have measured concentration of glyphosate in "bystanders" and people not involved in application of glyphosate. Bystanders are presumable exposed *via* food, water, and air (see above). It is also assumed that bystanders are exposed on a daily basis through the environment and/or food and drinking water, and that these exposures are constant and not episodic as in an applicator. Here, a single daily sample of urine is a reasonable surrogate for daily exposures, although uncertainty would be reduced with more frequent samples and analysis of total daily urinary output. Several of these studies were critically reviewed in 2015 (Niemann et al. 2015). This review was thorough, but the strengths of the methods of the original studies were variable. In addition, the authors did not correct for incomplete excretion of glyphosate (95%) as has been done for the applicator studies. In a study of farm and non-farm households in Iowa (Curwin et al. 2007), urine samples were analyzed from 95 adults and 117 children. A study in Europe (Mesnage et al. 2012) measured exposures in a farm family (two adults and three children). A report on the analysis of urine of 182 people from 18 countries (Hoppe 2013) provided data on concentrations in urine. In another study, urine concentrations of 40 male and female German students were measured (Markard 2014). The original study was in German and the value used here for the systemic dose is from the review of Niemann et al. (2015). A study using enzyme linked immunosorbent assay (ELISA) analysis with an unstated level of quantitation (LOQ) was used to measure the concentrations of glyphosate in samples of urine from more than 300 individuals in the EU (most from Germany) (Krüger et al. 2014). A report of a study in the US on 35 individuals using an ELISA analysis (Honeycutt and Rowlands 2014) provided data from which a systemic dose of glyphosate was estimated.

Where the systemic dose was calculated, it was used. Where dietary exposures were provided, the urinary concentration was used to calculate the systemic dose on the assumption of 2 L of urine per day and a 60 kg person (Niemann et al. 2015).

Under the auspices of the Food and Agricultural Organization of the United Nations, the Joint Meeting on Pesticide Residues (JMPR) conducts routine assessments of residues of pesticides in food (JMPR 2014). These are

evaluated in relation to diets in various regions of the world and exposure *via* food compared to an ADI. In 2013, the JMPR reviewed dietary exposures to glyphosate, its major metabolites, and breakdown products (N-acetyl glyphosate, AMPA, and N-acetyl AMPA) and calculated the international estimated daily intakes (IEDI) of glyphosate for 13 regional food diets (JMPR 2014). These IEDIs were based on estimated mean residues from supervised trails under normal or good agricultural practice. These values were for a 60 kg person but were used without modification.

The US Environmental Protection Agency (US EPA) has calculated exposures to glyphosate using the Dietary Exposure Evaluation Model (DEEM, ver 7.81), which is based on tolerance levels for all commodities and modeled estimates of exposures from food and drinking water for the overall US population (US EPA 2012).

There is some uncertainty in all of these studies and approaches. All of the monitoring studies used relatively few participants (<300), which increases uncertainty and lack of raw data in most studies does not allow variance to be fully characterized. Modeling approaches (US EPA and JMPR) based on maximum residue limits and assumptions of good agricultural practices are also subject to uncertainty; however, the assumptions used are more likely to result in overestimation. However, proportion of foods consumed is based on the statistical analyses of diets and this does incorporate, but not quantify, uncertainty.

Applicators

A relatively large number of studies on exposures of applicators to glyphosate have been conducted (see SI for a full list). Older studies tended to use passive dosimetry, either as whole-body dosimeters or patches. Some of the studies with dosimeters used tracers (dyes or other surrogates) and others analyzed dosimeters for glyphosate itself. Some more recent studies used biological monitoring and some a mixture of biological monitoring and dosimeter-patches. For compounds, such as glyphosate, where the excretion kinetics is well understood, biological monitoring provides a measure of the actual amount of the chemical in the body. For this reason, data from these studies are most appropriate for risk assessment. However, data from dosimetry studies can be used to estimate systemic dose. This allows comparison of exposures from different studies to a benchmark for exposure i.e. the reference dose (RfD) or ADI.

For studies using dosimetry, the normalization to systemic dose was conducted using the procedure outlined in Table 1. This was done for the dosimetry studies listed in SI Table 1. The estimated systemic doses were ranked from smallest to largest and a cumulative frequency distribution was derived. These values were plotted on a log-probability scale as above. The 90th centile values were calculated from the raw data using the Excel® function <=percentile>.

Where an applicator makes a single application, the systemic dose of glyphosate can be estimated from the total amount of glyphosate excreted in the urine over the four or five days following and including the day of application (Acquavella et al. 2004). Glyphosate is rapidly excreted and does not bioaccumulate. If applications are conducted every day, the amount excreted each day provides a time-weighted average for daily exposures. Because glyphosate is applied infrequently in normal agricultural practice, the assumption of a single initial exposure is appropriate for risk assessment.

The procedure of normalization for biomonitoring studies is complicated by the fact that many studies reported concentrations of glyphosate that are less than the LOQ, even on the day of application (d-0), when exposures would be expected to be greatest. Similarly, even if residues were detected on d-0, those on subsequent days might have values less than the LOQ. The common practice of using half the level of detection as a default value might be acceptable for the first observation day, but this fails to account for excretion that would reduce the amount in the body on each successive day. Use of half the LOQ on each day would grossly overestimate the systemic dose. Because of this, normalization of systemic doses was modeled using excretion kinetics and followed the steps outlined in Table 2.

If concentrations in urine are > LOQ for one or more days, the actual elimination rate for the individual can be used to correct for days where concentration is < LOQ. Unless already carried out in the study itself, these corrections were applied to the data in SI Table 2.

Because raw data were available for the studies on applicators, uncertainty could be considered. Total number of participants was large (249, See SI Table 2) and range of the values provided the upper and lower bounds of uncertainty. To be conservative, the 90th centiles of the data were used to characterize reasonable worst-case exposures.

Normalization of the RfD and ADI for systemic dose

Regulatory agencies set allowable limits for consumption of residues of glyphosate exposure based on toxicity studies. The US EPA RfD is 1.75 mg/kg body mass (b.m.)/day (US EPA 2012). The ADI for JMPR/WHO is 1 mg/kg b.m./d (JMPR 2014), while the ADI used by EFSA is 0.5 mg/kg b.m./d (EFSA 2015). In a recent review (summary published on 16 May 2016),

Table 1. Procedure for normalization of dosimetry data to estimate systemic dose.

Step	From		To	Explanation
1	Total residue on patches μg/cm^2)	to	Potential body exposure (μg)	2.1 m^2 surface area for a 70 kg male (US EPA 2009)
2	Potential body exposure (μg)	to	Actual body exposure (μg)	Measured penetration through clothing or default of 10%
3	Actual body exposure (μg)	to	Systemic body exposure (μg)	1% dermal penetration (from the value used by EFSA 2015)
4	Systemic body exposure (μg)	to	Systemic dose (mg/kg body weight/day)	70 kg adult

Table 2. Procedure for normalization of biomonitoring data to estimate systemic dose of glyphosate.

Step	Data	Action
1	LOD = 10 µg/kg urine	Assume half the LOD = 5 µg/kg
2	Adjust estimated dose to amount of urine	Multiple kg urine produced on day by 1/2 LOD
3	D-0 value amount estimated	C_0 amount
4	D-1 value estimated from remainder of d-0 concentration after excretion	Elimination rate constant (k) of 0.86 d^{-1} from (Acquavella et al. 2004) use $C_t = C_0 \times e^{-kt}$
5	D-2 value estimated from remainder of d-1 concentration after excretion	
6	D-3 value estimated from remainder of d-2 concentration after excretion	
7	D-4 value estimated from remainder of d-3 concentration after excretion	
8	D-5 value estimated from remainder of d-4 concentration after excretion	
9	Sum of amounts for each day of urine collected	
10	Correction for monitoring period from elimination rate constant and number of days	For example, 99% for 5 d, divide by 0.99
11	Correction for incomplete excretion (95%)	Based on observations in TK studies in monkeys, which showed that 95% of total systemic dose was excreted *via* urine (Wester et al. 1991), divided by 0.95
12	Correction for dosimeters, if used	Increase dose by percentage of body area represented by the dosimeters
13	Correction for hand wash or gloves, if used	Increase dose by percentage of body area represented by hands
14	Calculate systemic dose	Divide total systemic dose by body mass

C_0: initial concentration; C_t: concentration at time t; LOD: level of detection; TK: toxicokinetic.

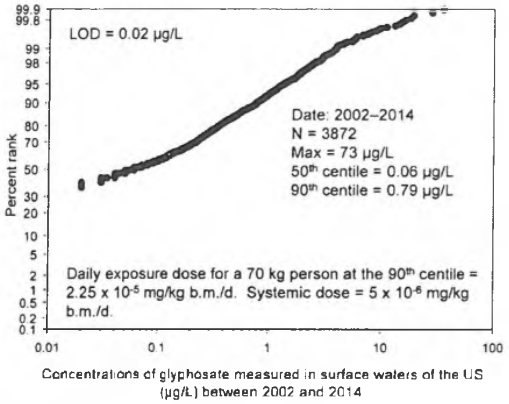


Figure 1. Distribution of concentrations of glyphosate measured in surface waters across the US.

JMPR (2016) has reaffirmed their ADI of 1 mg/kg b.m./d. These values are suitable for comparison to the dietary intake, but for comparison to systemic doses as estimated from biological monitoring (urinary excretion), the ADIs and RfD were divided by five to account for only 20% absorption from the GI tract (EFSA 2015). These normalized values are 0.35, 0.2, and 0.1 mg/kg b.m./d, for US EPA, JMPR, and EFSA, respectively.

Results

Air

Based on the above assumptions of respiratory volume and total absorption, inhaling glyphosate in air at the maximum measured concentration would result in an exposure dose of 1.04×10^{-6} mg/kg b.m./d. This is about five orders of magnitude less than the systemic ADI proposed by EFSA (2015).

Water

The cumulative frequency distribution of concentrations of glyphosate measured in surface waters of the US are shown in Figure 1. The 90th centile was 0.79 µg/L. The maximum concentration measured was 73 µg/L. Consumption of 2 L of drinking water by a 70 kg person at the 90th centile concentration is estimated to result in a consumed dose of 2.25×10^{-5} mg/kg b.m./d, more than four orders of magnitude less than the EFSA ADI.

Food and bystanders

Estimates of the systemic dose resulting from exposures of bystanders and the general public to glyphosate are shown in Table 3. All of these systemic doses are more than 150-times less than the EFSA ADI, normalized for reduced uptake from the gut.

Based on the estimates of daily intake from the FAO/JMPR, the minimum IEDI was 124 µg/person/d, the median was 301, and maximum was 762 (JMPR 2014). These values were normalized to a 60 kg person (0.002, 0.005, and 0.013 mg/kg b.m./d, respectively) for comparison to the ADI. Median exposures are 100-times less than the ADI suggested by EFSA.

The dietary exposure of the general population in the US was estimated by US EPA to be 0.088 mg/kg b.m./d and the range of values was from 0.058 to 0.23 mg/kg b.m./d across a range of age-groups from adults to toddlers. These values are all less than the ADI suggested by EFSA.

Applicators

For the applicator studies, the corrections were applied as in Table 1 or Table 2 and the results are presented graphically in Figure 2. Raw data are provided in SI Tables 1 and 2.

Table 3. Summary of exposures to glyphosate in bystanders and the general public.

Study	Source of exposure	Urinary concentration (µg/L)		Systemic dose (mg/kg b.m./d)		Comment
		Greatest mean	Maximum	Greatest mean	Maximum	
Table 2 from Curwin et al. 2007	Presumably food and water from non-farm households in Iowa	2.7	9.4	0.00009	0.00031	Highest mean and max was in non-farm children
Table 3 from Curwin et al. 2007	Bystanders from farm households in Iowa	2.1	–	0.00007	–	Highest median was in farm children. Max not reported.
Mesnage et al. 2012	Bystander, farm family of five	–	2	–	0.00007	Maximum concentration in child
Hoppe 2013	Presumably food and water	0.82	1.82	0.000027	0.000051	Highest mean was in samples from Malta
Markard 2014	Presumably food and water	–	0.65	–	0.000022	Maximum concentration
Krüger et al. 2014	Presumably food and water	–	5	–	0.00017	Maximum concentration
Honeycutt and Rowlands 2014	Presumably food and water	–	18.8	–	0.00063	Maximum concentration

Systemic dose (mg/kg b.m./d): Urinary concentration (µg/L) × 2 L urine/day ÷60 kg body mass ×1000. b.m.,.

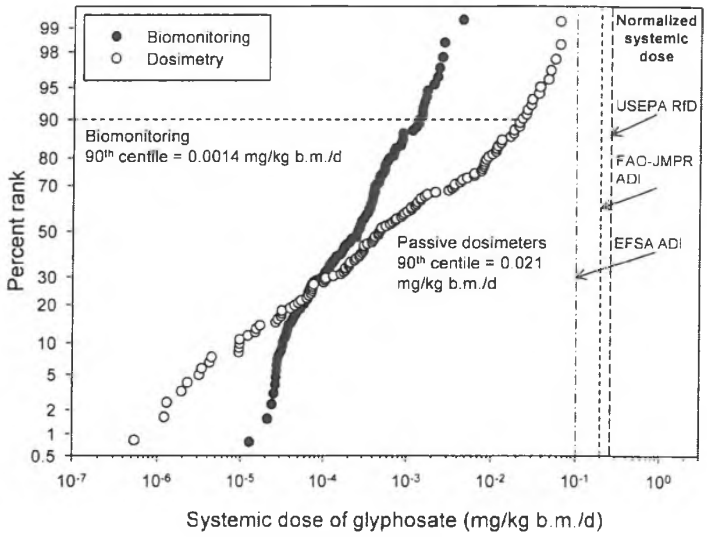


Figure 2. Systemic doses of glyphosate measured in exposure studies conducted in applicators.

The range of values for systemic doses measured in the dosimeter studies (90th centile =0.021 mg/kg b.m./d) was greater than in the biomonitoring studies (90th centile =0.0014 mg/kg b.m./d). Given the corrections applied to the data, this is surprising; however, there are a number of assumptions used in the normalization of the systemic doses that might result in overestimation of exposure. These are likely in the amount of absorption though skin and the penetration of clothing. The assumption of 1% penetration through the skin is greater than the value of 0.7% suggested from observations in an *in vitro* model with human skin (Bo Nielsen et al. 2009). The 90th centile in the dosimetry studies was 0.021 mg/kg b.m./d; about five-times less than the systemic EFSA ADI.

The range of values for the systemic doses determined by biomonitoring was smaller than for the passive dosimeters and more accurately reflects the true exposures. The 90th centile was 0.0014 mg/kg b.m./d; about 70-times less than the systemic EFSA ADI.

Conclusions

Even when using a number of reasonable worst-case assumptions, systemic doses of glyphosate in human applicators, bystanders, and the general public are small. Exposures to glyphosate in the general public are less than EFSA's ADI. The same conclusion applies to applicators. As an overall summary, exposures and ADIs are compared graphically in Figure 3. It should be noted that the ADIs and RFDs used in this assessment are derived from the most sensitive response in long-term feeding studies in the most sensitive laboratory test species and that an uncertainty factor is applied to these values. Furthermore, the biomonitoring exposures measured in applicators aggregate all sources of exposures (air, food, water, and dermal contact) and are still less than the most conservative ADI. Based on the current RfDs and ADIs, there is no hazard and no intolerable risk from exposure to glyphosate *via* its normal use in agriculture and management of weeds in landscapes.

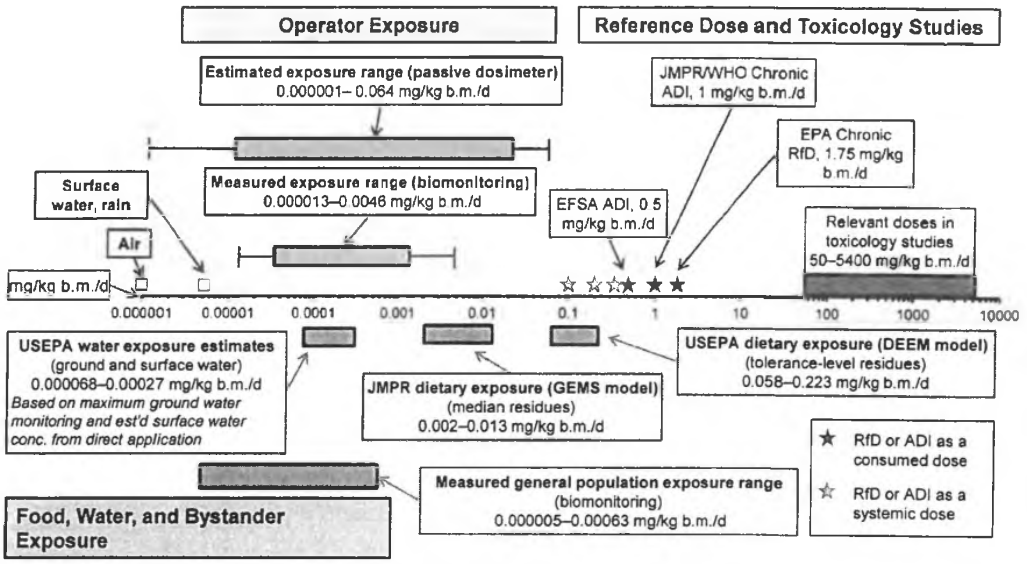


Figure 3. Illustration of measured and estimated exposures to glyphosate in applicators and the general public from various sources. Solid horizontal bars show 10–90th centiles, whiskers show minimum and maximum.

Acknowledgments

The author gratefully acknowledges the extensive comments offered by five reviewers selected by the Editor and presented anonymously to the author. These comments were useful in revising the paper. I thank Monsanto Inc. for providing access to reports from exposure studies for glyphosate in applicators. I wish to thank the authors of the other papers in this series for their constructive suggestions and comments.

Declaration of interest

The employment affiliation of the author is shown on the cover page. However, it should be recognized that the author participated in the review process and preparation of this paper as an independent professional and not as a representative of his employer. Keith R. Solomon previously served as an independent consultant for the Monsanto Company on the European Glyphosate Task Force. KS has not been involved in any litigation procedures involving Monsanto Company and glyphosate. KS's recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). KS acted as a consultant for Intertek. Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food and pharmaceutical industries.

While Intertek Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto Company, previous employees of Cantox had worked in this capacity. Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

Supplemental material

Supplemental material for this article is available online here.

References

Acquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, Chapman P, Bleeke M. 2004. Glyphosate biomonitoring for farmers and their families: results from the farm family exposure study. Environ Health Perspect. 112:321–326.

Bo Nielsen J, Ahm Sorensen J, Nielsen F. 2009. The usual suspects-influence of physicochemical properties on lag time, skin deposition, percutaneous penetration of nine model compounds. J Toxicol Environ Health A. 72:315–323.

Chang FC, Simcik MF, Capel PD. 2011. Occurrence and fate of the herbicide glyphosate and its degradate aminomethylphosphonic acid in the atmosphere. Environ Toxicol Chem. 30:548–555.

Curwin BD, Hein MJ, Sanderson WT, Striley C, Heederik D, Kromhout H, Reynolds SJ, Alavanja MC. 2007. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in Iowa. Ann Occup Hyg. 51:53–65.

EFSA. 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate (EFSA-Q-2014-00546, EFSA-Q-2015-00279, approved on 30 October 2015 by European Food Safety Authority). EFSA J. 13:4302; p. 107. doi:10.2903/j.efsa.2015.4302. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/4302.

Honeycutt Z, Rowlands H. 2014. Glyphosate testing report: findings in American mothers' breast milk, urine and water. Moms Across America & Sustainable Pulse; p. 19. Available from: https://d3n8a8pro7vhmx.cloudfront.net/yesmaam/pages/774/attachments/original/1396803706/Glyphosate__Final__in_the_breast_milk_of_American_women_Draft6_.pdf?1396803706.

Hoppe H-W. 2013. Determination of glyphosate residue in human urine samples from 18 European countries. Bremen (Germany): medical laboratory Bremen. (Report Glyphosate MLHB-2013-06-06); p. 18. Available from: https://www.bund.net/fileadmin/bundnet/pdfs/gentechnik/130612_gentechnik_bund_glyphosat_urin_analyse.pdf.

IARC. 2015. Glyphosate. In: Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, tetrachlorvinphos. IARC working group, March 3-10, 2015. Lyon (France): World Health Organization (WHO), International Agency for Research on Cancer (IARC). (IARC monographs on the evaluation of carcinogen risks to humans, vol 112); p. 1–92. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php.

JMPR. 2014. 5.21. Glyphosate (158) and metabolites. In: Pesticide residues in food 2013. Joint FAO/WHO meeting on pesticide residues and the WHO core assessment group on pesticide residues, Geneva, 17 to 26 September 2013. Rome: Food and Agriculture Organization of the United Nations/Geneva, World Health Organization (WHO). (FAO Plant Production and Protection Paper No. 219); p. 225–228, 484–486. Available from: http://www.fao.org/publications/card/en/c/299ca869-ae51-5093-8407-9cb30782b9f5/.

JMPR. 2016. Summary report for diazinon, glyphosate, malathion. Geneva, Switzerland: Food and agriculture organization of the United Nations/Geneva, World Health Organization (WHO). Joint FAO/WHO meeting on pesticide residues (JMPR); p. 6. Available from: http://www.who.int/foodsafety/jmprsummary2016.pdf?ua =1.

Jonsson J, Camm R, Hall T. 2013. Removal and degradation of glyphosate in water treatment: a review. Aqua. 62:395–408.

Krüger M, Schledorn P, Shrödl W, Wolfgang Hoppe H, Lutz W, Shehata AA. 2014. Detection of glyphosate residues in animals and humans. J Environ Anal Toxicol. 4:210. doi: 10.4172/2161-0525.1000210.

Markard C. 2014. Ergebnisse der Vorstudie HBM von Glyphosat. Dessau-Roßlau (Germany): Federal Environmental Agency (UBA), Umweltprobenbank des Bundes. [Unpublished Report provided to] Berlin (Germany): German Federal Institute for Risk Assessment (BfR).

Mesnage R, Moesch C, Grand R, Lauthier G, Vendômois J, Gress S, Séralini G. 2012. Glyphosate exposure in a farmer's family. J Environ Protect. 3:1001–1003.

Niemann L, Sieke C, Pfeil R, Solecki R. 2015. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. J Verbr Lebensm. 10:3–12.

Solomon KR, Takacs P. 2002. Probabilistic risk assessment using species sensitivity distributions. In: Posthuma L, Suter GW, Traas T, editors. Species sensitivity distributions in ecotoxicology. Boca Raton (FL): CRC Press; p. 285–313.

US EPA. 2009. Exposure factors handbook: review draft. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Research and Development, National Center for Environmental Assessment. (No. EPA/600/R-09/052A); p. 1265. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid =209866.

US EPA. 2012. Glyphosate. section 3 registration concerning the application of glyphosate to carrots, sweet potato, teff, oilseeds (crop group (CG) 20) and to update the CG definitions for bulb vegetable (CG 3-07), fruiting vegetable (CG 8-10), citrus fruit (CG 10-10), pome fruit (CG 11-10), berry (CG 13-07), human health risk assessment. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Chemical Safety and Pollution Prevention. (No. Decision No.: 459870); p. 28.

USGS. 2015. NAWQA Database. Reston (VA): United States Geological Survey (USGS); [cited 2015 Sep 2]. Available from: http://cida.usgs.gov/nawqa_public/apex/f?p=136:1:0.

Wester RC, Melendres J, Sarason R, McMaster J, Maibach HI. 1991. Glyphosate skin binding, absorption, residual tissue distribution, and skin decontamination. Fundam Appl Toxicol. 16:725–732.

CRITICAL REVIEWS IN TOXICOLOGY, 2016
VOL. 46, NO. S1, 28–43
http://dx.doi.org/10.1080/10408444.2016.1214681

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS

Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma

John Acquavella[a], David Garabrant[b], Gary Marsh[c], Tom Sorahan[d] and Douglas L. Weed[e]

[a]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; [b]EpidStat Institute, Emeritus Professor of Occupational Medicine and Epidemiology, University of Michigan, Ann Arbor, MI, USA; [c]Center for Occupational Biostatistics & Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA, USA; [d]Occupational Epidemiology, University of Birmingham, Birmingham, UK; [e]DLW Consulting Services, LLC, University of New Mexico School of Medicine, Albuquerque, NM, USA

ABSTRACT

We conducted a systematic review of the epidemiologic literature for glyphosate focusing on non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM) – two cancers that were the focus of a recent review by an International Agency for Research on Cancer Working Group. Our approach was consistent with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews. We evaluated each relevant study according to *a priori* criteria for study quality: adequacy of study size, likelihood of confounding, potential for other biases and adequacy of the statistical analyses. Our evaluation included seven unique studies for NHL and four for MM, all but one of which were case control studies for each cancer. For NHL, the case-control studies were all limited by the potential for recall bias and the lack of adequate multivariate adjustment for multiple pesticide and other farming exposures. Only the Agricultural Health (cohort) Study met our *a priori* quality standards and this study found no evidence of an association between glyphosate and NHL. For MM, the case control studies shared the same limitations as noted for the NHL case-control studies and, in aggregate, the data were too sparse to enable an informed causal judgment. Overall, our review did not find support in the epidemiologic literature for a causal association between glyphosate and NHL or MM.

ARTICLE HISTORY
Received 8 April 2016
Revised 25 May 2016
Accepted 15 July 2016

KEYWORDS
Glyphosate; non-Hodgkin's lymphoma; multiple myeloma; systematic reviews

Table of contents

Introduction

The epidemiologic literature for glyphosate was reviewed recently as part of a multi-disciplinary scientific review by the International Agency for Research on Cancer (IARC 2015). In the aftermath of the IARC review and the designation of glyphosate as probably carcinogenic to humans, the Monsanto Company requested expert reviews of the glyphosate literature in several technical areas, including epidemiology. IARC's working group concluded that there was limited epidemiologic evidence[1] in human studies for the carcinogenicity of glyphosate, based on a positive association observed for non-Hodgkin's lymphoma (NHL). The panel also noted that excesses had been observed for multiple myeloma (MM) in three studies, but felt these results were less reliable because of small numbers of cases in the available studies and the

CONTACT John Acquavella, PhD acquajohn@gmail.com 2040 Crestview Ct, Prescott, AZ 86305, USA

Table 1. Relevant studies for glyphosate review: non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM).

Author, year	Study location(s)	Study design	More recent analysis	Outcome
Cantor et al. 1992	Iowa + Minnesota	Case-control	De Roos et al. 2003	NHL
Nordstrom et al. 1998	Sweden	Case-control	Hardell et al. 2002	HCL
Hardell & Eriksson 1999	Sweden	Case-Control	Hardell et al. 2002	NHL excluding HCL
McDuffie et al. 2001	Canada	Case-control	n/a	NHL
Hardell et al. 2002	Sweden	Case-control (pooled)	n/a	NHL + HCL
De Roos et al. 2003	Nebraska Iowa/Minnesota Kansas	Case-control (pooled)	n/a	NHL
De Roos et al. 2005	Iowa, North Carolina	Cohort	n/a	NHL, MM
Eriksson et al. 2008	Sweden	Case-control	n/a	NHL
Orsi et al. 2009	France	Case-control	n/a	NHL, MM
Hohenadel et al. 2011	Canada	Case-control	Extension of McDuffie et al. 2001	NHL
Cocco et al. 2013	Czech Republic, France, Germany, Ireland, Italy, Spain	Case-control	n/a	B-cell lymphoma
Brown et al. 1993	Iowa	Case-control	n/a	MM
Landgren et al. 2009	Iowa North Carolina Minnesota	Prevalence Case-control	n/a	MGUS
Pahwa et al. 2012	Canada	Case-control	Kachuri et al. 2013	MM
Kachuri et al. 2013	Canada	Case-control	n/a	MM
Sorahan 2015	Iowa, North Carolina	Cohort	Reanalysis of De Roos et al. 2005	MM

HCL: hairy cell leukemia; MGUS: monoclonal gammopathy of undetermined significance.

related inability to adjust findings for other pesticide and farming exposures. Lastly, the panel concluded that there was no epidemiologic evidence of a relationship for other cancer sites with respect to glyphosate exposure.

In this epidemiology expert panel review, we focused on the possible relationship between glyphosate exposure and two cancers that were the focus of the IARC epidemiology review: NHL and MM. The focus of our review was qualitative. That is, we evaluated the published evidence according to widely accepted validity considerations and criteria for causality. When there were two or more publications with overlapping populations, we concentrated on the most recent publication noting the relationship to a previous publication(s) (see Table 1). Herein, in succeeding sections, we have presented our evaluation approach, reviewed the key validity issues for epidemiologic studies of pesticides, detailed some statistical considerations pertinent to the glyphosate literature, critically evaluated published studies, and, lastly, provided an overall weight of evidence assessment of the epidemiologic evidence for causality between glyphosate and NHL or MM.

Methods

The approach we took was informed by and consistent with the PRISMA guidelines for systematic reviews (Moher et al. 2009), standard approaches to critically evaluating epidemiologic studies (Aschengrau & Seage 2003a,b; Sanderson et al. 2007) and well-recognized interpretative methods – e.g. the criteria-based methods of causal inference (Hill 1965, 1971) – sometimes referred to as "weight of evidence" methods (Weed 2005). With this approach in mind, we address the following questions:

1. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and NHL?
2. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and MM?

Other types of scientific evidence are often evaluated when making causal determinations, including data on human exposure as well as animal studies and studies on mechanism. Since exposure assessment is critical for the validity of occupational epidemiologic studies and biologic plausibility is informed by presumed dose, the former were considered in our overall assessments.

Literature search and included/excluded published papers

A systematic search of the medical literature was performed to identify all analytic epidemiological studies that have examined the possible relationships between exposure to glyphosate and NHL and MM. The aim was to include all such publications – case control studies, cohort studies and pooled analyses – published to the present. In this process, other publications are typically identified, such as reviews, commentaries, methodological investigations, letters to the editor and case reports (or case series). Our primary concern here, however, was the evaluation of the published analytical epidemiological studies of glyphosate and either NHL or MM. To the extent that other types of publications inform our assessment, those papers will be cited in this report. The so-called "gray literature[2]" was not reviewed.

Medline (PubMed) and TOXLINE were searched for English-language publications (with no time constraints) as follows:

a. PubMed: (2 August 2015): search terms: "glyphosate" and "cancer" ($n = 31$);
b. TOXLINE: (2 August 2015): search terms: "glyphosate" and "cancer" ($n = 48$);
c. PubMed: (13 August 2015): search terms: "herbicide" and "cancer" and "lymphoma" and "epidemiology" ($n = 153$);
d. PubMed: (24 August 2015): search: "herbicide" and "cancer" and "multiple myeloma" and "epidemiology" ($n = 38$);

Table 2. Results for glyphosate: Non-Hodgkin's lymphoma (NHL).

Author, year (study design)	# cases, controls total or exposed	OR/RR (95% CI)	Multivariate adjustments	Outcome
McDuffie et al. 2001	517, 1506 [total]			NHL
(case-control)	51, 133	Any use OR = 1.2 (95% CI 0.8, 1.7)	Age, province, medical conditions	
	28, 97	≤2 days/year OR = 1.0 (95% CI 0.6, 1.6)	Age, province	
	23, 36	>2 days/year OR = 2.1 (95% CI 1.3, 2.7)		
Hardell et al. 2002	515, 1141 [total]			NHL + HCL
(case-control)	8, 8	Any use OR = 3.0 (95% CI 1.1, 8.5)	None	
	8, 8	Any use OR = 1.9 (95% CI 0.6, 6.2)	Multivariate (unspecified)	
De Roos et al. 2003	650, 1933 [total]			NHL
(case-control)	36, 61	Any use OR = 2.1 (95% CI 1.1, 4.0)	Age, other pesticides, study site	
	36, 61	Any use OR = 1.6 (95% CI 0.9, 2.8)	Age, other pesticides, study site, priors for chemical class and probability of being carcinogenic (hierarchical model)	
De Roos et al. 2005	71 exposed cases	Any use RR = 1.1 (95% CI 0.7, 1.9)	Age, education, smoking, alcohol, family history, state, 10 pesticides	NHL
(cohort, $n = 57\,311$)	21 unexposed cases			
	29 cases	1–20 days RR = 1.0 (referent)	same	
	15 cases	21–56 days RR = 0.7 (95% CI 0.4, 1.4)		
	17 cases	57–2678 days RR = 0.9 (95% CI 0.5, 1.6)		
Eriksson et al. 2008	910, 1016 [total]			NHL
(case-control)	29, 18	Any use OR = 2.0 (95% CI 1.1, 3.7)	Age, sex, year of diagnosis or enrollment	
	17, 9	>10 days OR = 2.4 (95% CI 1.0, 5.4)	Same	
Orsi et al. 2009	244, 436 total			NHL
(case-control)	12, 24	Any use OR = 1.0 (95% CI 0.5, 2.2)	Age, center, socioeconomic category	
Cocco et al. 2013	2348, 2462 [total]			B-cell lymphoma
(case-control)	4, 2	Any use OR = 3.1 (95% CI 0.6, 17.1)	Age, sex, education, study center	

CI: confidence interval; HCL: hairy cell leukemia; OR: odds ratio; RR: relative risk.

After removal of duplicates and examining the titles and abstracts, 11 publications were identified as relevant. Reasons for exclusions include: not analytical epidemiology, glyphosate not examined, and NHL and/or MM not examined.

An additional seven relevant analytic epidemiological studies were identified after examining reference lists from the publications above, the IARC Monograph 112 (2015) wherein glyphosate and cancer were evaluated, as well as personal collections of relevant papers by the expert panel. Upon further review, two of these references were excluded: Lee et al. (2005) because it did not focus on NHL or MM (only glioma) and the meta-analysis of Schinasi and Leon (2014) because our focus was on the primary literature. A meta-analysis by Chang and Delzell (2016) that was pending publication at the time of our review would have been excluded for the same reason.

The 16 relevant analytical epidemiological studies are listed in Table 1. Data collected from each study included the following: first author, year of publication, study design, number of cases and controls (for case-control studies), number of participants in cohort studies, results (typically in terms of an estimate of the relative risk [RR], e.g. an odds ratio [OR] with accompanying 95% confidence interval [95% CI]), exposure–response (if available), variables adjusted for in the analyses, and outcome (e.g. NHL, MM). See Tables 2 and 3 for details.

Each study was evaluated by the panel for the following key features that relate to study validity: recall bias (likely/unlikely[3]), exposure misclassification (likely/unlikely), exposure–response analyses with a trend test (yes/no), selection bias (likely/unlikely), adjustment for confounding by other (non-glyphosate) pesticides (yes/no), adjustment for confounding from other variables (yes/no), pathological review of cases (yes/no), proxy respondents (%cases/%controls), bias from sparse data (possible/no), blinding of interviews (yes/no/unclear) and consideration of induction/latency (yes/no). See Table 4 for details.

Validity considerations

Selection bias and recall bias

With the exception of one notable cohort study (De Roos et al. 2005), epidemiologists have employed the case control design to investigate glyphosate. Case control and cohort studies are related designs. Both study designs, if conducted with high quality, can produce valid results. In fact, the case control design is best thought of as including the cases that would have been detected in a hypothetical cohort study

Table 3. Results for glyphosate: multiple myeloma (MM).

Author, year (study design)	# cases, controls Total or exposed	OR/RR (95% CI)	Multivariate adjustments	Outcome
Brown et al. 1993 (case-control)	173, 650 [total] 11, 40	Any use OR = 1.7 (95% CI 0.8, 3.6)	Age, vital status	MM
De Roos et al. 2005 (cohort, $n = 57\,311$)	24 exposed cases Eight unexposed cases	Any use RR = 1.1 (95% CI 0.5, 2.4)	Age	MM
	Not specified	Any use RR = 2.6 (95% CI 0.7, 9.4)	Age, education, smoking, alcohol, family history, state, 10 pesticides	
	Eight exposed cases	1–20 days RR = 1.0 (referent)	Age, education, smoking, alcohol, family history, state, 10 pesticides	
	Five exposed cases	21–56 days RR = 1.1 (95% CI 0.4, 3.5)		
	Six exposed cases	57–2678 days RR = 1.9 (95% CI 0.6, 6.3)		
Orsi et al. 2009 (case-control)	56, 313 [total] 5, 18	Any use OR = 2.4 (95% CI 0.8, 7.3)	Age, center, socioeconomic category	MM
Kachuri et al. 2013 (case-control)	342, 1357 [total] 23, 108	Any use OR = 1.1 (95% CI 0.7, 1.9)	Age, province, smoking, selected medical conditions, family history of cancer	MM
			Same	
	11, 78	<2 days/year OR = 0.7 (95% CI 0.4, 1.4)		
	10, 26	>2 days/year OR = 2.1 (95% CI 0.95, 4.7)		
Sorahan 2015	24 exposed cases Eight unexposed cases	Any use RR = 1.1 (95% CI 0.5, 2.5)	Age	MM
Reanalysis of De Roos et al. 2005				
	24 exposed cases	Any use RR = 1.2 (95% CI 0.5, 2.9)	Age, sex, education, smoking, alcohol, family history of cancer, education, 10 pesticides	
	Eight unexposed cases			
	Eight cases	Never used RR = 1.0 (referent)	Age, sex, education, smoking, alcohol, family history of cancer, education, 10 pesticides	
	10 exposed cases	1–20 days RR = 1.1 (95% CI 0.4, 3.0)		
	Eight exposed cases	21–57 days RR = 1.5 (95% CI 0.5, 4.3)		
	Six exposed cases	57–2678 days RR = 1.4 (95% CI 0.4, 4.5)		

CI: confidence interval; HCL: hairy cell leukemia; OR: odds ratio; RR: relative risk.

1. Reanalysis of De Roos et al. to assess the exclusion of 14 000 with some missing covariate data as the explanation for the difference in RRs adjusted for age (RR = 1.1) versus adjusted for age, education, smoking alcohol, family history, state and 10 pesticides (OR = 2.6).

along with a sample of the source population (Rothman et al. 2008). The purpose of the control group is to determine the relative size of the exposed and unexposed populations that gave rise to the cases, so as to enable valid risk estimates for exposed versus unexposed populations. At times in case control studies, the control population is selected for convenience or practicality in a way that does not allow determining the relative size of the exposed and unexposed populations. For example, hospital controls may be less likely to have strenuous occupations than the general population; hence farmers and/or others with pesticide exposures might be under-represented among hospital controls. Poor or selective participation by potential controls can produce the same result. Both scenarios are examples of selection bias that would almost certainly generate spurious positive associations between farming exposures and cancers.

A particularly important and well-known potential bias in case control studies of pesticides is recall bias. That is, cases tend to be more likely to remember or report exposures than are study participants who have not been diagnosed with cancer. This bias results from the natural self-examination by cases of what might have caused their grievous illness. Recall bias is not a concern in the sole glyphosate cohort study (De Roos et al. 2005) because exposure was determined from study participants at study entry before follow-up began for health outcomes. Recall bias tends to produce spurious positive associations between exposure and disease.

Concern about recall bias also extends to next-of-kin who participate in epidemiologic studies in place of deceased or disabled family members. Analyses of next-of-kin or proxy respondents have been found to produce results similar to those of first-hand study subjects (e.g. Kachuri et al. 2013) or to show results quite different than those based on first-hand responders (e.g. Lee et al. 2005 – ORs for glyphosate and glioma were 0.4 based on primary respondents and 3.1 for proxy respondents); one never knows the impact of having appreciable numbers of next-of-kin respondents without a thorough analysis of data with/without proxy respondents (Johnson et al. 1993). This concern is noteworthy because the case-control studies for glyphosate frequently have a high proportion of next-of-kin participants and many studies did not evaluate the potential bias from next-of-kin responders.

Table 4. Validity considerations for glyphosate studies.

First author, year	Recall bias	Exposure misclassification	Exposure–response and trend test	Selection bias	Adjusted for confounding from other pesticides yes/no	Adjusted for confounding from other variables yes/no	Pathology review of cases	Proxies %cases/ %controls	Bias from sparse data	Blinding of interviews	Consideration of latency
Brown et al. 1993	Likely	Moderate ever/never	No	Unlikely	No	Yes	Yes	42% for cases; 30% for controls	No	Unclear	No
McDuffie et al. 2001	Likely	Moderate ever/never; appreciable days of use	Yes, no trend test	Likely	No	Yes and no	Yes	21% cases; 15% controls	No	Unclear	No
Hardell et al. 2002	Likely	Moderate ever/never; appreciable in days of use analysis	No	Unlikely	Yes, but variables not specified	Unclear	Yes for NHL, unclear for HCL	43% NHL cases and controls, 0% for HCL	Possible	Yes	No
De Roos et al. 2003	Likely in original publications	Moderate ever/never	No	Likely, in original publications	Yes	Yes	Yes	31% for cases; 40% for controls	No	Yes	No
De Roos et al. 2005	No	Moderate ever/never; appreciable in days of use analysis	Yes, yes	Unlikely	Yes	Yes	Yes	No	Possible in some analyses	N/A	No
Eriksson et al. 2008	Likely	Moderate ever/never	Yes, no trend test	Unlikely	Yes	Age, sex, year of diagnosis	Yes	No	Possible in some analyses	Yes	Yes
Orsi et al. 2009	Likely	Moderate ever/never	No	Likely	No	Yes	Yes	No	Possible	Yes	No
Cocco et al. 2013	Likely	Likely	No	Likely	No	No	20%	No	Possible	Unclear	No
Kachuri et al. 2013	Likely	Moderate ever/never; appreciable in days of use analysis	Yes, no trend test	Likely	No	Yes	Yes	Excluded	No	Unclear	No

NHL: non-Hodgkin's lymphoma.

Exposure assessment and misclassification

With few exceptions, epidemiologic studies of pesticides assess exposure by questioning participants or their next-of-kin about the prior use of specific pesticides and associated work practices. This practice has limitations compared with other branches of occupational research where epidemiologists often have access to objective documentation about past industrial workplace conditions to aid in exposure assessment (e.g. engineering diagrams, process descriptions, job descriptions, area or personal exposure-monitoring data).

A number of publications provide insights about the validity or reliability of self-reported pesticide information used in epidemiologic studies. In one study, approximately 60% of farmers' self-reports agreed with suppliers' records of purchases for specific pesticides (Hoar et al. 1986). In another article, researchers evaluated the repeatability of self-reported pesticide information on enrollment questionnaires for 4188 licensed pesticide applicators, primarily farmers, who filled out questionnaires in successive years (Blair et al. 2002). The year-to-year reliability for reporting any lifetime use of 11 widely used pesticides varied from 79 to 87%; categorical agreement varied from 50 to 59% for typical days of use per year and from 50 to 77% for years of use. Based on this literature, it is apparent that perhaps 10–20% or more of participants in epidemiologic studies may report incorrectly that they have used a specific pesticide and that reporting on frequency of use and years of use is even less certain.

There seems to be considerable under-appreciation of the implications of the acknowledged degree of exposure misclassification in the pesticide literature. Many consider exposure misclassification to almost always be non-differential (e.g. similar for cases and controls) and, therefore, to bias analyses toward the null (or no association between an exposure and a disease). However, even assuming the misclassification is non-differential overall over multiple analyses, the direction of the resulting bias can be uncertain for any specific analysis. As Rothman and Greenland (1998) pointed out, in any given study, random fluctuations can lead to bias away from the null (towards a positive or negative association) even if the classification method satisfies all the conditions for being non-differential (viz. on average). Hence, in the studies considered in this review, with hundreds of comparisons per study, some fraction of results likely will be biased away from the null even if misclassification is non-differential.

Finally, unlike the five days per week, 50 weeks per year routine for exposures in industrial settings, glyphosate and other pesticide applications are not a frequent occurrence for farmers and applicators. In fact, for most, application of a specific pesticide, like glyphosate, is seasonal and happens only a few days per year. The high exposure category in the glyphosate literature is usually two or more days per year – reflecting extremely infrequent use for the great majority of study subjects and, annually, long periods without exposure. This implies that pesticide exposures are much less frequent than other occupational exposures for those who use pesticides in their occupations and that these other, daily exposures need to be addressed comprehensively in any analysis of infrequently used pesticides.

Biomonitoring studies, implications for exposure assessment

Epidemiologists recognize that there is a difference between exposure (viz. reported use) and dose (the quantity of a substance that is absorbed). In fact, dose is of more interest than exposure in studying potential causal associations. For some chemicals, exposure and dose correlate well. For other chemicals, the correlation is low. Understanding the correlation between exposure and dose is essential for exposure–response analyses – an important indicator for a causal relationship.

The properties of a chemical affect dose. Glyphosate is usually formulated as the isopropylamine salt, which has an extremely low vapor pressure of 1.6×10^{-8} mm Hg (Tomlin 2003). Inhalation of spray droplets was found to be a minor route of glyphosate exposure in a study of glyphosate applicators in Finland (Jauhiainen et al. 1991), leaving dermal contact as the primary route of exposure. Dermal penetration experiments, where glyphosate was left undisturbed on skin surfaces of experimental animals and on human skin *in vitro*, indicate a percutaneous absorption of less than 2% (Wester et al. 1991).

Biomonitoring studies show results consistent with glyphosate's physical/chemical properties. In a study of 48 farmers in Minnesota and South Carolina during a normal day of glyphosate application on their farms, 60% of applicators were found to have quantifiable glyphosate in urine (the predominant route of excretion), while 40% of farmers did not (Acquavella et al. 2004). The distribution of urinary concentrations was highly skewed, with only a small percentage of values appreciably different than the one part per billion limit of detection. Nine farmers completed applications in excess of 100 acres and did not have detectable values for glyphosate in their urine. Evaluation of different approaches to exposure assessment used in epidemiologic studies has not shown good correlation with biomonitoring data for glyphosate (Acquavella et al. 2006), implying appreciable misclassification in studies that rely on traditional pesticide exposure assessment approaches.

The maximum systemic dose found in a review of all glyphosate biomonitoring studies completed to date is 0.004 mg/kg (Niemann et al. 2015). For comparison, the US Environmental Protection Agency (US EPA)'s reference dose (viz. the daily oral exposure to the human population, including sensitive subgroups such as children, that is not likely to cause harmful effects during a lifetime) is 500-fold higher at 2 mg/kg/day (US EPA 1993). The geometric mean systemic glyphosate dose for applicators is 0.0001 mg/kg/day.

Statistical considerations

In addition to the potential study biases discussed above, other threats to validity arise from the statistical procedures used (or not used) in the epidemiology studies reviewed for glyphosate. First, glyphosate risk estimates in several studies were based on small numbers of events in the exposure subcategories considered. For example, the case-control studies of NHL reported by Hardell et al. (2002), Cocco et al. (2013), and Eriksson et al. (2008) and of MM reported by Orsi et al. (2009) involved less than 10 exposed cases and/or controls

overall or in specific glyphosate exposure categories. Even the large cohort study of 57 311 pesticide applicators conducted by De Roos et al. (2005) and reanalyzed by Sorahan (2015) included sparse data (viz., 10 or fewer glyphosate-exposed MM cases in each of the three exposure categories considered).

Sparse data not only leads to imprecise risk estimates, but can decrease their validity when analyses are limited to asymptotic procedures (Greenland et al. 2000; Hirji 2006). The phenomenon of a bias away from the null due to small samples or sparse data is termed sparse data bias. It can occur if case-control or cohort studies are analyzed by conventional asymptotic methods such as logistic regression or Poisson regression rather than their counterparts based on exact estimation. For example, in the presence of sparse data, the estimated OR derived from asymptotic conditional logistic regression is substantially overestimated if the true OR is greater than one (Breslow & Day 1980). Sparse data bias also affects estimated CIs and p values (Greenland et al. 2000; Subbiah & Srinivasan 2008). It appears that all studies involving sparse data relied upon asymptotic procedures only, and were thus likely subject to sparse data bias and inflated risk estimates.

As shown in Table 4, with few exceptions, the statistical models used to evaluate NHL or MM risks among pesticide-exposed individuals were deficient at many levels. As all studies were exploratory (viz. not testing *a priori* hypotheses regarding specific pesticide exposures and NHL or MM risk), they produced a large number of risk estimates along with a high probability of some estimates being statistically significant simply due to chance alone. No attempt was made in any of the studies to adjust p values for these multiple comparisons, though one case control study (De Roos et al. 2003) used a two stage hierarchical modeling approach to adjust risk estimates based on pesticide class characteristics and extant carcinogenic classification to minimize false positives. Also, as shown in Table 4, most studies did not adjust glyphosate risk estimates for potential confounding by other pesticide exposures or relevant medical variables, and only one (Eriksson et al. 2008) considered latency period or the time between first (or last) glyphosate exposure and health outcome. Moreover, only one study (Hohenadel et al. 2011), considered the possible interaction or effect modification between pairs of commonly used pesticides.

Even among the few studies that incorporated potential confounding or effect modifying factors, little if any information was provided about the statistical model selection (e.g. asymptotic or exact), model building strategy (e.g. criteria for including/excluding co-variables) or the diagnostic procedures used to evaluate the fit or robustness of intermediate and final models. Thus, in most studies, reported glyphosate risk estimates remained relatively crude (viz. not fully adjusted) and likely biased due to residual confounding, poor model fit and in some cases, sparse data.

NHL studies

Cantor et al. (1992) conducted a NHL case control study in Iowa and Minnesota to evaluate possible causal factors, including pesticides. The data from this study were pooled with two other US NHL case control studies and subsequently reported by De Roos et al. (2003). We defer consideration to that more recent analysis.

Nordstrom et al. (1998) conducted a population-based case control study in Sweden that included 121 cases of hairy cell leukemia (HCL) and 484 general population controls. The intent of the study was to evaluate occupational exposures and smoking as risk factors for HCL. The data from this study are included with data from the Hardell and Eriksson (1999) study in a later publication (Hardell et al. 2002). We defer consideration of both primary studies to that more recent analysis.

McDuffie et al. (2001) conducted a trans-Canada multi-center case control study to evaluate the relationship between pesticide exposures and NHL. Cases ($n = 517$) were identified from provincial Cancer Registries except in Quebec, for which hospital ascertainment was used. Controls ($n = 1506$) were selected at random from the provincial Health Insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario) or voters' lists (British Columbia). Participation was much higher among invited cases (67%) than among invited controls (48%). Pesticide exposure was determined through telephone interviews of study participants or their proxies (21% of cases, 15% of controls). The authors used conditional logistic regression to estimate ORs. The OR for any reported glyphosate use was 1.2 (95% CI 0.8–1.7) controlling for age, province and medical variables associated with NHL. The strongest pesticide associations were with mecoprop (OR = 2.3) and dicamba (OR = 1.9). A subsequent analysis by reported days of use per year (none, $\leq$2 days/year, >2 days/year) showed glyphosate ORs of 1.0, 1.0 (95% CI 0.6–1.6), and 2.1 (95% CI 1.3–2.7), respectively. This latter analysis did not adjust for medical variables that were controlled in the analysis of any glyphosate use or for the effects of other pesticides.

> **Assessment:** The strengths of this study are the relatively large number of NHL cases and the likelihood that almost all cases were confirmed histologically. The limitations are likely residual confounding in the analysis by days of use by the uncontrolled effects of medical variables and other pesticides, selection bias (differential participation by cases and more proxies for cases), and possible recall bias.

Hardell et al. (2002) reported a pooled analysis of two case control studies; one of NHL and the other of HCL. Both of these studies were previously reported as separate case-control studies (Nordstrom et al. 1998; Hardell & Eriksson 1999). HCL is rare, comprising 2% of lymphoid leukemias, and typically affects middle aged to elderly men (Foucar et al. 2008). It is regarded as a mature B cell neoplasm, as are a high proportion of NHLs. It appears that the authors pooled the two separate studies principally to achieve a larger study size under the assumption that the two neoplasms could be treated as a homogeneous entity for etiologic research. However, the pooled analysis is thereby heavily weighted by HCL cases and the results not representative of NHL more broadly. The 404 NHL cases were males aged 25 and older, diagnosed in 1987–1990, and living in mid- and northern Sweden, drawn from regional cancer registries (viz.

histologically verified). Each case was matched on age and sex to two controls drawn from the National Population Registry. The 111 HCL cases were males diagnosed in 1987–1990, identified from the Swedish Cancer Registry covering the whole country. Each HCL case was matched on age, sex and county to four controls drawn from the National Population Registry. A total of 515 cases and 1141 controls were included in pooled analyses of NHL and HCL. A questionnaire was completed by study subjects or next-of-kin regarding complete working history and exposure to various chemicals. Exposure to each chemical was dichotomized, with at least one working day a year before diagnosis being regarded as positive for exposure. Conditional logistic regression was used to estimate ORs and 95% CIs, adjusted for study (NHL versus HCL), study area, and vital status. In the analyses, only subjects with no pesticide exposure were regarded as unexposed[4], whereas subjects who had not used glyphosate but had used other pesticides were excluded. Analysis for glyphosate, unadjusted for other pesticides, showed a positive association (OR = 3.0, 95% CI 1.1–8.5) based on eight exposed cases and eight exposed controls. Although multivariate analyses were done, it was not stated how variables were selected for inclusion or which variables were included in the multivariate models. The multivariate model for glyphosate indicated appreciable confounding in the unadjusted analysis and a reduced, statistically imprecise, positive association for glyphosate (OR = 1.9, 95% CI 0.6–6.2). Analyses based on increasing days of use were presented for some pesticides, but not for glyphosate.

Assessment: The strengths of this study were that cases were histologically confirmed and controls were population-based. The limitations of this publication were many. First, the investigators found a positive association for every class of pesticide and for every individual pesticide, suggesting a systematic bias in either the assessment of exposure (e.g. recall bias, interviewer or subject (inadvertent) unblinding), in the reporting of results, or due to selection bias. Second, the definition of unexposed (viz. no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate and precluded being able to control for possible confounding by other pesticides and farming exposures. Third, there seems to be some inconsistency in exposure assessment between the two studies that were pooled in this publication. The prevalence of exposure to glyphosate was three times higher among HCL cases and controls (1.3%) than it was among NHL study subjects (0.4%), even though both studies were contemporaneous and would be expected to have similar exposure prevalences.

De Roos et al. (2003) reported a pooled analysis of three NHL case-control studies of pesticides and other potential causal factors (Hoar et al. 1986; Zahm et al. 1990; Cantor et al. 1992). This analysis was limited to men and excluded cases and controls with a history of living or working on a farm before (but not after) age 18. Cases from the Nebraska study by Zahm et al. (1990) were diagnosed between July 1983 and June 1986 and were identified using the Nebraska Lymphoma Study Group as well as data from area hospitals. Cases from the Kansas study by Hoar et al. (1986) represented a random sample of cases diagnosed between 1979 and 1981 and selected from the Kansas Cancer Data Service. Cases from the study in Iowa and Minnesota by Cantor et al. (1992) were diagnosed between 1981 and 1983 and were identified from the Iowa State Health Registry along with a surveillance system established in Minnesota. Controls for these studies were randomly selected from population databases (e.g. Medicare, random digit dialing, and state mortality files for deceased cases) and frequency matched to cases on race, sex, age and vital status at time of interview. Cases and controls were interviewed (including next-of-kin when necessary) regarding use of pesticides and/or herbicides as well as other known or suspected risk factors for NHL. The final analysis dataset included 650 cases and 1933 controls, after exclusions of individuals for whom there was missing information. Forty-seven pesticides were included in the analysis after excluding pesticides for which there were not at least 20 persons exposed and data available from all three studies. The exposure metric in the analysis was restricted to any reported use of a specific pesticide, with no consideration of extent of use. Two types of statistical models were used to estimate ORs and 95% CIs: (1) standard logistic regression and (2) hierarchical regression, wherein logistic regression estimates were adjusted in a second stage based on expected similarities of effects within pesticide classes and the presumed *a priori* carcinogenic probability for specific pesticides as determined by external review bodies. For pesticides like glyphosate that were presumed to have a low probability of being carcinogenic, this second stage adjustment tended to draw positive associations toward the null. All analyses were adjusted for age and for the use of 46 other pesticides. Results for glyphosate showed an OR of 2.1 (95% CI: 1.1–4.0) in the logistic regression and a lesser association (OR = 1.6, 95% CI: 0.9–2.8) in the hierarchical regression.

Assessment: The strengths of this analysis were the histological confirmation of NHL cases and the large numbers of cases and controls that enabled simultaneous adjustment of the effects of 47 pesticides. The weaknesses of this study were the reliance on a relatively crude indicator of exposure (ever having used a pesticide with no consideration of the extent of use) and the limitations common to case control studies of pesticides – namely recall bias and, in this case, an appreciably higher proportion of proxy respondents for controls than cases (40% versus 31%).

De Roos et al. (2005) reported glyphosate findings from the Agricultural Health Study (AHS), a large prospective cohort study of health outcomes related to numerous pesticides among more than 53 000 licensed pesticide applicators in North Carolina and Iowa. Analyses for glyphosate considered potential exposure in a number of ways including: ever/never use, estimated cumulative exposure days (CED), and estimated intensity-weighted exposure days (IWED). The statistical approach was Poisson regression and effects were estimated as RRs with 95% CIs. After adjusting for age, findings for ever/never use of glyphosate showed a near null RR of 1.2 for NHL (95% CI 0.7–1.9), based on 92 cases. Further adjustment for education level, pack-years of smoking, alcohol use in last 12 months, family history of cancer, state of residence and 10 other pesticides that were correlated with glyphosate use, and excluding applicators who had missing data for any of these variables, had little effect on findings for NHL (RR 1.1 95% CI 0.7–1.9). Analyses of potential exposure–response effects using the first tertile of CEDs as a baseline category and with adjustments as described above, and

excluding the never-users from the analysis, found a slight non-significant negative trend (1–20 days: RR 1.0; 21–56 days: RR 0.7, 95% CI 0.4–1.4; 57–2678 days: RR 0.9, 95% CI 0.5–1.6). These categorical analyses were repeated for IWEDs and findings were little changed. De Roos et al. (2005) qualified their results as being based on small numbers, but concluded: "... the available data provided evidence of no association between glyphosate exposure and NHL incidence."

Assessment: The strengths of this study are the large size of the study cohort, the high quality assessment of cancer incidence based on statewide registries in Iowa and North Carolina, the lack of proxy respondents, the control for confounding by other pesticides, and the fact that collection of information about pesticide use could not be influenced by health status. The limitations of the study are the relatively short duration of follow-up for AHS cohort members, the relatively small number of NHL cases, and the likelihood of some degree of exposure misclassification in the various analyses.

Eriksson et al. (2008) reported a population based case control study of NHL in males and females aged 18–74 living in Sweden in 1999–2002. Cases were identified through physicians who diagnosed and treated NHL, and all cases were histologically verified. Controls were randomly chosen from population registries in the same health service regions as the cases, and were frequency matched in 10-year age and sex groups. A total of 910 NHL cases and 1016 controls were included in the analyses. The authors emphasized that, in contrast to their previous studies (Hardell et al. 1981; Hardell & Eriksson 1999), the analyses evaluated newer types of pesticides in relation to different histopathological subtypes of NHL. All subjects received a mailed questionnaire focusing on total work history and exposure to pesticides, solvents and other chemicals. For all pesticides, the number of years, number of days per year and length of exposure per day were questioned. Exposure to each chemical was dichotomized, with at least one working day at least a year before diagnosis being regarded as positive. In the analyses, only subjects with no pesticide exposure were regarded as unexposed[5], whereas subjects with other pesticide exposures were excluded. Unconditional logistic regression was used to calculate ORs and 95% CIs, adjusted for age, sex, and year of diagnosis. Analyses for individual herbicides showed positive associations for every agent and ORs were elevated for every other pesticide (although not in every analysis by NHL subtype or category of duration of exposure). In the model for glyphosate and all NHL (not adjusted for other exposures), the OR was 2.0, 95% CI 1.1–3.7 for ever/never exposure, based on 29 exposed cases and 18 exposed controls. Exposure to glyphosate for >10 days showed OR = 2.4, 95% CI 1.0–5.4 (not adjusted for other exposures). Analyses of glyphosate exposure and NHL subtypes (not adjusted for other exposures) were positive for every subtype of NHL, and were statistically significant for lymphocytic lymphoma/B-CLL (OR = 3.4, 95% CI 1.4–7.9) and unspecified NHL (OR = 5.6, 95% CI 1.4–22.0). Results for other NHL subtypes were not statistically significant: all B-cell NHL (OR = 1.9, 95% CI 0.998–3.5); follicular NHL (OR = 1.9, 95% CI 0.6–5.8); DLBCL (OR = 1.2, 95% CI 0.4–3.4); other B-cell NHL (OR = 1.6, 95% CI 0.5–5.0); unspecified B-cell NHL (OR = 1.5, 95% CI 0.3–6.6) and T-cell NHL (OR = 2.3, 95% CI 0.5–10.4). Multivariate analysis of glyphosate exposure was stated to include agents with statistically significant increased ORs or with an OR >1.5 and at least 10 exposed subjects. These models excluded subjects with exposure to pesticides that did not meet these conditions. The multivariate model for glyphosate and all NHL showed a non-significant positive association (OR = 1.5, 95% CI 0.8–2.9) for ever/never exposure, indicating substantial confounding in the analysis that were not adjusted for other pesticides.

Assessment: Strengths of the study include histological verification of cases and use of population-based controls. There were, however, a couple of major limitations. First, the investigators found a positive association for every herbicide and for every individual pesticide (although not in every sub-analysis), suggesting a systematic bias in either the assessment of exposure (e.g. recall bias, interviewer or subject [inadvertent] unblinding), in the reporting of results, or due to selection bias. Second, the definition of unexposed (viz. no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate for cases and controls and precluded being able to control for possible confounding by other pesticides and farming exposures.

Hohenadel et al. (2011) conducted a reanalysis of data included in the McDuffie publication to evaluate the relationship between exposure to specific pesticide combinations and NHL. The authors used unconditional logistic regression to estimate ORs for the total number of pesticides used by type and carcinogenic potential and for pairwise pesticide combinations (neither, either only or both). Where the OR for joint exposure was higher than the OR for exposure to either pesticide alone, interaction on the additive scale was evaluated using an interaction contrast ratio (ICR). Exposure to glyphosate alone yielded an estimated 8% deficit in NHL risk (OR = 0.92, 95% CI 0.5–1.6), whereas use of malathion only was associated with an elevated NHL risk (OR = 2.0, 95% CI 1.3–2.9). The OR of 2.1 (95% CI 1.3–3.4) for joint exposure to glyphosate and malathion was similar to that for malathion alone and there was no indication of a super additive joint effect (ICR <0.5).

Assessment: The strengths and limitations of this study are similar to those outlined for the related study by McDuffie et al. (2001). The re-analysis was more an exploratory assessment of joint exposures than it was a study of specific pesticides *per se* and is of limited relevance for a possible association between glyphosate and risk of NHL.

Orsi et al. (2009) reported a hospital-based case-control study of occupational exposure to pesticides and lymphoid neoplasms (including but not limited to NHL and MM) undertaken in France. Incident cases of NHL ($n = 244$) were identified from six French hospital center catchment areas between 2000 and 2004. A panel of pathologists and hematologists confirmed pathology. Controls ($n = 436$) were selected from the same hospitals as cases; controls had no history of lymphoid neoplasms and were primarily patients from rheumatology and orthopedic departments. Patients admitted for occupation-related diseases or diseases related to smoking and/or alcohol abuse were not eligible as controls although a past history of such diseases/conditions did not eliminate the control. Controls were matched to cases by center, age (±3 years) and gender. Information on cases and controls

involved a standardized self-administered questionnaire on socioeconomic status, family medical history, and lifelong residential and occupational histories. For additional information (on personal and family history), smoking, alcohol, tea and coffee consumption, use of pesticides (insecticides, fungicides, and herbicides) as well as detailed questions about work on farms, a trained interviewer performed a face-to-face interview with cases and controls. Two exposure definitions were used: definite or possible. Duration of exposure was estimated. ORs and 95% CIs were calculated using logistic regression. Results for any use of glyphosate and NHL showed no association (OR = 1.0, 95% CI: 0.5–2.2) based on 12 exposed cases and 24 exposed controls.

Assessment: A strength of this study is that the NHL cases were confirmed histologically. The limitations are no assessment of potential confounding due to the uncontrolled effects of other pesticides/exposures, possible recall bias and selection bias (controls were primarily selected from orthopedic and rheumatological departments where general population prevalence of pesticide exposure would likely be underrepresented). Scanning the ensemble of hundreds of effect estimates shows that the vast majority of estimates (though not for glyphosate) were greater than one, suggesting systematic error across the various analyses.

Cocco et al. (2013) reported results from the EPILYMPH case control study of NHL in six European countries, conducted in 1998–2004. The study included 2348 incident lymphoma cases and 2462 controls. Approximately 20% of the cases had their tissue slides reviewed by a central panel of pathologists. Controls were population-based in Germany and Italy, matched on gender, age (within five years) and residence area. Hospital controls were used in the Czech Republic, France, Ireland and Spain, excluding patients with diagnoses of cancer, infectious disease, and immunodeficiency. The participation rate was 88% in cases, 81% in hospital controls, but only 52% in population controls in Germany and Italy (Cocco et al. 2010). Trained interviewers conducted in-person interviews with a structured questionnaire regarding full time jobs held for a year or longer. Industrial hygienists coded the occupations to the ISCO, International Labour Office (1968) and the NACE, Statistical Office of the European Communities (1996) classifications. Subjects who reported having worked in agriculture were given a job-specific module inquiring in detail about tasks, kinds of crops, size of cultivated area, pests being treated, pesticides used, procedures of crop treatment, use of personal protective equipment, reentry after application and frequency of treatment in days/year. Hygienists reviewed the job modules to assess exposure to pesticides in categories. Exposure was scored in terms of confidence (probability and proportion of workers exposed), intensity and frequency. A cumulative exposure score was calculated. Subjects unexposed to any pesticide[6] were the referent category for all analyses. Unconditional logistic regression was used to calculate ORs and 95% CIs, adjusted for age, gender, education and study center. The authors reported a moderate association between glyphosate (ever/never exposure) and B-cell NHL (OR = 3.1, 95% CI 0.6–17.1) in a univariate analysis that was statistically imprecise being based on only four exposed cases and two exposed controls. Clearly, there were too few exposed cases and controls to estimate an OR for glyphosate controlling for other exposures.

Assessment: Glyphosate exposure was so infrequent in this study that it precluded an informative analysis. Were that not the case, there would have been obvious concerns about selection bias (esp. low participation for controls), confounding by other exposures (esp. solvent exposures found to be associated with NHL is a previous analysis of this data (Cocco et al. 2010), and recall bias. In addition, the definition of unexposed (viz. no exposure to any pesticide) used in the analysis distorted the exposure prevalence for glyphosate and would have precluded being able to control for possible confounding by other pesticides and farming exposures had such analyses been attempted.

MM studies

Brown et al. (1993) conducted a re-analysis of the National Cancer Institute Iowa population-based case-control study (Brown et al. 1990; Cantor et al. 1992) to evaluate the relationship between exposure to specific pesticides and MM. Cases ($n = 173$) were identified from the Iowa Health Registry. Controls ($n = 650$) were frequency matched to cases by age group and vital status at interview and selected from three sources: random digit dialing (living cases under age 65); Medicare records (living cases aged 65+) and state death certificate files (for deceased cases). Participation was relatively high and similar among cases (84%) and controls (78%). Pesticide exposure for 34 crop insecticides, 38 herbicides (including glyphosate) and 16 fungicides was determined from in-person interviews with subjects or their proxies. The authors used unconditional logistic regression to estimate ORs for pesticides handled by at least five cases. Subjects who did not farm[7] were the referent exposure category for these analyses. The OR for mixing, handling or applying glyphosate was 1.7 (95% CI 0.8–3.6) adjusted for vital status and age. Failure to use protective equipment (obtained from interviews) did not appreciably increase the risk for glyphosate (OR = 1.9, 95% CI not reported). None of the pesticides considered showed a statistically significant association with MM risk.

Assessment: Strengths of the study were the histological confirmation of cases and the high and similar participation for cases and controls. Study limitations were its exploratory nature (as noted by the authors), lack of control for potential confounding by possibly relevant personal characteristics or by exposure to other pesticides, and possible recall bias. In addition, the definition of unexposed (viz. non-farmers) used in the analysis excluded 64% of cases and 58% of controls, distorted the exposure prevalence for glyphosate, and would have precluded being able to control for possible confounding by other pesticides and farming exposures had the investigators sought to control potential confounding.

De Roos et al. (2005), based on data from the AHS cohort study described previously, estimated the age-adjusted RR for glyphosate and MM to be 1.1 (95% CI 0.5–2.4), based on 32 cases. Further adjustment for education level, pack-years of smoking, alcohol use in the last 12 months, family history of cancer and state of residence, together with the use of 10 other pesticides that were correlated with glyphosate use, and excluding approximately 14 000 applicators and 13 MM cases with missing data for any of these variables, markedly

increased the RR for MM (RR = 2.6, 95% CI 0.7–9.4). Analyses of exposure–response effects using the first tertile of CEDs as a baseline category and with adjustments as described above, and excluding the never-users from the analysis, produced a non-significant positive trend (1–20 days: RR = 1.0; 21–56 days: RR = 1.1, 95% CI 0.4–3.5; 57–2678 days: RR = 1.9, 95% CI 0.6–6.3; *p* values for trend 0.27). This MM CED analysis was based on 19 (of 32) cases, the other 41% of cases being excluded for any missing covariate information. These analyses were repeated for IWED categories and findings were little changed (RRs 1.0, 1.2, and 2.1; *p* values for trend = 0.17). The authors also repeated the exposure–response analyses for MM, using the never-use group as the baseline category and found a monotonic positive trend (tertile 1: RR = 2.3; 95% CI 0.6–8.9; tertile 2: RR = 2.6; 95% CI, 0.6–11.5; tertile 3: RR = 4.4; 95% CI 1.0–20.2; *p* values for trend = 0.09). The authors noted that the marked difference between the age adjusted MM findings and the more fully adjusted findings (viz. RR = 1.1 versus 2.6) could have been due to selection bias related to the 14 000 AHS cohort members who were dropped from the more fully adjusted analysis due to missing values for one or more variables.

Assessment: The strengths of this study are the large size of the study cohort, the high quality assessment of cancer incidence based on statewide registries in Iowa and North Carolina, the lack of proxy respondents, the control for confounding by other pesticides, and the fact that collection of information about pesticide use could not be influenced by health status. The limitations of the study are the short duration of follow-up for AHS cohort members, the relatively small number of MM cases, the likelihood of some degree of exposure misclassification in the various analyses, and the indications of selection bias affecting RR estimates due to the exclusion of so many cohort members and MM cases from the more fully adjusted analyses (addressed in a subsequent publication by Sorahan 2015).

Orsi et al. (2009) reported a French hospital-based case-control study of occupational exposure to pesticides and lymphoid neoplasms (including but not limited to NHL and MM), described previously. Included were 56 incident cases of MM and 313 controls matched to cases by center, age (±3 years) and gender. ORs and 95% CIs were calculated using logistic regression. Results for glyphosate and MM showed a moderate, but statistically imprecise, association (OR = 2.4, 95% CI: 0.8–7.3) based on five exposed cases and 18 exposed controls.

Assessment: A strength of this study is that the MM cases were confirmed histologically. The limitations are likely residual confounding due to the uncontrolled effects of other pesticides/exposures in the assessment of the OR for glyphosate, possible recall bias, and selection bias (controls were primarily selected from orthopedic and rheumatological departments where general population prevalence of pesticide exposure would likely be under-represented). Scanning the ensemble of hundreds of ORs shows that the vast majority was greater than 1.0, suggesting systematic error across the various analyses.

Landgren et al. (2009) estimated the age-specific prevalence of monoclonal gammopathy of undetermined significance (MGUS) (a medical condition that is sometimes a precursor to multiple myeloma) among a stratified random sample of 678 AHS participants selected based on lifetime organophosphate use. Subjects in the sample had completed all three phases of the AHS questionnaires, were enrolled into a neurobehavioral study nested within the AHS cohort, and had provided serum for analysis. The authors compared MGUS prevalence for this sample to that for the general population of Olmsted County, Minnesota (due to availability of Mayo Clinic MGUS screening data) and found higher prevalence for AHS participants. Within the AHS sample, associations between MGUS prevalence and pesticide exposures and subject characteristics were assessed in logistic regression models adjusted for age and education level. The prevalence OR for MGUS for glyphosate users versus non-users, adjusted for age and education level, was 0.5 (95% CI 0.2–1.0). None of the herbicides studied showed a strong association with MGUS.

Assessment: This is a small exploratory study of pesticide effects on a medical condition that is sometimes a precursor to MM. Taken at face value, the results provide evidence of a weak inverse association between risk of MGUS and glyphosate, though the exploratory nature of this study, the lack of adjustment for other pesticides in pesticide-specific analyses, the cross-sectional nature of the study, and the implied speculative hypothesis underlying the analysis (that pesticides might cause MM by causing MGUS first) limit conclusions that can be drawn from this work.

Pahwa et al. (2012) reported a trans-Canada, multi-center case control study regarding the relationship between pesticide exposures and MM. The publication is related to the trans-Canada NHL study reported initially by McDuffie et al. (2001) wherein there was a common control group for the study of several lymphopoietic cancers. Pahwa et al. (2012) was updated by Kachuri et al. (2013) and we defer consideration to that more recent publication.

Kachuri et al. (2013) presented a reanalysis and extension of Pahwa et al. (2012) in which they excluded 149 (of 1506) controls who did not have an age match with the MM cases. Kachuri et al. utilized unconditional logistic regression to estimate ORs and presented analyses including and excluding proxy respondents (15% of controls and 30% of cases) and adjusting for smoking, which was associated with MM. They also presented analyses by days of use for individual pesticides. Approximately 9% of cases and controls reported use of glyphosate. ORs adjusted for smoking were 1.2 (95% CI 0.8–1.9) including all cases and controls and 1.1 (95% CI 0.7–1.9) excluding cases and controls who had proxy respondents. ORs excluding proxy respondents for one and two days/year of glyphosate use and for two or more days/year were 0.7 (95% CI 0.4–1.3) in the lower use category and 2.0 (95% CI 0.98–4.2) in the higher use category. However, these results for days of use per year were not adjusted for the potential confounding effects of other pesticides or farm exposures.

Assessment: The strengths of this study are the relatively large number of MM cases, the likelihood that almost all cases were confirmed histologically, and the explicit consideration of proxy respondents in the analysis. The limitations are likely residual confounding in the days of use per year analysis by the uncontrolled effects of other pesticides/exposures, selection bias (58% participation for cases and 48% participation for controls), and possible recall bias.

Sorahan (2015) conducted a re-analysis of data from the AHS to assess the basis for the disparate age-adjusted and

more fully adjusted glyphosate MM findings reported by De Roos et al. (2005). The author used Poisson regression to estimate RRs for MM in relation to glyphosate exposure categorized as ever versus never exposed and by levels of CEDs and IWEDs. Applicators who had missing covariate data were included in the analysis in a "not known" category so that the entire AHS cohort could be maintained. The RR for any glyphosate use adjusted for age and gender was 1.1 (95% CI 0.5–2.5); further adjusting for lifestyle factors and use of 10 other pesticides yielded a similar RR of 1.2 (95% CI 0.5–2.9). RRs for MM tended to increase with increasing CED and IWED reaching a peak RR of 1.9 (95% CI 0.7–5.3; p values for trend = 0.2) in the highest category of IWED in the fully adjusted model; however, none of the trend tests or category-specific RRs was statistically significant. This reanalysis showed that selection bias was associated with inflated MM risk estimates in the paper by De Roos et al. (2005). Those excluded from the analysis included five of eight MM cases in the glyphosate never use category. Sorahan's secondary analysis of this AHS data does not support the hypothesis that glyphosate use is a risk factor for MM and indicates that the practice of restricting analyses to subjects with complete data for all variables can produce appreciable bias.

Assessment: This reanalysis answers some of the questions about the impact of selection bias in the MM analysis by De Roos et al. (2005). Given that there were only 32 MM cases in the original publication, there are obvious limitations to analyses by estimated extent of exposure that can only be addressed with analyses of the AHS cohort using more recent follow-up data.

A special consideration: selection bias in the analysis

According to accepted case control theory (Rothman et al. 2008), the validity of case control studies depends on accurately estimating the exposure prevalence in the population that gave rise to the cases. Exposure prevalence cannot be estimated accurately by excluding from the analysis cases and controls with farm exposures other than glyphosate as was done in several studies. This practice distorts the glyphosate exposure prevalence for cases and controls and biases OR estimates. We illustrate this bias using data from such a glyphosate analysis by Brown et al. (1993).

Brown et al. (1993) analyzed a case control study that had 173 MM cases and 650 controls. Of these, 11 of 173 cases (6%) and 40 of 650 controls (6%) reported use of glyphosate. Hence, there was no difference in exposure prevalence for cases and controls. However, the authors calculated ORs using non-farmers as the referent population with the rationale that they were not exposed to any farm activities. This seemingly well-intentioned modification of the referent population violates a fundamental premise that underlies the validity of case control studies – that controls should be drawn from the population that gave rise to the cases, which, of course, includes individuals with exposure to farm activities. With these exclusions 100 of 173 cases (58%) and 338 of 650 controls (52%), the glyphosate exposure prevalence for cases was increased to 15% (11 of 73 cases) and the glyphosate exposure prevalence for controls was increased a lesser amount to 13% (40 of 312 controls). This created a bias away from the null as illustrated in Tables 5 and 6 in our OR analysis of the Brown et al. data with and without restriction of the referent group to those not exposed to any farm related activities (using Stata version 14).

Table 5. Results as presented by Brown et al. (1993) for glyphosate exposure.

	Case	Control	Total
Exposed	11	40	51
Unexposed	62	272	334
Total	73	312	385

$OR_{unadjusted} = 1.2$, 95% CI 0.5, 2.6.

Table 6. Results for glyphosate exposure using all the cases and controls from Brown et al. (1993).

	Case	Control	Total
Exposed	11	40	51
Unexposed	162	610	772
Total	173	650	823

$OR_{unadjusted} = 1.0$, 95% CI 0.5, 2.1.

Ironically, the reason for the clear bias away from the null is that those with exposure to farm related activities and who did not use glyphosate had higher MM risks than farmers who used glyphosate. In addition, by excluding those without exposure to glyphosate and exposure to other farm exposures, the authors would have precluded being able to control fully for confounding had they attempted multivariate analyses of pesticide exposures. Hardell et al. (2002), Eriksson et al. (2008) and Cocco et al. (2013) made similar exclusions, defining their referent population as those not exposed to pesticides (other than glyphosate). The limited data presented in those papers did not permit us to address statistically the direction and extent of the bias as we have for Brown et al. (1993).

In a similar vein, Sorahan's reanalysis of the MM data from the cohort analysis by De Roos et al. (2005) provides another example of selection bias in the analysis that produced an appreciable bias away from the null. In this case, Sorahan (2015) showed that excluding those with any missing covariate data increased the adjusted RR from 1.1 to 2.6, largely by excluding five of eight MM cases from the glyphosate unexposed population.

Weight of evidence evaluation

Descriptive summary

We systematically collected, summarized and critiqued 16 analytical epidemiological publications examining aspects of the possible relationship between reported use of glyphosate and two cancer types: NHL and MM. We excluded redundant publications (Cantor et al. 1992; Nordstrom et al. 1998; Hardell & Eriksson 1999; Pahwa et al. 2012) in favor of more recent published analyses of the same subjects. This resulted in a final evaluative dataset of seven studies of glyphosate exposure and NHL (see Table 2) and four studies of glyphosate exposure and MM (see Table 3), considering the Sorahan publication (2015) as an extension of De Roos et al. (2005).

The descriptive characteristics of each of these studies were examined for the likely presence or absence of validity concerns (see Table 4). It is clear from Table 4 that only one study in the glyphosate literature (highlighted in Table 4) – the AHS cohort study (De Roos et al. 2005) – was designed to minimize selection bias and recall bias, had only firsthand respondents reporting about exposures (viz. no proxy respondents), and conducted analyses that controlled comprehensively for confounding by personal characteristics and occupational exposures. In addition, the AHS cohort study was the only study that attempted to look at exposure–response relationships while controlling for confounding exposures. As such, it deserves the highest weight in our assessment of the literature. The other studies have so many validity concerns that they cannot be interpreted at face value. Indeed, there is evidence in many of these studies that virtually every exposure studied was associated with NHL or MM – a clear indication of widespread systematic bias and the unreliability of any of the reported exposure-disease associations.

We note one potential limitation to our systematic review. Although we were careful to systematically search the existing literature using search terms and secondary sources to identify relevant studies, it is possible that some relevant studies were not identified. Given the focus on glyphosate epidemiology by IARC and the authors of two recent meta-analyses, included among our secondary sources, we think this potential limitation is unlikely to be consequential.

Assessment of causality

The assessment of causality is a complex process that relies upon a family of well-recognized methods: the general scientific method (familiar to all scientists), study design and statistical methods, and research synthesis methods (e.g. the systematic narrative review, meta-analysis and pooled analysis, and the so-called criteria-based methods of causal inference). Of these, the criteria-based methods are often described and considered in causal assessments, with the most familiar having been proposed by Hill (1965) and utilized extensively in the 1964 Surgeon General's Committee on Smoking and Health and the many publications on the topic that dotted the scientific landscape in the late 1950s and early 1960s (Surgeon General 1964; Weed 2005). These "criteria" or "considerations" are substantive components of the stated methodologies of agencies such as the US EPA (2005) and IARC (2015).

At the center of these methods is the fundamental scientific aim of selecting the best explanation from the alternative explanations that exist for any body of scientific observations, however carefully they were obtained. In epidemiological terms, those alternative explanations typically are defined as cause, bias, confounding (a type of bias) and chance. Some studies are better at excluding alternative explanations than others; cohort studies, for example, are typically better at avoiding recall bias than interview based case-control studies, and recall bias affects not only the exposure of interest (here, glyphosate) but also potential confounding factors (e.g. exposure to other pesticides). Similarly, any and all epidemiologic study designs can – and should – control statistically for factors believed to be potential alternative explanations, i.e. known and putative confounders. For example, studying glyphosate and any lymphohematopoietic cancer without controlling for the potential confounding effects of other pesticides and herbicides, as was widely the case for almost all of the case control studies, does not permit one to exclude those confounders as an alternative explanation. And finally, if the results of an epidemiologic study (whether case-control or cohort) fail to achieve conventional levels of statistical significance – whether defined in terms of "*p* values" or "95% CIs" – then the alternative explanation of chance cannot be excluded. Notably, however, as Greenland (1990) pointed out, interpretation of *p* values and CIs at face value requires the assumption that a particular OR or RR has been estimated without bias (e.g. recall bias, selection bias, or confounding), elevating the importance of concerns about study validity in the interpretation of results.

In essence, all the causal frameworks in epidemiology focus on whether the observed associations are strong (viz. the size of the OR or RR is appreciably different than 1.0), whether the associations appear to have been estimated without bias, whether the OR or RR increases or decreases with increasing exposure (viz. exposure–response), whether the temporal relationship between exposure and effect is considered appropriate, and whether the results are statistically robust enough to rule out chance as an explanation (Hill 1965; Bhopal 2002; Aschengrau & Seage 2003a, 2003b; Sanderson et al. 2007).

Assessment of the NHL studies

With these considerations in mind, for NHL, it is justified scientifically to rely most on the results of the De Roos et al. (2005) cohort study as those best suited to reveal the existence (or not) of an association between exposure to glyphosate and NHL. This cohort study was the only study where information about pesticide use was collected independently of the participants' knowledge of cancer status, where there were no proxies providing information about pesticide use, where exposure–response was evaluated extensively, and where there was statistical adjustment for other pesticide exposures and personal factors in estimating RRs for glyphosate. As De Roos et al. (2005) concluded "... the available data provided evidence of no association between glyphosate exposure and NHL incidence." On the other hand, all the case control studies had the potential limitation of recall bias, many had clear indications of selection bias (either in terms of subject participation or in the analysis), most had very small numbers of glyphosate exposed cases and controls, none showed evidence of an exposure–response relationship, and most did not control for the potential confounding effects of personal factors or other occupational exposures in their glyphosate risk estimates. We consider the case control studies to be inadequate for the assessment of a relationship between glyphosate and NHL and consider the AHS cohort study as the one reliable evaluation of NHL risk from glyphosate. The two limitations of the AHS study are the relatively small number of NHL cases ($n = 92$) and that the length of follow-up after enrollment was less than

a decade. Those limitations speak to statistical robustness, not validity.

Assessment for MM

The glyphosate literature for MM is appreciably sparser than the literature for NHL. Again, the AHS cohort study (De Roos et al. 2005) is the best source of evidence when compared with the three available case control studies. The AHS data indicate that glyphosate users had about the same rate of MM as non-users adjusting for confounding factors (factoring in Sorahan's (2015) reanalysis of the fully adjusted MM results from De Roos et al. (2005) to correct the inadvertent selection bias discussed previously). Exposure–response analyses by De Roos et al. (2005) and Sorahan (2015) were relatively uninformative in light of the few MM cases split among exposure categories. More informative analyses await additional follow-up of the AHS cohort to increase the number of MM cases. The three MM case control studies are based on very small numbers, have concerns about recall bias and selection bias, and did not control for confounding by other exposures. Overall, then, we consider this literature inadequate to make an informed judgment about a potential relationship between glyphosate and MM.

Conclusions

The purpose of this literature review was to address two questions:

1. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and NHL?
2. Does the current published epidemiologic evidence establish a causal relationship between glyphosate exposure and MM?

Our review of the glyphosate epidemiologic literature and the application of commonly applied causal criteria do not indicate a relationship with glyphosate exposure and NHL. In addition, we consider the evidence for MM to be inadequate to judge a relationship with glyphosate. Our conclusion for NHL differs from that of the IARC workgroup seemingly because we considered the null NHL findings from the AHS to be more convincing than the case control studies, in aggregate, with their major limitations. We utilized a structured systematic review approach, we formally addressed pre-specified validity criteria for each study, and our weight of evidence assessment employed widely utilized criteria for causal inference.

Notes

1. A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
2. Grey literature publications may include, but are not limited to the following types of materials: reports (pre-prints, preliminary progress and advanced reports, technical reports, statistical reports, memoranda, state-of-the art reports, market research reports, etc.), theses, dissertations, conference proceedings, technical specifications and standards, non-commercial translations, bibliographies, technical and commercial documentation, and official documents not published commercially (primarily government reports and documents) (Alberani et al. 1990).
3. Whether recall bias, exposure misclassification or selection bias was classified as likely or unlikely was based on a consensus after an in person discussion of each study by the authors.
4. According to accepted case control theory (see Rothman et al. 2008), the validity of case control studies depends on accurately estimating the exposure prevalence in the population that gave rise to the cases. Exposure prevalence cannot be estimated accurately by excluding from the analysis cases and controls with farm exposures other than glyphosate. This practice distorts the glyphosate exposure prevalence for cases and controls and biases OR estimates. We illustrate this in the section on selection bias in the analysis using data from such an analysis by Brown et al. (1993). In addition, excluding those with exposure to other pesticides hinders controlling for confounding by other farming exposures and pesticides in multivariate models.
5. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.
6. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.
7. Per footnote 2, defining the referent in this way distorts the glyphosate exposure prevalence for cases and controls, biases OR estimates, and precludes adequate control for confounding in multivariate models. See the section on selection bias in the analysis for additional details.

Acknowledgements

The authors gratefully acknowledge the very useful comments provided by seven reviewers who were selected by the Editor and anonymous to the authors. These comments helped improve the manuscript.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer. This expert panel evaluation was organized and conducted by Intertek Scientific & Regulatory Consultancy. Funding for this evaluation was provided by Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient. The authors had sole responsibility for the content of the paper, and the interpretations and opinions expressed in the paper are those of the authors.

JA worked for Monsanto from 1989 through 2004 and is a consultant on a legal case unrelated to glyphosate that involves a former Monsanto industrial chemical plant. DG serves on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate, and has consulted on behalf of Bayer Corp. on litigation matters concerning glyphosate and leukemia. GM has no additional declarations. TS has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112, as an Observer for the Monsanto Company. In addition, TS has consulted for Monsanto on litigation matters involving glyphosate. DW has consulted on litigation matters concerning Monsanto that did not involve glyphosate.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

Supplemental material

Supplemental material for this article is available online here.

ORCID

John Acquavella http://orcid.org/0000-0002-6455-9343
Gary Marsh http://orcid.org/0000-0002-2509-0490

References

Acquavella JF, Alexander BH, Mandel JS, Burns CJ, Gustin C, Baker B, Chapman P, Bleeke M. 2004. Glyphosate biomonitoring for farmers and their families: results from the farm family exposure study. Environ Health Perspect. 112:321–326.

Acquavella JF, Alexander BH, Mandel JS, Burns CJ, Gustin C. 2006. Exposure misclassification in studies of agricultural pesticides – insights from biomonitoring. Epidemiology. 17:69–74.

Alberani V, De Castro Pietrangeli P, Mazza AM. 1990. The use of gray literature in health sciences: a preliminary survey. Bull Med Libr Assoc. 78:358–363.

Aschengrau A, Seage GR III. 2003a. Bias. In: Essentials of epidemiology in public health. Sudbury (MA): Jones and Bartlett Publishers; p. 251–279.

Aschengrau A, Seage GR III. 2003b. Guide to the critical review of epidemiologic studies. In: Essentials of epidemiology in public health. Sudbury (MA): Jones and Bartlett Publishers; p. 348–374.

Bhopal R. 2002. Cause and effect: the epidemiological approach. In: Concepts of epidemiology. New York: Oxford University Press. p. 98–132.

Blair A, Tarone T, Sandler D, et al. 2002. Reliability of reporting on lifestyle and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology. 13:94–99.

Breslow NE, Day NE. 1980. Statistical methods in cancer research. Volume I – The analysis of case-control studies. Lyon (France): World Health Organization (WHO), International Agency for Research on Cancer (IARC) (IARC Scientific Publications, No. 32). p. 5–338.

Brown LM, Blair A, Gibson R, Everett GD, Cantor KP, Schuman LM, Burmeister LF, Van Lier SF, Dick F. 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res. 50:6585–6591.

Brown LM, Burmeister LF, Everett GD, Blair A. 1993. Pesticide exposures and multiple myeloma in Iowa men. Cancer Causes Control. 4:153–156.

Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, Schuman L, Dick FR. 1992. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res. 52:2447–2455.

Chang ET, Delzell E. 2016. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. J Environ Sci Health B. 51:402–428.

Cocco P, Satta G, Dubois S, Pili C, Pilleri M, Zucca M, 'tMannetje AM, Becker N, Benavente Y, de Sanjose S, et al. 2013. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occup Environ Med. 70:91–98.

Cocco P, t'Mannetje A, Fadda D, Melis M, Becker N, de Sanjose S, Foretova L, Mareckova J, Staines A, Kleefeld S, et al. 2010. Occupational exposure to solvents and risk of lymphoma subtypes: results from the Epilymph case-control study. Occup Environ Med. 67:341–347.

De Roos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, Sandler DP, Alavanja MC. 2005. Cancer incidence among glyphosate-exposed pesticide applicators in the agricultural health study. Environ Health Perspect. 113:49–54.

De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A. 2003. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med. 60:E11. doi:10.1136/oem.60.9.e11.

Eriksson M, Hardell L, Carlberg M, Akerman M. 2008. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. Int J Cancer. 123:1657–1663.

Foucar K, Falini B, Catovsky D, Stein H. 2008. Hairy cell leukemia. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. WHO classification of tumors of hematopoietic and lymphoid tissues. 4th ed. Lyon (France): World Health Organization (WHO), International Agency for Research on Cancer (IARC); p. 188–190.

Greenland S, Schwartzbaum JA, Finkle WD. 2000. Problems due to small samples and sparse data in conditional logistic regression analysis. Am J Epidemiol. 151:531–539.

Greenland S. 1990. Randomization, statistics, and causal inference. Epidemiology. 1:421–429.

Hardell L, Eriksson M, Lenner P, Lundgren E. 1981. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer. 43:169–176.

Hardell L, Eriksson M, Nordstrom M. 2002. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma. 43:1043–1049.

Hardell L, Eriksson M. 1999. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer. 85:1353–1360.

Hill AB. 1965. The environment and disease: association or causation. J R Soc Med. 58:295–300.

Hill AB. 1971. Statistical evidence and inference. In: A short textbook of medical statistics. London: Hodder and Stoughton; p. 283–296.

Hirji K. 2006. Exact analysis of discrete data. Boca Raton (FL): Chapman and Hall/CRC Press.

Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni JF. Jr. 1986. Agriculture herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA. 256:1141–1147.

Hohenadel K, Harris SA, McLaughlin JR, Spinelli JJ, Pahwa P, Dosman JA, Demers PA, Blair A. 2011. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. Int J Environ Res Public Health. 8:2320–2330.

IARC. 2015. Glyphosate. In: Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, tetrachlorvinphos. IARC Working Group, March 3–10, 2015. Lyon (France). World Health Organization (WHO), International Agency for Research on Cancer (IARC) (IARC Monographs on the Evaluation of Carcinogen Risks to Humans, vol. 112); p. 1–92. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php.

International Labor Office. 1968. The revised international standard classification of occupations. Geneva, Switzerland: International Labor Office (ILO) (ISCO-68). Cited In: Cocco et al. 2010 [Ref. #32].

Jauhiainen A, Rasanen K, Sarantila R, Nuutinen J, Kangas J. 1991. Occupational exposure of forest workers to glyphosate during brush saw spraying work. Am Ind Hyg Assoc J. 52:61–64.

Johnson RA, Mandel JS, Gibson RW, et al. 1993. Data on prior pesticide use collected from self- and proxy respondents. Epidemiology. 4:157–164.

Kachuri L, Demers PA, Blair A, Spinelli JJ, Pahwa M, McLaughlin JR, Pahwa P, Dosman JA, Harris SA. 2013. Multiple pesticide exposures and the risk of multiple myeloma in Canadian men. Int J Cancer. 133:1846–1858.

Landgren O, Kyle RA, Hoppin JA, Freeman LEB, Cerhan JR, Katzmann JA, Rajkumar SV, Alavanja MC. 2009. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood. 113:6386–6391.

Lee WJ, Colt JS, Heineman EF, McComb R, Weisenburger DD, Lijinsky W, Ward MH. 2005. Agricultural pesticide use and risk of glioma in Nebraska, United States. Occup Environ Med. 62:786–792.

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. 2001. Non-Hodgkin's lymphoma and specific pesticide exposures in men: Cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev. 10:1155–1163.

Moher D, Liberati A, Tetzlaff J, Altman DG. 2009. Preferred reporting items for systematic reviews and meta-analyzes: the PRISMA statement. Ann Intern Med. 151:264–269.

Niemann L, Sieke C, Pfeil R, Solecki R. 2015. A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers. J Verbr Lebensm. 10:3–12.

Nordstrom M, Hardell L, Magnuson A, Hagberg H, Rask-Andersen A. 1998. Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukemia evaluated in a case-control study. Br J Cancer. 77:2048–2052.

Orsi L, Delabre L, Monnereau A, Delval P, Berthou C, Fenaux P, Marit G, Soubeyran P, Huguet F, Milpied N, et al. 2009. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med. 66:291–298.

Pahwa P, Karunanayake CP, Dosman JA, Spinelli JJ, McDuffie HH, McLaughlin JR. 2012. Multiple myeloma and exposure to pesticides: a Canadian case-control study. J Agromed. 17:40–50.

Rothman KJ, Greenland S, Lash TL. 2008. Modern epidemiology. 3rd ed. Philadelphia (PA): Wolters Kluwer/Lippincott, Williams & Wilkins.

Rothman KJ, Greenland S. 1998. Modern epidemiology. 2nd ed. Philadelphia (PA): Lippincott Williams & Wilkins.

Sanderson S, Tatt LD, Higgins JPT. 2007. Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography. Int J Epidemiol. 36:666–676.

Schinasi L, Leon ME. 2014. Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis. Int J Environ Res Public Health. 11:4449–4527.

Sorahan T. 2015. Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study (AHS) data. Int J Environ Res Public Health. 12:1548–1559.

Statistical Office of the European Communities. 1996. Statistical classification of economic activities in the European community. Luxembourg: European Commission, Statistical Office of the European Communities (Eurostat) (NACE Rev. 1). Cited In: Cocco et al. 2010 [Ref. #33].

Subbiah M, Srinivasan MR. 2008. Classification of 2×2 sparse data sets with zero cells. Stat Probab Lett. 78:3212–3215.

Surgeon General. 1964. Smoking and health: report of the Advisory Committee to the Surgeon General of the Public Health Service. U.S. Department of Health and Human Welfare (DHHS), Public Health Service (Public Health Service Publication No. 64-1103). Available from: https://profiles.nlm.nih.gov/ps/access/NNBBMQ.pdf.

Tomlin C. 2003. 419. Glyphosate. In: The pesticide manual: a world compendium. 13th ed. Farnham, Surrey (UK): British Crop Protection Council; p. 513–516.

US EPA. 1993. Reregistration Eligibility Decision (RED): glyphosate. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Prevention, Pesticides, and Toxic Substances (EPA 738-R-93-014). Available from: http://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-417300_1-Sep-93.pdf.

US EPA. 2005. Guidelines for carcinogen risk assessment. Washington (DC): U.S. Environmental Protection Agency (US EPA), Risk Assessment Forum, National Center for Environmental Assessment (NCEA) (EPA/630/P-03/001F). Available from: http://www.epa.gov/risk/guidelines-carcinogen-risk-assessment.

Weed DL. 2005. Weight of evidence: a review of concept and methods. Risk Anal. 25:1545–1557.

Wester RC, Melendres J, Sarason R, McMaster J, Maibach HI. 1991. Glyphosate skin binding absorption residual tissue distribution and skin decontamination. Fundam Appl Toxicol. 16:725–732.

Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A. 1990. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology. 1:349–356.

CRITICAL REVIEWS IN TOXICOLOGY, 2016
VOL. 46, NO. S1, 44–55
http://dx.doi.org/10.1080/10408444.2016.1214679

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS

Glyphosate rodent carcinogenicity bioassay expert panel review

Gary M. Williams[a], Colin Berry[b], Michele Burns[c], Joao Lauro Viana de Camargo[d] and Helmut Greim[e]

[a]New York Medical College, Valhalla, NY, USA; [b]Queen Mary, University of London, London, UK; [c]Boston Children's Hospital, Boston, MA, USA; [d]Botucatu Medical School, São Paulo State University, UNESP, Sao Paulo, Brazil; [e]Technical University of Munich, Munich, Germany

ABSTRACT

Glyphosate has been rigorously and extensively tested for carcinogenicity by administration to mice (five studies) and to rats (nine studies). Most authorities have concluded that the evidence does not indicate a cancer risk to humans. The International Agency for Research on Cancer (IARC), however, evaluated some of the available data and concluded that glyphosate probably is carcinogenic to humans. The expert panel convened by Intertek assessed the findings used by IARC, as well as the full body of evidence and found the following: (1) the renal neoplastic effects in males of one mouse study are not associated with glyphosate exposure, because they lack statistical significance, strength, consistency, specificity, lack a dose-response pattern, plausibility, and coherence; (2) the strength of association of liver hemangiosarcomas in a different mouse study is absent, lacking consistency, and a dose-response effect and having in high dose males only a significant incidence increase which is within the historical control range; (3) pancreatic islet-cell adenomas (non-significant incidence increase), in two studies of male SD rats did not progress to carcinomas and lacked a dose-response pattern (the highest incidence is in the low dose followed by the high dose); (4) in one of two studies, a non-significant positive trend in the incidence of hepatocellular adenomas in male rats did not lead to progression to carcinomas; (5) in one of two studies, the non-significant positive trend in the incidence of thyroid C-cell adenomas in female rats was not present and there was no progression of adenomas to carcinomas at the end of the study. Application of criteria for causality considerations to the above mentioned tumor types and given the overall weight-of-evidence (WoE), the expert panel concluded that glyphosate is not a carcinogen in laboratory animals.

Abbreviations: APVMA: Australian Pesticides and Veterinary Medicines Authority; EC: European Commission; EFSA: European Food Safety Authority; FAO: Food and Agriculture Organization; IARC: International Agency for Research on Cancer; ICH: International Conference on Harmonization; IPCS: International Program on Chemical Safety; JMPR: Joint FAO/WHO Meeting on Pesticide Residues; OECD: Organization for Economic Co-operation and Development; US EPA: United States Environmental Protection Agency; US FDA: United States Food and Drug Administration; WHO: World Health Organization

ARTICLE HISTORY
Received 8 April 2016
Revised 7 June 2016
Accepted 15 July 2016

KEYWORDS
Glyphosate; aminomethylphosphoric acid; Roundup; herbicide; cancer; genotoxicity

Table of contents

Introduction

An expert panel was convened by Intertek, as described above (Williams et al. 2016) in response to the scientifically surprising conclusion of an International Agency for Research on Cancer (IARC 2015) panel's conclusion that data on glyphosate were sufficient to be classified by IARC as category 2a – "probably carcinogenic to humans". This conclusion contradicts a number of reviews and regulatory approvals that previously evaluated the carcinogenic and genotoxic potential of glyphosate (N-(phosphonomethyl)glycine) and its metabolite aminomethyl phosphonic acid. Glyphosate-based formulations (GBFs) were also in use prior to the

CONTACT Gary M. Williams, MD gary_williams@nymc.edu New York Medical College, Department of Pathology, BSB413, Valhalla, NY 10595, USA

development of IARC Monograph 112 (Health and Welfare Canada 1991; US EPA 1993a, 2013; WHO 1994; Williams et al. 2000; European Commission 2002; Kier & Kirkland 2013). The consensus among these reviews was that glyphosate was not considered to be an animal or human carcinogen and that the use of glyphosate and GBFs does not pose a genotoxic or carcinogenic hazard or risk. As a result, glyphosate-based herbicides have been approved for use in over 160 countries.

Background to the IARC evaluation

In this section, direct quotes from the IARC documentation are italicized so as to better define their stated objectives.

In examining what are called "agents", IARC refers to "specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioral practices, biological organisms and physical agents". A consistent pattern of consideration of this extraordinarily wide range of categories is clearly hard to achieve by a single mode of action (MoA).

Any of these categories might be considered in a *monograph*, which is stated to be the *first step in carcinogen risk assessment* – more precisely described as hazard identification. The monographs are intended to *identify cancer hazards even when* the perceived *risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.* In some IARC monographs, epidemiological studies used to identify a cancer hazard *can also be used to estimate a dose-response relationship.* The epidemiological review in the IARC document makes clear that this would not be appropriate regarding glyphosate.

IARC indicates that the outcome of these deliberations *represent only one part of the body of information on which public health decisions may be based.* It is nevertheless important that the data presented are the result of a set of deliberations, which acknowledge the characteristics of the scientific method in terms of the consideration of the available data.

Rodent carcinogenicity studies

Background

In considering any potential human carcinogen, information from many fields of science can be of value and none should be ignored, unless there are cogent and properly defined reasons for so doing. Studies that are poorly designed and thus inherently flawed may be excluded from consideration and developments in science subsequent to testing or new information may make it clear that the conclusions of earlier studies were not valid; this is how science progresses.

Animal testing over a significant portion of their lifespan is an integral part of the regulatory process and is clearly intended to provide information, which aids in the identification of potentially carcinogenic properties of a chemical. These properties are those that might result in an increased incidence of neoplasms in treated animals when compared with concurrent control groups. The studies may identify target organ(s) for carcinogenicity, characterize a tumor dose/response relationship, identify a no-observed-adverse-effect level (NOAEL) or point of departure for establishment of a benchmark dose, provide information allowing the extrapolation of carcinogenic effects to low-dose human exposure levels, and may also provide data to test hypotheses regarding a possible MoA (Williams et al. 2014).

Methods for evaluating the results of an extensive database of toxicology and carcinogenicity bioassays, as exist for glyphosate, have evolved from the application of WoE approaches (US EPA, 2005; Suter and Cormier, 2011) to approaches built on the systematic and rigorous methods of systematic evidence-based reviews (James et al. 2015). These approaches recommend that all reliable information be evaluated. Transparent descriptions of studies to be included and excluded are a key component of this approach. For example, if certain studies are determined to be invalid and thus not included, the reasons for these exclusions should be provided.

The majority of carcinogenicity studies are carried out in rodent species, most commonly with dosing *via* the oral route. In regulatory toxicology, the Organization for Economic Co-operation and Development (OECD) guidelines are commonly followed and these have been reviewed over a number of years, most recently in 2008 (OECD 2009). It therefore follows that in reviewing data on compounds that have been tested over many years, a careful examination of the precise nature of the studies reviewed must be made lest they fail to satisfy current standards of reliability. In any review, if any studies are to be ignored, the reasons for this should be provided.

The panel members were of the opinion that the IARC evaluation showed selectivity in the choice of data reviewed, with some omissions for which reasons were not clearly presented. These points will be considered below in more detail with regard to particular tumors, but an example of how an informative data set was not included in the IARC review is highlighted by the paper of Greim et al. (2015) who evaluated 14 carcinogenicity studies, nine chronic/carcinogenicity studies in the rat, including one peer-reviewed published study, and five carcinogenicity studies with glyphosate in mice. All were submitted to support glyphosate Annex I renewal in the European Union (European Commission, 2002) and were detailed in a supplement to the Greim et al. (2015) paper. The IARC Monograph reviewed only six rat and two mouse studies.

The dosing regimens in regulatory studies are determined on the basis of internationally agreed frameworks and in general, some evidence of an effect is sought. The attempt to demonstrate a potential toxic effect with a nontoxic compound, such as glyphosate has meant that the highest doses studied may utilize the compound at dosages of tens of thousands of parts per million in the diet, levels that are considered to be orders of magnitude greater than would be achieved from human exposure. Unusually, for glyphosate, there are also a number of studies in which lower doses are used.

Table 1 from Greim et al. (2015) provides a summary of the results of eight different rat studies conducted on glyphosate. As the studies used dietary exposure, the achieved dose levels in each study vary. Table 1 presents a tabulation of the

Table 1. Summary of select neoplasms in male rats (studies 1–8) listed in the legend*.

Select neoplasm	Tumor incidence/number of animals examined by dose in mg/kg bw/day (ppm diet)											
	Controls – 0 [range in %]	3† (30)	7.4§ (100)	10† (100)	10¶ (adjust)¶¶	31† (300)	73.9§ (1000)	86†† (1500)	89‡ (2000)	100¶ (adjust)¶¶	104# (3000)	121** (2000)
Pancreas islet cell adenoma	20/397 [0–14]	5/49	0/30	2/50	1/24	2/50	0/32	1/51	8/57	2/17	1/74	2/64
Pituitary adenoma	153/398 [6–57]	19/49	4/30	20/48	12/24	18/47	3/31	11/51	32/58	8/19	41/75	17/63
Pituitary carcinoma	4/98 [2–6]	2/49	NF	3/48	1/24	1/47	NF	NF	NF	0/19	NF	NF
Testes interstitial cell (Leydig)	14/447 [0–8]	3/50	0/37	1/50	1/25	6/50	2/32	3/51	0/60	0/19	2/75	2/63
Thyroid C cell adenoma	35/391 [4–18]	1/49	0/26	0/49	1/21	2/49	1/29	#1/51	5/58	1/17	10/74	#1/63
Hepatocellular adenoma	30/351 [0–48]	NF	22/50	NF	1/50	NF	10/48	2/51	2/60	1/49	0/75	2/64
Hepatocellular carcinoma	22/384 [0–42]	0/50	28/50	1/50	1/50	2/50	18/48	0/51	2/60	1/49	1/75	NF
Benign keratoacanthoma (skin)	8/250 [2–5]	NF	NF	NF	NF	NF	NF	3/51	3/60	NF	3/75	0/64

Select neoplasm	Tumor Incidence/number of animals examined by dose mg/kg bw/day (ppm diet)												
	150| (3000)	285†† (5000)	300¶ (adjust)¶¶	354# (10000)	361** (6000)	362† (8000)	740.6§ (10000)	780| (15000)	940‡ (20000)	1000¶ (adjust)	1077†† (15000)	1127# (30000)	1214** (20000)	1290| (25000)
Pancreas islet cell adenoma	NF	2/51	2/21	1/80	0/64	5/60	1/49	NF	7/59	1/49	1/51	1/78	1/64	NF
Pituitary adenoma	NF	10/51	7/21	33/80	18/64	34/58	5/49	NF	32/59	17/50	20/51	42/78	19/63	NF
Pituitary carcinoma	NF	NF	1/21	NF	NF	NF	NF	NF	NF	0/50	NF	NF	NF	NF
Testes interstitial cell (Leydig)	1/49	1/51	0/21	0/80	2/63	3/60	3/50	2/49	2/60	2/50	1/51	2/78	2/64	0/47
Thyroid C cell adenoma	NF	‡‡0/51	2/21	5/79	‡‡1/63	8/58	1/50	NF	7/60	8/49	‡‡3/51	6/78	‡‡0/64	NF
Hepatocellular adenoma	NF	0/51	2/50	2/80	0/64	3/60	21/50	NF	8/60	2/50	1/51	1/78	5/64	NF
Hepatocellular carcinoma	1/49	0/51	0/50	2/80	NF	1/60	24/50	0/49	2/60	0/50	0/51	1/78	NF	0/47
Benign keratoacanthoma (skin)	NF	0/51	NF	0/80	1/64	4/60	NF	NF	5/59	NF	6/51	7/78	1/63	NF

The 25 doses result from the multiple doses per individual study.
*Taken from Greim et al. 2015.
†Study 1 (Monsanto) (CD) SD rats, rated unreliable for carcinogenicity evaluation.
‡Study 2 (Monsanto) (CD) SD rats, including interim sacrifice groups.
¶Study 3 (Cheminova) SD rats.
§Study 4 (Feinchemic Schwebda) Wistar rats.
|Study 5 (Excel) SD rats, rated unreliable for carcinogenicity evaluation.
#Study 6 (Arysta Life Sciences) Crj:CD SD rats, including interim sacrifice groups.
**Study 7 (Syngenta) Alpk:APfSD Wistar rats, including interim sacrifice groups.
††Study 8 (Nufarm) Wistar Han Crl:WI rats.
‡‡Recorded as parafollicular adenoma.
¶¶Dietary concentrations adjusted weekly to achieve target mg/kg bw/day dose.
NF: not found/not reported.

relevant tumor data for each of these eight studies in ascending order of achieved dose (lowest to highest). This allows a comparison of the incidence of specific neoplasms in each of the eight studies at all dose levels. As can be seen from Table 1, some of the benign tumors in male rats that appear to concern IARC in terms of the potential risk to humans, are widely represented in non-exposed animals as well as those exposed to doses well below those that might be expected in standard carcinogenicity studies conducted for regulatory purposes. The incidence of tumors shows no clear or consistent pattern, either across dose or individual study. Such a distribution of findings strongly indicates that these incidences represent spontaneous variations.

Neoplasm data can be analyzed using a survival-adjusted trend test that discriminates among fatal, incidental, and palpable neoplasms (Peto et al., 1980). If one or more tumor types in a valid bioassay show a significant positive trend in incidence rates, the significance level (p value) for rare ($\leq 1\%$ background incidence) neoplasms would be 0.025 and for common neoplasms 0.005 (US FDA 2001; Williams et al. 2014). For pairwise comparisons (control vs high dose), the significance of rare neoplasms would be 0.05 and of common 0.01 (US FDA 2001; Williams et al. 2014).

In the Monograph, IARC concluded that there is *sufficient evidence in experimental animals* for the carcinogenicity of glyphosate, reaching this opinion by the use of trend analysis in the absence of statistical significance in pairwise comparisons. Furthermore, the level of significance which differs between rare and common tumors was not taken into account.

Evaluation of IARC's conclusions

IARC concluded that glyphosate induced:

1. A significant positive trend in the incidence ($p = .037$) of renal tubule carcinomas and of adenomas and carcinomas ($p = .034$) in male CD-1 mice of one study only. This is a rare tumor type.
2. In a second feeding study in the same strain of mice, a significant positive trend in the incidence ($p < .001$) of hemangiosarcomas in male mice.
3. In two dietary studies in SD rats, a significant positive trend ($p < .05$) in the incidence of pancreatic islet cell adenomas occurred in male rats.
4. In the first dietary study in SD rats, a significant positive trend ($p = .016$) in the incidence of hepatocellular adenomas occurred in males.
5. In the first dietary study in SD rats, a significant positive trend ($p = 031$) in the incidence of thyroid C-cell adenomas occurred in females.

The expert panel evaluated each of these conclusions further below.

Kidney tubular-cell neoplasia in mice

The expert panel noted that the conclusions of the IARC monograph 112 (IARC 2015) with respect to kidney neoplasms in male CD-1 mice were based on only one of two oral mouse two-year carcinogenicity studies (Monsanto 1983; Cheminova 1993a) excluding two additional 18-month oral studies in CD-1 mice (Arysta Life Sciences 1997; Nufarm 2009), and one 18-month oral study in Swiss Albino mice (Feinchemie Schwebda 2001). All of the mouse studies were considered by expert groups to meet the guidelines for carcinogenicity bioassay in mice (US EPA 1990; ICH 1997). The two mouse studies evaluated by IARC, which were the first two studies reported, were also reviewed by Williams et al. (2000).

This section examines the renal neoplasms that occurred in the first two-year, oral chronic toxicity, and carcinogenicity study in CD-1 mice (Monsanto 1983), which was subsequently reevaluated by a pathology working group (PWG) (Dr. R M Sauer, Dr. MR Anver, Dr. JD Strandberg, Dr. JM Ward, and Dr. DG Goodman) and peer review experts including Dr. Marvin Kuschner M.D., Dean, School of Medicine, State University of New York at Stony Brook; Dr. Robert A. Squire, Robert A. Squire Associates Inc., Ruxton Maryland; Klaus L. Stemmer M.D., Kettering Laboratory, University of Cincinnati Medical Center, and; Robert E. Olson, M.D., Ph.D., Professor of Medicine and Pharmacological Sciences, State University of New York at Stony Brook (Sauer 1985; US EPA 1985a, 1985b, 1986, 1991a; McConnell 1986) and compares these findings to the other four chronic toxicity and carcinogenicity mouse studies with oral glyphosate (GLY) administration. These latter four studies did not produce renal neoplasms (Cheminova 1993a; Arysta Life Sciences 1997; Feinchemie Schwebda 2001; Nufarm 2009).

In the first two-year bioassay reported by Monsanto in 1983, male and female CD-1 mice were dosed with GLY at 0 (M0/F0, control group), 1000 [157/190, low-dose (LD) group], 5000 [814/955, mid-dose (MD) group] or 30,000 [4841/5874 mg/kg/d, high-dose (HD) group] ppm in the diet. In this and all the other carcinogenicity studies, HD animal survival was high. Some of the pertinent, but not significant, GLY-related effects were observed only in the high-dose group in males. They included: decrease in body weight gain, a centrilobular hepatocellular hypertrophy, and a urinary bladder hyperplasia. In addition, initially, neoplastic (benign) renal tubule adenomas were found microscopically in male mice only (0/49, 0/49, 1/50 (2%), 3/50 (6%) at the terminal necropsy. The initial diagnosis in one MD mouse (mouse #3023), and three HD mice (mouse #'s 4029, 4032, 4041) was that of renal cell adenoma (Monsanto 1983). This rare neoplasm is designated as renal cell adenoma or tubular cell adenoma (Greaves 2012). Macroscopically, the location and dimensions of these adenomas were as follows: In #3023, a mass was found on the right kidney (2.4 × 1.8 cm), in #4029, a very small area was suspected (no location and dimensions were given), in #4032, a suspicious area was found on the left kidney (0.5 × 0.4 cm), in #4041, a suspicious area was found on the left kidney (0.6 cm in diameter). Subsequently, reevaluation was made by a PWG that resulted in a report by Sauer (1985) and McConnel (1986). This was also reflected in four US EPA submissions (US EPA 1985a, 1985b, 1986, 1991a). The final evaluation of the

Table 2. Final evaluation of pertinent renal histopathology findings from Monsanto Study (1983).

Diagnosis	Mouse and group identification	Group incidence
Tubular-cell adenoma	1028	Control 1/49
Tubular-cell carcinoma	**3023***,	Mid dose 1/50
	4029, 4032, 4041	High dose 3/50
Tubular-cell hyperplasia	1018,	Control 1/49
	3031, 3039,	Mid dose 2/50
	4008, 4049	High dose 2/50
Intercurrent† papillary hyperplasia	1008, 1041,	Control 2/49
	3008, 3050	Mid dose 2/50

Bold numbers indicate the original histopathological diagnosis of tubular-cell adenoma in four male mice; TCA/TCC, this combination was utilized in the IARC 2015 evaluation, only the trend analysis was $p = .034$, a value level, which is not significant for rare tumors (US FDA 2001); *, this neoplasm was the largest of all neoplasms; †, intercurrent occurring indicates while another process/renal toxic change was in progress.

kidney pathology produced the following incidences of pertinent renal findings detailed in Table 2.

The overall final incidence of renal neoplasms in male mice was as follows: 1/49, 0/49, 1/50, and 3/50, with the largest neoplasm being in the MD (#3023) group. The important non-neoplastic renal findings of hyperplasia were as follows: 3/49, 0/49, 4/50, and 2/50, indicating absence of a dose-response, with the highest incidence in the MD group, followed by the control group, and the HD group. The LD group had no renal findings.

Based on the pattern of pre-neoplasia and neoplasia described above, the PWG recommendation was that the renal neoplasms were not compound related, since they were not preceded by dose-related proliferative changes (hyperplasia). Thus, there was no dose-response for pre-neoplasia. In addition, no multiple renal neoplasms and no nephrotoxic lesions were found in any of the mice; many mice had proliferative/cystic lesions in the parietal layer of the Bowmans' capsule and proximal convoluted tubules. These changes, however, were more severe in controls. In addition, the females from the HD group of the study had no renal neoplasms and only proximal tubule epithelial basophilia and hypertrophy. No discrepancies were noted in any of the histopathology reporting among the various expert panel groups (Sauer 1985; US EPA 1985a, 1985b, 1986; McConnel 1986).

In addition to the PWG recommendations (above), a review of the renal lesions, which occurred only in 14 out of 198 male mice at the termination of the first (Monsanto 1983) study, showed clearly that none of the occurrences of hyperplasia (tubular-cell hyperplasia or intercurrent papillary hyperplasia were present in mice that had tubular-cell adenoma or tubular-cell carcinoma (Table 2). The absence of hyperplasia indicates that all renal proliferative and neoplastic lesions occurred *de novo* in male mice in all experimental groups (including controls), i.e. they were spontaneous or background lesions, and were not compound related. Moreover, the female mice, which had received 1.2-times, 1.1-times, or 1.2-times more GLY, within the LD, MD, or HD groups, respectively, had no renal neoplastic lesions.

Thus, the Monsanto (1983) report concluded that for male and female mice, the lower NOAEL was 157 mg/kg/d, and the lowest observed adverse effect level was 814 mg/kg/d.

Three additional oral carcinogenicity studies were conducted in CD-1 mice and one in Swiss Albino mice (Cheminova 1993a; Arysta Life Sciences 1997; Feinchemie Schwebda 2001; Nufarm 2009).

The Cheminova (1993a) report, was a two-year mouse study. In this study, no renal neoplasms were evident up to 1000 mg/kg/d (HD) of GLY in CD-1 mice of both sexes.

In an 18-month diet study in CD-1 mice, histopathological evaluations of groups dosed up to 4200 mg/kg/d of GLY (HD), did not show any evidence of renal neoplasms in male or female mice (Arysta Life Sciences 1997).

In an 18-month diet study in Swiss Albino mice, up to 1460 mg/kg/d (HD) of GLY produced no statistically significant neoplastic lesions (Feinchemie Schwebda 2001) and finally, in a 18-month diet study in CD-1 mice at dosages up to 946 mg/kg/d (HD) of GLY was shown not to be carcinogenic to the kidney (Nufarm 2009).

In the last four mouse carcinogenicity studies, multiple-section sampling of kidneys for histopathology was utilized according to Eustis et al. (1994).

Thus, for the five glyphosate mouse carcinogenicity studies, only the first conducted study showed any neoplastic renal lesions and these occurred only in male mice of the MD at 814 mg/kg/d, and HD groups at 4841 mg/kg/d. All of these general and renal neoplastic findings indicating a lack of a glyphosate renal carcinogenic response were reported in key regulatory submission updates (US EPA 1985a, 1985b, 1986, 1991a, 1993a, 1993b, 2012, 2013; JMPR 1987, 2006, 2014, 2016; IPCS 1996, 2005; European Commission 2002; EFSA 2009, 2015), and one review publication (Greim et al. 2015).

In conclusion, 14 GLY carcinogenicity studies (nine rat and five mouse) were evaluated for their reliability, and selected neoplasms were identified for further evaluation across all databases (Greim et al. 2015). The mouse renal neoplasms occurred only in males of the first study. In the other four, the HD of 1000 mg/kg/d (Cheminova 1993a), 4200 mg/kg/d (Arysta Life Sciences 1997), 946 mg/kg/d (Nufarm 2009), and 1460 mg/kg/d (Feinchemie Schwebda 2001) produced no renal neoplasms in either male or female mice.

The assessment of this study (Monsanto 1983) based on the PWG of the US EPA (1986) evaluation and which was reported by IARC (2015), concluded that the incidence of renal tubule adenoma: 1/49 (2%), 0/49, 0/50, 1/50 (2%), was not statistically significant, whereas, the incidence of renal tubule carcinoma: 0/49, 0/49, 1/50 (2%), 2/50 (4%), was significant at $p = .037$ (in the Cochran–Armitage trend test). When the adenomas and carcinomas were combined: 1/49 (2%), 0/49, 1/50 (2%), 3/50 (6%), then the value was $p = .034$ (in the Cochran–Armitage trend test). While both these p values ($p = .037$ and $p = .034$) were reported to be significant in this one study, it is important that these p values are not considered significant for rare neoplasms, for which authorities require a level of significance for trend at $p < .025$ (US FDA 2001).

Furthermore, the Panel applied to the kidney neoplasms noted within the Monsanto (1983) study a set of logical considerations for causation similar to those proposed for evaluation of epidemiologic data (Hill, 1965; Woodside & Davis, 2013) to assess whether an association between exposure

and effect (two variables) might be deemed strong, consistent, specific, temporal, plausible, coherent, and to demonstrate a dose-response pattern. Several conclusions following this evaluation were made:

1. The association is not strong, since the higher incidences of rare renal neoplasms in dosed groups are not considered to be statistically different from control group.
2. The association is not consistent, since four out of five mouse studies did not reproduce similar renal neoplasms at comparable doses.
3. The association is not specific, since females of this pivotal study, which have been exposed to higher levels of GLY did not develop renal neoplasms. Also, there were no renal findings (hyperplasia or neoplasia) in the LD group, whereas the control group had four incidences of hyperplasia or adenoma (Table 2).
4. The time required between exposure and effect, i.e. a reduced latency time was not present; all tumors were observed only at termination. Also, no mouse with neoplasia had also hyperplasia, and the largest tubular-cell carcinoma (#3023) was in the MD group.
5. The biological gradient of association or the dose-response curve was absent, since the females and the males in LD group had no neoplasms, whereas the controls had one.
6. A plausible explanation for the association was absent, since a MoA for induction of these renal neoplasms was not established.
7. Coherence of the association was also absent, female mice and male and female rats did not display kidney effects. Also, in the other four mouse carcinogenicity studies the mice did not develop similar neoplastic renal lesions.
8. The association does not demonstrate a dose-response pattern (see #5, 6), since the "in-study" females had neither neoplasms nor any of the other renal lesions, although they were exposed to higher levels of GLY.

Hemangiosarcomas in mice

This is a common neoplasm in this strain of mice with historical control values for both males and females ranging from 2 to 12%. This tumor was observed only in the liver.

The IARC conclusion was that "there was a significant ($p < .001$) positive trend in the incidence of hemangiosarcoma in high dose male CD-1 mice" (Control 0%, 0%, 0%, 8%) based on their interpretation of the Joint Meeting of the FAO panel of experts on Pesticide Residues in Food and the Environment (JMPR) 2006 study. Yet in females, the highest incidence (4%) was in the low-dose group followed by the high dose (2%) (Table 3).

In the CD-1 mouse study reported by Cheminova (1993a), the animals were fed diets providing intakes of glyphosate at dose levels of 100, 300, or 1000 mg/kg bw/d for 104 weeks. There were no treatment related effects on survival or body weight, nor were there any notable intergroup differences in the incidences of externally palpable masses. There were no statistically significant increases in the incidence of any tumors when compared with the control groups and no dose response was evident.

Based on their own statistical analysis, IARC concluded that there was an increase in the incidence of hemangiosarcoma in males [$p < .001$, Cochran–Armitage trend test].

IARC did not comment on the absence of hemangiosarcomas in Nufarm (2009), an 18-month diet study in CD-1 mice providing intakes up to 946 mg/kg bw/d of glyphosate similar to the previous study high dose. IARC also failed to note the historical control data, which have a range of 2–12% for both sexes (Charles River Labs 2000). Therefore, the statistically significant tumors were within the control data range (Table 3).

If the likelihood of the occurrence of hemangiosarcoma is considered in terms of the criteria for causality, it is clear that there is no strength in the association. For example, pairwise comparisons are not significant, there is no consistency (other mouse studies show no tumors of this type at all), a dose/response effect was not seen (some HD groups have a lower incidence than lower dose groups). In addition, the dose (about 170 mg/kg bw/d) associated with the highest incidence in males, did not produce any renal neoplasia in this study. Moreover, the female mice which have received higher doses of GLY had no significant incidence of hemangiosarcomas. Thus, despite the significantly positive trend in high dose males only, the incidence of this neoplasm was not compound related.

Pancreatic tumors in rats

Pancreatic islet cell tumors are common in this strain of rat (Williams et al. 2014). In two of the nine carcinogenicity studies in rats evaluated by IARC, tumors of islet cells of the pancreas were diagnosed in both males and females. Both studies were made available to IARC by the US EPA (1991a, 1991b, 1991c).

In the first study, SD rats received 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/d) ppm *ad libitum* in diet for 26 months. No pancreatic islet carcinomas were observed. The incidence of adenoma was found to have a positive trend ($p < .05$) in the study. However, the level of significance for common tumors should be $p < .005$. The following islet cell adenoma

Table 3. Incidences of hemangiosarcoma in CD-1 mouse study (Cheminova 1993b).

	Tumor incidence/number of animals examined (mg/kg bw/d)*							
	Males				Females			
	0	100	300	1000	0	100	300	1000
Hemangiosarcomas	0/50	0/50	0/50	4/50 (8%)	0/50	2/50 (4%)	0/50	1/50 (2%)

*Taken from Greim et al. (2015) supplemental data, doses were administered in the diet, with dietary concentrations adjusted regularly to achieve target mg/kg bw/day dose.

Table 4. Liver tumor incidences/number of Sprague–Dawley rats/group (Stout and Ruecker 1990).

	Males				Females			
mg/kg bw/d (ppm)	0 (0)	89 (2000)	362 (8000)	940 (20,000)	0 (0)	113 (2000)	457 (8000)	1183 (20,000)
Interim sacrifice (12th month)								
Hepatocellular adenoma	0/10	0/10	0/10	0/10	0/10	0/10	1/10	0/10
Hepatocellular carcinoma	0/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Unscheduled deaths								
Hepatocellular adenoma	2/36	1/31	0/33	4/33	0/28	1/28	2/33	1/32
Hepatocellular carcinoma	2/36	1/31	1/33	2/33	0/28	0/28	0/33	1/32
Scheduled sacrifices								
Hepatocellular adenoma	1/14	1/19	3/17	4/17	6/22	1/22	3/17	0/18
Hepatocellular carcinoma	1/14	1/19	0/17	0/17	1/22	0/22	1/17	1/18
All deaths								
Hepatocellular adenoma	3/60	2/60	3/60	8/60	6/60	2/60	6/60	1/60
Hepatocellular carcinoma	3/60	2/60	1/60	2/60	1/60	0/60	1/60	2/60

incidences were observed for controls, low, mid and high doses respectively in males: 0/50, 5/49 (10%), 2/50 (4%), 2/50 (4%). This incidence data shows no dose-response patterns and preneoplastic effects are absent. In addition, in the first study in males, the adenomas also did not progress to carcinomas. Thus, the pancreatic islet cell adenomas were not compound-related. In females, the corresponding values were: 2/50 (4%), 1/50 (2%), 1/50 (2%), and 0/50.

In the second study, male and female Sprague–Dawley (SD) rats were fed 0, 2000 (89/113), 8000 (362/457), or 20,000 (940/1183 mg/kg bw/d) ppm glyphosate (96.5% pure) *ad libitum* in diet for 24 months. The following islet cell tumor incidences were observed in males: adenomas – 1/58 (2%), 8/57 (14%), 5/60 (8%), 7/59 (12%); carcinomas – 1/58 (25%), 0/57, 0/60, 0/59. In females, the corresponding incidences were: adenomas – 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59; carcinomas – 0/60, 0/60, 0/60, 0/59. The historical control rates for pancreatic islet cell tumors at the testing laboratory were in the range 1.8–8.5%. The panel disagrees with the conclusion of IARC that there is a significant positive trend ($p < .05$) in the incidence of pancreatic adenomas in males, since the level of significance for trend should be $p < .005$ (US FDA 2001; Williams et al. 2014). Moreover, there was no progression of adenomas to carcinomas.

Four additional studies in rats, described by Greim et al. (2015), but not evaluated by IARC, similarly did not show pancreatic islet cell tumors. Based on this information, the panel concluded that there is no evidence that glyphosate induces islet cell neoplasia in the pancreas.

Liver tumors in rats

Hepatocellular neoplasms are common for this strain of rat (about 5% in males and 3% in female controls) (Williams et al. 2014). The IARC evaluation indicated that there was "... a significant positive trend ($p = .016$) in the incidences of hepatocellular adenoma in males ..." (IARC 2015). This opinion was based on its interpretation of the Stout and Ruecker (1990) study as presented by the US EPA's Peer Review of Glyphosate (US EPA 1991b, 1991c).

In the Stout and Ruecker (1990) carcinogenic bioassay, SD rats were exposed through the diet to 0, 2000, 8000, and 20,000 ppm of 96.5% pure glyphosate for 24 months. These dietary concentrations corresponded to 0, 89, 362, and 940 mg/kg bw/d for males and 0, 113, 457, and 1183 mg/kg bw/d for females, the highest tested dose (HTD) being close to the limit dose for long-term studies with rats (OECD 2009). No glyphosate-related clinical signs or influence on survival were observed. At term, there was no influence on body weights or body weight gain by males; in the females there was a 6.4% decreased body weight gain. The original data on tumor incidence in this study are available in Greim et al. (2015). The all-deaths incidences of hepatocellular adenomas or carcinomas in the glyphosate-exposed groups were not significantly different from the controls (Table 4). At the 12th month (interim sacrifice), no adenomas or carcinomas were observed in the male groups, but a single adenoma case was noted in a female at 457 mg/kg/d. The rates of hepatocellular adenomas in females and of hepatocellular carcinomas in each sex followed no dose-response pattern at any time. In males, the first liver adenoma and carcinoma were observed at week 88 and 85, respectively, in animals exposed to the HTD of 940 mg/kg/d. A non-significant numerically greater ($p = .101$, Fisher Exact) incidence of hepatocellular adenomas occurred in male rats exposed to the highest dose, since it is a common tumor type, the level of significance required is $p < .01$. There was no progression from adenoma to carcinoma. The authors did not highlight the occurrence of hepatocellular tumors in their final report and concluded that "an oncogenic effect was not observed".

The Stout and Ruecker (1990) study has been reviewed twice by the US EPA (1991b, 1991c). The US EPA memoranda indicate that the incidences of hepatocellular adenomas in males were within the range (1.4–18.3%) of historical controls from the Monsanto Environmental Health Laboratory (EHL), where the study was conducted. Additional statistical analyses developed by US EPA on liver tumor rates of male rats surviving after the 55th week indicated that the incidence of adenomas in the HTD males did not differ significantly from the control by the Fisher's Exact Test pair-wise comparison, but detected a significant trend ($p = .016$) by the Cochran–Armitage trend test (see also above) (Table 5). Since liver adenoma is a common tumor type, the significance level for trend should be 0.005 (US FDA 2001; Williams et al. 2014). It should be noted that the incidences of hepatocellular adenomas in animals exposed to the two intermediate doses were of the same magnitude as the controls, i.e. there was no linear ascending trend of incidence across doses, but a "hockey-stick"-type slope. The biological importance of the

Table 5. Sprague–Dawley male rats: hepatocellular tumor rates† and Cochran–Armitage trend and Fisher's exact tests results (p values).

	Dose mg/kg bw/d (ppm)			
Tumors	0 (0)	89 (2000)	362 (8000)	940 (20,000)
Carcinomas	3/34	2/45	1/49	2/48‡
(%)	(7)	(4)	(2)	(4)
p	.324	.489	.269	.458
Adenomas	2/44	2/45	3/49	7/48¶
(%)	(5)	(4)	(6)	(15)
p	.016*	.683	.551	.101
Adenoma + Carcinoma	5/44	4/45	4/49	9/48
(%)	(11)	(9)	(8)	(19)
p	.073	.486	.431	.245
Hyperplasia only	0/44	0/45	1/49§	0/48
(%)	(0)	(0)	(2)	(0)
p	.462	1.000	.527	1.000

Adapted from Table 3 (US EPA 1991a) or Table 7 (US EPA 1991b).
*($p < .05$) Significance of trend indicated at control (0 ppm). Significance of pair-wise comparison with control denoted at dose level, if occurred.
†Number of tumor-bearing animals/number of animals examined, excluding those that died or were sacrificed before week 55.
‡First carcinoma observed at week 85 at 20,000 ppm;
¶First adenoma observed at week 88 at 20,000 ppm;
§First hyperplasia observed at week 89 at 8000 ppm.

Table 6. Tumor Incidence/number of animals examined (mg/kg bw/d) (Stout and Ruecker 1990 all deaths reported).

	Males				Females			
	0	89	362	940	0	113	457	1183
Thyroid C cell adenoma	2/60	4/58	8/58	7/60	2/60	2/60	6/60	6/60
Thyroid C cell carcinoma	0/60	2/58	0/58	1/58	0/60	0/60	1/60	0/60

observed data should be taken into account (OECD 2012) and in this case the result of the trend test should not override the absence of significance found by the pair-wise test.

The final interpretation of the US EPA Review committee was appropriate: "Despite the slight dose-related increase in hepatocellular adenomas in males, this increase was not significant in the pair-wise comparison with controls and was within the historical control range. Furthermore, there was no progression from adenoma to carcinoma and incidences of hyperplasia were not compound-related. Therefore, the slight increased occurrence of hepatocellular adenomas in males is not considered compound-related" (US EPA 1991b). As noted previously, the US EPA ultimately concluded that glyphosate should be classified as a Group E (evidence of non-carcinogenicity for humans) chemical (US EPA 1991b, 1991c).

There are other aspects of the Stout and Ruecker (1990) data that support the conclusion that glyphosate did not exert an oncogenic effect on the liver of SD rats. For example, chemical-induced rat hepatocellular carcinogenesis is a multiple stage process characterized by progressive functional, morphological and molecular changes that indicate or precede the full establishment of neoplasia, such as enzyme induction, hepatocyte hypertrophy, degeneration and necrosis, hepatocyte proliferation, hyperplasia, and preneoplasia, i.e. altered hepatocellullar foci, and malignant tumors (Williams 1980; Bannasch et al. 2003; Maronpot et al. 2010). Identification and analyses of these liver changes – that span from adaptative to irreversible adverse effects – can support characterization of key events along the carcinogenesis process and inform the MoA of the tested chemical (Williams & Iatropoulos 2002; Holsapple et al. 2006; Carmichael et al. 2011). None of these alterations were significantly found in this study.

It is clear that there was a non-significant numerically greater incidence of liver adenomas in a long-term bioassay with male rats exposed to glyphosate, at a dose that was close to the limit dose. There was no progression to malignancy and no compound-associated pre-neoplastic lesions were induced.

In the last 30 years, the systemic carcinogenic potential of glyphosate has been assessed in at least eight studies in Sprague–Dawley or Wistar rats (Greim et al. 2015); a ninth could not be evaluated because of a high mortality and the low doses used (Chruscielska et al. 2000). Considered jointly, these animals were exposed through the diet to 24 different doses distributed across a wide range of 3.0–1290.0 mg/kg bw/d. In exposed males, the incidences of hepatocellular adenomas across the doses showed no dose-response relationship and varied within the same range as the controls. Similar rates were also seen for hepatocellular carcinomas. These observations confirm the absence of carcinogenic potential of glyphosate on the rat liver.

Thyroid tumors in rats

C-cell tumors of the thyroid are a common tumor in this strain of rat (Williams et al. 2014).

The incidence of thyroid C-cell adenoma in females was reported in the Monograph (IARC 2015) to have a significant positive trend ($p = .031$). IARC based their opinion, again, on its interpretation of the Stout and Ruecker (1990) study and the US EPA's Second Peer Review of Glyphosate (US EPA 1991a).

In the Stout and Ruecker (1990) study, no statistically significant difference was reported in the incidence of thyroid C-cell neoplasms, as shown in Table 6. Additionally, the US EPA (1991a) concluded that "the C-cell adenomas in males and females are not considered compound-related." Although the C-cell adenomas were slightly numerically greater in male and female mid- and high-dose groups, there was no dose related progression to carcinoma and no significant dose-related increase in severity of grade or incidence of hyperplasia in either sex. However, IARC concluded that "there was also a statistically significant positive trend in the incidence of thyroid C-cell adenoma in females ($p = .031$)." But, because this is a common tumor type, the trend significance value should be $p < .005$ (US FDA 2001; Williams et al. 2014). Thus, the incidence of this tumor is not statistically significant.

In the Arysta Life Sciences (1997) study, no increase in C-cell adenomas up to 1247 mg/kg/d was reported. The Chruscielska et al. (2000) study in Wistar rats is not informative and this work fails to meet appropriate standards for inclusion.

Thus, in one of the two studies, the significant trend in the incidence of thyroid C-cell adenomas in female rats did not materialize, although the adenomas were only slightly increased in mid and high doses, but there was no progression to malignancy. Thus, only one out of nine life-time

studies in rats showed a slight not significant increase in C-cell adenomas, which however did not progress to carcinomas.

Evaluations by regulatory agencies, scientific bodies and third party experts

A number of scientific groups, regulatory agencies and individuals have evaluated and commented on these data with the latter grouping from third party experts appearing in peer reviewed documents. The expert panel agrees with the opinions expressed below that glyphosate was not carcinogenic to rodents.

Regulatory agencies

- EFSA 2015: "No evidence of carcinogenicity was confirmed by the large majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pair-wise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/maximum tolerated dose, lack of preneoplastic lesions and/or being within historical control range. The statistical significance found in trend analysis (but not in pair-wise comparison) *per se* was balanced against the former considerations." (EFSA 2015)
- APVMA (2013) – "The weight and strength of evidence shows that glyphosate is not genotoxic, carcinogenic, or neurotoxic."
- US EPA (2013) – "No evidence of carcinogenicity was found in mice or rats."
- US EPA (2012) – "No evidence of carcinogenicity was found in mice or rats."
- European Commission (2002) – "No evidence of carcinogenicity."
- US EPA (1993a, 1993b) – "The Agency has classified glyphosate as a Group E carcinogen (signifies evidence of non-carcinogenicity in humans)."
- Health and Welfare Canada (1991) – "Health and Welfare Canada has reviewed the glyphosate toxicology data base, which is considered to be complete. The acute toxicity of glyphosate is very low. The submitted studies contain no evidence that glyphosate causes mutations, birth defects or cancer."

Scientific bodies

- JMPR (2016) – "Glyphosate is not carcinogenic in rats, but could not exclude the possibility that it is carcinogenic in mice at very high doses."
- JMPR (2006) – "In view of the absence of a carcinogenic potential in animals and the lack of genotoxicity in standard tests, the meeting concluded that glyphosate is unlikely to pose a carcinogenic risk to humans."
- WHO (1994) – "The available studies do not indicate that technical glyphosate is mutagenic, carcinogenic or teratogenic."
- JMPR (1987) – "The chronic toxicity of glyphosate is low ... There is no evidence of carcinogenicity."

Independent experts

- Williams et al. (2000) – "It was concluded that, under present and expected conditions of use, Roundup herbicide does not pose a health risk to humans."
- Greim et al. (2015) – "There was no evidence of a carcinogenic effect related to glyphosate treatment. The lack of a plausible mechanism, along with published epidemiology studies, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans."

Conclusions

After review of all available glyphosate carcinogenicity data, the panel concluded:

i. The rare renal tubule tumors in one male (CD-1) mouse study were not associated with glyphosate exposure, because they lacked statistical significance, strength, consistency, specificity, dose-response patterns, plausibility, and coherence.
ii. In a different mouse (CD-1) study, there was a lack of association of exposure to glyphosate and a statistically significant positive trend for the incidence of liver hemangiosarcoma (a common tumor) because the findings were inconsistent, there was no dose-response effect, and the incidences were within the historical control range.
iii. The strength of association of pancreatic islet-cell adenomas (a common tumor) to glyphosate exposure in two studies of male SD rats was absent. There was a lack of a dose-response pattern (the highest incidence is in the low dose followed by the high dose), plausibility and absence of pre-neoplastic effects and progression to islet-cell carcinomas.
iv. In one of two studies, a significant positive trend in the incidence of hepatocellular adenomas (a common tumor) in male SD rats did not occur, and no progression to carcinomas was evident and no glyphosate-associated pre-neoplastic lesions were present.
v. In one of two studies, the significant positive trend in the incidence of thyroid C-cell adenomas in female SD rats was not evident. The adenomas were only slightly increased in mid and high doses, within the historical ranges. Also, there was no progression to carcinomas.

Application of criteria for causality considerations to the above mentioned tumor types and given the overall WoE, the expert panel concluded that glyphosate is not a carcinogen in laboratory animals.

Acknowledgements

The authors gratefully acknowledge the extensive comments received from seven independent reviewers selected by the Editor and who were

anonymous to the authors. Their comments were very helpful in revising the manuscript.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer.

The expert panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The expert panelists were engaged by, and acted as consultants to, Intertek, and were not directly contacted by the Monsanto Company. Funding for this evaluation was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorneys reviewed any of the expert panel's manuscripts prior to submission to the journal.

Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food, and pharmaceutical industries. While Intertek has not previously worked on glyphosate related matters for the Monsanto Company, previous employees (Ian Munro, Barry Lynch) of Cantox, have worked in this capacity. These employees of Cantox, and Gary Williams, prepared a safety and risk assessment, including the carcinogenicity, of Roundup herbicide (glyphosate), which was published in 2000 (Williams GM, Kroes R, Munro IC (2000). Safety evaluation and risk assessment of the herbicide roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol 31(2):117–165).

Gary Williams, Sir Colin Berry, João Lauro Viana de Camargo, and Helmut Greim have previously served as independent consultants for the Monsanto Company, some on the European Glyphosate Task Force. Gary Williams has consulted for Monsanto on litigation matters involving glyphosate. Michele Burns has not previously been employed by the Monsanto Company or previously been involved in any activity involving glyphosate and as such declare no potential conflicts of interest. Furthermore, other than Gary Williams, none of the aforementioned authors have been involved in any litigation procedures involving glyphosate.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

References

APVMA. 2013. A review of the earth open source (EOS) report roundup and birth defects: is the public being kept in the dark?. Prepared by Canberra (Australia): scitox assessment services for Canberra (Australia): Australian pesticides and veterinary medicine authority (APVMA). Available from: http://archive.apvma.gov.au/news_media/docs/glyphosate_scitox_review_july_2013.pdf.

Arysta Life Sciences. 1997. HR-001: 18-month oral oncogenicity study in mice. Tokyo (Japan): The Institute of Environmental Toxicology (Cited in: Greim et al. 2015).

Bannasch P, Haertel T, Su Q. 2003. Significance of hepatic preneoplasia in risk identification and early detection of neoplasia. Toxicol Pathol. 31:134–139.

Carmichael N, Bausen M, Boobis AR, Cohen SM, Embry M, Fruijtier-Polloth C, Greim H, Lewis R, Meek ME, Mellor H, et al. 2011. Using mode of action information to improve regulatory decision-making: an ECETOC/ILSI RF/HESI workshop overview. Crit Rev Toxicol. 41:175–186.

Charles River Labs. 2000. Spontaneous neoplastic lesions in the crl:CD-1® BR mouse. Wilmington (MA): Charles River Laboratories Inc.

Cheminova. 1993a. Glyphosate: 104 week dietary carcinogenicity study in mice. [Unpublished Report] Tranent (Scotland): inveresk research international Ltd. Submitted to WHO by Lemvig (Denmark): Cheminova A/S. (Report No. 7793, IRI project No. 438618).

Cheminova. 1993b. 104 week combined chronic feeding/oncogenicity study in rats with 52 week interim kill (results after 104 weeks). [Unpublished report] Tranent (Scotland): inveresk research international Ltd. Submitted to WHO by Lemvig (Denmark): Cheminova A/S. (Report No. 7867, IRI project No. 438623).

Chruscielska K, Brzezinski J, Kita K, Kalhorn D, Kita I, Graffstein B, Korzeniowski P. 2000. Glyphosate – evaluation of chronic activity and possible far-reaching effects. Part 1. Studies on chronic toxicity. Pestycydy (Warsaw). (3/4):11–20.

EFSA. 2009. 2007 Annual report on pesticide residues according to article 32 of regulation (EC) no 396/2005 (reasoned opinion of EFSA prepared by the pesticides unit/PRAPeR) (EFSA-Q-2008-714). Parma (Italy): European food safety authority (EFSA). EFSA scientific report 305, p. 1–106; [cited 2009 Jun 10]. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/305r.

EFSA. 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate (EFSA-Q-2014-00546, EFSA-Q-2015-00279, by European food safety authority). EFSA J. 13:4302 [107 p.]. doi:10.2903/j.efsa.2015.4302; [cited 2015 Oct 30]. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/4302.

European Commission. 2002 Review report for the active substance glyphosate. Finalized in the standing committee on plant health at its meeting on 29 June 2001 in view of the inclusion of glyphosate in annex I of directive 91/414/EEC. Brussels (Belgium): European commission (EC), health and consumer protection directorate general. (6511/VI/99-final). Available from: http://ec.europa.eu/food/fs/sfp/ph_ps/pro/eva/existing/list1_glyphosate_en.pdf.

Eustis SL, Hailey JR, Boorman GA, Haseman JK. 1994. The utility of multiple-section sampling in the histopathological evaluation of the kidney for carcinogenicity studies. Toxicol Pathol. 22:457–472.

Excel. 1997. Combined chronic toxicity/carcinogenicity study of glyphosate technical in Sprague–Dawley rats. Pune, India: Indian Institute of Toxicology.

Feinchemie Schwebda. 2001. Carcinogenicity study with glyphosate technical in Swiss Albino mice. [Unpublished report]. Bangalore (India): Rallis India, Ltd.

Greaves P. 2012. Urinary tract [renal neoplasms] (chapter 10). In: Histopathology of preclinical toxicity studies. 4th ed. New York (NY): Elsevier B.V. p. 545–626 [See p. 593].

Greim H, Saltmiras D, Mostert V, Strupp C. 2015. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. Crit Rev Toxicol. 45:185–208.

Health and Welfare Canada. 1991. Preharvest application of glyphosate (roundup) herbicide. Ottawa (ON): health and welfare Canada, pest management regulatory agency (PMRA), plant industry directorate. Pesticide information division. (pesticides directorate discussion document). 91. p. 92.

Hill AB. 1965. The environment and disease: association or causation. J R Soc Med. 58:295–300.

Holsapple MP, Pitot HC, Cohen SM, Boobis AR, Klaunig JE, Pastoor T, Dellarco VL, Dragan YP. 2006. Mode of action in relevance of rodent liver tumors to human cancer risk. Toxicol Sci. 89:51–56.

IARC. 2015. Glyphosate. In: Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, tetrachlorvinphos. IARC working group, Lyon (France). Lyon (France): World Health Organization (WHO), International Agency for Research on Cancer (IARC). (IARC monographs on the evaluation of carcinogen risks to humans, vol 112). p. 1–92; [cited 2015 Mar 3–10]. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php.

ICH. 1997. Testing for carcinogenicity of pharmaceuticals: S1B. Geneva: International Conference on harmonization of technical requirements for registration of pharmaceuticals for human use (ICH). (ICH harmonized tripartite guideline – current step 4 version); [cited 1997 Jul 16]. Available from: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html [Open S1B].

IPCS. 1996. Glyphosate. (Geneva: World Health Organization (WHO), International program on chemical safety (IPCS). WHO/FAO data sheets on pesticides no 91; WHO/PCS/DS/96.91). Available from: http://apps.who.int/iris/handle/10665/63290.

IPCS. 2005. Glyphosate. Luxembourg: commission of the European union/International program on chemical safety (IPCS). (international chemical safety card, ICSC-0160). Available from: http://www.inchem.org/documents/icsc/icsc/eics0160.htm.

James RC, Britt JK, Haimes NC, Guzelian PS. 2015. Evidence-based causation in toxicology: a 10-year retrospective. Hum. Exp. Tox. 34:1245–1252.

JMPR. 1987. Glyphosate. In: pesticide residues in food – 1986: part II – toxicology. Joint meeting of the FAO panel of experts on pesticide residues in food and the environment (JMPR) and the WHO expert group on pesticide residues, Sep. 29-Oct. 8, 1986, Rome. Rome: food and agriculture organization of the United Nations (FAO)/FAO panel of experts on pesticide residues in food and the environment/WHO expert group on pesticide residues joint FAO/WHO meeting on pesticide residues (JMPR). (FAO plant production and protection paper, vol 78). p. 63–76. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v86pr08.htm.

JMPR. 2006. Glyphosate. In: pesticides residues in food – 2004. Evaluations 2004 part II-toxicological. Joint meeting of the FAO panel of experts on pesticide residues in food and the environment and the WHO core assessment group (JMPR), Sep 20–29, 2004, Rome. Rome: food and agriculture organization of the United Nations (FAO)/Geneva: World Health Organization (WHO), International program on chemical safety (IPCS). (WHO/PCS/06.1). p. 95–169; [cited 2004 Sep 20–29]. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v2004pr01.pdf.

JMPR. 2014. 5.21. Glyphosate ('158) and metabolites. In: pesticide residues in food 2013. Joint FAO/WHO meeting on pesticide residues and the WHO core assessment group on pesticide residues, Geneva. Rome: food and agriculture organization of the United Nations/Geneva, World Health Organization (WHO). (FAO plant production and protection paper No. 219). p. 225–228, 484–486; [cited 2013 Sep 17–26]. Available from: http://www.fao.org/publications/card/en/c/299ca869-ae51-5093-8407-9cb0782b9f5/.

JMPR. 2016. Diazinon, glyphosate and malathion. Summary report from a core assessment group on pesticide residues (JMPR) held at WHO headquarters, Geneva, Switzerland, from 9 to 13 of May, 2016; [cited 2016 May 16].

Kier LD, Kirkland DJ. 2013. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol. 43:283–315.

Maronpot RR, Yoshizawa K, Nyska A, Harada T, Flake G, Mueller G, Singh B, Ward JM. 2010. Hepatic enzyme induction: histopathology. Toxicol Pathol. 38:776–795.

McConnel R. 1986. A chronic feeding study of glyphosate (Roundup® technical) in mice: pathology report on additional kidney sections. final report. Confidential. [Unpublished report] prepared by Bio/dynamics Inc. Division of biology and safety evaluation for St Louis (MO): Monsanto Company for submission to Washington (DC): Washington (DC): U.S. environmental protection agency (US EPA), office of pesticides, and toxic substances. (Project No. 77-2061A; BDN-77-420).

Monsanto. 1983. A chronic feeding study of glyphosate (roundup® technical) in mice. [Unpublished report]. East Millstone (NJ): Bio/dynamics Inc. (project #77-2062, 1981).

Nufarm. 2009. Glyphosate technical: dietary carcinogenicity study in the mouse [Unpublished Report] Derbyshire (UK): Harlan Laboratories Ltd (Cited by Greim et al. 2015).

OECD. 2009. Combined chronic toxicity\carcinogenicity studies. In: OECD guidelines for the testing of chemicals. Paris (France): organization for economic co-operation and development (OECD). (OECD guideline no 453); [cited 2009 Sep 7]. Available from: http://www.oecd-ilibrary.org/environment/test-no-453-combined-chronic-toxicity-carcinogenicity-studies_9789264071223-en.

OECD. 2012. Guidance document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453. 10th ed. Joint meeting of the chemicals committee and the working party on chemicals, pesticides, and biotechnology. Paris (France): organization for economic co-operation and development (OECD), environment directorate, health and safety publications. (OECD series on testing and assessment; ENV/JM/MONO(2011)47). Available from: http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/JM/MONO(2011)47&doclanguage=en.

Peto R, Pike MC, Day NE, Gray RG, Lee PN, Parish S, Peto J, Wahrendorf J. 1980. Guidelines for simple, sensitive significance test for carcinogenic effects in long-term animal experiments. In: Long-term and short-term screening assays for carcinogens: a critical appraisal, edited by R Montesano, H Bartsh, L Tomatis, IARC monogrphas on the evaluation of the carcinogenic risk of chemicals to humans, Suppl. 2, pp. 311–426 Lyon Franc: International Agency for Research on Cancer.

Sauer RM. 1985. Pathology working group report on glyphosate in CD-1 mice. (10/10/85). Reported In: http://www.cdpr.ca.gov/docs/risk/toxsums/pdfs/1855.pdf [See p. 16].

Stout LD, Ruecker FA. 1990. Chronic study of glyphosate administered in feed to Albino rats. [Unpublished report] St Louis (MO): Monsanto agricultural company (No. MSL-10495, job/project No. ML-87-148/EHL 87122).

Suter GWII, Cormier SM. 2011. Why and how to combine evidence in environmental assessments: weighing evidence and building cases. Sci Total Environ. 409:1406–1417.

US EPA. 1985a. Glyphosate; EPA Reg.#: 524-308; mouse oncogenicity study [memo]. Washington (DC): U.S. environmental protection agency (US EPA). (Document No. 004370). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1985b. EPA Reg.#: 524-308; Roundup; glyphosate; pathology report on additional kidney sections [memo]. Washington (DC): U.S. Environmental protection agency (US EPA). (document No. 004855). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1986. Glyphosate; EPA Reg.#: 524-308; roundup; additional histopathological evaluations of kidneys in the chronic feeding study of glyphosate in mice [memo]. Washington (DC): U.S. Environmental protection agency (US EPA). (Document No. 005590). Page 7, point 5. Letter of October 10, 1985, from pathology working group (PWG) to Monsanto. Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1990. Determination of glyphosate in drinking water by direct-aqueous-injection HPLC, post column derivatization, and fluorescence detection. In: methods for the determination of organic compound in drinking water – supplement I. Washington (DC): U.S. Environmental protection agency (US EPA), office of research and development. (EPA/600/4-90/020). Available from: http://nepis.epa.gov/Exe/ZyPDF.cgi/30000UX8.PDF?Dockey=30000UX8.PDF.

US EPA. 1991a. Second peer review of glyphosate [memo]. Washington (DC): U.S. Environmental protection agency (US EPA). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1991b. Glyphosate; 2-year combined chronic toxicity/carcinogenicity study in Sprague–Dawley rats – list A pesticide for reregistration [memo]. Washington (DC): U.S. Environmental protection agency (US EPA). (Document No. 008390). Available from: http://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/html/103601.html.

US EPA. 1991c. Peer review on glyphosate [memo]. Washington (DC): U.S. environmental protection agency (US EPA), office of pesticides, and toxic substances.

US EPA. 1992. Determination of glyphosate in drinking water by direct-aqueous-injection HPLC, post column derivatization, and fluorescence detection. In: Methods for the determination of organic compound in drinking water – supplement II. Washington (DC): U.S. environmental protection agency (US EPA), office of pesticides, and toxic substances. (EPA/600/R-92-129).

US EPA. 1993a. Reregistration eligibility decision (RED): glyphosate. U.S. environmental protection agency (US EPA), office of prevention, pesticides, and toxic substances. (EPA 738-R-93-014). Washington (DC). Available from: http://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/red_PC-417300_1-Sep-93.pdf.

US EPA. 1993b. RED facts: glyphosate. Washington (DC): U.S. environmental protection agency (US EPA), office of prevention, pesticides, and

toxic substances. (EPA 738-F-93-011). Available from: http://archive.epa.gov/pesticides/reregistration/web/pdf/0178fact.pdf.

US EPA 2005. Guidelines for carcinogen risk assessment [EPA/630/P-03/001F]. Washington (DC): US. Environmental Protection Agency (U.S. EPA), Risk assessment forum, National Center for Environmental Assessment (NCEA). Available from: http://www.epa.gov/risk/guidelines-carcinogen-risk-assessment.

US EPA. 2012. Memo from Tom Bloem et al. (RAB/HED) through Charles W. Smith III, George F. Kramer (RA/HED) to Barbara Madden and Andrew Ertman (RD) Re: glyphosate. section 3 registration concerning the application of glyphosate to carrots, sweet potato, teff and oilseeds (crop group (CG) 20) and to update the CG definitions for bulb vegetable (CG 3-07), fruiting vegetable (CG 8-10), citrus fruit (CG 10-10), pome fruit (CG 11-10, berry (CG 13-07). Washington (DC): U.S. environmental protection agency (US EPA), office of chemical safety and pollution prevention. (D398547).

US EPA. 2013. Glyphosate pesticide tolerances; final rule (40 CFR Part 180) [EPA-HQ-OPP-2012-0132; FRL-9384-3]. Fed regist (US). 78:25396-25401. Available from: http://www.regulations.gov/#%21documentDetail;D=EPA-HQ-OPP-2012-0132-0009.

US FDA. 2001. Draft guidance for industry on the statistical aspects of the design, analysis, and interpretation of chronic rodent carcinogenicity studies of pharmaceuticals. Availability [Docket No. 01N-0006]. Fed Regist (US). 66:23266-23267.

WHO. 1994. Glyphosate. Geneva: World Health Organization (WHO)/International program on chemical safety (IPCS)/United Nations environment program (UNEP). (Environmental health criteria, no 159). Available from: http://www.inchem.org/documents/ehc/ehc/ehc159.htm.

Williams GM. 1980. The pathogenesis of rat liver cancer caused by chemical carcinogens. Biochem Biophy Acta. 605:167-189.

Williams GM, Iatropoulos MJ. 2002. Alteration of liver cell function and proliferation: differentiation between adaptation and toxicity. Toxicol Pathol. 30:41-53.

Williams GM, Kroes R, Munro IC. 2000. Safety evaluation and risk assessment of the herbicide roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol. 31:117-165.

Williams GM, Iatropoulos MJ, Enzmann HG, Deschl UF. 2014. Carcinogenicity of chemicals. In Hayes' principles and methods of toxicology. In: Hayes AW, Kruger CL, editors. Boca Raton, FL, USA: CRC Press Taylor & Francis Group. pp 1251-1303.

Williams G, Aardema M, Acquavella J, Berry C, Brusick D, Viana de Camargo JL, Garabrant D, Greim H, Kier L, Kirkland D, et al. 2016. A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. Crit Rev Toxicol., in this issue. doi: 10.1080/10408444.2016.1214677.

Woodside FC III, Davis AG. 2013. The Bradford Hill criteria: the forgotten predicate. Thomas Jefferson Law Rev. 35:103-125.

CRITICAL REVIEWS IN TOXICOLOGY, 2016
VOL. 46, NO. S1, 56–74
http://dx.doi.org/10.1080/10408444.2016.1214680

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS

Genotoxicity Expert Panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid

David Brusick[a], Marilyn Aardema[b], Larry Kier[c], David Kirkland[d] and Gary Williams[e]

[a]Toxicology Consultant, Bumpass, VA, USA; [b]Marilyn Aardema Consulting, LLC, Fairfield, OH, USA; [c]Private Consultant, Buena Vista, CO, USA; [d]Kirkland Consulting, Tadcaster, UK; [e]Pathology, New York Medical College, Valhalla, NY, USA

ABSTRACT

In 2015, the International Agency for Research on Cancer (IARC) published a monograph concluding there was strong evidence for genotoxicity of glyphosate and glyphosate formulations and moderate evidence for genotoxicity of the metabolite aminomethylphosphonic acid (AMPA). These conclusions contradicted earlier extensive reviews supporting the lack of genotoxicity of glyphosate and glyphosate formulations. The IARC Monograph concluded there was strong evidence of induction of oxidative stress by glyphosate, glyphosate formulations, and AMPA. The Expert Panel reviewed the genotoxicity and oxidative stress data considered in the IARC Monograph, together with other available data not considered by IARC. The Expert Panel defined and used a weight of evidence (WoE) approach that included ranking of studies and endpoints by the strength of their linkage to events associated with carcinogenic mechanisms. Importantly, the Expert Panel concluded that there was sufficient information available from a very large number of regulatory genotoxicity studies that should have been considered by IARC. The WoE approach, the inclusion of all relevant regulatory studies, and some differences in interpretation of individual studies led to significantly different conclusions by the Expert Panel compared with the IARC Monograph. The Expert Panel concluded that glyphosate, glyphosate formulations, and AMPA do not pose a genotoxic hazard and the data do not support the IARC Monograph genotoxicity evaluation. With respect to carcinogenicity classification and mechanism, the Expert Panel concluded that evidence relating to an oxidative stress mechanism of carcinogenicity was largely unconvincing and that the data profiles were not consistent with the characteristics of genotoxic carcinogens.

ARTICLE HISTORY
Received 8 April 2016
Revised 24 May 2016
Accepted 15 July 2016

KEYWORDS
Glyphosate; formulations; AMPA; genotoxicity; mutagenicity; oxidative stress; carcinogenesis mechanism; weight of evidence; Roundup

Table of contents

CONTACT David Brusick, PhD brusick41@aol.com ATS, Toxicology Consultant, 123 Moody Creek Rd., Bumpass, VA 23023, USA

Executive summary

Overall, extensive reviews of the genotoxicity of glyphosate, aminomethylphosphonic acid (AMPA) and glyphosate based formulations (GBFs) that were available prior to the development of the International Agency for Research on Cancer (IARC) Glyphosate Monograph all support a conclusion that glyphosate (and related materials) is inherently not genotoxic. Further, evidence indicative of an oxidative stress mechanism of carcinogenicity is largely unconvincing. The Expert Panel concluded that there is no new, valid evidence presented in the IARC Monograph that would provide a basis for altering these conclusions.

The differences between the conclusions of the IARC review and the Expert Panel review were in large part due to IARC exclusion of numerous available studies and in some cases differences in interpretation of study results reported in the IARC Monograph. Another significant source of difference was the Expert Panel's weighting of different studies and endpoints by the strength of their linkage to mutagenic events associated with carcinogenic mechanisms. The Expert Panel concluded that without critically evaluating all available data, it is not possible to make an accurate weight of evidence (WoE) assessment.

The IARC review process does not allow for use of data from reports that are not published or accepted for publication in the open scientific literature or data from government reports that are not publicly available. However, detailed primary data were extracted and published in reviews such as Kier and Kirkland (2013), although the study reports themselves are unpublished. The Expert Panel concluded that these data along with regulatory studies of GBFs and AMPA summarized in Williams et al. (2000) should have been considered by IARC, and should be considered by all stakeholders going forward in evaluating the genetic toxicology of glyphosate and GBFs. A critical review of the complete dataset by the Expert Panel supports a conclusion that glyphosate (including GBFs and AMPA) does not pose a genotoxic hazard and therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen.

Introduction

In 2015, IARC published the Glyphosate Monograph of Volume 112 (IARC 2015) which concluded that there was strong evidence supporting that "glyphosate can operate through two key characteristics of known human carcinogens" including genotoxicity and induction of oxidative stress. This was viewed as providing strong support for IARC classifying glyphosate as probably carcinogenic to humans, Group 2A. A number of published and regulatory approval reviews of the carcinogenic and genotoxic potential of glyphosate, AMPA and GBFs were available prior to the development of the IARC Monograph (Health and Welfare Canada 1991; US EPA 1993; WHO 1994; Williams et al. 2000; European Commission 2002; Kier & Kirkland 2013; US EPA 2013). The consensus among these reviews was that proper use of glyphosate and GBFs does not pose a genotoxic or carcinogenic hazard/risk with hazard indicating potential for adverse effects and risk indicating potential for adverse effects under actual conditions and amounts of exposure. As a result, glyphosate based herbicides have been approved for use in over 160 countries. The recent IARC conclusion was therefore inconsistent with these other reviews. Consequently, the Monsanto Company commissioned Intertek Scientific & Regulatory Consultancy to assemble a panel of experts to conduct a thorough review in the four areas considered by IARC including mechanistic data (focused on genotoxicity and oxidative stress). This review section reports the views of the Expert Panel of genetic toxicologists on the genotoxicity of glyphosate, GBFs and AMPA and discusses how they relate to the IARC opinions. The views and conclusions represent those of the Expert Panel of genetic toxicologists as independent scientific consultants and neither employees of the Monsanto Company nor attorneys reviewed this manuscript prior to submission.

Proper methods to accurately evaluate and interpret complex sets of genetic toxicology data

Characteristics of genetic toxicology tests and genetic testing data sets

Due to interest in understanding the potential to produce adverse effects, chemicals such as glyphosate, for which there is widespread human exposure, are typically subjected to extensive testing for genotoxic activity. The resultant database will contain studies that encompass diverse phylogenetic boundaries, types of genetic alterations, and exposure methods. Some of the more common test methods are often represented by multiple entries in the database. Proper evaluation of such data sets requires an approach that is both systematic and critical.

In large datasets, there are always likely to be some positive responses that are described as "false" or "misleading" positives from the standpoint of predicting carcinogenicity or relevance to carcinogenic mechanism (Waters et al. 1988; Mendelsohn et al. 1992; Jackson et al. 1993). False or misleading responses generally fall into one of three types:

1. Non-predictive – positive responses produced by non-carcinogenic agents. It is well documented that misleading positive responses are more frequent in certain genotoxicity tests (particularly in *in vitro* mammalian cells) due to their inherent lack of specificity (Kirkland et al. 2005; Pfuhler et al. 2011; Walmsley & Billinton 2011) and artifacts resulting from *in vitro* treatment conditions (Halliwell 2003).

2. Secondary response – the positive response is not associated with direct DNA-reactivity of the agent or metabolites of the agent but is a downstream or indirect consequence of high levels of cytotoxicity (Kirsch-Volders et al. 2003; Pratt & Barron 2003) or extreme treatment conditions such as high osmotic conditions or significant variations in pH (Scott et al. 1991). Such responses may not be relevant to *in vivo* prediction because they involve effects generated by exposures that exceed potential *in vivo* exposures.
3. Technical deficiencies – positive responses may be produced by inadequate study designs, mistakes made during the conduct of a test or inappropriate evaluation of data. This type includes cases where there is reason to question whether a positive experimental result has actually been obtained.

An understanding of possible actions leading to false or misleading responses with respect to carcinogenicity prediction or carcinogenic mechanism must be incorporated into the design, conduct, evaluation, and interpretation of genotoxicity assays. As a consequence, new standard test guidelines for *in vitro* mammalian assays published by the Organization for Economic Cooperation and Development (OECD) and other organizations indicate that treatment conditions must be monitored for maintenance of normal physiological parameters.

Therefore, it is expected that a chemical as heavily tested as glyphosate would exhibit some positive responses in its genotoxicity database that would be considered "misleading" and therefore not predictive of its true genotoxic or carcinogenic hazard/risk potential.

Methods applicable to evaluation and interpretation of complex data sets

The universally recommended method for evaluating the databases of the type associated with glyphosate (including GBFs and AMPA), involves the application of a WoE approach as discussed recently for genetic toxicology testing (US FDA 2006; Dearfield et al. 2011). Many of the principles of the WoE analysis indicated here are consistent with and included in the very recently issued endpoint specific guidance document of the European Chemicals Agency (ECHA 2015).

While numerous attempts to develop a standard WoE method to evaluate large, complex data sets have not found universal acceptance, some critical performance requirements for WoE approaches have been identified by the US EPA (Suter & Cormier 2011). One of the most important requirements is that individual test methods should be assigned a weight that is consistent with their contribution to the overall evidence, and different types of evidence or evidence categories must be weighted before they are combined into a WoE.

The weight of a category of evidence used in the Expert Panel evaluation is based on four considerations:

1. **Different categories of evidence (i.e. assay types) have different weights**. Genotoxicity tests measuring mutations and chromosome damage have greater weight than "indicator" assays that measure DNA damage. For example, for human pharmaceuticals, ICH S2 (R1) (ICH 2011) states that "fixation of damage to DNA in the form of gene mutations, larger scale chromosomal damage or recombination is generally considered to be essential for heritable effects and in the multi-step process of malignancy". The following comments are taken from the "Overview of the Set of OECD Genetic Toxicology Test Guidelines and Updates Performed in 2014–2015" (OECD 2015): *"There are tests that detect primary DNA damage (i.e. the first in the chain of events leading to a mutation), but not the consequences of this genetic damage. The endpoint measured in these tests does not always lead to a mutation, a change that can be passed on to subsequent generations (of cells or organisms). The DNA damage measured in the comet assay, or the unscheduled DNA synthesis (UDS) test, may lead to cell death, or it may initiate DNA repair, which can return the DNA either to its original state or result in mutation. When evaluating the mutagenic potential of a test chemical, more weight should be given to the measurement of permanent DNA changes (i.e. mutations) than to DNA damage events that are reversible."*
2. **The aggregate strength (robustness of protocols and reproducibility) and quality of evidence in the category also influence the weight.** It is generally acknowledged that studies conducted in compliance with Good Laboratory Practice (GLP) Regulations and studies conducted according to OECD guidelines have greater weight than studies lacking these attributes. These are fundamental features of the Klimisch scoring system, which is widely used to assess the reliability of study data, particularly for regulatory purposes (Klimisch et al. 1997).
3. **The number of pieces of evidence within a category influences the weight.** A single (or few) divergent responses (positive or negative) within a majority of studies exhibiting concordant findings would be insufficient to alter the direction and strength of the WoE. This component of the overall WoE is an aggregate of the weights of all the pieces of evidence within a single test category (e.g. tests for gene mutation).
4. **Tests with greater ability to extrapolate results to humans carry greater weight.** Test responses able to more accurately predict potential hazard in humans, such as *in vivo* tests, will generally be weighted more heavily than evidence developed from tests conducted *in vitro* or in non-mammalian models.

Human versus non-human test results

Using a variety of different methods, genotoxicity test data can be derived from human populations exposed under typical use conditions. Human population monitoring studies, if performed with sufficient sample sizes, knowledge of exposure levels and adjusted appropriately for confounding variables, can offer highly relevant information. Poorly controlled human biomonitoring studies, however, can lead to erroneous conclusions (Schmid & Speit 2007; Dusinska & Collins

2008). Adjustments that need to be considered in human biomonitoring studies for genotoxicity must extend beyond age, gender, smoking, alcohol, tobacco use, and medicines used. Diet, disease status (e.g. presence of inflammatory diseases), seasonal variation, and physical stress are all important confounding factors that influence an individual's background level for any parameter under consideration (Moller 2005; Battershill et al. 2008; Bonassi et al. 2011; Fenech et al. 2011; Tenorio et al. 2013; Collins et al. 2014). There is evidence that different factors may have different impact depending on the specific genotoxic endpoints (e.g. Fenech et al. 2011 for the cytokinesis block MN endpoint; Collins et al. 2014 for the comet endpoint).

It is worth noting that there is currently considerable debate concerning the relevance of increased levels of micronuclei in human biomonitoring studies. Speit (2013) suggested that micronuclei induced in the cytochalasin B micronucleus assay used in human biomonitoring studies, do not represent micronuclei that were induced during exposure, but rather represent DNA damage that generates micronuclei during the *in vitro* culturing required for the assay. As such, this bioassay could be classified as an "indicator test" of DNA damage with lower relevance for genotoxic risk. Kirsch-Volders et al. (2014), however, considered gaps in the knowledge regarding the source of micronuclei observed in human biomonitoring studies, but considers the assay, especially with modifications, to have utility for human genotoxic hazard/risk measurements. For the purposes of this review, the Expert Panel adopted a conservative approach and the measurement of micronuclei detected in studies of exposed humans was assigned a high weight.

It is also possible to conduct genetic tests using human derived cell lines or in primary lymphocyte cultures. With respect to results from cell lines of different origin, the benefits of using human rather than rodent derived cell lines are not as compelling as one might presume. Cell lines (human or rodent origin) with mutations affecting how cells handle initial DNA damage (e.g. p53 mutations) are typically more susceptible to genetic damage. Consequently, human cell lines with altered responsiveness to DNA damaging mechanisms may be expected to generate results not dissimilar to those produced in rodent cell lines. At this time there are not enough data available to reliably determine if the use of p53-competent cell lines of human origin (as opposed to p53-competent rodent derived lines) or other human cells confer greater accuracy (Walmsley & Billinton 2011; Fowler et al. 2014).

The most current OECD *in vitro* mammalian cell chromosomal aberration and micronucleus test guidelines indicate that either human or rodent cell lines or primary cultures may be used (OECD 2014a, 2014d). These guidelines also state that: *"At the present time, the available data do not allow firm recommendations to be made but suggest it is important, when evaluating chemical hazards to consider the p53 status, genetic (karyotype) stability, DNA repair capacity and origin (rodent* versus *human) of the cells chosen for testing."*

Thus, any *in vitro* mammalian cell results should be interpreted with caution, and the weight they contribute to an overall assessment of genotoxic activity should take account of the potential limitations.

A summary of assumptions, results, and conclusions regarding the IARC genotoxicity evaluation of glyphosate, GBFs, and AMPA

The Expert Panel used the considerations discussed above when assigning weights to genotoxicity endpoints and to the responses present in the glyphosate (and related materials) dataset. The results of this review indicate some areas of agreement with IARC, but also identified some major differences between the conclusions of the two assessments.

An evaluation of IARC and expert panel review processes

The Expert Panel agreed that there was sufficient evidence to conclude that glyphosate and GBFs appeared to induce DNA strand breaks and possibly micronuclei in *in vitro* mammalian and non-mammalian systems and sister chromatid exchanges (SCEs) in *in vitro* mammalian systems. These results provide some evidence of genotoxicity, but it is not possible to accurately characterize or classify genotoxic hazard/risk or carcinogenesis mechanisms based on these results alone. As noted earlier and further stated in the OECD overview comments (OECD 2015) regarding test weights, *"When evaluating the mutagenic potential of a test chemical, more weight should be given to the measurement of permanent DNA changes (i.e. mutations) than to DNA damage events that are reversible."* Consequently, positive responses in genotoxic endpoints identified above as "indicator tests" (i.e. DNA strand breaks, SCEs) are evidence of compound exposure but not sufficient to determine compound effect. In order to determine compound effect, consideration must be given to available evidence clearly demonstrating the induction of gene mutations or stable chromosomal alterations, particularly *in vivo* in mammalian systems.

Evidence weighting

Weights assigned to individual assays represent the strength of evidence assigned to an endpoint or category and may be derived from validation studies supporting the endpoint's involvement in carcinogen prediction as well as its relevance to mechanisms involved with initiation of malignancy (ICH 2011). In general human and *in vivo* mammalian systems have the highest test system weight, with a lower degree of weighting applied to *in vitro* mammalian cell systems and *in vivo* non-mammalian systems and lowest weight to *in vitro* non-mammalian systems (with the exception of the well validated bacterial reverse mutation "Ames" tests using mammalian metabolic activation). Other considerations, such as response reproducibility or GLP compliance, may influence the weight of a particular study result. GLP compliance indicates a high degree of, and standard for, detailed documentation of experimental conditions and data.

Section 4.2.1 of the IARC Monograph does not provide sufficient information to its readers regarding the strategy

employed by IARC reviewers in assessing the WoE; therefore, it is not possible to know if, for example, studies were assigned variable weights in accordance with the criteria discussed above. While the Expert Panel agrees that data from a well conducted human population biomonitoring study might carry more weight in a WoE assessment, it appears that IARC considered *in vitro* studies in human cells as carrying more weight than rodent *in vivo* studies as evidenced by the order of discussion topics in Section 4.2.1, and the inclusion of a separate table for human *in vitro* studies. The overall IARC Monograph evaluation (Section 6.0) and rationale (Section 6.4) indicate that the conclusion of strong evidence of genotoxicity is based on "studies in humans *in vitro* and studies in experimental animals." As discussed above, the Expert Panel evaluation considered *in vitro* studies using cells of human origin to be weighted as equivalent to any other *in vitro* mammalian cell assay using the same endpoint.

There did not, however, appear to be additional weight assigned by IARC to other criteria such as relevance of the endpoint to neoplastic initiation, quality of study performance, *in vitro* versus *in vivo* or reproducibility of responses.

Table 1 summarizes the Expert Panel's endpoint weighting assumptions. Weights represent strength, relevance and reliability of evidence and are based on a compilation of information regarding the endpoint's reversibility and susceptibility to false or misleading positive responses with respect to carcinogenicity prediction or relevance to mechanisms involved in initiation of malignancy (Solomon et al. 1991; Pierotti et al. 2003; Petkov et al. 2015).

The endpoint and test system weighting categories are defined as follows:

- **Negligible weight** – the endpoint is not linked to any adverse effect relevant to genetic or carcinogenic hazard/risk and as such is not given weight as evidence of genotoxicity.
- **Low weight** – the end point is indicative of primary DNA damage, is not unequivocally linked to mechanisms of tumorigenicity, and the test system has low specificity.
- **Moderate weight** – the endpoint is potentially relevant to tumorigenicity or may be subject to secondary, threshold-dependent mechanisms of induction (e.g. cytotoxic clastogens, aneugens) or the test system exhibits a high rate of misleading positives with respect to carcinogenicity predictivity or carcinogenic mechanism.
- **High weight** – the endpoint is one that has been demonstrated with a high level of confidence to play a critical role in the process of tumorigenicity.

Chemical structure and chemistry of GBFs

Chemical structures of glyphosate and AMPA are presented in Figure 1. IARC did not consider the chemical structure of glyphosate in its mechanistic section; however, IARC Monograph Section 5.3 states that glyphosate is not electrophilic. Many guidelines recommend that the presence of structural alerts be considered in evaluation of or testing for genotoxicity (Cimino 2006; Eastmond et al. 2009; EFSA 2011; ICH 2011). As reported in Kier and Kirkland (2013) analysis of the glyphosate structure by DEREK software identified no structural alerts for chromosomal damage, genotoxicity, mutagenicity, or carcinogenicity. Analysis of structural alerts for genotoxicity inherently includes consideration of potential

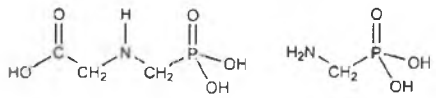


Figure 1. Chemical structures of glyphosate and AMPA. Glyphosate: N-(phosphonomethyl)glycine, acid form, CAS 1071-83-6; AMPA: aminomethylphosphonic acid; CAS 1066-51-9.

Table 1. Expert Panel's evidence weighting assumptions for mammalian (plus selected microbial test) endpoints.

Endpoint*	Negligible weight	Low weight	Moderate weight	High weight
DNA binding (adduct formation) *in vitro*		■		
DNA binding (adduct formation) *in vivo*		■		
SSB/DSB *in vitro (including comet)*		■		
SSB/DSB *in vivo (including comet)*			■	
SCEs *in vitro*	■			
SCEs *in vivo*	■			
Oxidative DNA		■		
Damage *in vitro*		■		
Oxidative DNA			■	
Damage *in vivo* (detection of 8-OHdG adducts)			■	
DNA repair effects *in vitro*		■		
DNA repair effects *in vivo*			■	
Micronuclei *in vitro*			■	
Micronuclei *in vivo*				■
Chromosomal aberrations *in vitro*			■	
Chromosomal aberrations *in vivo*				■
Gene mutation in bacteria (Ames Test)				■
Gene mutation mammalian *in vitro*			■	
Gene mutation *in vivo*				■

*Shaded box indicates weight for the endpoint. SSB: single strand breaks; DSB: double strand breaks; SCE: sister chromatid exchange.

metabolites. Although formal analysis is not available, it does not appear likely that the metabolite AMPA (glyphosate without a carboxymethyl group) has structural alerts. While structural alerts are not as definitive as experimental data, they serve as part of a WoE (Dearfield et al. 2011). The lack of structural alerts in the glyphosate molecular structure suggests lack of genotoxicity or that genotoxic effects might well be secondary to toxicity or resulting from mechanisms other than DNA-reactivity.

Another aspect of chemistry that should be recognized is the fact that GBFs, while containing glyphosate (often present as a sodium or potassium salt) also contain other components which frequently include surfactants. Specific formulations differ in composition and differences may exist between GBFs identified with a common brand name. Frequently, GBFs are observed to have greater toxicities than glyphosate. Evaluation of genotoxicity results for glyphosate and GBFs should always consider the possibility that effects observed with GBFs may be due to GBF components other than glyphosate and that there may be chemical differences between various GBFs.

The case for including other published results in the IARC genotoxicity evaluation

Although IARC policies and Working Group decisions excluded consideration of additional data from unpublished studies or publicly unavailable governmental reports, it was the Expert Panel's conclusion that the genetic toxicology studies published in reviews such as Kier and Kirkland (2013), in particular the supplementary primary data submitted with the paper, should have been considered by IARC in evaluating the genetic toxicology of glyphosate and GBFs. Though the primary study reports from which the data were extracted were not available to IARC, detailed data were provided in the Kier and Kirkland (2013) review and exceed the weight of data in most published reports that were considered by IARC. Regulatory studies of GBFs and AMPA summarized in Williams et al. (2000) should also have been considered and information on these studies is presented in Appendices A and B.

Inclusion of the studies in these publications would have filled data gaps, supplemented study categories for which there were limited numbers of test responses and would have added a very high level of confirmation to other core assay results. Table 2 summarizes an additional 90 studies covering a range of test categories that were available for review if the regulatory studies in the Kier and Kirkland (2013) publication and other published or publicly available studies had been included. Among the 90 studies not included in the IARC Monograph, only nine were reported as positive. Inclusion of these studies in a WoE produces a much clearer, more reliable and balanced assessment of the genotoxicity of glyphosate, GBFs and AMPA.

The rationale supporting the inclusion of these 90 additional studies is that the supplementary tables presented in the Kier and Kirkland (2013) paper, and presented in Supplemental Information, Appendix A of this publication, do contain sufficient detail concerning the robustness of the studies. For the regulatory studies, which were the key studies not reviewed by IARC, the Kier and Kirkland (2013) paper clearly states:

> Each study examined was stated to have been conducted in accordance with GLP standards with almost all studies citing the OECD Principles of Good Laboratory Practice (OECD GLP 1982, 1997). Reports also cited compliance with various national and regional GLP Guidelines (e.g European Commission GLP Directives 87/18/EEC or 88/320/EEC; U.S. Environmental Protection Agency GLP Standards, 40 CFR Part 160; Japanese Ministry of Agriculture, Forestry, and Fisheries (MAFF) GLP Standards, 11 Nousan No. 6283). Variations from GLPs were considered not to have significantly impacted the study results.
>
> Almost all of the studies were reported to have been conducted in accordance with the relevant OECD test guidelines applicable at the time of the study. Study reports were examined to determine that the protocols and experimental methods for the report were consistent with the OECD guidelines and any deviations were noted and considered. Report data were examined to confirm the conclusion of the report regarding whether treatment-related activity had been observed.

Thus, the methods used were generally as specified in OECD guidelines, or any deviations were noted. Moreover, the studies were performed under GLP conditions, which would ensure protocol compliance and high quality data. The key aspects of each test method were detailed in the first few pages of the supplementary material in Kier and Kirkland (2013) so it is easy to see how top concentrations were chosen, what measures of cytotoxicity were used, how many cells were scored etc. Links to the guidelines were provided.

The rationale given by IARC for not including the regulatory studies in Kier and Kirkland (2013) was that the primary study reports were not available, and that the information provided in the supplementary tables was insufficient regarding topics such as details of statistical methods, choice of

Table 2. Summary of test categories, number of studies, and study responses available from Kier and Kirkland (2013) and other publically available studies not included in the IARC Monograph (details for all studies provided in Supplemental Information, Appendix A).

Test category	Endpoint	Glyphosate (Pos/Neg)	GBFs (Pos/Neg)	AMPA (Pos/Neg)	Total (Pos/Neg)
Non-mammalian (Bacterial Reverse Mutation)	Gene mutation	0/19	0/20	0/1	0/40
Mammalian *In Vitro*	Gene mutation	0/2	ND	ND	0/2
	Chromosomal aberrations	1/5	1/0	ND	2/5
	Micronucleus	2/0*	1/0	ND	3/0
	UDS	0/1	ND	0/1	0/2
	SCE	ND	1/0	ND	1/0
Mammalian *In Vivo*	Chromosomal aberrations	0/1	2/0*	ND	2/1
	Micronucleus	0/13*	0/17	0/1	0/31
	SCE	ND	1/0	ND	1/0
Total		3/41	6/37	0/3	9/81

*Inconclusive studies not included in count; AMPA: aminomethylphosphonic acid; GBFs: glyphosate based formulations; ND: not done

highest dose tested, and verification of the target tissue exposure.

This rationale for exclusion is unjustified for the following reasons.

For bacterial reverse mutation assays the concentrations tested were detailed in every table, as were critical aspects of the methods (e.g. plate incorporation or pre-incubation for the Ames tests, inducing agent for the S9 and its final concentration, and number of replicate cultures). Thus, it is clear what top concentrations were used, whether they complied with the maximum concentration/dose as recommended in OECD guidelines, or whether they were defined by toxicity.

Almost all of the many Ames tests on glyphosate used a top concentration of the maximum required, 5000 μg/plate unless contraindicated by toxicity. All of the required strains, including either TA102 or *Escherichia coli*, have been used in the regulatory studies included in Kier and Kirkland (2013). The Ames tests on GBFs used quite variable top concentrations. Some went as high as the maximum required (5000 μg/plate) but others only reached <100 μg/plate, seemingly limited by toxicity. Since we know glyphosate *per se* is not very toxic in the bacterial tests, the toxicity is presumably caused by the other components of the formulations, which were more toxic in some GBFs than in others.

The mammalian cell assays on glyphosate generally reached top concentrations in the range 500–5000 μg/mL, even when prolonged (48 h) treatments were performed in the chromosomal aberration studies. Thus, many of these studies exceeded 10 mM (1690 μg/mL for glyphosate), the top concentration currently recommended in OECD guidelines for nontoxic substances. There were no regulatory mammalian cell tests on GBFs.

All except one of the regulatory *in vivo* micronucleus (MN) tests on glyphosate that used oral dosing achieved a top dose of at least 2000 mg/kg, which is the top dose for a nontoxic substance recommended in OECD guidelines. One oral study achieved a top dose of only 30 mg/kg, seemingly because severe toxicity and lethality was seen at higher doses. It is unclear why such lethal effects were seen in this study when much higher doses were tolerated in other studies using the same acute dosing regimen. Several studies using intraperitoneal (i.p.) injection had lower top doses because of greater toxicity when using the intraperitoneal route. Thus, all of the regulatory MN studies on glyphosate met or exceeded the required top dose.

The *in vivo* bone marrow MN and chromosomal aberration regulatory studies of Kier and Kirkland (2013) generally did not report evidence of target organ toxicity (e.g. %PCE, which would be a measure of bone marrow toxicity) or include analyses to demonstrate presence of glyphosate in plasma. Therefore, the issue of whether the bone marrow was exposed needs verification by evidence other than target organ toxicity.

The IARC Monograph states that about 1/3 of glyphosate administered orally to rodents is absorbed and excreted, largely unchanged, in urine. This provides evidence that it is likely that the bone marrow, a well-perfused tissue, is exposed to glyphosate in rodents treated orally. Definitive evidence of absorption and systemic distribution of glyphosate in rodents is also contained in a summary of regulatory toxicokinetic studies (JMPR 2006). These studies demonstrated absorption of glyphosate and systemic distribution, including distribution in bone marrow, in rats dosed intraperitoneally or orally. Published reports have also indicated absorption and systemic distribution of glyphosate administered by the intravenous (i.v.) or oral route in rats (Brewster et al. 1991; Anadon et al. 2009) and by the oral (dietary) route in mice (Chan & Mahler 1992). Thus, in the regulatory rodent *in vivo* MN and chromosomal aberration tests, target organ exposure would have been achieved.

If statistical analysis was performed (not commonly performed or required for Ames tests) this is given as a footnote to the supplementary tables (Kier & Kirkland 2013, supplementary tables; Appendix B, this report), together with the statistical method used, and whether the results were significant.

Thus, in view of the Expert Panel, the exclusion of these studies was not justified. Failure to evaluate and consider the large number of results included in the publication by Kier and Kirkland (2013) as well as other publicly available studies not reviewed by IARC, resulted in an inaccurate assessment of glyphosate, GBFs and AMPA's genotoxic hazard/risk potential.

Expert panel's critique of selected studies: impact on IARC evaluation

Genetic toxicology tests relied upon by most regulatory bodies to support decisions focus on a set of core endpoints that are known to be involved either in direct activation of genes responsible for neoplastic initiation in somatic cells or alteration of the genetic information in germ cells (EFSA 2011; ICH 2011; Kirkland et al. 2011). Therefore, the endpoints given the greatest weight in Table 1 include gene mutation and chromosomal aberrations.

MN formation *in vivo* was also assigned a high weight (Table 1), as it is considered an indication of chromosome breakage but could also result from aneuploidy (Kirsch-Volders et al. 2003). However, aneugenic effects are usually thresholded (Parry et al. 1994). For instance, MN may be induced by alterations in normal mitosis produced by various kinases. It was demonstrated that GBFs activate mitotic kinase CDK-1 (Marc et al. 2002) which could possibly play a role in MN induction through a separate mechanism believed to be threshold based (Terasawa et al. 2014). Although a thresholded mechanism may be considered of less weight than a non-thresholded mechanism, most *in vivo* MN studies did not investigate this. In the absence of information on clastogenic or aneugenic mode of action, the panel considered that a high weight should be applied to all *in vivo* MN studies.

Human genotoxicity biomonitoring studies

The results provided for GBFs in Table 4.1 (human studies) of the IARC Monograph concluded positive evidence of DNA breakage as determined by results in humans using the comet assay Paz-y-Miño et al. (2007), negative induction of

chromosomal aberrations (Paz-y-Miño et al. 2011), and positive induction of MN (Bolognesi et al. 2009). Due to the importance of these studies in the IARC review, these papers were critically reviewed by the Expert Panel as described in detail below.

Paz-y-Miño et al. (2007) reported increased DNA damage (comet assay) in individuals recently exposed to GBF spraying, but only "suggested" this implied a genotoxic risk. The comet assay, as discussed earlier is an "indicator" endpoint and primary DNA damage does not accumulate, so the consequences of the observed DNA breaks remain unknown (Faust et al. 2004).

The Expert Panel review of this study identified a number of issues that questioned the validity of the interpretation of results. For example, it is not clear which blood cells were scored for comets, or if it was all cells in the blood. Also, the observation of a median comet tail length of exactly 25.0 μm for 20/21 unexposed control individuals in this publication questions the quality of data collection. This unusual observation was not noted in the IARC Monograph. The Paz-y-Miño et al. (2007) publication indicated that signs of clinical toxicity were reported in the population and that the GBF application rate was reported to be some 20 times higher than recommended. The clinical signs were consistent with acute intoxication associated with severe exposures (Menkes et al. 1991) and these factors suggest that comet effects might have been secondary to toxicity from very high exposure to GBF. The Paz-y-Miño et al. (2007) report seems to qualify the conclusiveness of the results by indicating that the results "suggest" a genotoxic effect. Due to uncertainties regarding the negative control data, and particularly because of uncertainties regarding the mechanistic role of cytotoxicity in generating the effects the Panel regarded this study as inconclusive evidence for *in vivo* human genotoxic effects relevant to induction of mutations or carcinogenesis.

In a follow-up study, Paz-y-Miño et al. (2011) reported negative results for induction of chromosomal changes in individuals from areas where GBF spraying had occurred two years previously. The absence of chromosomal aberrations supports the presumption that the DNA strand breaks identified in the Paz-y-Miño et al. (2007) study were either repaired or lethal and did not persist as lesions which could be expressed as chromosomal aberrations in cultured lymphocytes in the follow-up study.

Bolognesi et al. (2009) reported a significant but small, transient and inconsistent effect of glyphosate spraying on MN induction in individuals living in areas where aerial spray application of glyphosate occurred (Figure 1 in Bolognesi et al. 2009), but concluded that any risk was "low". Of greater importance however, is the observation that no statistically significant increase in the frequency of micronucleated binucleated cells (BNMN) was observed in individuals that actually reported direct exposure to the spray compared to individuals who lived in the spray area but were not present during spraying (Bolognesi et al. 2009, Table 4). These results are shown graphically in Figure 2 (graph provided by K. Solomon). As indicated in Table 4 of Bolognesi et al. (2009), statistical analysis did not indicate a significant difference ($p < .05$, ANOVA) in post-spray BNMN frequency between

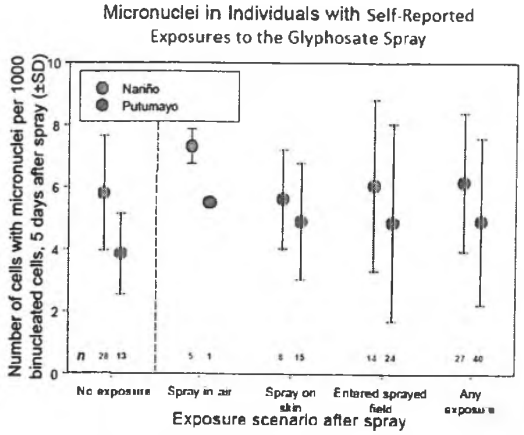


Figure 2. Mean frequency of binucleated cells with micronuclei (BNMN) in self-reported exposures to glyphosate spray in areas where aerial application occurred. From Bolognesi et al. (2009); Table 4. Data from Valle del Cauca not shown in graph since only one individual reported exposure. Graph provided by K. Solomon.

different categories of self-reported spray exposure and there was no statistically significant difference ($p < .05$) between no exposure and any self-reported spray exposure for any of the three regions. The Valle del Cauca region, which exhibited the highest post-spraying increase, only had 1/26 persons self-reporting spray exposure and the GBF spray application rate was substantially lower than the application rates in the other two regions.

Although results were temporally consistent with GBF spraying, the lack of significant correlation between increased post-spraying BNMN frequencies and self-reported spray exposure, and inconsistency with application rates, indicate that the MN effects observed in this study cannot be associated with GBF exposure (Figure 2) and therefore the Expert Panel concluded the results to be negative. The panel agrees with the statement made in the discussion section of Bolognesi et al. (2009) that based on the Bradford Hill criteria (Hill 1965) it is not possible to assign causality to the BNMN increases observed in their study and notes that elsewhere in this publication the authors seemed to qualify their conclusions with terms like "suggest" and "potentially". Lack of clear evidence of causality indicates that it is inappropriate to conclude that GBF induces MN in humans. The Bolognesi et al. (2009) results were considered negative by the Expert Panel because there were no statistically significant increases in MN frequency associated with self-reported spray exposure. This conclusion is subject to the limitation of the use of self-reporting as a measure of exposure.

The Expert Panel conclusion for the Bolognesi et al. (2009) results seems to be quite different from the IARC Monograph. The qualifications about lack of consistency with exposure rates or statistically significant association with self-reported spray exposure are noted in the discussion of this study in IARC Monograph Section 4.2.1(a)(i). However, these qualifications are not evident in IARC Monograph Section 5.4 which presents these results as positive without qualification. IARC Monograph Section 6.4 not only presents the results as

positive without qualification but seems to give this study a high weight in arriving at their conclusion of a genotoxic mode of action.

Due to the deficiencies cited in the biomonitoring studies above, along with the lack of scientific consensus regarding the relevance of MN found in exposed humans, the Expert Panel concluded that there was little or no reliable evidence produced in these studies that would support a conclusion that GBFs, at levels experienced across a broad range of end-user exposures, poses any human genotoxic hazard/risk.

Studies in mammalian in vitro and in vivo assays

The number of studies conducted in mammalian models both *in vitro* and *in vivo* was relatively extensive but with some notable data deficiencies and gaps. However, looking for evidence consistent with a concern for genotoxic hazard finds little or no compelling support among test methods that assess relevant endpoints.

Gene mutation

IARC noted one negative *in vitro* mammalian gene mutation result for glyphosate (IARC Monograph Table 4.4). Additionally there are two negative results for glyphosate in the mouse lymphoma tk locus assay (Kier & Kirkland 2013). These provide a clear WoE that glyphosate does not induce gene mutation in mammalian cell systems. There are no *in vitro* mammalian cell gene mutation results for GBFs or AMPA.

Chromosomal effects in vitro

In *in vitro* mammalian cell chromosomal aberration assays (IARC Monograph Tables 4.2 and 4.4) glyphosate was reported positive in one study and negative in two other studies. Regulatory studies and published studies, not considered by IARC, provide one additional positive result and five additional negative results (see Supplemental Information, Appendix A, Table 2 of this paper). One of the positive studies (Lioi et al. 1998a) is not considered valid due to the fact that there was excessive cytotoxicity (>50% reductions in mitotic index at all concentrations tested, exceeding current regulatory guidelines for a valid assay). Several of the published studies did not include exogenous mammalian metabolic activation. Most importantly, the negative studies tested glyphosate at dose levels well in excess of those reported positive by Lioi et al. (1998a, 1998b) and included several human and bovine lymphocyte studies. In addition to the negative chromosomal aberration assays the two negative results in the mouse lymphoma tk locus assay also add weight to a conclusion that glyphosate is not clastogenic in *in vitro* mammalian cell assays. Overall these results provide sufficient evidence that glyphosate is not clastogenic in mammalian cells when studied under appropriate *in vitro* treatment conditions.

No *in vitro* mammalian chromosomal aberration studies of GBFs and one positive *in vitro* mammalian chromosomal aberration study with AMPA were reported by IARC. The latter study by Sivikova and Dianovsky (2006), reported as a GBF study in IARC, is considered to be a study of a manufacturing batch of an isopropyl salt of glyphosate from a Monsanto source (Kier & Kirkland 2013). An additional positive *in vitro* mammalian chromosomal aberration study was not considered by IARC (Amer et al. 2006; see Supplemental Information, Appendix A, Table 2 of this paper). The positive GBF study tested an unusual GBF and employed very high dose levels. These single studies do not provide a strong WoE for induction of chromosomal aberrations for GBFs or AMPA in mammalian cells *in vitro*.

IARC reported two positive *in vitro* mammalian cell MN studies of glyphosate. However, another four positive or equivocal *in vitro* mammalian cell MN studies of glyphosate were identified in the literature that were not reported in IARC but were summarized in Kier and Kirkland (2013). Several of the studies had weak or inconsistent responses. Piesova (2004, 2005), not in IARC, reported statistically significant increases in MN in bovine lymphocytes only with 48-h incubation without S9 metabolic activation but the responses were not consistent between donors. Two papers by Mladinic et al. (2009a, 2009b) reported weak responses in human lymphocytes at the highest dose tested in the presence of S9 metabolic activation. MN results for Mladinic et al. (2009a) were not reported in IARC. One of these studies (Mladinic et al. 2009a) had a very high control MN frequency and in both publications it appears that cells were treated prior to mitogen stimulation which would mean cells would have been exposed in G0 cell stage. This treatment regimen is not considered appropriate according to current test guidelines. The MN induced at high doses were predominantly centromere positive suggesting the possibility of an aneugenic effect. These responses were considered of limited quality by IARC and the publication authors indicated that the high dose effects might have been at a dose level exceeding a threshold and possibly associated with high toxicity. Koller et al. (2012), MN results not evaluated by IARC, reported positive *in vitro* MN results in human-derived buccal epithelial cells for glyphosate in the absence of S9 metabolic activation. An unusual feature of this paper was indication of significant cytotoxicity at very low dose levels (20 µg/mL) and with very short exposure times (20 min). Although the authors speculated their epithelial cells might be more sensitive than cells of the hematopoietic system such as lymphocytes, a large number of other studies using non-hematopoietic cells used much higher doses and longer exposure times. A study by Roustan et al. (2014) reported increases in MN frequency in CHO-K1 cells only in the presence of S9 activation. There was very little dose response observed over an order of magnitude of concentrations (10–100 µg/mL). Thus, although positive (or equivocally positive) responses were observed for glyphosate in several studies these responses were not consistent in terms of dose levels or requirement for an S9 metabolic activation system. The possibility of a threshold aneugenic effect in the presence of S9 metabolic activation might be suggested by the results of Mladinic et al. (2009a, 2009b) but other studies cannot confirm this possibility because presence or absence of centromeres was not

measured. It should be noted that there is a report that glyphosate is essentially unchanged by incubation with rat liver homogenate which would indicate that S9 activation dependent responses might not be due to metabolites of glyphosate (Gohre et al. 1987).

Overall these studies provide only very limited evidence of the possibility of MN induction by glyphosate in *in vitro* mammalian cell assays and this observation, coupled with the negative profile for clastogenicity in *in vitro* mammalian cell assays, would suggest this low possibility is limited to aneugenic effects that are likely to be indirect and thresholded.

Although IARC reports one negative *in vitro* mammalian cell assay with a GBF (Sivikova & Dianovsky 2006), as noted above this assay is likely to have been performed with a technical glyphosate preparation rather than a formulation. Koller et al. (2012) report a positive *in vitro* MN result for a GBF (result not included in IARC) in buccal epithelial cells derived from a human-neck metastatic tumor. The authors noted that these cells have not been used for genotoxicity assessments and the Expert Panel considered the results in this non-validated system to be of unknown relevance. IARC reported one positive result for AMPA in an *in vitro* mammalian cell MN assay in CHO-K1 cells (Roustan et al. 2014). An unusual feature of the Roustan et al. (2014) study was that AMPA apparently exhibited much higher cytotoxicity than glyphosate. Although complete cytotoxicity data are not presented, the maximum AMPA concentrations evaluated for MN, appearing to produce less than 50% reduction in cytokinesis blocked proliferation index, were 1000-fold lower than glyphosate concentrations in the absence of S9 metabolic activation, 20-fold lower in the presence of S9 metabolic activation and 100,000-fold lower with light activation. These very large cytotoxicity differences are dramatically different from the relative toxicities of AMPA and glyphosate observed in other mammalian cell studies, e.g. Chaufan et al. (2014); Manas et al. (2009a, 2009b); Li et al. (2013); Kwiatkowska et al. (2014). These individual studies, particularly the Roustan et al. (2014) study, appear to exhibit technical problems and do not present a convincing WoE for *in vitro* mammalian cell MN effects of GBFs or AMPA.

Chromosomal effects in vivo

As a general point, it was noted earlier that there is adequate evidence available from toxicology studies demonstrating absorption and distribution of glyphosate to bone marrow in the rat (i.p., i.v., and oral routes) and absorption and distribution of glyphosate in blood by the oral route in the mouse. This information provides evidence for target organ exposure in the rodent bone marrow studies discussed below, which is particularly important when negative results are obtained.

Table 4.3 in the IARC Monograph reported one negative *in vivo* rat bone marrow chromosomal aberration result and one negative mouse dominant lethal result for glyphosate. In addition there is one negative regulatory *in vivo* mouse bone marrow chromosomal aberration study of glyphosate not evaluated by IARC (Suresh 1994; see Supplemental Information, Appendix A, Table 3). These studies provide *in vivo* evidence complementing the larger number of *in vitro* studies (discussed above) indicating glyphosate is not clastogenic when tested in mammalian assays.

IARC reported two positive results and one negative result for glyphosate in *in vivo* MN assays. In one of the positive studies reported by IARC (Bolognesi et al. 1997), relatively low increases in MN frequency were observed which might well be within the historical range of many laboratories (Salamone & Mavournin 1994). The other positive study (Manas et al. 2009a) had an unusual feature in that it is reported that erythrocytes were scored for MN, but in the bone marrow and at an early sampling time. Historical control data were not reported in the publication so the relevance of this result cannot be determined. By contrast, there are an additional 13 published, publicly available or regulatory *in vivo* MN studies with glyphosate in the mouse (12 studies) or rat (one study), all of which gave negative results (see Supplemental Information, Appendix A, Table 3 of this paper). These negative results were obtained in multiple studies at dose levels that exceeded those at which positive results had been reported in the IARC reviewed studies mentioned above using the same (i.p.) route of administration. With respect to a route of exposure, the negative MN results in a glyphosate mouse feeding study (Chan & Mahler 1992) that was not reported in IARC are of particular relevance to carcinogenic potential. The Expert Panel's conclusion is that there is a strong WoE that glyphosate does not induce MN *in vivo* in mammals.

IARC reported one positive and one negative rodent bone marrow chromosomal aberration study for GBFs. An additional two published positive rodent chromosomal aberration studies on GBFs were identified that were not reported in IARC. One mouse study with positive results (Prasad et al. 2009) employed sampling times for a chromosomal aberration assay quite different from those currently recommended (OECD 2014c). Moreover, the GBF was administered i.p. using dimethylsulfoxide (DMSO) as a vehicle and the use of this vehicle and route has unusual toxicity properties (Heydens et al. 2008). This assay was also unusual in that dose-responsive increases were observed at multiple sampling times, which is difficult to explain since cells damaged at early sampling times have usually died and disappeared from the bone marrow by later sampling times. Another positive publication (Amer et al. 2006), not reported in IARC, found positive chromosomal aberration results in mouse bone marrow and spermatocytes with treatments that included repeated oral and i.p. dosing. The test material was reported to be a formulation containing 84% glyphosate which is very unusual and raises the possibility that observed effects were due to some unusual or unique component of this formulation. Another published positive GBF study (Helal & Moussa 2005) uniquely involved rabbits exposed to GBF (750 ppm) in drinking water for 60 days. Using extended repeat dosing for a bone marrow chromosomal aberration assay is questionable because cells with chromosome breaks usually do not accumulate and any cytogenetic effects would likely be due to the final one or two doses. Total aberrations reported for this study included some nonstandard and questionable categories such as gaps and centromeric attenuations. Thus, most of the positive *in vivo* chromosomal aberration studies with

GBF's are all subject to concerns regarding the reliability or biological relevance of the results. While they cannot be ignored, they do not warrant undue weight, and do not support a conclusion of strong evidence of genotoxicity.

IARC reported two positive and three negative *in vivo* rodent bone marrow MN results for GBFs. One of the two positive studies (Bolognesi et al. 1997) had low negative control MN frequencies and the MN frequencies in treated groups were within historical control ranges for many laboratories (Salamone & Mavournin 1994) although historical control ranges for the laboratory were not reported in the publication. The other positive study (Prasad et al. 2009) was unusual in using DMSO as a vehicle by the i.p. route which, as noted above, may have led to unusual toxicity. However, there are an additional 17 rodent bone marrow studies with GBFs that were not considered by IARC, and all were negative (see Supplemental Information, Appendix A, Table 3 of this paper). The negative studies included use of both oral and i.p. routes and maximum dose levels frequently were limit doses of 2000 mg/kg (OECD 2014b). The overwhelming majority of *in vivo* MN studies on GBFs, therefore, gave negative results. In the studies reported positive, there are indications that the results may not be biologically meaningful, or that artifacts may have resulted from use of DMSO as vehicle.

For AMPA, IARC reported one positive mouse bone marrow MN study. There was one negative regulatory mouse bone marrow MN study of AMPA not reported in IARC. Both studies used the i.p. route. The positive study used a top dose of 200 mg/kg administered on two occasions, 24 h apart. The negative study used a single top dose of 1000 mg/kg which produced signs of toxicity. There is no obvious explanation for these conflicting results and the limited data do not allow reasonable WoE conclusions for AMPA in terms of the *in vivo* MN endpoint.

DNA damage in vitro

As noted above, the Expert Panel is in agreement with IARC reviewers that there are several *in vitro* mammalian cell studies of glyphosate which show DNA strand break effects (more specifically the alkaline single cell gel electrophoresis or comet endpoint). However, as also noted above, these studies should be assigned low weights compared to other more relevant endpoints in evaluating genotoxic risk, particularly when the results for relevant endpoints are more abundant. An assumption that the DNA damage observed *in vitro* might be secondary to toxicity rather than leading to DNA-reactive or persistent genotoxicity is underscored by cases where the same publication reports DNA damage effects but not chromosomal alterations, e.g. Sivikova and Dianovsky (2006); Manas et al. (2009a); Mladinic et al. (2009a) without metabolic activation. Other publications reported both DNA damage and chromosomal effects, e.g. Lioi et al. (1998a); Koller et al. (2012).

For GBFs there are only two positive *in vitro* mammalian cell comet results reported by IARC. These provide limited evidence for GBF-induced DNA damage effects *in vitro* in mammalian cells.

There are a few positive *in vitro* mammalian cell SCE reports for glyphosate and GBFs reported in IARC. Since the OECD guideline for the SCE test has recently been deleted because of a lack of understanding of the mechanism(s) detected by the test, the biological relevance of SCE is unclear, and these studies have not been further considered by the Expert Panel for a WoE evaluation.

One negative primary hepatocyte UDS result is reported by IARC for glyphosate, but there are also negative primary hepatocyte UDS results for glyphosate and AMPA (one each) not reported by IARC.

DNA damage/adducts in vivo

One *in vivo* mammalian DNA damage and one *in vivo* mammalian DNA adduct study of glyphosate were reported by IARC. No additional regulatory or published studies were identified. Results for 8-hydroxydeoxyguanosine (8-OHdG) measurements are considered in the oxidative stress section (Section IIIB).

Bolognesi et al. (1997) reported transient (4 h after dosing) increases in alkali-labile DNA strand breaks in liver and kidneys of mice treated i.p. with glyphosate. Interpretation of the genotoxic significance of these observations is difficult because such effects might be due to arrest of cells in S-phase or secondary to cytotoxicity (Williams et al. 2000). Peluso et al. (1998) reported no induction of adducts in mouse liver or kidney detectable by ^{32}P-postlabelling methodology after i.p. administration of glyphosate.

There is one positive *in vivo* SCE report for a GBF by Amer et al. (2006) which was not evaluated by IARC. For reasons of relevancy noted above, this study has not been further considered by the Expert Panel in a WoE evaluation.

One *in vivo* mammalian DNA damage and one *in vivo* mammalian DNA adduct studies of GBFs were reported by IARC. No additional regulatory or published studies were identified.

Bolognesi et al. (1997) reported transient (4 h after dosing) increases in alkali-labile DNA strand breaks in liver and kidneys of mice treated i.p. with a GBF. Similar conclusions about interpretation of these results apply as for the glyphosate results by the same authors discussed above. Peluso et al. (1998) observed ^{32}P-postlabelling adducts in liver and kidneys of mice dosed with a GBF. The source or identity of the adducts were not characterized although such adducts were not observed in studies with glyphosate in their publication.

No *in vivo* mammalian DNA damage studies of AMPA were reported in IARC or identified.

The paucity of data as well as the limited significance of the primary DNA damage endpoints on tumor initiation did not warrant that these observations should have a significant WoE impact.

Weight of evidence (WoE) for genotoxic effects in mammalian systems

In summary, the WoE from *in vitro* and *in vivo* mammalian tests for genotoxicity indicates that:

- Glyphosate does not induce gene mutations *in vitro*. There are no *in vitro* mammalian cell gene mutation data for GBFs or AMPA, and no gene mutation data *in vivo*.
- Glyphosate, GBFs, and AMPA are not clastogenic *in vitro*. Glyphosate is also not clastogenic *in vivo*. Some positive *in vivo* chromosomal aberration studies with GBFs are all subject to concerns regarding their reliability or biological relevance.
- There is limited evidence that glyphosate induces MN *in vitro*. Although this could be a reflection of increased statistical power in the *in vitro* MN studies, the absence of clastogenic effects in a large majority of *in vitro* chromosomal studies suggests the possibility of threshold-mediated aneugenic effects. However, there is strong evidence that glyphosate does not induce MN *in vivo*.
- Limited studies and potential technical problems do not present convincing evidence that GBFs or AMPA induce MN *in vitro*. The overwhelming majority of *in vivo* MN studies on GBFs gave negative results, but conflicting and limited data do not allow a conclusion on *in vivo* induction of MN by AMPA.
- There is evidence that glyphosate and GBFs can induce DNA strand breaks *in vitro*, but these might be secondary to toxicity since they did not lead to chromosome breaks. There is limited evidence of transient DNA strand breakage for glyphosate and GBFs *in vivo*, but for glyphosate at least these are not associated with DNA adducts. These results are assigned a lower weight than results from other more relevant endpoints, which were in any case more abundant.
- There is evidence that glyphosate and AMPA do not induce UDS in cultured hepatocytes.
- Some reports of induction of SCE *in vitro* by glyphosate and GBFs, and one positive report of SCE induction *in vivo* by a GBF, do not contribute to the overall evaluation of genotoxic potential since the mechanism of induction and biological relevance of SCE are unclear.

Studies in non-mammalian test systems

With the exception of the bacterial reverse mutation test, global genotoxicity testing guidelines such as those issued by OECD (2015) and other regulatory bodies do not recommend routine use of non-mammalian assays. Recently, OECD guidelines for two non-mammalian tests have been deleted because mammalian cell tests are considered more biologically relevant, and non-mammalian tests (with the exception of the bacterial reverse mutation test) are rarely used for regulatory test batteries.

Table 4.6 in the IARC Monograph summarized results from two bacterial reverse mutation test publications. One publication (Li & Long 1988) reviewed by IARC reported no mutagenic activity associated with glyphosate in a bacterial reverse mutation test but a publication by Rank et al. (1993) indicated a positive finding with a glyphosate formulation.

Rank et al. (1993) reported positive mutagenicity in TA98 only without S9 and positive mutagenicity in TA100 only with S9. At the outset this combination of responses is problematic as it is an unlikely combination and suggests that either one or both strain/S9 responses would be in error. The study data shown in Table 2 of the Rank et al. (1993) publication indicates that the positive responses reported for TA98 and TA100 were neither dose related nor were they reproduced in repeat data sets. The authors called the results indicative of gene mutation capabilities for a GBF; however, the data should never have been accepted for publication without additional testing over a narrower range of doses and as they currently stand, do not meet commonly used criteria for declaring Ames test results positive. The data from this one publication are not in agreement with 19 bacterial reverse mutation assays of GBFs presented in Supplemental Information, Appendix A, Table 1 that were not included in the IARC Monograph. The Expert Panel considered the results of this study to be inconclusive.

A large number (20) of negative bacterial reverse mutation assays of GBFs are presented in Supplemental Information, Appendix A, Table 1. None of these were included in the IARC Monograph. There is also one negative regulatory study of AMPA.

In contrast to the two bacterial reverse studies considered in the IARC Monograph there are actually abundant data from 40 additional studies (Supplemental Information, Appendix A, Table 1) that glyphosate and GBFs are negative in the one genetic test for gene mutation considered overall to be the best non-mammalian predictor of mammalian carcinogenesis.

Publications in which glyphosate or GBFs have been tested for genotoxicity in a variety of non-mammalian species other than bacterial reverse mutation appear to be included in the IARC Monograph, with only a few regulatory or published studies not included. With the exception of two positive and one negative chromosomal aberration assays in plants for glyphosate, chromosomal effect assay results have mainly been published for GBFs and showed predominantly positive results for MN in fish and amphibians.

A larger number of DNA damage comet assays in fish and other non-mammalian species *in vitro* are reported as exhibiting predominantly positive results for glyphosate. Larger numbers of positive comet results are available for GBFs in fish and amphibian/reptile studies. One positive fish comet study is reported for AMPA.

Some general features of these non-mammalian tests should be noted. First, both major endpoints measured in the majority of non-mammalian tests (i.e. MN and comet) might well be secondary to toxic effects. Second, many of these tests involve exposure by immersion in or surface contact with the test material in water. This is certainly not a standard or relevant route of exposure for *in vivo* mammalian systems and may introduce route-specific unique toxicity and genotoxic effects. This is particularly a concern for GBFs which commonly contain surfactants.

As a consequence, the Expert Panel did not consider data from a majority of the non-mammalian systems and nonstandard tests with glyphosate, GBF, and AMPA to have significant weight in the overall genotoxicity evaluation, especially given the large number of standard core studies in the gene mutation and chromosomal effects categories available in mammalian systems. Rationale supporting this consideration

is the absence of internationally accepted guidelines for such non-mammalian test systems, lack of databases of acceptable negative control data or positive control responses, and no results from validation studies suggesting concordance with carcinogenicity. OECD guidelines specifically state that use of any nonstandard test requires justification along with stringent validation including establishing robust historical negative and positive control databases. Therefore, results in these tests, when conflicting with findings obtained in well validated test systems for which OECD guidelines exist, and where the biological relevance of the results can be evaluated, do not carry a significant WoE.

Critique of the classifications and mode of action (MoA) proposed in the IARC monograph for glyphosate and related agents

Genotoxicity classification and MoA

Based on the results of the WoE critique detailed above and the wealth of negative regulatory studies reviewed by Kier and Kirkland (2013) and Williams et al. (2000), the Expert Panel does not agree with IARC's conclusion that there is strong evidence for genotoxicity across the glyphosate or GBFs database. In fact the Expert Panel WoE assessment provides strong support for a ***lack*** of genotoxicity, particularly in study categories closely associated with indications of potential genetic and carcinogenic hazard.

In order to demonstrate how the evidence from all sources was used to develop the Expert Panel's WoE conclusions for glyphosate, GBFs, and AMPA, the results from all study types were compiled in Table 3. Wherever possible, positive or negative responses were assigned to the individual studies in Table 3 according to the conclusions given in the original publication or report. In a small number of studies the Expert Panel concluded that there were significant issues regarding data analysis and interpretation of results and either changed the positive call given by IARC, e.g. Bolognesi et al. (2009) or, if the impact of the issues on the overall conclusions of the study was considered inconclusive, the data from that paper were excluded from Table 3, e.g. Paz-y-Miño et al. (2007) and Rank et al. (1993).

It should also be noted that the weight indicated in this table primarily reflects the endpoint of the publication or report. As noted above, there are significant test system (experimental protocol and data interpretation) considerations for some specific studies that significantly lowered the weight of these studies independently of the endpoint measured.

An evaluation of the studies in Table 3 according to their relative contributions to a WoE produced the following results:

- Test methods identified as providing low contribution (Low Weight) to the WoE produced the highest frequency of positive responses, regardless of whether the responses were taken from the results of IARC evaluated studies alone (eight of nine) or from all studies combined (eight of 11).
- The highest frequencies of positive responses were reported for test endpoints and systems considered most likely to yield false or misleading positive results with respect to carcinogenicity prediction or carcinogenic mechanism due to their susceptibility to secondary effects. This relationship was constant regardless of whether the results were taken from IARC evaluated studies alone or all studies combined.
- The numbers of studies providing strong evidence of relevant genotoxicity (High Weight) were in the minority for both the IARC and Expert Panel evaluations, with six out of 15 studies identified as High Weight being positive for the IARC evaluation, and only eight out of 92 studies identified as High Weight being positive for all studies combined by the Expert Panel.

Contrary to IARC's conclusion that there is strong evidence of genotoxicity, the Expert Panel's WoE analysis of the complete database (or the IARC subset alone) using the weighting categories proposed in Suter and Cormier (2011) indicates that glyphosate and GBFs should not be classified as genotoxic. The panel does not agree with IARC's conclusion of moderate evidence for genotoxicity of AMPA. The data needed to make an assessment of the genetic hazard of AMPA are too limited and conflicting to reliably support such a classification.

To provide greater emphasis to the Expert Panel's WoE conclusion, Table 4 provides a comparison between a set of characteristics found in confirmed genotoxic carcinogens (Bolt et al. 2004; Petkov et al. 2015) and the genotoxic activity profiles for glyphosate, AMPA, and GBFs. There is virtually no concordance between the two sets of characteristics.

Oxidative stress classification and MoA

Oxidative stress was the second characteristic considered by IARC as operative in human carcinogens and thus supporting their classifying glyphosate as probably carcinogenic to humans. Publications investigating the relationship between oxidative DNA damage and cancer (Wu et al. 2004; Klaunig et al. 2010) have demonstrated that following exposure to oxidative stress-inducing agents, a common adaptive response induced in mammalian cells is the up-regulation of stress-response genes. The resultant toxic response is threshold dependent.

It has been shown that reactive oxygen species (ROS) are genotoxic in principle, and the question arises as to whether GBFs that increase ROS production will add to an endogenously produced background level of DNA lesions or whether compensatory mechanisms may result in non-linear dose-effects. Halliwell (2003) reported that alteration to DNA molecules triggers repair, and frequent activation may increase the general repair capacity, irrespective of the cause of the damage. Thus, repeated exposure to ROS may lead to an adaptive response, mitigating the mutagenicity of oxidative DNA lesions. Moreover, as suggested by Deferme et al. (2015) oxidative stress is not uniquely associated with a genotoxic carcinogens and simple measurements of ROS are insufficient

Table 3. Summary of Expert Panel's evaluation of human, non-human mammalian, and selected microbial genotoxicity studies from IARC Section 4.2.1 and other published sources.

Source	Test category	Endpoint	Weight	Glyphosate (Pos/Neg)	GBFs (Pos/Neg)	AMPA (Pos/Neg)	Total (Pos/Neg)
Kier and Kirkland (2013) and other published studies not included in IARC	Bacterial Reverse Mutation	Gene mutation	High	0/19	0/20	0/1	0/40
	Mammalian *In Vitro*	Gene mutation	Moderate	0/2	ND	ND	0/2
		Chromosomal aberrations	Moderate	1/5	1/0	ND	2/5
		Micronucleus	Moderate	2/0	1/0	ND	3/0
		UDS	Low	0/1	ND	0/1	0/2
		SCE	None	ND	1/0	ND	1/0
	Mammalian *In Vivo*	Chromosomal aberrations	High	0/1	2/0	ND	2/1
		Micronucleus	High	0/13	0/17	0/1	0/31
		SCE	None	ND	1/0	ND	1/0
IARC Monograph 112	Bacterial Reverse Mutation	Gene mutation	High	0/1	0/0	ND	0/1
	Mammalian *In Vitro*	Gene mutation	Moderate	0/1	ND	ND	0/1
		Chromosomal aberrations	Moderate	1/2	ND	1/0	2/2
		Micronucleus	Moderate	2/0	ND	1/0	3/0
		Comet/DNA breaks	Low	5/0	2/0	1/0	8/0
		UDS	Low	0/1	ND	ND	0/1
		SCE	None	3/0	2/0	ND	5/0
	Mammalian *In Vivo*	Chromosomal aberrations	High	0/1	1/1	ND	1/2
		Micronucleus	High	2/1	2/3	1/0	5/4
		Comet/DNA breaks	Moderate	1/0	1/0	ND	2/0
		Dominant lethal	High	0/1	ND	ND	0/1
	Human *In Vivo*	Chromosomal aberrations	High	ND	0/1	ND	0/1
		Micronucleus	High	ND	0/3	ND	0/3
	High Weight *Combined Totals*			2/37	5/45	1/2	8/84
	(IARC results only)			(2/4)	(3/5)	(1/0)	(6/9)
	Moderate Weight *Combined Totals*			7/10	3/0	2/0	12/10
	(IARC results only)			(4/3)	(1/0)	(2/0)	(7/3)
	Low Weight *Combined Totals*			5/2	2/0	1/1	8/3
	(IARC results only)			(5/1)	(2/0)	(1/0)	(8/1)

AMPA: aminomethylphosphonic acid; GBFs: glyphosate based formulations; ND: no data.
All responses based on study critiques and conclusions of Expert Panel members.
Non-mammalian responses from IARC monograph in this table did not include four positive studies measuring DNA strand breaks in bacteria and one negative Rec assay in bacteria from IARC monograph Table 4.6.

Table 4. Comparison of test response profiles from glyphosate, GBFs, and AMPA to the profile characteristics of confirmed genotoxic carcinogens.

Characteristic	Carcinogens with a proven genotoxic mode of action	Glyphosate, GBFs, AMPA study data in Section 4.2.1
Profile of test responses in genetic assays	Positive effects across multiple key predictive endpoints (i.e. gene mutation, chromosomal aberrations, aneuploidy) both *in vitro* and *in vivo*	No valid evidence for gene mutation in any test; no evidence for chromosomal aberrations in humans and equivocal findings elsewhere.
Structure activity relationships	Positive for structural alerts associated with genetic activity	No structural alerts for glyphosate or AMPA suggesting genotoxicity
DNA binding	Agent or breakdown product are typically electrophilic and exhibit direct DNA binding	No unequivocal evidence for electrophilic properties or direct DNA binding by glyphosate or AMPA
Consistency	Test results are highly reproducible both *in vitro* and *in vivo*	Conflicting and/or non-reproducible responses in the same test or test category both *in vitro* and *in vivo*
Response kinetics	Responses are dose dependent over a wide range of exposure levels	Many positive responses do not show significant dose-related increases
Susceptibility to confounding factors (e.g. cytotoxicity)	Responses are typically found at nontoxic exposure levels	Positive responses typically associated with evidence of overt toxicity

evidence supporting a genotoxic causal MoA for carcinogenicity (Arai et al. 2006).

The evidence for oxidative stress induction summarized by IARC comes from studies employing a variety of endpoints and test systems, but in the IARC Monograph the data on oxidative stress are comingled with data from other endpoints, and data on glyphosate and GBFs are also comingled. It is therefore difficult to obtain a clear picture of the oxidative stress effects.

Indirect measures of oxidative stress vs. measures of oxidative damage

In some respects, measures (endpoints) of oxidative effects can be weighted in a manner similar to that applied to measures of genotoxicity. For example, in the majority of the studies reviewed by IARC, the endpoints assessed were only indirect measures of oxidative stress, in the form of antioxidant suppressive effects, changes in endogenous levels of protective molecules or enzymes (e.g. glutathione, superoxide dismutase) or changes in ROS (e.g. H_2O_2). The experiments *in vitro* in mammalian cells produced conflicting results and some positive results were observed only at very high dose levels which could be problematic for reliable evaluation of the potential for *in vivo* oxidative stress (Halliwell 2003). Long et al. (2007) demonstrated that reactive oxygen can be produced as an artifact by chemical reactions with components of the culture media, a possibility not evaluated in the studies reviewed by IARC. Overall, IARC's assessment did not appear to consider the relative importance of different

biomarkers of oxidative stress with the exception of noting limitations of using dihydrofluorescein acetate as a marker of oxidative stress.

A more meaningful endpoint for identification of oxidative damage, particularly as it pertains to identification of a possible genotoxic mechanism of cancer, would be the identification and application of a biomarker relevant to oxidative stress-induced damage to DNA. While a number of biochemical and physiological changes in cells can be produced during oxidative stress, the most extensively studied oxidative DNA lesion produced is 8-OHdG. This adduct has been widely used as a biomarker of oxidative DNA damage, and determination of 8-OHdG levels may be useful in defining a chemical's MoA.

Oxidative damage studies evaluated in the IARC monograph

Peluso et al. (1998) reported ^{32}P-postlabelling adducts in rats treated with GBFs (but not glyphosate). The nature or source of the adducts was not identified but Williams et al. (2000) noted that the solvent system used by Peluso et al. (1998) could not detect oxidative DNA damage. Evidence for increased DNA damage in Bolognesi et al. (1997) as measured by 8-OHdG DNA adducts was both limited and contradictory. Glyphosate was reported to induce 8-OHdG adducts in liver but not kidney tissues whereas a GBF (with an equivalent level of glyphosate) was reported to induce 8-OHdG adducts in kidney but not in liver tissue. Results of the Bolognesi et al. (1997) study are contradicted by another published study (Heydens et al. 2008) that was not considered by IARC. In this study no statistically significant increases in 8-OHdG were observed in liver or kidneys of mice 24 h after treatment by i.p. injection with 600 and 900 mg/kg of a GBF of the same composition as those used by Peluso et al. (1998) and Bolognesi et al. (1997).

The only other cited mammalian study examining oxidative DNA damage was a measurement of the effect of human 8-oxoguanine DNA N-glycosylase 1 (hOGG1) on the comet endpoint in human lymphocytes exposed to glyphosate (Mladinic et al. 2009a). This study showed a small but statistically significant effect on comet tail intensity at only a low mid-dose level in the absence of an S9 metabolic activation system and at the highest dose level tested (580 µg/mL) in the presence of S9. The observation of an effect at the highest dose level only in the presence of S9 is unusual because statistically significant increases in other markers of oxidative stress were observed at the high dose levels in either the presence or absence of S9. The authors indicated that their results were not considered an unequivocal indication of the oxidative potential of glyphosate. As noted above there does not appear to be any significant *in vitro* metabolism of glyphosate with rat liver homogenate (Gohre et al. 1987).

A series of studies in eels examined oxidative DNA damage of glyphosate, GBF, and AMPA by measurement of comet endpoints with and without treatment of samples with endonucleases that cleave at sites of oxidative damage (Guilherme et al. 2012a, 2012b; Guilherme et al. 2014a, 2014b; Marques et al. 2014a, 2014b). When considering net effects of endonuclease treatment there were varied responses in different conditions, tissues, and treatments ranging from no statistically significant effect to relatively small but statistically significant effects. These studies did not provide consistent strong evidence of oxidative DNA damage in a non-mammalian system.

In addition there was a human biomonitoring study measuring blood 8-OHdG which did not indicate a statistically significant association between previous GBF exposure and high 8-OHdG levels (Koureas et al. 2014, not evaluated in IARC). There are concerns with this study, particularly the relationship between the timing of exposure and a presumably transient marker of exposure. While some other agents did show associations, the lack of a statistically significant association between 8-OHdG and past GBF exposure does not provide support for GBF-related oxidative DNA damage in humans.

Many more oxidative stress studies are available for GBFs than for glyphosate or AMPA. Unlike glyphosate, most of the GBF studies show evidence of oxidative stress suggesting that GBFs contain compounds that are likely to be toxic under some treatment conditions leading to ROS followed by normal cellular protective responses. Comparison of GBF oxidative stress study results with predicted human exposure levels (e.g. calculated 90th percentile for applicators of 0.064 mg/kg body weight/day and much lower for other exposures), suggests that it is not likely that GBFs would induce oxidative stress likely to exceed endogenous detoxification capacities.

IARC claims of strong evidence supporting oxidative stress from AMPA seem to result from glyphosate and particularly GBF results rather than AMPA results. In fact, oxidative stress studies of AMPA are very limited. In the section on oxidative stress, IARC only cites one negative *in vitro* mammalian cell study of AMPA (Chaufan et al. 2014) and one positive *in vitro* mammalian cell study (Kwiatkowska et al. 2014). There is one other positive human cell study (Roustan et al. 2014) that was not cited; however, AMPA had unusually high toxicity in this report compared to other *in vitro* mammalian studies (see above) and no dose response was observed over an order of magnitude concentrations. The paucity and inconsistency of cited data does not seem to justify a conclusion of strong evidence for oxidative stress induction by AMPA.

Research on oxidative stress induced genotoxicity suggests that it is often a secondary response to toxicity and characterized by a threshold (Pratt & Barron 2003). Therefore the most appropriate conclusion supported by the oxidative stress data presented in IARC Monograph Section 4.2 is that there is not a strong WoE that glyphosate, GBFs, or AMPA produce oxidative damage to DNA that would lead to induction of endpoints predictive of a genotoxic hazard or act as a mechanism for the induction of cancer in experimental animals or humans.

Summary and conclusions

Detection of genotoxic activity or induction of oxidative stress/damage in any test conducted with a chemical does

not, *a priori*, mean that the agent has a carcinogenic potential, induces key events leading to tumor development or represents an *in vivo* genotoxic risk. A systematic and critical assessment of the WoE is required before genotoxic hazard and MoA conclusions can be reached. The IARC process leading to conclusions suggesting modes of action involving genotoxicity and oxidative stress was incomplete (excluding valuable data) and did not appear to critically evaluate some of the key studies it relied upon. A meaningful WoE evaluation depends on an assessment of all available data using an appropriate weighting process.

A number of reviews of the carcinogenicity, genotoxicity, and oxidative stress/damage for glyphosate, AMPA, and GBFs were available prior to the development of the IARC Glyphosate Monograph (see Introduction). These prior reviews included much of the data available to IARC reviewers involved in the evaluation presented in the IARC Monograph. In general, genetic toxicology data evaluated in these prior reviews all support a conclusion that glyphosate (and related materials) is inherently not genotoxic. The Expert Panel concluded that there is no new, valid evidence presented in the IARC Monograph that would provide a basis for altering these conclusions and that including the study results reviewed by Kier and Kirkland (2013) would provide considerable additional support to the conclusion of absence of inherent genotoxic potential.

- The Expert Panel concluded that glyphosate, GBFs, and AMPA genotoxicity response profiles are not consistent with characteristics of genotoxic carcinogens (Table 4).
- There is substantial evidence, particularly in bacterial reverse mutation assays, demonstrating that glyphosate, GBFs, or AMPA do not induce gene mutation from either direct or oxidative induced mechanisms.
- The evidence indicating that glyphosate can produce chromosomal aberrations in mammalian systems is very limited, conflicting, and potentially due to secondary mechanisms.
- The absence of evidence indicating that glyphosate or GBFs induced lesions characteristic of genotoxic carcinogens, in well-validated test systems with robust experimental protocols, invalidates conclusions that glyphosate or GBFs might act via a genotoxic MoA.
- The evidence for oxidative stress/damage as a mechanism or predictor of carcinogenesis is unconvincing. Repeated exposure to ROS most likely leads to adaptive responses, mitigating the mutagenicity of oxidative DNA lesions. Studies directed toward a better understanding of this relationship for glyphosate or GBF related exposures have not been reported.
- There is little or no reliable evidence that GBFs, at levels experienced across a broad range of end-user exposures, poses any human genotoxic hazard/risk.

The Expert Panel concluded that the IARC assessment of classifications regarding strong evidence of genotoxicity and oxidative stress capabilities of glyphosate, GBFs, and AMPA is not supported by the available data. A critical review of the complete dataset by the Expert Panel supports a conclusion that glyphosate (including GBFs and AMPA) does not pose a genotoxic hazard and therefore, should not be considered support for the classification of glyphosate as a genotoxic carcinogen. These conclusions are supportive of recent reviews that have occurred during the preparation of this review. A European Food Safety Authority peer review concluded that glyphosate is unlikely to pose a carcinogenic hazard to humans (EFSA 2015) and a Joint FAO/WHO Meeting on Pesticide Residues concluded that glyphosate is unlikely to be genotoxic at anticipated dietary exposures and unlikely to cause a carcinogenic risk to humans from dietary exposure (JMPR 2016).

Acknowledgements

The authors gratefully acknowledge the extensive comments received from seven independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the manuscript.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer. Gary Williams, David Brusick, and David Kirkland have previously served as independent consultants for the Monsanto Company on the European Glyphosate Task Force. Gary Williams has consulted for Monsanto on litigation matters involving glyphosate. Larry Kier was previously an employee of the Monsanto Company. Marilyn Aardema has not previously been employed in the Monsanto Company or previously been involved in any activity involving glyphosate and as such declares no potential conflicts of interest. Furthermore, other than Gary Williams, none of the aforementioned authors have been involved in any litigation procedures involving glyphosate.

The Expert Panel Members recruitment and evaluation of the data were organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists acted as consultants for Intertek. Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food, and pharmaceutical industries. While Intertek Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto Company, previous employees of Cantox had worked in this capacity.

Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

Supplemental material

Supplemental material for this article is available online here.

References

Amer SM, Aly FAE, Farghaly AA, Ibrahim AAE. 2006. In vitro and in vivo evaluation of the genotoxicity of the herbicide glyphosate in mice. Bull Natl Res Center Egypt (Cairo). 31:427–446.

Anadon A, Martinez-Larranaga MR, Martinez MA, Castellano VJ, Martinez M, Martin MT, Nozal MJ, Bernal JL. 2009. Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats. Toxicol Lett. 190:91–95.

Arai T, Kelly VP, Minowa O, Noda T, Nishimura S. 2006. The study using wild-type and ogg1 knockout mice exposed to potassium bromate shows no tumor induction despite an extensive accumulation of 8-hydroxyguanine in kidney DNA. Toxicology. 221:179–186.

Battershill JM, Burnett K, Bull S. 2008. Factors affecting the incidence of genotoxicity biomarkers in peripheral blood lymphocytes: impact on design of biomonitoring studies. Mutagenesis. 23:423–437.

Bolognesi C, Bonatti S, Degan P, Gallerani E, Peluso M, Rabboni R, Roggieri P, Abbondandolo A. 1997. Genotoxic activity of glyphosate and its technical formulation Roundup. J Agric Food Chem. 45:1957–1962.

Bolognesi C, Carrasquilla G, Volpi S, Solomon KR, Marshall EJP. 2009. Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: association to occupational exposure to glyphosate. J Toxicol Environ Health A. 72:986–997.

Bolt HM, Foth H, Hengstler JG, Degen GH. 2004. Carcinogenicity categorization of chemicals-new aspects to be considered in a European perspective. Toxicol Lett. 151:29–41.

Bonassi S, Coskun E, Ceppi M, Lando C, Bolognesi C, Burgaz S, Holland N, Kirsh-Volders M, Knasmueller S, Zeiger E, et al. 2011. The human micronucleus project on exfoliated buccal cells (HUMNxL): the role of life-style, host factors, occupational exposures, health status, and assay protocol. Mutat Res. 728:88–97.

Brewster DW, Warren J, Hopkins WE. II. 1991. Metabolism of glyphosate in Sprague-Dawley rats tissue distribution identification and quantitation of glyphosate-derived materials following a single oral dose. Fundam Appl Toxicol. 17:43–51.

Chan P, Mahler J. 1992. Toxicity studies of glyphosate (CASRN 1071-83-6) administered in dosed feed to F344/N rats and B6C3F$_1$ mice. Research Triangle Park (NC): National Toxicology Program (NTP) (Toxicity Report Series, No. 16; NIH Publication 92-3135). Available from: http://ntp.niehs.nih.gov/results/pubs/shortterm/reports/abstracts/tox016/index.html

Chaufan G, Coalova I, del Carmen Rios de Molina M. 2014. Glyphosate commercial formulation causes cytotoxicity, oxidative effects, and apoptosis on human cells: differences with its active ingredient. Int J Toxicol. 33:29–38.

Cimino MC. 2006. Comparative overview of current international strategies and guidelines for genetic toxicology testing for regulatory purposes. Environ Mol Mutagen. 47:362–390.

Collins A, Koppen G, Valdiglesias V, Dusinska M, Kruszewski M, Moller P, Rojas E, Dhawan A, Benzie I, Coskun E, et al. 2014. The comet assay as a tool for human biomonitoring studies: the ComNet project. Mutat Res Rev Mutat Res. 759:27–39.

Dearfield KL, Thybaud V, Cimino MC, Custer L, Czich A, Harvey JS, Hester S, Kim JH, Kirkland D, Levy DD, et al. 2011. Follow-up actions from positive results of in vitro genetic toxicity testing. Environ Mol Mutagen. 52:177–204.

Deferme L, Wolters J, Claessen S, Briede J, Kleinjans J. 2015. Oxidative stress mechanisms do not discriminate between genotoxic and nongenotoxic liver carcinogens. Chem Res Toxicol. 28:1636–1646.

Dusinska M, Collins AR. 2008. The comet assay in human biomonitoring: gene–environment interactions. Mutagenesis. 23:191–205.

Eastmond DA, Hartwig A, Anderson D, Anwar WA, Cimino MC, Dobrev I, Douglas GR, Nohmi T, Phillips DH, Vickers C. 2009. Mutagenicity testing for chemical risk assessment: update of the WHO/IPCS Harmonized Scheme. Mutagenesis. 24:341–349.

ECHA. 2015. Chapter R.7a: Endpoint Specific Guidance. In: Guidance on information requirements and chemical safety assessment. Helsinki, Finland: European Chemical Agency (ECHA) (Version 4.1 October 2015). Available from: http://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf.

EFSA. 2011. Scientific opinion on genotoxicity testing strategies applicable to food and feed safety assessment (EFSA Scientific Committee) (Question no. EFSA-Q-2009-00782, adopted on 13 September 2011 by European Food Safety Authority, 3 October 2012, replaces the earlier version). EFSA J. 9:2379 [69 pp.]. doi:10.2903/j.efsa.2011.2379. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/2379.htm.

EFSA. 2015. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate (EFSA-Q-2014-00546, EFSA-Q-2015-00279, approved on 30 October 2015 by European Food Safety Authority). EFSA J. 13:4302 [107 pp.]. doi:10.2903/j.efsa.2015.4302. Available from: http://www.efsa.europa.eu/en/efsajournal/pub/4302.

European Commission. 2002. Review report for the active substance glyphosate. Finalized in the Standing Committee on Plant Health at its meeting on 29 June 2001 in view of the inclusion of glyphosate in Annex I of Directive 91/414/EEC. Brussels (Belgium): European Commission (EC), Health and Consumer Protection Directorate General (6511/VI/99-Final). Available from: http://ec.europa.eu/food/fs/sfp/ph_ps/pro/eva/existing/list1_glyphosate_en.pdf

Faust F, Kassie F, Knasmuller S, Boedecker RH, Mann M, Mersch-Sundermann V. 2004. The use of the alkaline comet assay with lymphocytes in human biomonitoring studies. Mutat Res. 566:209–229.

Fenech M, Holland N, Zeiger E, Chang WP, Burgaz S, Thomas P, Bolognesi C, Knasmueller S, Kirsch-Volders M, Bonassi S. 2011. The HUMN and HUMNxL international collaboration projects on human micronucleus assays in lymphocytes and buccal cells-past, present and future. Mutagenesis. 26:239–245.

Fowler P, Smith R, Smith K, Young J, Jeffrey L, Carmichael P, Kirkland D, Pfuhler S. 2014. Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. III: Sensitivity of human cell types to known genotoxic agents. Mutat Res Genet Toxicol Environ Mutagen. 767:28–36.

Gohre K, Casida JE, Ruzo LO. 1987. N oxidation and cleavage of the amino acid derived herbicide glyphosate and anilino acid of the insecticide fluvalinate. J Agric Food Chem. 35:388–392.

Guilherme S, Gaivao I, Santos MA, Pacheco M. 2012a. DNA damage in fish (*Anguilla anguilla*) exposed to a glyphosate-based herbicide – elucidation of organ-specificity and the role of oxidative stress. Mutat Res Genet Toxicol Environ Mutagen. 743:1–9.

Guilherme S, Santos MA, Barroso C, Gaivao I, Pacheco M. 2012b. Differential genotoxicity of Roundup® formulation and its constituents in blood cells of fish (*Anguilla anguilla*): considerations on chemical interactions and DNA damaging mechanisms. Ecotoxicology. 21:1381–1390.

Guilherme S, Santos MA, Gaivao I, Pacheco M. 2014a. Are DNA-damaging effects induced by herbicide formulations (Roundup® and Garlon®) in fish transient and reversible upon cessation of exposure? Aquat Toxicol. 155:213–221.

Guilherme S, Santos MA, Gaivao I, Pacheco M. 2014b. DNA and chromosomal damage induced in fish (*Anguilla anguilla* L.) by aminomethylphosphonic acid (AMPA) – the major environmental breakdown product of glyphosate. Environ Sci Pollut Res Int. 21:8730–8739.

Halliwell B. 2003. Oxidative stress in cell culture: an under-appreciated problem? FEBS Lett. 10:3–6.

Health and Welfare Canada. 1991. Preharvest application of glyphosate (Roundup) herbicide. Ottawa (ON): Health and Welfare Canada, Pest Management Regulatory Agency (PMRA), Plant Industry Directorate, Pesticide Information Division (Pesticides Directorate Discussion Document, Vol. 91, Iss. 1), 92 p.

Helal AD, Moussa HM. 2005. Chromosomal aberrations induced by glyphosate isopropylamine herbicide and trials for diminuting its toxicity using some chemical inactivators and antioxidant. Vet Med J Giza. 53:169–187.

Heydens WF, Healy CE, Hotz KJ, Kier LD, Martens MA, Wilson AGE, Farmer DR. 2008. Genotoxic potential of glyphosate formulations: mode-of-action investigations. J Agric Food Chem. 56:1517–1523.

Hill AB. 1965. The environment and disease: association or causation? Proc R Soc Med. 58:295–300.

IARC. 2015. Glyphosate. In: Some organophosphate insecticides and herbicides: diazinon, glyphosate, malathion, parathion, tetrachlorvinphos. IARC Working Group, March 3–10, 2015, Lyon (France). Lyon (France): World Health Organization (WHO), IARC (IARC Monographs on the Evaluation of Carcinogen Risks to Humans, vol. 112). p. 1–92. Available from: http://monographs.iarc.fr/ENG/Monographs/vol112/index.php.

ICH. 2011. Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use: S2(R1). Geneva (Switzerland): International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (ICH Harmonized Tripartite Guideline – Current Step 4 version [Combines S2A & S2B]). Available from: http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html.

Jackson MA, Stack HF, Waters MD. 1993. The genetic toxicology of putative nongenotoxic carcinogens. Mutat Res. 296:241–277.

JMPR. 2006. Glyphosate. In: Pesticides residues in food – 2004. Evaluations 2004 Part II – Toxicological. Joint Meeting of the FAO Panel of Experts on Pesticide residues in Food and the Environment and the WHO Core Assessment Group (JMPR), Sep 20–29, 2004, Rome. Rome: Food and Agriculture Organization of the United Nations (FAO)/Geneva: World Health Organization (WHO), International Program on Chemical Safety (IPCS) (WHO/PCS/06.1). p. 95–169. Available from: http://www.inchem.org/documents/jmpr/jmpmono/v2004pr01.pdf.

JMPR. 2016. 1.2 Glyphosate (158). In: Summary report. Joint FAO/WHO Meeting on Pesticide Residues, May 9–13, 2016, Geneva, Switz. Rome: Food and Agriculture Organization of the United Nations/Geneva, World Health Organization (WHO) (Issued May 16, 2016). Available from: http://www.who.int/foodsafety/jmprsummary2016.pdf.

Kier LD, Kirkland DJ. 2013. Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit Rev Toxicol. 43:283–315.

Kirkland DJ, Henderson L, Marzin D, Muller L, Parry JM, Speit G, Tweats DJ, Williams GM. 2005. Testing strategies in mutagenicity and genetic toxicology: an appraisal of the guidelines of the European scientific committee for cosmetics and non-food products for the evaluation of hair dyes. Mutat Res. 588:88–105.

Kirkland DJ, Reeve L, Gatehouse D, Vanparys P. 2011. A core in vitro genotoxicity battery comprising the Ames test plus the in vitro micronucleus test is sufficient to detect rodent carcinogens and in vivo genotoxins. Mutat Res. 721:27–73.

Kirsch-Volders M, Bonassi S, Knasmueller S, Holland N, Bolognesi C, Fenech MF. 2014. Commentary: critical questions, misconceptions and a road map for improving the use of the lymphocyte cytokinesis-block micronucleus assay for in vivo biomonitoring of human exposure to genotoxic chemicals – a HUMN project perspective. Mutat Res Rev Mutat Res. 759:49–58.

Kirsch-Volders M, Vanhauwaert A, Eichenlaub-Ritter U, Decordier I. 2003. Indirect mechanisms of genotoxicity. Toxicol Lett. 140:63–74.

Klaunig JE, Kamendulis LM, Hocevar BA. 2010. Oxidative stress and oxidative damage in carcinogenesis. Toxicol Pathol. 38:96–109.

Klimisch H-J, Andreae M, Tillmann U. 1997. A systematic approach for evaluating the quality of experimental toxicological and ecotoxicological data. Regul Toxicol Pharmacol. 25:1–5.

Koller VJ, Fuerhacker M, Nersesyan A, Misik M, Eisenbauer M, Knasmueller S. 2012. Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells. Arch Toxicol. 86:805–813.

Koureas M, Tsezou A, Tsakalof A, Orfanidou T, Hadjichristodoulou C. 2014. Increased levels of oxidative DNA damage in pesticide sprayers in Thessaly region (Greece). Implications of pesticide exposure. Sci Total Environ. 496:358–364.

Kwiatkowska M, Huras B, Bukowska B. 2014. The effect of metabolites and impurities of glyphosate on human erythrocytes (in vitro). Pestic Biochem Physiol. 109:34–43.

Li AP, Long TJ. 1988. An evaluation of the genotoxic potential of glyphosate. Fundam Appl Toxicol. 10:537–546.

Li Q, Lambrechts MJ, Zhang Q, Liu S, Ge D, Yin R, Xi M, You Z. 2013. Glyphosate and AMPA inhibit cancer cell growth through inhibiting intracellular glycine synthesis. Drug Des Dev Ther. 7:635–643.

Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Di Berardino D, Ursini MV. 1998a. Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures in vitro. Mutat Res. 403:13–20.

Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Salvemini F, Di Berardino D, Ursini MV. 1998b. Cytogenetic damage and induction of pro-oxidant state in human lymphocytes exposed in vitro to glyphosate, vinclozolin, atrazine, and DPX-E9636. Environ Mol Mutagen. 32:39–46.

Long LH, Kirkland D, Whitwell J, Halliwell B. 2007. Different cytotoxic and clastogenic effects of epigallocatechin gallate in various cell-culture media due to variable rates of its oxidation in the culture medium. Mutat Res. 634:177–183.

Manas F, Peralta L, Raviolo J, Garcia Ovandoa H, Weyers A, Ugnia L, Gonzalez Cid M, Larripa I, Gorla N. 2009a. Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests. Environ Toxicol Pharmacol. 28:37–41.

Manas F, Peralta L, Raviolo J, Ovando HG, Weyers A, Ugnia L, Cid MG, Larripa I, Gorla N. 2009b. Genotoxicity of AMPA, the environmental metabolite of glyphosate, assessed by the comet assay and cytogenetic tests. Ecotoxicol Environ Saf. 72:834–837.

Marc J, Mulner-Lorillon O, Boulben S, Hureau D, Durand G, Belle R. 2002. Pesticide Roundup provokes cell division dysfunction at the level of CDK1/cyclin B activation. Chem Res Toxicol. 15: 326–331.

Marques A, Guilherme S, Gaivao I, Santos MA, Pacheco M. 2014a. Erratum to: "Progression of DNA damage induced by a glyphosate-based herbicide in fish (*Anguilla anguilla*) upon exposure and post-exposure periods – insights into the mechanisms of genotoxicity and DNA repair". Comp Biochem Physiol C Toxicol Pharmacol. 168C:1. doi: 10.1016/j.cbpc.2014.10.008.

Marques A, Guilherme S, Gaivao I, Santos MA, Pacheco M. 2014b. Progression of DNA damage induced by a glyphosate-based herbicide in fish (*Anguilla anguilla*) upon exposure and post-exposure periods-insights into the mechanisms of genotoxicity and DNA repair. Comp Biochem Physiol C Toxicol Pharmacol. 166:126–133.

Mendelsohn ML, Moore DH II, Lohman PHM. 1992. A method for comparing and combining short-term genotoxicity test data results and interpretation. Mutat Res. 266:43–60.

Menkes DB, Temple WA, Edwards IR. 1991. Intentional self-poisoning with glyphosate-containing herbicides. Hum Exp Toxicol. 10:103–107.

Mladinic M, Berend S, Vrdoljak AL, Kopjar N, Radic B, Zeljezic D. 2009a. Evaluation of genome damage and its relation to oxidative stress induced by glyphosate in human lymphocytes in vitro. Environ Mol Mutagen. 50:800–807.

Mladinic M, Perkovic P, Zeljezic D. 2009b. Characterization of chromatin instabilities induced by glyphosate, terbuthylazine and carbofuran using cytome fish assay. Toxicol Lett. 189:130–137.

Moller P. 2005. Genotoxicity of environmental agents assessed by the alkaline comet assay. Basic Clin Pharmacol Toxicol. 96:1–42.

OECD. 2014a. In vitro mammalian chromosomal aberration test. In: OECD Guidelines for the Testing of Chemicals. Paris (France): Organization for Economic Co-operation and Development (OECD) (OECD Guideline no. 473) [Adopted: 26 September 2014]. Available from: http://www.oecd-ilibrary.org/environment/test-no-473-in-vitro-mammalian-chromosomal-aberration-test_9789264224223-en.

OECD. 2014b. Mammalian erythrocyte micronucleus test. In: OECD Guidelines for the Testing of Chemicals. Paris (France): Organization for Economic Co-operation and Development (OECD) (OECD Guideline no. 474) [Adopted: 26 September 2014]. Available from: http://www.oecd-ilibrary.org/environment/test-no-474-mammalian-erythrocyte-micronucleus-test_9789264224292-en.

OECD. 2014c. Mammalian bone marrow chromosomal aberration test. OECD Guidelines for the Testing of Chemicals. Paris (France): Organization for Economic Co-operation and Development (OECD) (OECD Guideline no. 475) [Adopted: 26 September 2014]. Available from: http://www.oecd-ilibrary.org/environment/test-no-475-mammalian-bone-marrow-chromosomal-aberration-test_9789264224407-en.

OECD. 2014d. In vitro mammalian cell micronucleus test. OECD Guidelines for the Testing of Chemicals. Paris (France): Organization for Economic Co-operation and Development (OECD) (OECD Guideline no. 487) [Adopted: 26 September 2014]. Available from: http://www.oecd-ilibrary.org/environment/test-no-487-in-vitro-mammalian-cell-micronucleus-test_9789264224438-en

OECD. 2015. Overview of the Set of OECD Genetic Toxicology Test Guidelines and Updates Performed in 2014–2015. Paris (France): Organization for Economic Co-operation and Development (OECD), Environment Directorate, Health and Safety Publications Available

from: http://www.oecd.org/env/ehs/testing/series-testing-assessment-publications-number.htm

Parry JM, Fiedler RJ, McDonald A. 1994. Thresholds for aneuploidy-inducing chemicals. Advisory Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment of the UK Department of Health. Mutagenesis. 9:503–504.

Paz-y-Miño C, Muñoz MJ, Maldonado A, Valladares C, Cumbal N, Herrera C, Robles P, Sánchez ME, López-Cortés A. 2011. Baseline determination in social, health, and genetic areas in communities affected by glyphosate aerial spraying on the northeastern Ecuadorian border. Rev Environ Health. 26:45–51.

Paz-y-Miño C, Sánchez ME, Arévalol M, Muñoz MJ, Wittel T, Oleas De-la-Carreral G, Leonel PE. II. 2007. Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate. Genet Mol Biol. 30:456–460.

Peluso M, Munnia A, Bolognesi C, Parodi S. 1998. 32P-postlabeling detection of DNA adducts in mice treated with the herbicide Roundup . Environ Mol Mutagen. 31:55–59.

Petkov PI, Patlewicz G, Schultz TW, Honma M, Todorov M, Kotov S, Dimitrov SD, Donner EM, Mekenyan OG. 2015. A feasibility study: can information collected to classify for mutagenicity be informative in predicting carcinogenicity? Regul Toxicol Pharmacol. 72:17–25.

Pfuhler S, Fellows M, van Benthem J, Corvi R, Curren R, Dearfield K, Fowler P, Froetschl R, Elhajouji A, Le Hegarat L, et al. 2011. In vitro genotoxicity test approaches with better predictivity: summary of an IWGT workshop. Mutat Res. 723:101–107.

Pierotti MA, Sozzi G, Croce CM. 2003. Oncongenes: mechanisms of oncogene activation. In: Kufe DW, Pollock RE, Weichselbaum RR, Bast RC Jr, Gansler TS, Holland JF, Frei E III, editors. Holland-Frei cancer medicine. 6th ed. Hamilton (ON): B.C. Decker. Available from: http://www.ncbi.nlm.nih.gov/books/NBK12538/.

Piesova E. 2004. The influence of different treatment length on the induction of micronuclei in bovine lymphocytes after exposure to glyphosate. Folia Vet Lat. 48:130–134.

Piesova E. 2005. The effect of glyphosate on the frequency of micronuclei in bovine lymphocytes in vitro. Acta Vet (Beogr). 55:101–109.

Prasad S, Srivastava S, Singh M, Shukla Y. 2009. Clastogenic effects of glyphosate in bone marrow cells of Swiss albino mice. J Toxicol. 2009:308985. doi: 10.1155/2009/308985.

Pratt IS, Barron T. 2003. Regulatory recognition of indirect genotoxicity mechanisms in the European Union. Toxicol Lett. 140: 53–62.

Rank J, Jensen AG, Skov B, Pedersen LH, Jensen K. 1993. Genotoxicity testing of the herbicide Roundup and its active ingredient glyphosate isopropylamine using the mouse bone marrow micronucleus test, salmonella mutagenicity test, and allium anaphase-telophase test. Mutat Res. 300:29–36.

Roustan A, Aye M, De Meo M, Di Giorgio C. 2014. Genotoxicity of mixtures of glyphosate and atrazine and their environmental transformation products before and after photoactivation. Chemosphere. 108:93–100.

Salamone MF, Mavournin KH. 1994. Bone marrow micronucleus assay: a review of the mouse stocks used and their published mean spontaneous micronucleus frequencies. Environ Mol Mutagen. 23:239–273.

Schmid O, Speit G. 2007. Genotoxic effects induced by formaldehyde in human blood and implications for the interpretation of biomonitoring studies. Mutagenesis. 22:69–74.

Scott D, Galloway SM, Marshall RR, Ishidate JM, Brusick D, Ashby J, Myhr BC. 1991. Genotoxicity under extreme culture conditions: a report from ICPEMC task group 9. Mutat Res Genet Toxicol Environ Mutagen. 257:147–205.

Sivikova K, Dianovsky J. 2006. Cytogenetic effect of technical glyphosate on cultivated bovine peripheral lymphocytes. Int J Hyg Environ Health. 209:15–20.

Solomon E, Borrow J, Goddard AD. 1991. Chromosome aberrations and cancer. Science. 254:1153–1160.

Speit G. 2013. Does the recommended lymphocyte cytokinesis-block micronucleus assay for human biomonitoring actually detect DNA damage induced by occupational and environmental exposure to genotoxic chemicals? Mutagenesis. 28:375–380.

Suresh TP. 1994. Genetic toxicology – in vivo mammalian bone marrow cytogenetic test – chromosomal analysis [Unpublished Regulatory Study] (Report Identification Number: TOXI:890-MUTCH. AB).

Suter GWII, Cormier SM. 2011. Why and how to combine evidence in environmental assessments: weighing evidence and building cases. Sci Total Environ. 409:1406–1417.

Tenorio NM, Ribeiro DA, Alvarenga TA, Fracalossi ACC, Carlin V, Hirotsu C, Tufik S, Andersen ML. 2013. The influence of sleep deprivation and obesity on DNA damage in female Zucker rats. Clinics (Sao Paulo). 68:385–389.

Terasawa M, Shinohara A, Shinohara M. 2014. Double-strand break repair-adox: restoration of suppressed double-strand break repair during mitosis induces genomic instability. Cancer Sci. 105:1519–1525.

US EPA. 1993. RED facts: glyphosate. Washington (DC): U.S. Environmental Protection Agency (US EPA), Office of Prevention, Pesticides, and Toxic Substances (EPA 738-F-93-011). Available from: http://archive.epa.gov/pesticides/reregistration/web/pdf/0178fact.pdf

US EPA. 2013. Glyphosate pesticide tolerances; Final rule (40 CFR Part 180) [EPA-HQ-OPP-2012-0132; FRL-9384-3]. Fed Regist (US). 78:25396–25401. Available from: http://www.regulations.gov/#%21documentDetail;D=EPA-HQ-OPP-2012-0132-0009.

US FDA. 2006. Guidance for industry and review staff: recommended approaches to integration of genetic toxicology study results. Rockville (MD): U.S. Food and Drug Administration (US FDA), Center for Drug Evaluation and Research (CDER). Available from: http://www.fda.gov/downloads/Drugs/... /Guidances/ucm079257.pdf.

Walmsley RM, Billinton N. 2011. How accurate is in vitro prediction of carcinogenicity? Br J Pharmacol. 162:1250–1258.

Waters MD, Bergman HB, Nesnow S, 1988. The genetic toxicology of Gene-Tox non-carcinogens. Mutat Res. 205:139–182.

WHO. 1994. Glyphosate. Geneva: World Health Organization (WHO)/ International Program on Chemical Safety (IPCS)/United Nations Environment Program (UNEP) (Environmental Health Criteria, no. 159). Available from: http://www.inchem.org/documents/ehc/ehc/ehc159.htm.

Williams GM, Kroes R, Munro IC. 2000. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol. 31:117–165.

Wu LL, Chiou C-C, Chang P-Y, Wu JT. 2004. Urinary 8-ohdg: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta. 339:1–9.

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2018.1522786

Taylor & Francis
Taylor & Francis Group

Expression of Concern

Critical Reviews in Toxicology, 46(S1): 'An Independent Review of the Carcinogenic Potential of Glyphosate'

We, the Editor-in-Chief and Publisher of the journal, have been informed of concerns over the completeness of acknowledged contributions to the above supplement, and in the declarations of interest provided by the named contributors, for the following articles:

Williams, G. M., Aardema, M., Acquavella, J., Berry, C., Brusick, D., Burns, M. M., de Camargo, J. L. V., Garabrant, D., Greim, H. A., Kier, L. D., Kirkland, D. J., Marsh, G., Solomon, K. R., Sorahan, T., Roberts, A., & Weed, D. L. (2016). A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. *Critical Reviews in Toxicology*, 46(S1), pp. 3–20.

Solomon, K. R. (2016). Glyphosate in the general population and in applicators: a critical review of studies on exposures. *Critical Reviews in Toxicology*, 46(S1), pp. 21–27.

Acquavella, J., Garabrant, D., Marsh, G., Solomon, K. R., Sorahan, T., & Weed, D. L. (2016). Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. *Critical Reviews in Toxicology*, 46(S1), pp. 28-43.

Williams, G. M., Berry, C., Burns, M. M., de Camargo, J. L. V., & Greim, H. A. (2016). Glyphosate rodent carcinogenicity bioassay expert panel review. *Critical Reviews in Toxicology*, 46(S1), pp. 44–55.

Brusick, D., Aardema, M., Kier, L. D., Kirkland, D. J., & Williams, G. (2016). Genotoxicity Expert Panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. *Critical Reviews in Toxicology*, 46(S1), pp. 56–74.

We have requested corrigenda from the authors to provide additional disclosure as to contributions to the articles. To date, we have only received corrigenda for three of the five articles that have been agreed by all authors. We have not received an adequate explanation as to why the necessary level of transparency was not met on first submission. We thank those who brought this matter to our attention. When reading the articles, we recommend that readers take this context into account. We will continue to work to update these articles and ensure full disclosure of all contributions to them.

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2018.1539570

Taylor & Francis
Taylor & Francis Group

Expression of Concern

Critical Reviews in Toxicology, 46(S1): 'An Independent Review of the Carcinogenic Potential of Glyphosate'

With the cooperation of the authors, we, the Editor-in-Chief and Publisher of the journal, have published corrigenda for each of the following articles:

Williams GM, Aardema M, Acquavella J, Berry C, Brusick D, Burns MM, de Camargo JLV, Garabrant D, Greim HA, Kier LD, et al. 2016. A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. Crit Rev Toxicol. 46(S1):3–20.

Solomon KR. 2016. Glyphosate in the general population and in applicators: a critical review of studies on exposures. Crit Rev Toxicol. 46(S1):21–27.

Acquavella J, Garabrant D, Marsh G, Solomon KR, Sorahan T, Weed DL. 2016. Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. Crit Rev Toxicol. 46(S1):28–43.

Williams GM, Berry C, Burns MM, de Camargo JLV, Greim HA. 2016. Glyphosate rodent carcinogenicity bioassay expert panel review. Crit Rev Toxicol. 46(S1):44–55.

Brusick D, Aardema M, Kier LD, Kirkland DJ, Williams G. 2016. Genotoxicity Expert Panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. Crit Rev Toxicol. 46(S1):56–74.

After investigation into the completeness of the original declarations of interest provided by the authors, it was found that these did not fully represent the involvement of Monsanto or its employees or contractors in the authorship of the articles.

These corrigenda provide additional disclosure as to contributions to the articles, in some places in contradiction to the statements originally supplied.

We have not received an adequate explanation as to why the necessary level of transparency was not met on first submission and welcome the opportunity to address this. We regret that these corrections were necessary and thank those who brought this matter to our attention.

To the best of our knowledge, the scholarly record is now accurate; however, we recommend that readers take the additional context the corrected disclosures provide into account when reading the articles.

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2018.1522175

Correction

Article tiltle: A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment.

Authors: Williams, G. M., Aardema, M., Acquavella, J., Berry, C., Brusick, D., Burns, M. M., de Camargo, J. L. V., Garabrant, D., Greim, H. A., Kier, L. D., Kirkland, D. J., Marsh, G., Solomon, K. R., Sorahan, T., Roberts, A., & Weed, D. L.

Journal: *Critical Reviews in Toxicology*

Bibliometrics: Volume 46(S1), pages 3–20, Year 2016

DOI: http://dx.doi.org/10.1080/10408444.2016.1214677

When this article was originally published on 28th September 2016, the contributions, contractual status and potential competing interests of all authors and non-author contributors were not fully disclosed to Critical Reviews in Toxicology. Specifically, the Acknowledgements and Declaration of Interest were not complete. After further clarification from the authors, these sections are corrected to reflect the full contributions, contractual status and, potential competing interests of all authors and non-author contributors and read as follows:

Acknowledgements

The authors gratefully acknowledge the extensive comments received from nine independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the manuscript. Ashley Roberts would like to thank his colleague at Intertek, Barry Lynch, for assistance in the preparation of the manuscript and William Heydens of Monsanto for providing a regulatory history overview for use by the authors in the preparation of this overview paper and his review of a preliminary draft of the overview manuscript and the final manuscript. The authors welcome the opportunity to correct the omission of the contributions of Barry Lynch, Intertek, and William Heydens, Monsanto in the original Acknowledgments. These individuals were not considered for authorship because they did not participate in the deliberations of the Panel and did not contribute to the conclusions drawn by the Panel. The conclusions were independently formulated by each of four Panel Sub-Groups as detailed in the individual papers.

Declaration of Interest

This overview paper (paper) is part of a supplement, the preparation of which was coordinated by Intertek Scientific & Regulatory Consultancy (Intertek) under the leadership of Ashley Roberts. It was prepared subsequent to completion of the four manuscripts as an overview and presented the opinions and conclusions of four groups of the expert panel.

The expert panels were organized and supported administratively by Intertek. Funding was provided to Intertek by Monsanto Company, which is a primary producer and marketer of glyphosate and related products. All the expert panelists other than John Acquavella and Larry D. Kier were compensated through a contract with Intertek. John Acquavella and Larry D. Kier were compensated through existing consulting contracts with Monsanto Company. The employment affiliations of the authors are as shown on the cover page. The authors participated in the review process and preparation of this overview paper as independent professionals and not as representatives of their employers.

Monsanto also supported presentation of the Panel's findings and conclusions by Gary Williams and Tom Sorahan as a poster entitled "Expert Panel Review of the Carcinogenic Potential of the Herbicide Glyphosate" at the Society for Risk Analysis Annual Meeting in Arlington, VA, December 6-10, 2015, prior to the publication of the manuscripts.

William Heydens of Monsanto reviewed a draft of this overview paper and suggested wording changes but did not comment on the opinions and conclusions of the expert panel. The opinions expressed, and final conclusions set out in this overview paper were those of the listed authors and no one else.

While Intertek (formerly Cantox) has not previously worked on glyphosate-related matters for the Monsanto Company, previous employees (Ian Munro and Douglass Bryant) of Cantox, have worked in this capacity. Ian Munro and Gary Williams, with the assistance of Douglass Bryant, prepared a safety and risk assessment of Roundup® herbicide (glyphosate), which was supported by Monsanto (Williams et al, 2000).

Gary Williams, Sir Colin Berry, David Brusick, Joao Lauro Viana de Camargo, Helmut A. Greim, David J. Kirkland, and Tom Sorahan have previously served as independent consultants for the Monsanto Company, some serving on the European Glyphosate Task Force. Keith R. Solomon previously served as an independent consultant for the Monsanto Company on the deregulation of RR alfalfa in the US (2012-2014). In collaboration with Cantox, Dr. Solomon contributed to an ecotoxicological risk assessment for Roundup® herbicide, which was published (Giesy et al, 2000). In addition, between 2014 and 2016, he served on a scientific advisory board to Dow AgroSciences, which markets pesticides, including glyphosate. John Acquavella and Larry D. Kier have also served as independent consultants and were previously employees of the Monsanto Company. John Acquavella was employed by Monsanto between the years 1989 and 2004. He is a consultant on a legal case unrelated to glyphosate that involved a former Monsanto industrial chemical plant. Larry Kier was employed as a consultant by Monsanto to provide support for the Glyphosate Expert Panel in the areas of genotoxicity and oxidative stress. Larry Kier did review the report as it was being written and provided his expertise when requested by the panel members. After the final draft of the report was written Larry was added as a co-author and genotoxicity Expert Panel member based on a unanimous decision of the original genotoxicity Expert Panel Members.

Helmut Greim has previously reviewed the available long-term studies in rodents and has published a paper (Greim et al., 2015) together with three coauthors. One of them, an employee of Monsanto, provided the original data from the studies conducted by Monsanto, the other two authors were independent consultants, one of them a member of the glyphosate task force.

David Garabrant served in 2014-16 on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate. He was jointly retained by Bayer Corporation; Bayer CropScience LP; Bayer CropScience Holding, Inc.; Dow AgroSciences, L.L.C.; BASF Corporation; Syngenta Crop Protection, Inc., Deere & Company, Lesco, Inc.; and Monsanto in litigation matters concerning glyphosate and leukemia. He also provided consultation in February 2016 to an attorney representing Pharmacia (formerly Monsanto) in litigation that did not involve glyphosate. Tom Sorahan has consulted for Monsanto on litigation matters involving glyphosate. Tom Sorahan has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112, as an Observer for the Monsanto Company. Douglas L. Weed has consulted on litigation matters for Monsanto that did not involve glyphosate.

Other than David Garabrant and Tom Sorahan, none of the authors had previously been involved in any litigation procedures involving Monsanto and glyphosate.

Marilyn Aardema, Michele M. Burns, Gary Marsh and Ashley Roberts had not been previously involved in any activity involving glyphosate and as such declare no potential conflicts of interest.

The authors apologize for any errors or omissions in the original disclosure.

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2018.1522751

Taylor & Francis
Taylor & Francis Group

Corrigendum

Solomon KR, (2016). Glyphosate in the general population and in applicators: a critical review of studies on exposures. *Crit Rev Toxicol.* 46(S1), pp. 21–27.

http://dx.doi.org/10.1080/10408444.2016.1214678

When this article was originally published on 28th September 2016, the contributions, contractual status and potential competing interests of all authors and non-author contributors were not fully disclosed. Specifically, the Declaration of Interest were not complete. These sections should read as follows:

Acknowledgment

The author gratefully acknowledges the extensive comments offered by five reviewers selected by the Editor and presented anonymously to the author. These comments were useful in revising the paper. I thank Monsanto Inc. for providing access to reports from exposure studies for glyphosate in applicators and Dr. Marian Bleeke (of Monsanto Inc.) for clarification of some of the methods used. I wish to thank the authors of the other papers in this series for their constructive suggestions and comments.

Declaration of interest

The employment affiliation of the author is shown on the cover page. However, it should be recognized that the author participated in the review process and preparation of this paper as an independent professional and not as a representative of his employer. Keith R. Solomon previously served as an independent consultant for the Monsanto Company on the deregulation of RR alfalfa in the US (2012–2014). In collaboration with Cantox, the predecessor company to Intertek Scientific and Regulatory Consultancy (Intertek) KRS contributed to an ecotoxicological risk assessment for Roundup® herbicide, which was published (Giesy et al., 2000). In addition, between 2014 and 2016, he served on a scientific advisory board to Dow AgroSciences, which markets pesticides including glyphosate. KRS has not been involved in any litigation procedures involving Monsanto Company and glyphosate. KRS's recruitment and evaluation of the data was organized and conducted by Intertek. acted as a consultant for Intertek. Intertek is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food and pharmaceutical industries. Intertek prepared the paper for submission to the journal, made some formatting and editorial changes prior to submission, and, after review provided the comments from the reviewers to KRS. KRS was not provided with comments from William Heydens of Monsanto Inc., either directly or via Intertek.

While Intertek Scientific & Regulatory Consultancy (Intertek) has not previously worked on glyphosate related matters for the Monsanto Company, previous employees of Cantox, the predecessor company to Intertek, had worked in this capacity. Funding for this evaluation was provided to Intertek by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

The author apologizes for these errors.

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2018.1522142

Corrigendum

Acquavella J, Garabrant D, Marsh G, Sorahan T, Weed DL. (2016). Glyphosate epidemiology expert panel review: a weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. Crit Rev Toxicol. 46(S1). pp. 28–43.

http://dx.doi.org/10.1080/10408444.2016.1214681

When this article was originally published on 28th September 2016, the contributions, contractual status and potential competing interests of all authors and non-author contributors were not fully disclosed. Specifically, the Acknowledgements and Declaration of Interest were not complete. These sections should read as follows:

Acknowledgements

The authors gratefully acknowledge the very useful comments provided by seven reviewers who were selected by the Editor and anonymous to the authors. These comments helped improve the manuscript. William Heydens of Monsanto reviewed the initial draft of our manuscript and commented that the section on analytic selection bias was unclear to him and that we might define the term "grey literature." He also pointed out some typographical errors. Based on his feedback, the authors decided to clarify the section on analytic selection bias, define grey literature in a footnote, and correct the typos. All additions, deletions, and changes to the draft manuscript were made only by the authors, with unanimous agreement.

Declaration of Interest

The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer. This expert panel evaluation was organized and conducted by Intertek Scientific & Regulatory Consultancy. Funding for this evaluation was provided by Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient. The authors had sole responsibility for the content of the paper, and the interpretations and opinions expressed in the paper are those of the authors.

JA worked for Monsanto from 1989 through 2004. He is currently a consultant on a legal case unrelated to glyphosate that involves a former Monsanto industrial chemical plant. DG serves on a scientific advisory board to Dow Agro Sciences, which markets pesticides including glyphosate. He was jointly retained by Bayer Corporation; Bayer CropScience LP; Bayer CropScience Holding, Inc.; Dow AgroSciences, L.L.C.; BASF Corporation; Syngenta Crop Protection, Inc., Deere & Company, Lesco, Inc.; and Monsanto in litigation matters concerning glyphosate and leukemia. He also provided consultation in February 2016 to an attorney representing Pharmacia (formerly Monsanto) in litigation that did not involve glyphosate. That consultation consisted of 0.3 hours of professional services, after which he did no further work on the litigation. GM has no additional declarations. TS has received consultancy fees and travel grants from Monsanto Europe SA/NV as a member of the European Glyphosate Toxicology Advisory Panel and participated in the IARC Monograph Meeting for volume 112 which reviewed the literature and provided a carcinogenic hazard assessment for glyphosate as an Observer for the Monsanto Company. In addition, TS has consulted for Monsanto on litigation matters involving glyphosate. DW has consulted on litigation matters concerning Monsanto that did not involve glyphosate. This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient. JA was paid directly by Monsanto for his work on this expert panel through an existing consultant contract. The other authors (DG, GM, TS, DW) were paid by Intertek, which was funded by Monsanto.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

The authors apologize for these errors.

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2018.1522784

Taylor & Francis
Taylor & Francis Group

Corrigendum

Williams, G. M., Berry, C., Burns, M. M., de Camargo, J. L. V., & Greim, H. A. (2016). Glyphosate rodent carcinogenicity bioassay expert panel review. *Critical Reviews in Toxicology,* 46(S1), pp. 44–55.

http://dx.doi.org/10.1080/10408444.2016.1214679

When this article was originally published on 28th September 2016, the contributions, contractual status and potential competing interests of all authors and non-author contributors were not fully disclosed. Specifically, the Acknowledgements and Declaration of Interest were not complete. These sections should read as follows:

Acknowledgements

The authors gratefully acknowledge the extensive comments received from nine independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the manuscript. Materials for consideration for use in the preparation of this paper were provided by Intertek. The authors thank Barry Lynch of Intertek for writing the Introduction to the paper. Dr. Williams thanks his colleague, Dr. Michael J. Iatropoulos for assistance in writing the section on mouse kidney tumors, and Ms. Sharon Brana for typing the manuscript.

Declaration of Interest

This paper is part of a series on glyphosate, which was sponsored and supported by Intertek Scientific & Regulatory Consultancy (Intertek) under the leadership of Ashley Roberts. Funding for preparation of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

The employment affiliations of the authors of the carcinogenicity group of the expert panel are as shown on the cover page. Each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer.

The carcinogenicity group members recruitment and the evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The group panelists were engaged by Intertek, and acted as consultants to Intertek and were not directly contacted by the Monsanto Company. Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food, and pharmaceutical industries. While Intertek has not previously worked on glyphosate-related matters for the Monsanto Company, previous employees (Ian Munro, Douglass W. Bryant, Barry Lynch) of Cantox, have worked in this capacity. Gary Williams coauthored a review of Roundup herbicide (glyphosate) (Williams et al, 2000), which was supported by Monsanto. Gary Williams, Sir Colin Berry, Jo~ao Lauro Viana de Camargo, and Helmut Greim have previously served as independent consultants for the Monsanto Company, some on the European Glyphosate Task Force. Helmut Greim has previously reviewed the available long-term studies in rodents and has published a paper (Greim et al., 2015) together with three coauthors. One of them, an employee of Monsanto, provided the original data of the Monsanto studies, the other two were independent consultants, one of them a member of the glyphosate task force. Michele Burns has not previously been involved in any activity involving glyphosate and as such declares no potential conflict of interest. None of the aforementioned authors have been involved in any litigation procedures concerning glyphosate.

Neither any Monsanto company employees nor any attorney provided any review of the Expert Panel's manuscript analysis and conclusions prior to submission to the journal.

The authors apologize for these errors.

CRITICAL REVIEWS IN TOXICOLOGY
https://doi.org/10.1080/10408444.2018.1522133

Taylor & Francis
Taylor & Francis Group

Corrigendum

Brusick D, Aardema M, Kier LD, Kirkland DJ, Williams G. (2016). Genotoxicity Expert Panel review: weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. Crit Rev Toxicol. 46(S1). pp. 56–74.

http://dx.doi.org/10.1080/10408444.2016.1214680

When this article was originally published on 28th September 2016, the contributions, contractual status and potential competing interests of all authors and non-author contributors were not fully disclosed. Specifically, the Acknowledgements and Declaration of Interest were not complete. These sections should read as follows:

Acknowledgements

The authors gratefully acknowledge the extensive comments received from seven independent reviewers selected by the Editor and who were anonymous to the authors. These comments were very helpful in revising the original submitted manuscript. The authors also gratefully acknowledge the clerical assistance of Anna Bickel, a Monsanto employee, in formatting the final paper prior to submission to the journal.

Declaration of interest

The employment affiliation of the authors is as shown on the cover page. Each individual participated in the review process and preparation of this paper as an independent professional. No individuals other than the cited authors were involved in developing the analysis and conclusions of the manuscript prior to its submission to the journal.

The Expert Panel Member recruitment was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek) and the initial Expert Panelists worked under individual consulting contracts with Intertek. Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food, and pharmaceutical industries. While Intertek Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto Company, previous employees of Cantox had worked in this capacity.

Larry Kier did not have a consulting contract with Intertek; he was employed as a consultant by Monsanto to provide support for the Glyphosate Expert Panel in the areas of genotoxicity and oxidative stress. LK did review the report as it was being written and provided his expertise when requested by the panel members. After the final draft of the report was written Larry was added as a co-author and genotoxicity Expert Panel member based on a unanimous decision of the original genotoxicity Expert Panel Members.

Gary Williams, David Brusick, and David Kirkland have previously served as independent consultants for the Monsanto Company, some serving on the European Glyphosate Task Force. Larry Kier was previously an employee of the Monsanto Company (1974-2000) and has also served as an independent consultant for Monsanto Company. As consultants to the Glyphosate Task Force LK and DK prepared and published a review of the genotoxicity of glyphosate and glyphosate-based formulations (Kier and Kirkland, 2013) and as a consultant to Monsanto LK prepared and published a review of genotoxicity biomonitoring studies of glyphosate-based formulations (Kier, 2015). Marilyn Aardema has not previously been employed in the Monsanto Company or previously been involved in any activity involving glyphosate and as such declares no potential conflicts of interest. Ian Munro, Douglass W. Bryant, and Gary Williams prepared a safety and risk assessment paper of Roundup herbicide (glyphosate) (Williams G.M. et al., 2000).

Except for assistance with final formatting, neither any Monsanto company employees nor any attorney provided any review of the Expert Panel's manuscript analysis and conclusions prior to submission to the journal.

This article is part of a supplement, sponsored and supported by Intertek Scientific & Regulatory Consultancy. Funding for the sponsorship of this supplement was provided to Intertek by the Monsanto Company, which is a primary producer of glyphosate and products containing this active ingredient.

The authors apologize for these errors.

(6) All communications with Monsanto related to GBFs, AMPA, and/or surfactants for GBFs.

Response:

Roger O. McClellan has had no communications with Monsanto personnel related to GBFs. AMPA and/or surfactants for GBFs except as related to specific manuscripts submitted to Critical Reviews in Toxicology and disclosed below.

(7) All communications with Intertek, Inc related to GBFs, AMPA, and/or surfactants for GBFs.

Response:

The only communications between Roger O. McClellan and Intertek, Inc. personnel related to GBFs, AMPA and/or surfactants for GBFs are those with Ashley Roberts in his role coordinating the preparation and publication of five papers included in the Special Supplement to Volume 46 (2016) of Critical Reviews in Toxicology as noted in Item 10 below.

(8) All communications with Dr. Larry Kier related to GBFs, AMPA, and/or surfacants for GBFs.

Response:

The only communications Roger O. McClellan has had with Dr. Larry Kier related to GBFs, AMPA, and/or surfactants for GBFs are communications in McClellan's role as Editor-in-Chief of Critical Reviews in Toxicology and specifically relate to manuscripts authored or co-authored by Dr. Kier as identified below:

Larry D. Kier and David J. Kirkland (2013). Review of genotoxicity studies of glyphosate and glyphosate-basd formulations. Crit. Rev. in Toxicol. 43(4):283-315.

Larry D. Kier (2015). Review of genotoxicity biomonitoring studies of glyphosate-based formulations. Crit. Rev. in Toxicol. 45(3):209-218.

Brusick, D., Aardema, M., Kier, L., Kirkland, D. and William, G. (2016). Genotoxicity expert panel review: Weight of evidence evaluation of the genotoxicity of glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid. Crit. Rev. in Toxicol. 46 (Special Supplement): 56-74.

Copies of those published papers were provided in response to Item 5.

The third paper listed, authored by Brusick et al. (2016), which included Dr. Larry Kier as a co-author, was included in a special investigation addressed in Item 15.

Roger McClellan

From: Roger McClellan <[redacted]@att.net>
Sent: Monday, February 25, 2013 8:52 AM
To: Claire Summerfield
Cc: Bridget Sheppard; Lindsay Duncan; Mildred Morgan; Roger O. McClellan
Subject: Fw: Revised Proof Corrections/ Like to see it

Claire:
Welcome back> I was surprized I did not receive the revised galley's for review. Please send me a copy. I am curious as to how they turned out. I appreciate everyone's help with this manuscript.
Regards,
Roger

----- Forwarded Message ----
From: Larry Kier <[redacted]@q.com>
To: Roger O. McLellan <[redacted]att.net>
Sent: Mon, February 25, 2013 8:16:34 AM
Subject: Revised Proof Corrections

Roger,

I received the revised proof on Friday and submitted corrections on Saturday morning. The corrections certainly weren't anything major but they were definitely worthwhile.

They were received and I believe they are being processed which shouldn't take much time at all.

Thanks for your help with this process.

Larry Kier

Roger McClellan

From: SALTMIRAS, DAVID A (AG/1000) <[redacted]@monsanto.com>
Sent: Thursday, January 9, 2014 2:35 PM
To: roger.o.mcclellan@[redacted]
Subject: Glyphosate carcinogenicity review manuscript

Roger,

I have been meaning to update you for some time on our progress on a glyphosate carcinogenicity review manuscript. We are making a few modifications since the Seralini paper was recently retracted by *Food & Chemical Toxicology*. We are also hard at work evaluating the tumor data tables on the thirteen industry studies (8 rat and 5 mouse). However, we just received the EU Rapporteur's Reevaluation Assessment Report (RAR) for glyphosate's EU Annex I Renewal, which will soon open up for a two month public comment period. The European Glyphosate Task Force (I chair the Toxicology Technical Working Group) will first complete our comments back to the German BvL. Then I will turn my attention to final tuning of our manuscript for submission to *Critical Reviews in Toxicology*.

Thanks for your patience.

Best wishes for 2014.

David Saltmiras, PhD, D. ABT.
Toxicology Manager
Regulatory, Toxicology and Nutrition Center
Monsanto
ph [redacted]

comply with all
applicable U.S. export laws and regulations.

Roger McClellan

From: SALTMIRAS, DAVID A (AG/1000) <[redacted]@monsanto.com>
Sent: Wednesday, October 1, 2014 10:00 AM
To: roger.o.mcclellan@[redacted]
Subject: Declaration of Interest

Roger,

I have framed the following declaration of interest similar to that of the Larry Kier & David Kirkland paper, but I am not sure this as granular as you were requesting over the phone. Please let me know if this is acceptable or whether more details are necessary.

Declaration of Interest

Volker Mostert was a consultant involved in the preparation of the 2012 glyphosate Annex I Renewal dossier for the Glyphosate Task Force (GTF), a consortium of European glyphosate registrants (http://www.glyphosatetaskforce.org/). Volker Mostert and Helmut Greim have been reimbursed by the GTF for their work on this manuscript. The selection and interpretation of the data presented here were the sole responsibility of the four authors. David Saltmiras and Christian Strupp are employed by member companies of the GTF, Monsanto and Feinchemie Schwebda GmbH (Makhteshim Agan Industries Ltd.) respectively. David Saltmiras is also Chair of the Toxicology Technical Working Group of the Glyphosate Task Force. Monsanto Company was the original producer and marketer of glyphosate formulations. The authors had sole responsibility for the writing and content of the paper and the interpretations and opinions expressed in the paper are those of the authors and may not necessarily be those of the member companies of the Glyphosate Task Force.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all applicable U.S. export laws and regulations.

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[redacted]@monsanto.com>
Sent: Thursday, November 6, 2014 4:39 PM
To: roger.o.mcclellan@[redacted]
Subject: FW: Critical Reviews in Toxicology - Manuscript ID BTXC-2014-0081

Roger,

Finally submitted! Confirmation email below. Please let me know if you have any questions ore require additional details, information, etc.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead Toxicology and Nutrition Center Monsanto ph[redacted]

-----Original Message-----
From: onbehalfof+mbmorgan[redacted]@manuscriptcentral.com
[mailto:onbehalfof+mbmorgan+hargray.com@manuscriptcentral.com] On Behalf Of mbmorgan@[redacted]
Sent: Thursday, November 06, 2014 5:37 PM
To: SALTMIRAS, DAVID A [AG/1000]
Cc: mbmorgan@[redacted]
Subject: Critical Reviews in Toxicology - Manuscript ID BTXC-2014-0081

06-Nov-2014

Dear Dr Saltmiras:

Your manuscript entitled "Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies" has been successfully submitted online and is presently being given full consideration for publication in Critical Reviews in Toxicology.

Your manuscript ID is BTXC-2014-0081.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to Manuscript Central at https://mc.manuscriptcentral.com/btxc and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to https://mc.manuscriptcentral.com/btxc.

Thank you for submitting your manuscript to Critical Reviews in Toxicology.

Sincerely,
Critical Reviews in Toxicology Editorial Office

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[redacted]@monsanto.com>
Sent: Friday, December 19, 2014 4:37 PM
To: roger.o.mcclellan@[redacted]
Attachments: Author Responses to Reviewer Comments.docx; Glyphosate Carcinogenic Potential - REVISED CRT Manuscript_12-19-2014.docx

Roger,

As discussed this afternoon, I have uploaded the responses to reviewer comments, the revised glyphosate carcinogenicity review manuscript, revised tables and a revised data supplement on manuscript central. I have also attached are my responses to reviewers comments and the revised manuscript in MS Word with tracked changes.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
m: [redacted]

Roger McClellan

From: Roger McClellan <roger.o.mcclellan[redacted]>
Sent: Tuesday, January 13, 2015 11:31 AM
To: Larry Kier
Cc: mbmorgan@[redacted]; Roger McClellan
Subject: Re: Critical Reviews in Toxicology

Larry:
Your interpretation is correct. Please do not submit a revised manuscript until you receive the third reviewers comments or I give you a green light. Best regards, Roger

On Tuesday, January 13, 2015 11:25 AM, Larry Kier <[redacted]@q.com> wrote:

Roger and Mildred,

Thanks so much for sending the reviews and thanks to both you and the reviewers for their remarkably prompt responses.

I will get to work on these right away but assume I should wait for the third review to submit reviewer reponses.

Thanks.

Larry Kier

-----Original Message-----
From: onbehalfof+roger.o.mcclellan+[redacted]@manuscriptcentral.com
[mailto:onbehalfof+roger.o.mcclellan+[redacted]@manuscriptcentral.com] On Behalf Of roger.o.mcclellan[redacted]
Sent: Tuesday, January 13, 2015 10:44 AM
To: ldkier@[redacted]
Cc: mbmorgan[redacted]; roger.o.mcclellan[redacted]
Subject: Critical Reviews in Toxicology

13-Jan-2015

BTXC-2015-0001 - Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

Dear Dr Larry Kier:

I have have received two reviews of your paper and I am waiting for a third review. The two reviews received are quite positive. I am asking my assistant , Mildred Morgan, to send copies of the review to you so you can begin considering revisions to the text you submitted. In particular one reviewer suggests adding a table to clarify your findings. I concur with his recommendation. I will be sending you the third review as soon as it is received.

Best regards

Sincerely,

Roger

Dr Roger McClellan, Editor
Critical Reviews in Toxicology

Claire.summerfield@informa.com
http://www.tandfonline.com

From: Roger McClellan [mailto:roger.o.mcclellan@att.net]
Sent: 31 January 2015 17:10
To: Summerfield, Claire
Cc: Mildred; Roger McClellan
Subject: Fw: Submitted Corrections for Manuscript ID: BTXC 1010194/ Questions

Claire:

What is going on with the Production People on the Conflict of Interest / Declaration of Interest front? Queries like number 4 on the Kier manuscript are confusing to authors. I thought we had this issue resolved. Has CRT been shifted to another Production Company? If I am off base on this issue let me know.

Best regards,

Roger

On Saturday, January 31, 2015 10:01 AM, Roger McClellan <roger.o.mcclellan@att.net> wrote:

Larry:

Ignore the Query related to Conflict of Interest ?Declaration of Interest. What you provided and I approved is just fine. I think the Production People are confused and are use to using "eye wash statements" like "the authors declare no conflict of interest".

Best regards,

Roger

On Saturday, January 31, 2015 9:54 AM, "claire.summerfield@informa.com" <claire.summerfield@informa.com> wrote:

This e-mail confirms that you have submitted your corrections to your proofs. Please review the journal and article/content titles below to make sure they are correct.
If any of this information is incorrect, please contact the Production Editor.
Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations
By: Kier
Journal: BTXC Critical Reviews in Toxicology
Comments From: Roger McClellan
Date Returned: 31 Jan 2015

Correction#: 1
Query#: 4
Page#: 9
Line#: 39
This is exactly the same Declaration of Interest as provided by the author and approved by the Editor. I do NOT understand what the Production stff is doing inserting a Query like this that is pure NONSENSE. What is going on????
After your article has been published online, you will receive 15 eprints to share with colleagues. You will receive an email from us to let you know that it has been published. If you wish to order reprints, please place your order at the Rightslink website:

http://cats.informa.com/PTS/go?t=rl&m=1010194
Yours sincerely,
Claire Summerfield
Informa Business Information
Christchurch Court
10-15 Newgate Street
London
EC1A 7AZ
UNITED KINGDOM
Email:claire.summerfield@inform[redacted]
Phone:+4[redacted]

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[redacted]@monsanto.com>
Sent: Thursday, February 19, 2015 10:57 AM
To: roger.o.mcclellan@att[redacted]
Subject: Recently Accepted Glyphosate Manuscripts

Hello Roger,

I trust the weather your way has been a little more amenable than what we have been experiencing!

I have a little inquiry of you. Monsanto's public affairs & scientific affairs folk asked whether *Critical Reviews in Toxicology* will be issuing a press release on the glyphosate papers recently accepted. If so, what does the press release entail?

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[redacted]@monsanto.com>
Sent: Thursday, February 19, 2015 1:22 PM
To: roger.o.mcclellan@[redacted]
Subject: vol112-participants
Attachments: vol112-participants.pdf

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[redacted]@monsanto.com>
Sent: Thursday, February 19, 2015 8:36 PM
To: Roger McClellan
Cc: Larry Kier
Subject: Re: Greim et al. (2015) & Kier (2015) summaries, abstracts and sound bytes

Roger,

Thank you for looping me into the conversation. The two summaries were initially prepared by our Scientific Affairs personnel. I completely understand and empathize with Larry's concerns on his paper's "summary" as I had to prepare some significant rewording to ensure my paper's summary was an accurate reflection of the work. I was remiss in not first routing this by Larry and my sincere apologies go out to him.

Larry, I would like to discuss further if you are available tomorrow to see if we can come up with acceptable summaries for both of your recent publications, which you may be comfortable sharing with Roger.

Regards,

David

Sent from my iPhone

On Feb 19, 2015, at 6:21 PM, "Roger McClellan" <[redacted]@att.net> wrote:

> Larry:
> What I forwarded to T and F (Charles Whalley) is what I received from David Saltmiras. I assumed you were in the loop on what had been developed at Monsanto. I suggest you get in touch ASAP with David. In the mean time I will ask T and F to let me review whatever they develop prior to its release. IF T and F does something to publicize the two papers I suspect it will be very brief.
> Thanks for your input.
> Roger
>
> On Thursday, February 19, 2015 5:12 PM, Larry Kier <[redacted]@a.com> wrote:
>
> Dear Dr. McClellan (Roger):
>
> I'm a little cautious about high levels of publicity for the biomonitoring review and have concerns about some of the suggested publicity material.
>
> I don't know who wrote the "Summary" for my paper and certainly don't want to offend them but it is not the way I would have worded it and I would personally not want this used to characterize my paper. I have a revision below but I don't know whether these summaries are appropriate for publication authors:
>
> Summary

A recent review examined several studies that measure damage to the DNA (genotoxicity) in cells collected from people exposed to pesticides including glyphosate-based herbicides. The author concluded that these studies do not indicate significant genotoxic risks to humans from glyphosate-based herbicides under normal exposure conditions. These findings are consistent with an earlier review of an extensive number of laboratory studies that indicated little likelihood of significant genotoxic risk or reaction with DNA under normal exposure conditions.

I also don't think the "Sound bytes for social media" are accurately worded. They are way too absolute for my taste and place undue emphasis on the strength of the biomonitoring study data. Unfortunately, I can't readily suggest alternatives that fit nicely into the "sound byte" format.

Frankly, the biomonitoring studies that are informative for GBF exposure were few in number (arguably 5) and the robustness of the results is pretty low (not unexpected for biomonitoring studies). My conclusion, as stated, was that the limited data from biomonitoring studies do not contradict the much more extensive and robust data from experimental studies that suggest no significant genotoxic risk or DNA-reactive mechanism, especially under expected much lower actual real-world exposures compared to experimental exposures. I would personally place much more emphasis on the experimental study data but the Summary and particularly the "Sound bytes for social media" don't do this and place undue emphasis on the strength of the biomonitoring data. This focus is understandable for publicity directed at the biomonitoring study but I still am not comfortable with this.

Please note that I believe this qualification applies particularly to the biomonitoring review and I support a stronger conclusion regarding low genotoxic risk from glyphosate and GBF's based on the experimental study review.

Thanks very much for the communication and please let me know if I can be of further assistance.

Larry Kier

From: Roger McClellan [mailto:[redacted]@att.net]
Sent: Thursday, February 19, 2015 3:43 PM
To: Whalley Charles
Cc: DAVID A (AG/1000) SALTMIRAS; Mildred; Claire; Roger McClellan; Larry Kier
Subject: Fw: Greim et al. (2015) & Kier (2015) summaries, abstracts and sound bytes

Publicity for Glyphosate Papers

Charles:

I spoke to David Saltmiras today concerning the two Glyphosate papers that will be the lead papers in the next issue of Critical Reviews in Toxicology with regard to F and F putting out any publicity on these two papers. The e-mail below includes complete citations for the papers, abstracts and some information developed by Monsanto Company on the papers.

As you may be aware, these papers have been forwarded to the International Agency for Research on Cancer (IARC) in Lyon, France. IARC at a meeting in early March will be considering the carcinogenic hazard classification of Glyphosate and some other phosphate containing agricultural chemicals. These papers will be a topic of discussion at that meeting. IARC will announce its carcinogenic hazard classification for all the chemical agents reviewed at the meeting, this will probably be done at a Press Conference on March 10. A brief paper describing the results of the meeting will also be published within a few weeks after the meeting concludes. A large Monograph documenting the reviews will be published in early 2016.

As a bottom line the two papers published on line in CRT are likely to attract some attention in the scientific and regulatory community and, possibly, by lay media. I am uncertain as to the policy of T and F on publicizing articles published in Journals such as CRT. If T and F is doing so , these two articles would be excellent candidates.

Please let me know your views on this matter and how you plan to proceed. Let me know if I can be assistance.

On a related matter, I am uncertain as to how T and F would like to handle access to these two papers. I suspect that Monsanto would be interested in purchasing "open access" if that is an option.

Best regards,
Roger

On Thursday, February 19, 2015 1:16 PM, "SALTMIRAS, DAVID A [AG/1000]" <[redacted]@monsanto.com> wrote:

Roger – FYI on press releases.

Greim, H., D. Saltmiras, V. Mostert, and C. Strupp. 2015. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Crit.* Rev. Toxicol. In press

Summary: A new scientific publication examining 14 separate cancer studies in rats and mice conducted over the last several decades concludes that there is no evidence that glyphosate, the active ingredient in Roundup branded herbicides, causes cancer. The article, in Critical Reviews in Toxicology, evaluated the data from these long term studies to determine whether there were any patterns to suggest humans exposed to glyphosate would have any concern about developing cancer. Other scientifically relevant information such as expert regulator evaluations, human dietary exposures and epidemiological studies were also discussed. The clear and consistent view across over 30 years of relevant information continues to support the first expert opinions from the 1980's, that glyphosate does not cause cancer.

Abstract: Glyphosate, an herbicidal derivative of the amino acid glycine, was introduced to agriculture in the 1970s. Glyphosate targets and blocks a plant metabolic pathway not found in animals, the shikimate pathway, required for the synthesis of aromatic amino acids in plants. After almost forty years of commercial use, and multiple regulatory approvals including toxicology evaluations, literature reviews, and numerous human health risk assessments, the clear and consistent conclusions are that glyphosate is of low toxicological concern, and no concerns exist with respect to glyphosate use and cancer in humans. This manuscript discusses the basis for these conclusions. Most toxicological studies informing regulatory evaluations are of commercial interest and are proprietary in nature. Given the widespread attention to this molecule, the authors gained access to carcinogenicity data submitted to regulatory agencies and present overviews of each study, followed by a weight of evidence evaluation of tumor incidence data. Fourteen

carcinogenicity studies (nine rat and five mouse) are evaluated for their individual reliability, and select neoplasms are identified for further evaluation across the data base. The original tumor incidence data from study reports are presented in the online data supplement. There was no evidence of a carcinogenic effect related to glyphosate treatment. The lack of a plausible mechanism, along with published epidemiology studies, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans.

Sound bytes for social media:

- New scientific review examines over 30 years of data, concludes glyphosate does not cause cancer in animals and poses no cancer risk to humans
- Over 30 years of data: no evidence that glyphosate causes cancer
- New glyphosate scientific review: over 30 years of data, demonstrates it does not cause cancer in animals and poses no cancer risk to humans

---

Kier, L. D. (2015). Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations. Crit. Rev. Toxicol., in press

Summary: A recent review examined several studies that allege damage to the DNA in cells collected from people after self-reported exposures to glyphosate-based herbicides. The author concluded that there are no direct risks to human DNA under normal exposure conditions. These findings are consistent with an earlier review of an extensive number of laboratory studies that also demonstrated no direct effect on DNA. Taken together, these results confirm previous conclusions that glyphosate-based herbicides do not damage DNA in humans following real world exposures.

Abstract: Human and environmental genotoxicity biomonitoring studies involving exposure to glyphosate-based formulations (GBFs) were reviewed to complement an earlier review of experimental genotoxicity studies of glyphosate and GBF's (Kier and Kirkland, 2013). The environmental and many of the human biomonitoring studies were not informative because there was either a very low frequency of GBF exposure or exposure to a large number of pesticides. One human biomonitoring study indicated no statistically significant correlation between frequency of GBF exposure reported for the last spraying season and oxidative DNA damage. Negative results for the lymphocyte cytokinesis-block micronucleus (CBMN) endpoint were observed in a second human monitoring study with exposure to several pesticides including GBF. There were three studies of human populations exposed to GBF aerial spraying. One study found increases for the CBMN endpoint but these increases did not correlate with self-reported spray exposure or application rates. A second study found increases for the blood cell comet endpoint at high exposures causing toxicity. However, a follow-up to this study two years after spraying did not indicate chromosomal effects. The results of the biomonitoring studies do not contradict an earlier conclusion derived from experimental genotoxicity studies that typical GBF's do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

Sound bytes for social media:

- New analysis of human data: glyphosate-based herbicides do not damage cellular DNA following realistic human exposures
- Human data: glyphosate-based herbicide following realistic human exposure not associated with DNA damage in human cells

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

This e-mail message may contain privileged and/or confidential information, and is intended to be received only by persons entitled to receive such information. If you have received this e-mail in error, please notify the sender immediately. Please delete it and all attachments from any servers, hard drives or any other media. Other use of this e-mail by you is strictly prohibited.

All e-mails and attachments sent and received are subject to monitoring, reading and archival by Monsanto, including its subsidiaries. The recipient of this e-mail is solely responsible for checking for the presence of "Viruses" or other "Malware". Monsanto, along with its subsidiaries, accepts no liability for any damage caused by any such code transmitted by or accompanying this e-mail or any attachment.

The information contained in this email may be subject to the export control laws and regulations of the United States, potentially

including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all applicable U.S. export laws and regulations.

Roger McClellan

From: Larry Kier <[redacted]@q.com>
Sent: Thursday, February 19, 2015 2:31 PM
To: Summerfield, Claire
Cc: Roger O. McLellan; Mildred B. Morgan
Subject: Revised Proof and Publication Process

Ref:

Journal: BTXC Critical Reviews in Toxicology
Manuscript ID: 1010194
Manuscript Title: Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

Dear Ms. Summerfield:

I was somewhat surprised to see that the above has appeared on the InformaHealthcare CRC website as an early online publication.

It was my understanding from an earlier email that I would see a revised proof on Monday. As far as I know this was not available and I sent an email inquiry yesterday but didn't receive a response.

When I now attempt to access the CATS system (http://cats.informa.com/PTS/go?t=rl&m=1010194) to see if the revised proof is there (it wasn't earlier this week) I somehow get redirected to the https://s100.copyright.com/ site. My CATS user name and password doesn't work on this copyright.com page.

I would please like to see a copy of the proof or publication of my article. In my Wednesday (yesterday) email I asked for another one word change (the word "detectable" on page 8 line 94 of the original proof be replaced with "significant"). I would please like this considered for the publication.

While I certainly understand and appreciate the need to process manuscripts into publications efficiently and rapidly I think that there may have been a communication gap in this case.

I would also appreciate information on publication charges (e.g. page charges) when convenient.

Thanks for your help.

Larry Kier

Roger McClellan

From: Larry Kier <[redacted]@q.com>
Sent: Thursday, February 19, 2015 3:36 PM
To: Summerfield, Claire
Cc: Roger O. McLellan; Mildred B. Morgan
Subject: Publication Proof Revision

Ref:

Journal: BTXC Critical Reviews in Toxicology
Manuscript ID: 1010194
Manuscript Title: Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

Dear Ms. Summerfield:

I just checked my other email account (author correspondence account) and found that a notice of publication and an email token was sent on February 17.

I have checked the publication with my proof corrections and all corrections were successfully made with one minor exception too minor to change now. I suspect that changing "detectable" to "significant" [Page 8, right column, line 28] is not convenient now. Hopefully, this will not be a significant point.

Although I expected a revised proof on Monday I acknowledge the validity of all's well that ends well.

Thanks for your help and that of your team.

Larry Kier

Roger McClellan

From: Larry Kier <[redacted]@q.com>
Sent: Friday, February 20, 2015 8:02 AM
To: 'Summerfield, Claire'
Cc: 'Roger O. McLellan'; 'Mildred B. Morgan'
Subject: RE: Publication Proof Revision

Claire,

Thanks for the note and there is no problem here. You guys did a great job of addressing the proof corrections.

If it's not too much trouble I would really appreciate the word change from "detectable" to "significant" [Page 8, right column, line 28 of the publication pdf: These results provide limited evidence for this indirect genotoxic mechanism not operating at a significant level in humans using GBFs.]. This is admittedly fussy on my part but having accurate and precise wording is important to me.

I did notice that the Greim et al. (2015) is still an "in press" citation in the References section so maybe this could be updated when appropriate citation information is available but I would certainly defer to you on whether that is appropriate or necessary.

Thanks again.

Larry Kier

From: Summerfield, Claire [mailto[redacted]@tandf.co.uk]
Sent: Friday, February 20, 2015 3:27 AM
To: Larry Kier
Cc: Roger O. McLellan; Mildred B. Morgan
Subject: RE: Publication Proof Revision
Importance: High

Dear Larry (if I may),
Bless you, many thanks for your understanding.
I experienced some major changes in my working status on Monday and have been given some additional resources this week to ensure everything is running smoothly by Monday next week. Unfortunately/fortunately your article was one of the items that was prioritised because of its imminent inclusion in this month's issue.

Despite the minor amendment not being included in the online file, I am happy to make this amendment in the printed file and online issue files, should you so wish.

I apologise once again for the confusion
Kindest regards,

Claire

Claire Summerfield
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group
an Informa Business

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line: [redacted]
Fax: [redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

From: Larry Kier [mailto:[redacted]@g.com]
Sent: 19 February 2015 22:36
To: Summerfield, Claire
Cc: Roger O. McLellan; Mildred B. Morgan
Subject: Publication Proof Revision

Ref:

Journal: BTXC Critical Reviews in Toxicology
Manuscript ID: 1010194
Manuscript Title: Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations

Dear Ms. Summerfield:

I just checked my other email account (author correspondence account) and found that a notice of publication and an email token was sent on February 17.

I have checked the publication with my proof corrections and all corrections were successfully made with one minor exception too minor to change now. I suspect that changing "detectable" to "significant" [Page 8, right column, line 28] is not convenient now. Hopefully, this will not be a significant point.

Although I expected a revised proof on Monday I acknowledge the validity of all's well that ends well.

Thanks for your help and that of your team.

Larry Kier

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[redacted]@monsanto.com>
Sent: Saturday, February 21, 2015 8:58 AM
To: Summerfield, Claire
Cc: roger.o.mcclellan[redacted]
Subject: RE: BTXC 1003423 - Issue 3 Lead article

Claire,

I have been very pleased our interactions throughout the editorial process and commend you on your acumen and diligence. Thank you for ensuring the corrections will be included in the final version.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

From: Summerfield, Claire [mailto:[redacted]@tandf.co.uk]
Sent: Friday, February 20, 2015 4:40 PM
To: SALTMIRAS, DAVID A [AG/1000]
Cc: roger.o.mcclellan[redacted]t
Subject: RE: BTXC 1003423 - Issue 3 Lead article

The proof was the revised proof from those corrections you sent via CATS only. I trust these were all fine. The 3 additional ones will be included in the issue revises so as to be correct in the final issue. I will double check the 3 corrections are in before proceeding with finalising the issue.

Kind regards,
Claire

Claire Summerfield
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line: +[redacted]
Fax: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

From: SALTMIRAS, DAVID A [AG/1000] [mailto:[redacted]@monsanto.com]
Sent: 19 February 2015 18:05
To: Summerfield, Claire
Cc: roger.o.mcclellan@[redacted]
Subject: RE: BTXC 1003423 - Issue 3 Lead article

Clare,

I left you a voice message – perhaps you sent me the wrong "final version"? None of the three items I mentioned in my last email on Saturday, below, were addressed.

Claire,

Sorry I couldn't reply on Friday as I was out of town and couldn't manage to review/respond on my phone. I have three small corrections.

1. Page 4, Table 1, line 16, column 2, change "197" to "300"
2. An essential rewording on page 17, lines 57-68. Please change from "unrelated to treatment" to "inconclusive but unrelated to treatment in the context of similar higher dosed studies"
3. Page 23, line 39. Please change the year (2013c) to (2015c).

Many Thanks,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
New Chemistry and Molecular Product Lead
Toxicology and Nutrition Center
Monsanto
c: [redacted]

From: Summerfield, Claire [mailto:[redacted]@tandf.co.uk]
Sent: Friday, February 13, 2015 9:30 AM
To: SALTMIRAS, DAVID A [AG/1000]
Subject: BTXC: Issue 3 Lead article - final confirmation
Importance: High

Dear Author,
As you know your article is going to be the lead in the next issue of BTXC. I am about to send it off for issue revises but wanted to send you this last version in case there is anything minor to amend prior to final files. If you can e-mail me by REPLY email, I will double check my inbox prior to requesting final files.

Claire Summerfield
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group
an Informa business

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line:: +[redacted]
Fax: +[redacted]
[redacted]@tandf.com
www.tandfonline.com

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph: [redacted]

From: Summerfield, Claire [mailto:[redacted]@tandf.co.uk]
Sent: Thursday, February 19, 2015 4:18 AM
To: SALTMIRAS, DAVID A [AG/1000]
Cc: Summerfield, Claire
Subject: RE: BTXC 1003423 - Issue 3 Lead article
Importance: High

Please find the final proof for final confirmation ☺

Claire Summerfield
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group
an Informa business

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line:: +[redacted]
Fax: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

From: SALTMIRAS, DAVID A [AG/1000] [mailto:[redacted]@monsanto.com]
Sent: 18 February 2015 14:57
To: Summerfield, Claire
Subject: BTXC 1003423 - Issue 3 Lead article

Hi Claire,

I'm just following up to make sure you received my final three comments over the weekend. Do you have an ETA for incorporation of these small changes and online posting?

Thanks,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph[redacted]

All e-mails and attachments sent and received are subject to monitoring, reading and archival by Monsanto, including its
subsidiaries. The recipient of this e-mail is solely responsible for checking for the presence of "Viruses" or other "Malware".
Monsanto, along with its subsidiaries, accepts no liability for any damage caused by any such code transmitted by or accompanying
this e-mail or any attachment.

The information contained in this email may be subject to the export control laws and regulations of the United States, potentially
including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of
Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all
applicable U.S. export laws and regulations.

This e-mail message may contain privileged and/or confidential information, and is intended to be received only by persons entitled
to receive such information. If you have received this e-mail in error, please notify the sender immediately. Please delete it and
all attachments from any servers, hard drives or any other media. Other use of this e-mail by you is strictly prohibited.

All e-mails and attachments sent and received are subject to monitoring, reading and archival by Monsanto, including its
subsidiaries. The recipient of this e-mail is solely responsible for checking for the presence of "Viruses" or other "Malware".
Monsanto, along with its subsidiaries, accepts no liability for any damage caused by any such code transmitted by or accompanying
this e-mail or any attachment.

The information contained in this email may be subject to the export control laws and regulations of the United States, potentially
including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of
Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all
applicable U.S. export laws and regulations.

Roger McClellan

From: Guengerich, Frederick P <[redacted]@Vanderbilt.Edu>
Sent: Sunday, February 22, 2015 1:18 PM
To: Roger McClellan
Cc: Larry Kier; Whalley Charles; Mildred; Herman Bolt; Russell; David Dorman; Gunnar Johanson; David Warheit; Shuji Tsuda
Subject: Re: Review Publication Concerns

Good points, Roger. Thanks for sharing. Fred

On Feb 22, 2015, at 1:07 PM, Roger McClellan <[redacted]@att.net> wrote:

Larry:
You make a number of important points in your letter. It is critical that all of us (authors, co-authors, editors, reviewers and publishers) who are involved with the publication of scientific papers adhere to several key principles to protect the confidential nature of the process.

First, it is critical that the peer review process be anonymous with all aspects treated with the highest degree of confidentiality. It is important that the names of reviewers and review comments not be released under any circumstances. In my opinion, a break down in confidentiality would do irreparable harm to the scientific process. In that vein, I have filed document attesting to my position in a court case where lawyers were attempting to gain access to peer review comments related to a publication in another scientific journal.

Second, it is important to recognize the responsibility of the Editor in selecting peer reviewers for any paper. As a matter of routine, I provide authors the opportunity to propose potential reviewers. For me, this is just the starting point. I read the paper and give particular attention to papers that are reviewed to identify potential reviewers. I also use my own knowledge of the subject matter to identify potential reviewers who will focus on the science being reviewed absent any particular ideological orientation or bias. At the end of the process I recognize my substantial responsibility as an Editor to select a final slate of reviewers. Moreover, when review comments are returned I use them to help guide my decision on accept, revise or reject AND, most importantly, convey the comments to authors in an anonymous manner anticipating that attention to the comments will help the authors revise and further improve the paper thereby enhancing its value to the scientific community and Society at large.

Again, thanks for your comments and for allowing me to elaborate on them. Because of the importance of this exchange I am forwarding a copy of your letter and my response with members of the CRT Editorial Advisory Board and Charles Whalley, Managing Editor, Medicine and Health Science Journals, Taylor and Francis Group, Oxford , England. I am confident that Mr Whalley and Taylor and Francis , as a Publisher, share my views as to the importance of maintaining the confidential nature of the peer review process and that T and F will resist any attempts to breach the process.

With best regards,
Roger

Roger O. McClellan, Editor
Critical Reviews in Toxicology

On Saturday, February 21, 2015 11:51 AM, Larry Kier <[redacted]@q.com> wrote:

Dear Editor McClellan:

Hopefully this communication won't be considered too presumptuous or a waste of your time. It certainly isn't intended as such.

A recent article in Science ("Agricultural researchers rattled by demands for documents", Science, 13 February 2015, p. 699.) indicates an aggressive campaign by a nonprofit organization to discredit academic scientists by demanding documentation of their interactions with industry.

Given the aggressive nature of this campaign I wonder if such organizations might consider a tactic of taking legal actions against authors, sponsors, editors and publishers of publications that represent industrial products as being of low risk where the authors) have industry connections.

While anonymous scientific peer review could represent a reasonable defense against accusations of improper bias I wonder if such legal actions could eventually include demands for legal discovery of the identities of the reviewers and the contents of their reviews. Of course, this is speculation and I am certainly not an attorney but I did want to bring this to your attention.

These concerns prompted me to think about and offer a specific example and generic suggestion. I could have suggested the three first authors (Bolognesi, Paz-y-Mino and Koureas) of the five informative papers on GBF biomonitoring results as potential reviewers of the GBF genotoxicity biomonitoring review manuscript. This simply didn't occur to me at the time and these particular individuals may not have agreed or been appropriately responsive but considering this as a generic approach may be useful.

The concept of considering significant primary publication authors as potential reviewers for a review publication seems to be a worthwhile suggestion. This could address bias issues for reviews, especially if authors of the primary review papers might have different affiliations, interpretations and conclusions than the authors of the review manuscript. The primary paper authors would have a chance to have their viewpoints considered by the review authors and editor as reviewer comments.

Thanks.

Larry Kier

F. Peter Guengerich, Ph. D.
Tadashi Inagami Professor of Biochemistry
Department of Biochemistry
Vanderbilt University School of Medicine
638 Robinson Research Bldg.
2200 Pierce Avenue
Nashville, TN 37232-0146
Telephone: [redacted]
FAX: [redacted]
E-mail: [redacted]@vanderbilt.edu

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[redacted]@monsanto.com>
Sent: Wednesday, February 25, 2015 5:30 PM
To: Summerfield, Claire
Cc: roger.o.mcclellan@[redacted]
Subject: FW: BTXC 1003423 - Issue 3 Lead article

Hello Claire,

Do you know when we can expect the glyphosate carcinogenicity manuscript to be available online this week?

Cheers,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

From: SALTMIRAS, DAVID A [AG/1000]
Sent: Saturday, February 21, 2015 9:58 AM
To: 'Summerfield, Claire'
Cc: roger.o.mcclellan@[redacted]
Subject: RE: BTXC 1003423 - Issue 3 Lead article

Claire,

I have been very pleased our interactions throughout the editorial process and commend you on your acumen and diligence. Thank you for ensuring the corrections will be included in the final version.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

> **From:** Summerfield, Claire [mailto:[redacted]@tandf.co.uk]
> **Sent:** Friday, February 20, 2015 4:40 PM
> **To:** SALTMIRAS, DAVID A [AG/1000]
> **Cc:** roger.o.mcclellan@[redacted]
> **Subject:** RE: BTXC 1003423 - Issue 3 Lead article
>
> The proof was the revised proof from those corrections you sent via CATS only. I trust these were all fine. The 3 additional ones will be included in the issue revises so as to be correct in the final issue. I will double check the 3 corrections are in before proceeding with finalising the issue.
>
> Kind regards,
> Claire

Claire Summerfield
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line: [redacted]
Fax: [redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

From: SALTMIRAS, DAVID A [AG/1000] [mailto:[redacted]@monsanto.com]
Sent: 19 February 2015 18:05
To: Summerfield, Claire
Cc: roger.o.mcclellan@[redacted]
Subject: RE: BTXC 1003423 - Issue 3 Lead article

Clare,

I left you a voice message – perhaps you sent me the wrong "final version"? None of the three items I mentioned in my last email on Saturday, below, were addressed.

Claire,

Sorry I couldn't reply on Friday as I was out of town and couldn't manage to review/respond on my phone. I have three small corrections.

1. Page 4, Table 1, line 16, column 2, change "197" to "300"
2. An essential rewording on page 17, lines 57-68. Please change from "unrelated to treatment" to "inconclusive but unrelated to treatment in the context of similar higher dosed studies"
3. Page 23, line 39. Please change the year (2013c) to (2015c).

Many Thanks,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

RM 000213

From: Summerfield, Claire [mailto:[redacted]@tandf.co.uk]
Sent: Friday, February 13, 2015 9:30 AM
To: SALTMIRAS, DAVID A [AG/1000]
Subject: BTXC: Issue 3 Lead article - final confirmation
Importance: High

Dear Author,
As you know your article is going to be the lead in the next issue of BTXC. I am about to send it off for issue revises but wanted to send you this last version in case there is anything minor to amend prior to final files. If you can e-mail me by REPLY email, I will double check my inbox prior to requesting final files.

Claire Summerfield
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line: [redacted]
Fax: +4[redacted]
[redacted]@tandf.com
www.tandfonline.com

David Saltmiras, Ph.D., D_A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

From: Summerfield, Claire [mailto:[redacted]@tandf.co.uk]
Sent: Thursday, February 19, 2015 4:18 AM
To: SALTMIRAS, DAVID A [AG/1000]
Cc: Summerfield, Claire
Subject: RE: BTXC 1003423 - Issue 3 Lead article
Importance: High

Please find the final proof for final confirmation ☺

Claire Summerfield
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group
an informa business

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

Direct line: [redacted]
Fax: [redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

From: SALTMIRAS, DAVID A [AG/1000] [mailto:[redacted]@monsanto.com]
Sent: 18 February 2015 14:57
To: Summerfield, Claire
Subject: BTXC 1003423 - Issue 3 Lead article

Hi Claire,

I'm just following up to make sure you received my final three comments over the weekend. Do you have an ETA for incorporation of these small changes and online posting?

Thanks,

David Saltmiras, Ph.D., DABT
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
p: [redacted]

The information contained in this email may be subject to the export control laws and regulations of the United States, potentially including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all applicable U.S. export laws and regulations.

The information contained in this email may be subject to the export control laws and regulations of the United States, potentially including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all applicable U.S. export laws and regulations.

This e-mail message may contain privileged and/or confidential information, and is intended to be received only by persons entitled to receive such information. If you have received this e-mail in error, please notify the sender immediately. Please delete it and all attachments from any servers, hard drives or any other media. Other use of this e-mail by you is strictly prohibited.

All e-mails and attachments sent and received are subject to monitoring, reading and archival by Monsanto, including its subsidiaries. The recipient of this e-mail is solely responsible for checking for the presence of "Viruses" or other "Malware". Monsanto, along with its subsidiaries, accepts no liability for any damage caused by any such code transmitted by or accompanying this e-mail or any attachment.

The information contained in this email may be subject to the export control laws and regulations of the United States, potentially including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of

Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all applicable U.S. export laws and regulations.

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Tuesday, February 24, 2015 12:32 PM
To: Roger McClellan
Subject: RE: Greim et al. (2015) & Kier (2015) summaries, abstracts and sound bytes

Dear Roger,

Thank you for this. T&F's policy on publicising individual articles is, in short, that we're very much in favour! I'll discuss with my Marketing team. As for Open Access, we'll see if we can come up with a price for the authors. We're currently working on revising OA policy across all of the former Informa Healthcare journals, including your journal, so there's more to come on this point.

Best wishes,
Charles

From: Roger McClellan [mailto:[redacted]@att.net]
Sent: 19 February 2015 22:43
To: Whalley, Charles
Cc: DAVID A (AG/1000) SALTMIRAS; Mildred; Summerfield, Claire; Roger McClellan; Larry Kier
Subject: Fw: Greim et al. (2015) & Kier (2015) summaries, abstracts and sound bytes

Publicity for Glyphosate Papers

Charles:

I spoke to David Saltmiras today concerning the two Glyphosate papers that will be the lead papers in the next issue of Critical Reviews in Toxicology with regard to F and F putting out any publicity on these two papers. The e-mail below includes complete citations for the papers, abstracts and some information developed by Monsanto Company on the papers.

As you may be aware, these papers have been forwarded to the International Agency for Research on Cancer (IARC) in Lyon, France. IARC at a meeting in early March will be considering the carcinogenic hazard classification of Glyphosate and some other phosphate containing agricultural chemicals. These papers will be a topic of discussion at that meeting. IARC will announce its carcinogenic hazard classification for all the chemical agents reviewed at the meeting, this will probably be done at a Press Conference on March 10. A brief paper describing the results of the meeting will also be published within a few weeks after the meeting concludes. A large Monograph documenting the reviews will be published in early 2016.

As a bottom line the two papers published on line in CRT are likely to attract some attention in the scientific and regulatory community and, possibly, by lay media. I am uncertain as to the policy of T and F on publicizing articles published in Journals such as CRT. If T and F is doing so , these two articles would be excellent candidates.

Please let me know your views on this matter and how you plan to proceed. Let me know if I can be assistance.

On a related matter, I am uncertain as to how T and F would like to handle access to these two papers. I suspect that Monsanto would be interested in purchasing "open access" if that is an option.

Best regards,
Roger

On Thursday, February 19, 2015 1:16 PM, "SALTMIRAS, DAVID A [AG/1000]" <[redacted]@monsanto.com> wrote:

Roger – FYI on press releases.

Greim, H., D. Saltmiras, V. Mostert, and C. Strupp. 2015. Evaluation of carcinogenic potential of the herbicide glyphosate, drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies. *Crit.* Rev. Toxicol. In press

Summary: A new scientific publication examining 14 separate cancer studies in rats and mice conducted over the last several decades concludes that there is no evidence that glyphosate, the active ingredient in Roundup branded herbicides, causes cancer. The article, in Critical Reviews in Toxicology, evaluated the data from these long term studies to determine whether there were any patterns to suggest humans exposed to glyphosate would have any concern about developing cancer. Other scientifically relevant information such as expert regulator evaluations, human dietary exposures and epidemiological studies were also discussed. The clear and consistent view across over 30 years of relevant information continues to support the first expert opinions from the 1980's, that glyphosate does not cause cancer.

Abstract: Glyphosate, an herbicidal derivative of the amino acid glycine, was introduced to agriculture in the 1970s. Glyphosate targets and blocks a plant metabolic pathway not found in animals, the shikimate pathway, required for the synthesis of aromatic amino acids in plants. After almost forty years of commercial use, and multiple regulatory approvals including toxicology evaluations, literature reviews, and numerous human health risk assessments, the clear and consistent conclusions are that glyphosate is of low toxicological concern, and no concerns exist with respect to glyphosate use and cancer in humans. This manuscript discusses the basis for these conclusions. Most toxicological studies informing regulatory evaluations are of commercial interest and are proprietary in nature. Given the widespread attention to this molecule, the authors gained access to carcinogenicity data submitted to regulatory agencies and present overviews of each study, followed by a weight of evidence evaluation of tumor incidence data. Fourteen carcinogenicity studies (nine rat and five mouse) are evaluated for their individual reliability, and select neoplasms are identified for further evaluation across the data base. The original tumor incidence data from study reports are presented in the online data supplement. There was no evidence of a carcinogenic effect related to glyphosate treatment. The lack of a plausible mechanism, along with published epidemiology studies, which fail to demonstrate clear, statistically significant, unbiased and non-confounded associations between glyphosate and cancer of any single etiology, and a compelling weight of evidence, support the conclusion that glyphosate does not present concern with respect to carcinogenic potential in humans.

Sound bytes for social media:

- New scientific review examines over 30 years of data, concludes glyphosate does not cause cancer in animals and poses no cancer risk to humans
- Over 30 years of data: no evidence that glyphosate causes cancer
- New glyphosate scientific review: over 30 years of data, demonstrates it does not cause cancer in animals and poses no cancer risk to humans

Kier, L. D. (2015). Review of Genotoxicity Biomonitoring Studies of Glyphosate-Based Formulations. Crit. Rev. Toxicol., in press

Summary: A recent review examined several studies that allege damage to the DNA in cells collected from people after self-reported exposures to glyphosate-based herbicides. The author concluded that there are no direct risks to human DNA under normal exposure conditions. These findings are consistent with an earlier review of an extensive number of laboratory studies that also demonstrated no direct effect on DNA. Taken together, these results confirm previous conclusions that glyphosate-based herbicides do not damage DNA in humans following real world exposures.

Abstract: Human and environmental genotoxicity biomonitoring studies involving exposure to glyphosate-based formulations (GBFs) were reviewed to complement an earlier review of experimental genotoxicity studies of glyphosate and GBF's (Kier and Kirkland, 2013). The environmental and many of the human biomonitoring studies were not informative because there was either a very low frequency of GBF exposure or exposure to a large number of pesticides. One human biomonitoring study indicated no statistically significant correlation between frequency of GBF exposure reported for the last spraying season and oxidative DNA damage. Negative results for the lymphocyte cytokinesis-block micronucleus (CBMN) endpoint were observed in a second human monitoring study with exposure to several pesticides including GBF. There were three studies of human populations exposed to GBF aerial spraying. One study found increases for the CBMN endpoint but these increases did not correlate with self-reported spray exposure or application rates. A second study found increases for the blood cell comet endpoint at high exposures causing toxicity. However, a follow-up to this study two years after spraying did not indicate chromosomal effects. The results of the biomonitoring studies do not contradict an earlier conclusion derived from experimental genotoxicity studies that typical GBF's do not appear to present significant genotoxic risk under normal conditions of human or environmental exposures.

Sound bytes for social media:

- New analysis of human data: glyphosate-based herbicides do not damage cellular DNA following realistic human exposures
- Human data: glyphosate-based herbicide following realistic human exposure not associated with DNA damage in human cells

David Saltmiras PhD DABT

subsidiaries. The recipient of this e-mail is solely responsible for checking for the presence of "Viruses" or other "Malware".
Monsanto, along with its subsidiaries, accepts no liability for any damage caused by any such code transmitted by or accompanying
this e-mail or any attachment.

The information contained in this email may be subject to the export control laws and regulations of the United States, potentially
including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of
Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all
applicable U.S. export laws and regulations.

Roger McClellan

From: Roger McClellan <[redacted]@att.net>
Sent: Monday, July 27, 2015 2:28 PM
To: Mildred B. Morgan
Subject: Fw: Follow up questions on CRT manuscript "Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies"?

On Monday, July 27, 2015 3:50 PM, "SALTMIRAS, DAVID A [AG/1000]" <[redacted]@monsanto.com> wrote:

Hi Roger,

I hope this note finds you well in the absence of the humidity we face here in St Louis. I have a few follow up inquiries regarding the glyphosate *in vivo* cancer data review manuscript published several months ago in CRT, which I coauthored.

1. I have had a number of requests for this paper. Is there a way to pay to have this changed to "open access"? This wasn't a clear option when submitting, perhaps due to something with the change of publisher from Informa to Taylor & Francis, or more likely, ineptitude on my part. If open access is not an option, how may I order author copies for me to distribute? I can't seem to order these through Scholar One now.

2. In recently experiencing a few computer issues, I can no longer find the original supplementary materials I uploaded with the manuscript submission, which are posted online with the manuscript. Since I do not have a subscription to CRT and thus do not have a user name and password, I do not have access the online data supplement. Is there a way I can either access the online supplement or obtain a copy of the data supplement that I uploaded on Scholar One (it is now electronically archived by T&F)?

3. I am curious as to the volume and quality of correspondence you may have received, particularly in light of the IARC opinion that glyphosate is a "2a" probably human carcinogen.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Leader
Novel Chemistry and Alternatives Process Lead
Toxicology and Nutrition Center
Monsanto
P: [redacted]

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Thursday, March 5, 2015 3:58 AM
To: Roger McClellan; Larry Kier
Cc: Mildred; Herman Bolt; Russell; David Dorman; F. Guengerich; Gunnar Johanson; David Warheit; Shuji Tsuda
Subject: RE: Review Publication Concerns

Dear all,

Thank you for the interesting discussion. To confirm Roger's points below, Taylor & Francis believes rigorous, anonymous peer review to be of the utmost importance, and do everything we can to support our editors and reviewers in maintaining the integrity of this process.

Best wishes,
Charles

Charles Whalley – Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Tel: [redacted]
Web: www.tandfonline.com
E-mail: [redacted]@tandf.co.uk

From: Roger McClellan [mailto:[redacted]@att.net]
Sent: 22 February 2015 19:07
To: Larry Kier
Cc: Whalley, Charles; Roger McClellan; Mildred; Herman Bolt; Russell; David Dorman; F. Guengerich; Gunnar Johanson; David Warheit; Shuji Tsuda
Subject: Re: Review Publication Concerns

Larry:
You make a number of important points in your letter. It is critical that all of us (authors, co-authors, editors, reviewers and publishers) who are involved with the publication of scientific papers adhere to several key principles to protect the confidential nature of the process.

First, it is critical that the peer review process be anonymous with all aspects treated with the highest degree of confidentiality. It is important that the names of reviewers and review comments not be released under any circumstances. In my opinion, a break down in confidentiality would do irreparable harm to the scientific process. In that vein, I have filed document attesting to my position in a court case where lawyers were attempting to gain access to peer review comments related to a publication in another scientific journal.

Second, it is important to recognize the responsibility of the Editor in selecting peer reviewers for any paper. As a matter of routine, I provide authors the opportunity to propose potential reviewers. For me, this is just the starting point. I read the paper and give particular attention to papers that are reviewed to identify potential reviewers. I also use my own knowledge of the subject matter to identify potential reviewers who will focus on the science being reviewed absent any

particular ideological orientation or bias. At the end of the process I recognize my substantial responsibility as an Editor to select a final slate of reviewers. Moreover, when review comments are returned I use them to help guide my decision on accept, revise or reject AND, most importantly, convey the comments to authors in an anonymous manner anticipating that attention to the comments will help the authors revise and further improve the paper thereby enhancing its value to the scientific community and Society at large.

Again, thanks for your comments and for allowing me to elaborate on them. Because of the importance of this exchange I am forwarding a copy of your letter and my response with members of the CRT Editorial Advisory Board and Charles Whalley, Managing Editor, Medicine and Health Science Journals, Taylor and Francis Group, Oxford , England. I am confident that Mr Whalley and Taylor and Francis , as a Publisher, share my views as to the importance of maintaining the confidential nature of the peer review process and that T and F will resist any attempts to breach the process.

With best regards,
Roger

Roger O. McClellan, Editor
Critical Reviews in Toxicology

On Saturday, February 21, 2015 11:51 AM, Larry Kier <[redacted]@g.com> wrote:

Dear Editor McClellan:
Hopefully this communication won't be considered too presumptuous or a waste of your time. It certainly isn't intended as such.
A recent article in Science ("Agricultural researchers rattled by demands for documents", Science, 13 February 2015, p. 699.) indicates an aggressive campaign by a nonprofit organization to discredit academic scientists by demanding documentation of their interactions with industry.
Given the aggressive nature of this campaign I wonder if such organizations might consider a tactic of taking legal actions against authors, sponsors, editors and publishers of publications that represent industrial products as being of low risk where the authors) have industry connections.
While anonymous scientific peer review could represent a reasonable defense against accusations of improper bias I wonder if such legal actions could eventually include demands for legal discovery of the identities of the reviewers and the contents of their reviews. Of course, this is speculation and I am certainly not an attorney but I did want to bring this to your attention.
These concerns prompted me to think about and offer a specific example and generic suggestion. I could have suggested the three first authors (Bolognesi, Paz-y-Mino and Koureas) of the five informative papers on GBF biomonitoring results as potential reviewers of the GBF genotoxicity biomonitoring review manuscript. This simply didn't occur to me at the time and these particular individuals may not have agreed or been appropriately responsive but considering this as a generic approach may be useful.
The concept of considering significant primary publication authors as potential reviewers for a review publication seems to be a worthwhile suggestion. This could address bias issues for reviews, especially if authors of the primary review papers might have different affiliations, interpretations and conclusions than the authors of the review manuscript. The primary paper authors would have a chance to have their viewpoints considered by the review authors and editor as reviewer comments.
Thanks.

Larry Kier

Roger McClellan

From: Ashley Roberts Intertek <[redacted]@intertek.com>
Sent: Wednesday, July 11, 2018 11:35 AM
To: Roger McClellan
Subject: RE: An Independent Review of the Carcinogenic Potential of Glyphosate

Roger,

Sorry I missed your call but I was in the UK on business (addressing questions in the houses of parliament but not related to glyphosate).

I must admit I do not remember making any recommendation to Charles that the title of the journal should have included the term "independent".

Regarding the other matters, maybe we can discuss when we are both in town. Unfortunately, I leave on business again on Saturday for a while and will not be back in the office until July 25th.

Hope to speak to you then.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President – Food & Nutrition Health, Environmental & Regulatory Services (HERS)

Direct [redacted]
Office [redacted]
Skype [redacted]
www.intertek.com

Intertek, 2233 Argentia Rd., Suite 201, Mississauga, ON L5N 2X7

-----Original Message-----
From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: October-16-16 2:28 AM
To: [redacted]@tandf.co.uk
Cc: Ashley Roberts Intertek <[redacted]intertek.com>
Subject: Fw: An Independent Review of the Carcinogenic Potential of Glyphosate

Charles:
You will find this of interest. Can you tell me how many times the Supplement has been accessed and the number of downloads on each article ? Best regards, Roger

Roger McClellan

From:	roger.o.mcclellan <roger.o.mcclellan@[redacted]>
Sent:	Wednesday, July 29, 2015 2:12 AM
To:	Charles Whalley
Cc:	mbmorgan@hargray[redacted] roger.o.mcclellan@[redacted]
Subject:	Fwd: Follow up questions on CRT manuscript "Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies"?

Charles Please help Dr Saltmiras out with the access issue. I would also like your views on giving additional publicity to the several papers on glyphosate published in CRT.
The controversial decision by IARC makes these papers even more important. Roger
Sent via the Samsung Galaxy S® 6, an AT&T 4G LTE smartphone
-------- Original message --------
From: "SALTMIRAS, DAVID A [AG/1000]" <[redacted]@monsanto.com>
Date: 07/27/2015 9:49 PM (GMT+01:00)
To: roger.o.mcclellan@[redacted]
Subject: Follow up questions on CRT manuscript "Evaluation of Carcinogenic Potential of the Herbicide Glyphosate, Drawing on Tumor Incidence Data from Fourteen Chronic/Carcinogenicity Rodent Studies"?

Hi Roger,

I hope this note finds you well in the absence of the humidity we face here in St Louis. I have a few follow up inquiries regarding the glyphosate *in vivo* cancer data review manuscript published several months ago in CRT, which I coauthored.

1. I have had a number of requests for this paper. Is there a way to pay to have this changed to "open access"? This wasn't a clear option when submitting, perhaps due to something with the change of publisher from Informa to Taylor & Francis, or more likely, ineptitude on my part. If open access is not an option, how may I order author copies for me to distribute? I can't seem to order these through Scholar One now.

2. In recently experiencing a few computer issues, I can no longer find the original supplementary materials I uploaded with the manuscript submission, which are posted online with the manuscript. Since I do not have a subscription to CRT and thus do not have a user name and password, I do not have access the online data supplement. Is there a way I can either access the online supplement or obtain a copy of the data supplement that I uploaded on Scholar One (it is now electronically archived by T&F)?

3. I am curious as to the volume and quality of correspondence you may have received, particularly in light of the IARC opinion that glyphosate is a "2a" probably human carcinogen.

Regards,

David Saltmiras, PhD., DABT, RAC
Science Fellow

Novel Chemistry and Microbial Product Lead
Toxicology and Nutrition Center
Monsanto
cell: [redacted]

Roger McClellan

From: Roger McClellan <[redacted]@att.net>
Sent: Wednesday, October 21, 2015 11:13 AM
To: SALTMIRAS, DAVID A [AG/1000]; Elaine Roberts; Charles Whalley
Cc: Mildred B. Morgan; Roger McClellan
Subject: Re: Glyphosate Papers

David:

I am confident Charles Whalley, the Managing Editor for CRT will be able to work out "open access" for the Greim article on Glyphosate. I will notify him of your interest by copy of this e-mail since the fee for "open access" is a business matter and outside of my purview as the Scientific Editor for CRT. As an aside, did you purchase 'open access" for the earlier articles?

If you are interested in Taylor and Francis providing some publicity for these papers I suggest you compile a set of key points for each article and send them to Elaine Roberts at Tand F with a copy to me and Charles Whalley. I would encourage Monsanto to note the availability of the important review papers published in CRT. Alternatively, I am sure Tand F (Elaine Roberts) would be pleased to work with you on a press release coming from T and F. Since, this issue is clearly of international interest I am sure they cab make certain the press release receives international distribution.

Best regards,

Roger

On Wednesday, October 21, 2015 9:41 AM, "SALTMIRAS, DAVID A [AG/1000]" <david.a.saltmiras@monsanto.com> wrote:

Roger,

Thank you for opening this discussion.

I would like to procure open access for the Greim et al. (2015) publication. This was my original intent upon submission of the manuscript. However, in the transition from Informa to Taylor and Francis, I was not able to navigate this request online. Please let me know if and how I can pay for open access to help facilitate broader reader distribution.

Regards,

David Saltmiras, Ph.D., D.A.B.T.
Science Fellow
Novel Chemistry and Microbials Product Lead
Toxicology and Nutrition Center
Monsanto
ph [redacted]

From: Roger McClellan [mailto[redacted]@att.net]
Sent: Wednesday, October 21, 2015 10:28 AM
To: Elaine Roberts; Charles Whalley
Cc: SALTMIRAS, DAVID A [AG/1000]; Mildred B. Morgan; Roger McClellan
Subject: Glyphosate Papers

Elaine and Charles:

During the last several years several review papers on the very important chemical, Glyphosate, the key ingredient in the herbicide, Roundup, were published in Critical Reviews in Toxicology. These papers were considered by the International Agency for Cancer Research review in early 2015 of the carcinogenic hazard of the chemical. Much to the surprise of many scientists IARC classified Glyphosate as a "probable human carcinogen". This decision is still being discussed around the world . For example, the decision will be the focus of a US Senate Hearing this week.

This causes me to raise the question of whether Taylor and Francis might give the Glyphosate papers some publicity. The decision by IARC and the underlying science is going to be a topic of debate for some time.

My principal contact on the Glyphosate papers has been Dr David Saltmiras at Monsanto. If T and F were interested in publicizing the papers I am sure David could provide some key talking points as to the key conclusions in the papers. I have copied him on this memo.

You should be aware that Monsanto has asked an independent organization based in Canada to review the Glyphosate science relevant to evaluating its carcinogenic hazard including the IARC decision. A paper describing the review panel's work is in preparation. I have advised David that I will be pleased to consider that paper for publication in CRT.

Please let me know your views on this matter including if you want some key summary points from the papers.

Best regards,

Roger

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Thursday, October 22, 2015 4:54 AM
To: Roger McClellan
Cc: Mildred B. Morgan; Roberts, Elaine
Subject: RE: Glyphosate Papers

Dear Roger,

I've emailed Dr Saltmiras about Open Access for the Greim et al. article.

Can you please confirm that the relevant articles in *CRT*, besides the recent Greim et al., are the following?

Kimmel et al. in 43(4)
Kier et al. in 43(4)
Kier in 45(3)

Of these, only the later Kier article is not currently Open Access.

Best wishes,
Charles

From: Roger McClellan [mailto:[redacted]@att.net]
Sent: 21 October 2015 16:28
To: Roberts, Elaine; Whalley, Charles
Cc: DAVID A (AG/1000) SALTMIRAS; Mildred B. Morgan; Roger McClellan
Subject: Glyphosate Papers

Elaine and Charles:

During the last several years several review papers on the very important chemical, Glyphosate, the key ingredient in the herbicide, Roundup, were published in Critical Reviews in Toxicology. These papers were considered by the International Agency for Cancer Research review in early 2015 of the carcinogenic hazard of the chemical. Much to the surprise of many scientists IARC classified Glyphosate as a "probable human carcinogen". This decision is still being discussed around the world . For example, the decision will be the focus of a US Senate Hearing this week.

This causes me to raise the question of whether Taylor and Francis might give the Glyphosate papers some publicity. The decision by IARC and the underlying science is going to be a topic of debate for some time.

My principal contact on the Glyphosate papers has been Dr David Saltmiras at Monsanto. If T and F were interested in publicizing the papers I am sure David could provide some key talking points as to the key conclusions in the papers. I have copied him on this memo.

You should be aware that Monsanto has asked an independent organization based in Canada to review the Glyphosate science relevant to evaluating its carcinogenic hazard including the IARC decision. A paper describing the review panel's work is in preparation. I have advised David that I will be pleased to consider that paper for publication in CRT.

Please let me know your views on this matter including if you want some key summary points from the papers.

Best regards,
Roger

Roger McClellan

From: Roger McClellan <[redacted]@att.net>
Sent: Thursday, October 22, 2015 11:08 AM
To: Whalley, Charles
Cc: Mildred B. Morgan; Roberts, Elaine; DAVID A (AG/1000) SALTMIRAS; Roger McClellan
Subject: Re: Glyphosate Papers

Charles
I believe these are the only recent articles in CRT on Glyphosates that are of interest. I am including David Saltmiras on this e=mail so he can weigh in if I have missed any articles. As an aside, the Kimmel etal paper is in Volume 43, issue 2. Thanks for your help on this matter. Roger

On Thursday, October 22, 2015 3:54 AM, "Whalley, Charles" <Charles.Whalley@tandf[redacted]> wrote:

Dear Roger,

I've emailed Dr Saltmiras about Open Access for the Greim et al. article.

Can you please confirm that the relevant articles in *CRT*, besides the recent Greim et al., are the following?

Kimmel et al. in 43(4)
Kier et al. in 43(4)
Kier in 45(3)

Of these, only the later Kier article is not currently Open Access.

Best wishes,
Charles

From: Roger McClellan [mailto:[redacted]@att.net]
Sent: 21 October 2015 16:28
To: Roberts, Elaine; Whalley, Charles
Cc: DAVID A (AG/1000) SALTMIRAS; Mildred B. Morgan; Roger McClellan
Subject: Glyphosate Papers

Elaine and Charles:
During the last several years several review papers on the very important chemical, Glyphosate, the key ingredient in the herbicide, Roundup, were published in Critical Reviews in Toxicology. These papers were considered by the International Agency for Cancer Research review in early 2015 of the carcinogenic hazard of the chemical. Much to the surprise of many scientists IARC classified Glyphosate as a "probable human carcinogen". This decision is still being discussed around the world . For example, the decision will be the focus of a US Senate Hearing this week.
This causes me to raise the question of whether Taylor and Francis might give the Glyphosate papers some publicity. The decision by IARC and the underlying science is going to be a topic of debate for some time.

My principal contact on the Glyphosate papers has been Dr David Saltmiras at Monsanto. If T and F were interested in publicizing the papers I am sure David could provide some key talking points as to the key conclusions in the papers. I have copied him on this memo.

You should be aware that Monsanto has asked an independent organization based in Canada to review the Glyphosate science relevant to evaluating its carcinogenic hazard including the IARC decision. A paper describing the review panel's work is in preparation. I have advised David that I will be pleased to consider that paper for publication in CRT.

Please let me know your views on this matter including if you want some key summary points from the papers.

Best regards,

Roger

Roger McClellan

From: SALTMIRAS, DAVID A [AG/1000] <[redacted]@monsanto.com>
Sent: Tuesday, December 1, 2015 7:17 PM
To: Roger McClellan
Subject: Correction SRA (not ACT) Glyphosate Expert Panel Poster

Roger,

Correction, poster at SRA, not ACT.

David

Sent from my iPhone

Begin forwarded message:

> **From:** "SALTMIRAS, DAVID A [AG/1000]" <[redacted]@monsanto.com>
> **Date:** December 1, 2015 at 6:47:27 PM CST
> **To:** Roger McClellan <[redacted]att.net>
> **Subject: Glyphosate Expert Panel Poster**
>
> Roger,
>
> FYI, attached is the poster that an Expert Panel is presenting at ACT on Monday. Four different sub-committee sections reviewing the corresponding glyphosate IARC review panels are exposure, animal bioassays, epidemiology and genetic toxicology/oxidative stress (mechanisms). This poster summarizes the Expert Panel subcommittee and overall conclusions. Details of the Expert Panel subcommittee reviews are in the process of being consolidated into a multipart manuscript or manuscripts.
>
> Regards,
>
> *David Saltmiras, Ph.D., D. ABT*
> Science Fellow
> Novel Chemistry and Mechanism Product Lead
> Toxicology and Nutrition Center
> Monsanto
> ph [redacted]
>
> <Expert Panel Poster proof.pdf>

Monsanto, along with its subsidiaries, accepts no liability for any damage caused by any such code transmitted by or accompanying
this e-mail or any attachment.

The information contained in this email may be subject to the export control laws and regulations of the United States, potentially
including but not limited to the Export Administration Regulations (EAR) and sanctions regulations issued by the U.S. Department of
Treasury, Office of Foreign Asset Controls (OFAC). As a recipient of this information you are obligated to comply with all
applicable U.S. export laws and regulations.

(9) All communications with Wallace Hayes related to GBFs, AMPA and/or surfactants for GBFs.

Response:

I do not recall any communications with Wallace Hayes related to GBFs, AMPA and/or surfactants for GBFs.

(10) All communications with Ashley Roberts related to GBFs, AMPA, and/or surfactants for GBFs.

Response:

The communications I have had with Ashley Roberts related to GBFs, AMPA, and/or surfactants for GBFs relate to the five papers published in the Special Supplement to Volume 46 (2016).

(11) All medical literature, studies, journal articles, tests and/or scientific analyses authored and/or conducted by You related to the potential adverse human health effects of GBFs, AMPA, and/or surfactants for GBFs. This request includes drafts.

Response:

I have not conducted independent research on the potential adverse health effects of GBFs, AMPA, and/or surfactants for GBFs and, thus, have not published on these topics. I did prepare a "Foreword" to the Special Supplement to Volume 46 of Critical Reviews in Toxicology in my role as Editor-in-Chief of the Journal. The Foreword, noted in the response to Item 5, was intended to provide an editorial context to the five papers published in the Supplement.

(12) All communications with Monsanto related to the documents in Request No. 9.

Response:

I had no communications with Wallace Hayes as I noted in my response to Request No. 9. I did have a communication from David Saltmiras of Monsanto (January 9, 2014) related to preparation of a "glyphosate carcinogenicity review manuscript" for submission to Critical Reviews in Toxicology. This manuscript, authored by Greim, Saltmiras, Mostert and Strupp (2015) was ultimately submitted to Critical Reviews in Toxicology and was noted in my response to Item 5. A second manuscript, authored by Larry Kier (2015), is also noted in the communications with David Saltimiras.

(13) All documents and communications related to Williams, et al., *A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels and Comparison to the IARC Assessment* 46 Crit. Rev. Toxicol. 3-20 (2016), including all documents and communications related to the four contemporaneously published companion papers by the expert panel organized by Intertek, Inc ("Inertek Expert Panel"). This request includes drafts.

Response:

The five papers referred to in Item 13 were previously noted in Item 5 and are listed below:

Williams, Gary, Marilyn Aardena, John Acquavella, Sir Colin Berry, David Brusick and Michele M. Burns (2016). A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels & Comparison to IARC Assessment. Crit. Rev. Toxicol. 46(S1): 3-20.

Solomon, Keith R. (2016). Glyphosate in the General Population and in Applications: A Critical Review of Studies on Exposures. Crit. Rev. Toxicol. 46(S1): 21-27.

Acquavella, John, David Garabrant, Gary Marsh, Tom Sorahan and Douglas L. Weed. (2016). Glyphosate Epidemiology Expert Panel Review: A Weight of Evidence Systematic Review of the Relationship Between Glyphosate Exposure and Non-Hodgkin's Lymphoma or Multiple Myeloma. Crit. Rev. Toxicol. 46(S1): 28-43.

Williams, Gary, Colin Berry, Michele Burns, Joao LauroViana de Camargo and Helmut Greim. (2016). Glyphosate Rodent Carcinogenicity Bioassay Expert Panel Review. Crit. Rev. Toxicol. 46(S1): 44-55.

Brusick, David, Marilyn Aardema, Larry Kier, David Kirkland and Gary Williams. (2016). Genotoxicity Expert Panel Review: Weight of Evidence Evaluation of the Genotoxicity of Glyphosate, Glyphosate-Based Formulations, and Aminomethylphosphonic Acid. Crit. Rev. Toxicol. 46(S1): 56-74.

As noted earlier, these papers were all submitted to Critical Reviews in Toxicology through the Manuscript Central/Scholar One portal. Each of the manuscripts was reviewed by from 5 to 9 reviewers with the review comments provided to the authors to assist in revising the manuscripts. In total, the five manuscripts were reviewed by 27 different reviewers who provided 36 sets of review comments.

The reviewers were all selected and contacted by the Editor-in-Chief via the Manuscript Central/Scholar One System. The identity of the reviewers was not made known to the authors, a "single blind" review system. The review comments are considered to be confidential communications among the authors, the Editor and reviewers as discussed in response to Item 5.

The Editor does not retain an independent file of reviewer comments on individual papers. The author does not retain a file of original manuscripts nor revised manuscripts.

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Tuesday, March 8, 2016 7:23 AM
To: Roger McClellan
Cc: Mildred
Subject: RE: Glyphosate Manuscripts --Potential Supplement

Dear Roger,

Thank you for this, and my apologies for being slow to respond.

First off, the download figures for the glyphosate papers (unless I've missed some) are as follows:

Kimmel et al in 43(2)	847
Kier & Kirkland in 43(4)	2,688
Kier in 45(3)	272
Greim et al in 45(3)	732

These download figures understate their impact, as all have been discussed on news sites and blogs, etc. It is, as you say, a controversial topic of some public interest.

With that in mind, I'm grateful for your usual diligence in pursuing a thorough Declaration of Interest.

As for your plans on how to publish this series of papers should they be accepted, I agree that combining the introduction and summary makes sense, with the others split out into separate papers. As ever, I'm grateful to be kept informed and happy to be guided by your judgement! As for the question of a supplement, I can take this up with Dr Roberts as appropriate.

I'll try giving you a ring later today, as I want to catch up about SoT. If you see this email before I get hold of you, do give me a tinkle, as we say over here.

All best wishes,
Charles

From: Roger McClellan [mailto[redacted]@att.net]
Sent: 26 February 2016 22:05
To: Whalley, Charles
Cc: Mildred; Roger McClellan
Subject: Fw: Glyphosate Manuscripts --Potential Supplement

Charles:
I have been in discussions with multiple parties over the past year on publishing one or a series of review papers on the evaluation of the human carcinogenic potential of "glyphosate". Several excellent reviews on the toxicity of this compound have been published previously in CRT. Can you tell me how many times those papers have been accessed?
As you know this compound is a leading agro-chemical. Moreover, the IARC has recently evaluated the compound and made a determination as to its carcinogenicity that is very controversial. That lead to the work covered in these six papers. As an aside , much of my discussions have relates to whether this might be published as one or multiple papers.
At this stage, I am leaning to recommending that for the initial review what has been billed as an introduction and a second paper billed as a summary should be rolled together as a single paper. That single paper and the

other six papers would be sent for external review with the reviewers of each paper being given access to all the papers.
I have already alerted the coordinating author, Ashley Roberts, to the need for more robust Declarations of Interest. The topic is controversial and the papers when published are likely to be controversial.
At his stage I would envision the papers being published as a single issue Supplement. At he appropriate juncture it will be useful for you to make contact with Dr Roberts to negotiate terms and conditions for publication of the Supplement, assuming it moves through the rigorous review process.
The purpose of this e-mail is to alert you to this large project and ask if you have any special advice to offer at this time.
Best regards,
Roger

--- On Fri, 2/26/16, Ashley Roberts Intertek <[redacted]@intertek.com> wrote:

> From: Ashley Roberts Intertek <[redacted]@intertek.com>
> Subject: Glyphosate Manuscripts
> To: "Roger.o.mcclellan@[redacted]" <Roger.o.mcclellan@[redacted]>
> Date: Friday, February 26, 2016, 11:41 AM
>
>
>
>
>
>
>
>
>
> Dear Dr. McClellan,
>
> In follow-up to our
> discussions this morning, please find attached the
> individual manuscripts covering the Expert panels responses
> to the IARC Monograph. I have not included all of the
> figures and supplemental information at this stage
> for risk of clogging up your email.
>
> If you have any
> comments/questions, please do not hesitate to contact
> me.
>
> Looking forward to hearing
> from you
>
> Many Best Wishes
>
> Ashley
>
> Ashley Roberts,
> Ph.D.
>
> Senior Vice President
>

> Food & Nutrition Group
>
> Intertek Scientific
> & Regulatory Consultancy
>
> Tel: +1
> [redacted]
>
>
> Fax: +1 [redacted]
>
> E-mail: [redacted]@intertek.com
>
> 2233 Argentia Road,
> Suite 201
>
> Mississauga, Ontario Canada L5N 2X7
>
>
>
>
> Valued Quality. Delivered.
>
> CONFIDENTIALITY NOTICE
> This email may contain confidential or privileged
> information, if you are not the intended recipient, or the
> person responsible for delivering the message to the
> intended recipient then please notify us by return email
> immediately. Should you have received
> this email in error then you should not copy this for any
> purpose nor disclose its contents to any other person.
> http://www.intertek.com
>
>
>

Roger McClellan

From: Ashley Roberts Intertek [redacted]@intertek.com>
Sent: Friday, March 11, 2016 10:36 AM
To: Roger.o.mcclellan@[redacted]
Subject: RE: Glyphosate Manuscripts

Dear Roger,

Nice to talk to you the other day about our current very interesting scientific climate!!! I have put together a declaration of interest preamble below (in red,) which would cover all of the authors of the introductory manuscript. This would obviously be revised for the individual groups publications. Please could you let me know if this is in line with your thinking and the Journals requirements?

The authors of the manuscript is as shown on the cover page. The authors had sole responsibility for the writing and the content of the article, and the interpretations and opinions expressed in the paper are those of the authors.

Gary Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company, while Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed declare no potential conflicts of interest.

The Expert Panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists acted as consultants for Intertek. Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food and pharmaceutical industries. While Intertek Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto company, previous employees of Cantox had worked in this capacity.

Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither Monsanto nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

If you think some revisions/amendments are required, I would be most happy to receive your suggestions.

I will be sending you the introductory chapter on Monday as I have just been told that one of the authors is going to work on this over the weekend. I gave him over a week to do this and gave him a deadline of today but what can you do!!!

All the Best

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [redacted]
Fax: +1 [redacted]
E-mail: [redacted]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

Roger McClellan

From: Ashley Roberts Intertek <[redacted]@intertek.com>
Sent: Monday, March 14, 2016 10:26 AM
To: Roger.o.mcclellan@[redacted]
Subject: FW: Glyphosate Manuscripts
Attachments: Summary March 10 FINAL.docx

Dear Roger,

In follow-up to our chat on Friday, please find attached the final introductory manuscript to go alongside the 4 main papers sent previously.

Also I amended the declaration of interest slightly as per your recommendations. Please see below. I hope this is more along the lines you were looking for?

Gary Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company. Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed have not previously been employed the Monsanto Company or previously been involved in any activity involving glyphosate and as such declare no potential conflicts of interest. Furthermore, none of the afore mentioned authors have been involved in any litigation procedures involving glyphosate.

The Expert Panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists acted as consultants for Intertek. Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food and pharmaceutical industries. While Intertek Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto company, previous employees of Cantox had worked in this capacity.

Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

I am out of the office today but would be happy to call you if you think necessary. Just send me a quick email and I will respond.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [redacted]
Fax: +1 [redacted]
E-mail: [redacted]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Ashley Roberts Intertek
Sent: March-11-16 12:36 PM
To: 'Roger.o.mcclellan@[redacted]
Subject: RE: Glyphosate Manuscripts

Dear Roger,

Nice to talk to you the other day about our current very interesting scientific climate!!! I have put together a declaration of interest preamble below (in red,) which would cover all of the authors of the introductory manuscript. This would obviously be revised for the individual groups publications. Please could you let me know if this is in line with your thinking and the Journals requirements?

The authors of the manuscript is as shown on the cover page. The authors had sole responsibility for the writing and the content of the article, and the interpretations and opinions expressed in the paper are those of the authors.

Gary Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company, while Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed declare no potential conflicts of interest.

The Expert Panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists acted as consultants for Intertek. Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food and pharmaceutical industries. While Intertek Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto company, previous employees of Cantox had worked in this capacity.

Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither Monsanto nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

If you think some revisions/amendments are required, I would be most happy to receive your suggestions.

I will be sending you the introductory chapter on Monday as I have just been told that one of the authors is going to work on this over the weekend. I gave him over a week to do this and gave him a deadline of today but what can you do!!!

All the Best

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [redacted]
Fax: +1 [redacted]
E-mail: [redacted]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Ashley Roberts Intertek
Sent: February-26-16 5:19 PM
To: 'Roger.o.mcclellan@[redacted]
Subject: RE: Glyphosate Manuscripts

Dear Dr. McClellan,

I received your voice mail message. Thank you.

Unfortunately, I will not be attending the SOT this year. I have young staff members hungry to learn and grow within the industry, so I feel that it much more worthwhile for them to attend than myself. We have 9 people going from our group and some will be presenting posters etc.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [redacted]
Fax: +1 [redacted]
E-mail: [redacted]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Ashley Roberts Intertek
Sent: February-26-16 1:41 PM
To: 'Roger.o.mcclellan@[redacted]
Subject: Glyphosate Manuscripts

Dear Dr. McClellan,

In follow-up to our discussions this morning, please find attached the individual manuscripts covering the Expert panels responses to the IARC Monograph. I have not included all of the figures and supplemental information at this stage for risk of clogging up your email.

If you have any comments/questions, please do not hesitate to contact me.

Looking forward to hearing from you

Many Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [redacted]
Fax: +1 [redacted]
E-mail: [redacted]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

Valued Quality. Delivered.

http://www.intertek.com

Roger McClellan

From: Roger McClellan <[redacted]@att.net>
Sent: Friday, March 20, 2015 2:17 PM
To: Mildred Morgan; Susan Felter
Cc: Roger McClellan
Subject: Re: Roger O. McClellan's Note on CRT Journal

Susan:
Thanks for your quick response. The exact position of Taylor and Francis with regard to the 'Open Access" policy is still evolving. I will be meeting with the Taylor and Francis Managing Editor , Charles Whalley, who I report to at the SOT meeting and discussing the details of the "open access" policy with him. After that meeting on Saturday evening I will be able to give you an up date on the "open access" policy for CRT. If you should stop by the Taylor and Francis / CRC Press booth at SOT and see Mr Whaley please convey to him your expectations on "open access". I hope to see you in San Diego
Best regards,
Roger

On Friday, March 20, 2015 10:39 AM, Mildred Morgan <[redacted]@hargray.com> wrote:

Susan would like for you to respond to her.

From: Felter, Susan [mailto[redacted]@pg.com]
Sent: Friday, March 20, 2015 11:55 AM
To: Mildred Morgan
Subject: RE: Roger O. McClellan's Note on CRT Journal

Hi Mildred,
Thanks for the email below. I am interested in the details of the open access policies for Taylor and Francis. I just hit "reply" to this email and then realized it was going to you and not Roger. Please let me know if I should contact him directly, or if you can send this. Thanks!

Best regards,
Susan

From: Mildred Morgan [mailto[redacted]@hargray.com]
Sent: Friday, March 20, 2015 11:12 AM
To: ken.unice@cardno[redacted]; lmsweeney@[redacted]Antonis Christou; 'James Bus'; 'Robertson, Larry'; FGrimm@cvm.tamu[redacted] Felter, Susan; edonovan@cardno[redacted] Annahita.ghassemi@churchdwight[redacted] Lewis, R Jeffrey; sherilyn.gross@cardno[redacted] C.R.Tyler@exeter.ac[redacted] 'Brooke Tvermoes'; brent.finley@cardno[redacted] JL Mauderly
Subject: Roger O. McClellan's Note on CRT Journal

Critical Reviews in Toxicology

I am writing to you as a recent author of a paper published in Critical Reviews in Toxicology (CRT) and/or a reviewer of a paper published in CRT. I anticipate seeing many of you next week at the Society of Toxicology (SOT) meeting in San Diego. Please seek me out if you wish to discuss any potential review manuscript submissions with me.

In preparation for a meeting of the Editorial Advisory Board for CRT at next week's SOT Meeting, I have reviewed the most recent Publisher's Report. The Report confirms that CRT continues to be ranked in the top 10% of Journals published in the Toxicology category. In addition, the Report confirms our tradition of prompt and rigorous review of manuscripts, received from around the world, on contemporary topics in toxicology and risk/safety assessment.

It was a special pleasure to note the download statistics for recently published papers on a diverse range of agents such as chrysotile asbestos, atrazine, glyphosate, bisphenol A, phthalates, aflatoxins and nanomaterials. Other papers focused on new methods for evaluating the risk/safety of chemicals and other agents and improved human risk assessment approaches. Other papers that were frequently downloaded were concerned with over-arching issues such as exposure(dose)-response extrapolations and weight of evidence approaches to evaluating diverse data sets. These papers are already being widely cited in the global peer-reviewed literature ensuring that the Citation Impact Factor for CRT will remain high in the future.

Most importantly, Critical Reviews in Toxicology is now being managed as one of the Journals within Taylor and Francis' portfolio of more than 2,200 Journals. The move of CRT to this portfolio will result in some changes to the Journal's open access policy. I am confident that these new open access policies will be well received by authors and their founders. Please let me know if you are interested in the details of these open access policies.

Best regards to all and best wishes for safe travel if you are heading to San Diego.

Roger

Roger O. McClellan
Editor, Critical Review in Toxicology
[redacted]
Albuquerque, NM 87111
Tel: [redacted]
E-mail: roger.o.mcclellan@[redacted]

Roger McClellan

From:	Roger McClellan <roger.o.mcclellan@[redacted]>
Sent:	Friday, March 20, 2015 11:08 AM
To:	Samuel M. Cohen; Russell Cattley; David Dorman; Gunnar Johanson; F. Guengerich; David Warheit; Herman Bolt; Shuji Tsuda; Mildred B. Morgan
Cc:	Roger McClellan; Charles Whalley; Claire Summerfield; mbmorgan@hargray[redacted]
Subject:	Publisher's Report - March 2015

To all:

Attached is a copy of the Publisher's Report (March 2015) that I just received from Charles Whalley, Managing Editor, Taylor and Francis Group. Charles is now my primary Editorial contact at T and F. On a very regular basis basis, I have continuing contact with our superb Production Editor, Claire Summerfield. I am looking forward to meeting Charles, face to face, over dinner in San Diego on Saturday evening. I am personally very excited about Critical Reviews in Toxicology moving under the main Taylor and Francis umbrella effective January 1, 2015 to the Taylor and Francis portfolio of some 2,200 journals. They are very experienced in the world of scientific publishing.

I urge you to treat this as a confidential report and not share it with others. We will discuss the contents at our breakfast meeting on Tuesday morning at the Marriott Hotel in San Diego. I believe you will agree with me that the report is very comprehensive and professional in tone. It contains some very positive information about Critical Reviews in Toxicology.. I have conveyed that view in a message sent out this morning to over 300 individuals (authors who have previously published in the Journal and past reviewers).

One of the topics I will be discussing with Charles is the Journals "open Access" policy. As you know , I was concerned that a change in the journals "open access" policy imposed by the former Informa Health Care management would have potential negative impact on the Journal's manuscript flow. Indeed that has happened. One of the primary topics I will be discussing with Charles is the "open access" policy under T and F management. A glimpse in to this policy is apparent on page 7 of the Publisher's Report. I am optimistic that the "open policy" under T and F management will be more favorably received by authors and sponsors than the previous policy. I will likely be sending a memo to authors and reviewers on this new policy after I meet with Charles. My e-mail earlier this morning has already stimulated queries back to me on the new "open access" policy.

The importance of "open access" is apparent when one notes that three of the articles in Issue 44, Supplement 3 have been down loaded more than 1,000 time. As an aside, Sam is a co-author on those articles and was very helpful in facilitating their publication in CRT. Thanks, Sam!

I am flying from Albuquerque to San Diego on Saturday morning. I will be staying at the Marriott, the SOT headquarters hotel. As soon as I can identify a location for our Tuesday morning breakfast meeting I will let you know.

Thanks again for all your help with Critical Reviews in Toxicology.

Best regards,

Roger

Roger McClellan

From:	Mildred Morgan <mbmorgan@[redacted]>
Sent:	Tuesday, August 30, 2016 3:40 PM
To:	bolt@ifado[redacted] rcc0022@auburn[redacted] scohen@unmc[redacted] Vicki Dellarco; david_dorman@ncsu[redacted] f.guengerich@vanderbilt[redacted] 'Gunnar Johanson'; Shuji Tsuda; David Warheit
Cc:	Roger McClellan
Subject:	Editorial Draft for Glyphosates Papers
Attachments:	Special Supplemental Issue on Glyphosates Document for CRT.docx

Dear Board Members:

Attached is a draft editorial for the Special Supplemental Issue on "An Independent Review of the Carcinogenic Potential of Glyphosates." Dr. McClellan would appreciate your reviewing this draft and provide him any comments, additions, changes, etc.

Thanks.

Mildred B. Morgan
Assistant to Dr. Roger O. McClellan
Tel: [redacted]
Fax: [redacted]

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Tuesday, April 5, 2016 8:53 AM
To: Roger McClellan ([redacted]@att.net)
Subject: Glyphosate papers

Dear Roger,

I hope this finds you very well.

I spoke to Ashley Roberts at Intertek today about the options for publishing a supplement in *CRT*. It was my understanding that we were waiting for some changes to the Declaration of Interest statements on the glyphosate manuscripts before they were submitted to ScholarOne, but it seems things have progressed beyond that. Dr Roberts thought he was waiting for contact from me.

We can negotiate a supplement whilst the manuscripts are in review, on the assumption (as I made clear to Dr Roberts) that any discussion is conditional on acceptance. With this in mind, is there anything else waiting for Dr Roberts to address, or should we advise him to submit his group's manuscripts into ScholarOne?

Best wishes as ever,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]
Sent: Tuesday, April 5, 2016 2:36 PM
To: Ashley Roberts Intertek
Cc: Charles.Whalley@[redacted] roger.o.mcclellan@[redacted] Mildred
Subject: Re: FW: Glyphosate Manuscripts

Ashley:

I understand that you and Charles Whalley have initiated discussions with regard to publishing the glyphosate manuscripts as a Supplement to Critical Reviews in Toxicology conditioned on the papers all being accepted for publication in CRT after external scientific review. Both Charles and I agree that we should proceed with the scientific review of the papers in parallel with you and Charles working out the details including costs associated with publication of the Supplement.

Hence, I urge you to enter the papers in the Scholar One system. For each paper please enter the names of 10 potential reviewers. In addition, please send me an e-mail listing the suggested reviewers for each paper including their *name, affiliation, e-mail address, area of expertise and whether or not their work is cited in the particular review paper.* It is Ok to recommend a specific reviewer to review more than one paper. As always, I retain the right as Editor to select the reviewers for any particular paper.

In addition to submitting the papers via Scholar One please send me an e-mail with each of the papers as an attachment.

Each paper should include a comprehensice Declaration of Interest as we have discussed.

I am looking forward to receiving the papers via Scholar One and as attachments to your e-mail to me.

Best regards,

Roger

On Mon, 3/14/16, Ashley Roberts Intertek <[redacted]@intertek.com> wrote:

Subject: FW: Glyphosate Manuscripts
To: "Roger.o.mcclellan@[redacted] <Roger.o.mcclellan@[redacted]>
Date: Monday, March 14, 2016, 9:25 AM

Dear Roger,

In follow-up to our chat on Friday,
please find attached the final introductory manuscript to go alongside the 4 main papers sent previously.

Also I amended the declaration of
interest slightly as per your recommendations. Please see below. I hope this is more along the lines you were looking for?

Gary Williams, Sir Colin Berry, David Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company. Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed have not previously been employed the Monsanto Company or previously been involved in any activity involving glyphosate and as such declare no potential conflicts of interest. Furthermore, none of the afore mentioned authors have been involved in any litigation procedures involving glyphosate.

The Expert Panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists acted as consultants for Intertek. Intertek (previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food and pharmaceutical industries. While Intertek Scientific & Regulatory Consultancy has not previously worked on glyphosate related matters for the Monsanto company, previous employees of Cantox had worked in this capacity.

Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

I am out of the office today but would be happy to call you if you think necessary. Just send me a quick email and I will respond.

Best Wishes

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1 [redacted]

Fax: +1 [redacted]

E-mail: [redacted]@intertek.com

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

From: Ashley
Roberts Intertek

Sent: March-11-16 12:36 PM

To: 'Roger.o.mcclellan@a[redacted]

Subject: RE: Glyphosate Manuscripts

Dear Roger,

Nice to talk to you the other day
about our current very interesting scientific climate!!! I have put together a declaration of interest preamble below (in red,) which would cover all of the authors of the introductory
manuscript. This would obviously be revised for the individual groups publications. Please could you let me know if this is in line with your thinking and the Journals requirements?

The authors of the manuscript is as shown on the cover page. The authors had sole responsibility for the writing and the content of the article, and the interpretations and opinions expressed in the paper are those
of the authors.

Gary Williams, Sir Colin Berry, David
Brusick, João Lauro Viana de Camargo, Helmut Greim, David Kirkland, Keith Solomon and Tom Sorahan have previously served as independent consultants for the Monsanto Company or
the European Glyphosate Task Force. John Acquavella and Larry Kier were previously employees of the Monsanto Company, while Marilyn Aardema, Michele Burns, David Garabrant, Gary Marsh, Ashley Roberts and Douglas Weed declare no potential conflicts of interest.

The Expert Panel Members recruitment and evaluation of the data was organized and conducted by Intertek Scientific & Regulatory Consultancy (Intertek). The Expert Panelists acted as consultants for Intertek. Intertek
(previously Cantox) is a consultancy firm that provides scientific and regulatory advice, as well as safety and efficacy evaluations for the chemical, food and pharmaceutical industries. While Intertek Scientific & Regulatory Consultancy has not previously
worked on glyphosate related matters for the Monsanto company, previous employees of Cantox had worked in this capacity.

Funding for this evaluation was provided by the Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient.
Neither Monsanto nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal.

If you think some revisions/amendments are required, I would be most happy to receive your suggestions.
I will be sending you the introductory chapter on Monday as I have just been told that one of the authors is going to work on this over the weekend. I gave him over a week to do this and gave him a deadline of today but what can you do!!!
All the
Best
Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1 [redacted]

Fax: +1[redacted]

E-mail: [redacted]@intertek.com

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

From: Ashley Roberts Intertek

Sent: February-26-16 5:19 PM

To: 'Roger.o.mcclellan@[redacted]'

Subject: RE: Glyphosate Manuscripts

Dear Dr. McClellan,

I received your voice mail
message. Thank you.

Unfortunately, I will not be
attending the SOT this year. I have young staff members hungry to learn and grow within the industry, so I feel that it much more worthwhile for them to attend than myself. We have
9 people going from our group and some will be presenting posters etc.

Best Wishes

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1
[redacted]

Fax: +1[redacted]

E-mail: [redacted]@intertek.com

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

From: Ashley
Roberts Intertek

Sent: February-26-16 1:41 PM

To: 'Roger.o.mcclellan@[redacted]'

Subject: Glyphosate Manuscripts

Dear Dr. McClellan,

In follow-up to our
discussions this morning, please find attached the individual manuscripts covering the Expert panels responses to the IARC Monograph. I have not included all of the figures and supplemental information at this stage
for risk of clogging up your email.

If you have any
comments/questions, please do not hesitate to contact me.

Looking forward to hearing
from you

Many Best Wishes

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1 [redacted]

Fax: +1 [redacted]

E-mail: [redacted]@intertek.com

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

Valued Quality. Delivered.

this email in error then you should not copy this for any purpose nor disclose its contents to any other person.
http://www.intertek.com

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Friday, April 15, 2016 5:25 AM
To: Roger McClellan
Cc: mbmorgan@[redacted]
Subject: RE: Any legal requests to T and F or related companies

Dear Roger,

Further to the below, I can confirm that our current understanding is that Taylor & Francis has not disclosed any reviewer comments on this article. We're still investigating with the various parties who could've had access to the reviewer comments. I'll update you on our findings.

As for your broader question, for now I can only refer you to mine and Didi's previous emails to you on T&F's policy on this issue. I'll get back to you on this soon. I'm still seeking further legal guidance.

In return, could you let me know the nature of the litigation in which these reviewer comments have been raised, and your understanding of how this relates to the journal? I'd be grateful for whatever background you can give here.

Best wishes,
Charles

-----Original Message-----
From: Whalley, Charles
Sent: 15 April 2016 08:14
To: 'Roger McClellan'
Cc: mbmorgan@[redacted]
Subject: RE: Any legal requests to T and F or related companies

Dear Roger,

Thanks for passing this on. I'm going to need to consult internally on this, I'm afraid. I'll get back to you as soon as I can.

I'm working from home today, so won't be reachable via telephone, but I'm back at my desk next week.

All best wishes as ever,
Charles

-----Original Message-----
From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]]
Sent: 14 April 2016 22:48
To: Whalley, Charles
Cc: roger.o.mcclellan@[redacted] mbmorgan@[redacted]
Subject: Any legal requests to T and F or related companies

Charles:
I was very disturbed to recently learn that reference was made in US Federal Court to "confidential review comments" for a paper Paustenbach etal, A review of the health hazards of cobalt, CRT, 43; 316-362 (2013). Does T and F have a record of releasing "confidential review comments" for this or any other paper published by Dr Dennis Paustenbach

and/or his associates in CRT? It is possible that the lawyers might have attempted to use a subpoena or merely made contact by telephone or e-mail. It is possible the lawyers used some means other than contacting T and F to obtain the "confidential review comments", possibly contacting a reviewer. This case is remarkable since the lawyers apparently had copies of multiple review comments on the paper.

I am hoping that this does not occur again in the future. Can you provide me assurance that in the event T and F receives a legal or any inquiry for release of "confidential review comments" that T and F will immediately contact me before taking any action with regard to release of the "confidential review comments"?

As you know, I have strongly held views that all transactions between authors, reviewers and the Editor concerning a paper are confidential and private. Moreover, if this curtain of confidentiality is removed it can cause irreparable harm to the review process and , in doing so, to the author(s), Editor, reviewers and publisher. Hence, I will personally strongly object to release of any "confidential review comments" even if served a legal subpoena. I would hope T and F and its affiliates would hold similar views and support me and my position as an Editor under contract to T and F.

I welcome your response to my specific question on release of comments on this specific paper. Moreover, I welcome your comments on the larger issue.

Best regards,

Roger

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Friday, April 15, 2016 12:39 PM
To: Charles.Whalley@tandf[redacted]
Cc: roger.o.mcclellan@[redacted] mbmorgan@hargray[redacted] Didi.Peng@informa[redacted]
Subject: Fw: RE: Any legal requests to T and F or related companies
Attachments: jj trial scan 2.pdf

Charles:

Thanks for the quick response on this matter. I left a telephone message for you before I read your e-mail indicating you were working from your home today. Your message is re-assuring.

The official tile of the legal case is shown on the top of the transcript which I have attached. You can obtain additional details by goggling on key words such as hip implants, Depuy, Johnson and Johnson, etc. It is my understanding that more than 6000 cases have been filed alleging failure of the implant and/or harm to health from these particular "metal on metal" implants which have now been removed from the market.

In this specific case the court consolidated several cases. It is my understanding the Jury awarded the plaintiffs represented by Attorney Mark Lanier about $500 million. Other cases are in the "pipeline. It is my understanding that Johnson and Johnson has set aside about $2.5 billion in US dollars to cover potential losses related to these cases.

What I know about the case is derived from the transcript I have attached. The paper by Paustenbach etal (2013) was apparently introduced as evidence by the Defendants in the case just tried. The paper concludes that systemic toxicity from Cobalt reaching the blood occurs only when very high blood levels of Cobalt are encountered. As I understand it, the Plaintiff's counsel apparently tried to trash the Defendants expert, Dr Boyer, by indicating he had not considered the negative review comments (reviewer 3) on the paper thereby under-mining the credibility of Dr Boyer and the paper. Dr Boyer was obviously surprised because he had never seen the reviewers comments. The key question is how did the plaintiffs lawyer, Mark Lanier, gain access to the review comments?

As an aside, I have reviewed the process and specifics of how the paper was submitted, reviewed and accepted. I feel confident that the paper was rigorously reviewed and the authors appropriately responded to review comments which helped improve the paper resulting in its acceptance. Indeed, one could argue the Journal comes out OK in the exchange. .

My concern relative to the Journal is whether a breach occurred in the review / production process that allowed release of "confidential review comments". This could cause authors and reviewers to lose confidence in the Editor, the journal and publisher.

I appreciate what you have done to date. Moreover, I will appreciate further efforts by you, Didi and Taylor and Francis to identify any potential breaches in the confidentiality of the review and production system.

Best regards,
Roger

> From: Whalley, Charles <Charles.Whalley@tandf[redacted]>
> Subject: RE: Any legal requests to T and F or related companies
> To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
> Cc: "mbmorgan@hargray[redacted] <mbmorgan@hargray[redacted]
> Date: Friday, April 15, 2016, 4:24 AM
> Dear Roger,
>
> Further to the below, I can
> confirm that our current understanding is that Taylor & Francis has
> not disclosed any reviewer comments on this article. We're still
> investigating with the various parties who could've had access to the
> reviewer comments. I'll update you on our findings.

>
> As for your broader question,
> for now I can only refer you to mine and Didi's previous emails to you
> on T&F's policy on this issue.
> I'll get back to you on this soon. I'm still seeking further legal
> guidance.
>
> In
> return, could you let me know the nature of the litigation in which
> these reviewer comments have been raised, and your understanding of
> how this relates to the journal? I'd be grateful for whatever
> background you can give here.
>
> Best wishes,
> Charles
>
> -----Original Message-----
> From: Whalley, Charles
> Sent:
> 15 April 2016 08:14
> To: 'Roger
> McClellan'
> Cc: mbmorgan@hargray[redacted]
> Subject: RE: Any legal requests to T and F or related companies
>
> Dear
> Roger,
>
> Thanks for passing
> this on. I'm going to need to consult internally on this, I'm afraid.
> I'll get back to you as soon as I can.
>
> I'm working from
> home today, so won't be reachable via telephone, but I'm back at my
> desk next week.
>
> All best wishes as ever,
> Charles
>
> -----Original Message-----
> From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]
>
> Sent: 14 April 2016 22:48
> To: Whalley, Charles
> Cc: roger.o.mcclellan@[redacted];
> mbmorgan@hargray[redacted]
> Subject: Any legal requests to T and F or related companies
>
> Charles:
> I was
> very disturbed to recently learn that reference was made in US Federal
> Court to "confidential review comments"

> for a paper Paustenbach etal, A review of the health hazards of
> cobalt, CRT, 43; 316-362 (2013). Does T and F have a record of
> releasing "confidential review comments"
> for this or any other paper published by Dr Dennis Paustenbach and/or
> his associates in CRT? It is possible that the lawyers might have
> attempted to use a subpoena or merely made contact by telephone or
> e-mail. It is possible the lawyers used some means other than
> contacting T and F to obtain the "confidential review comments",
> possibly contacting a reviewer. This case is remarkable since the
> lawyers apparently had copies of multiple review comments on the
> paper.
> I am hoping
> that this does not occur again in the future. Can you provide me
> assurance that in the event T and F receives a legal or any inquiry
> for release of "confidential review comments" that T and F will
> immediately contact me before taking any action with regard to release
> of the "confidential review comments"?
>
> As you know, I have strongly held views that all transactions
> between authors, reviewers and the Editor concerning a paper are
> confidential and private. Moreover, if this curtain of confidentiality
> is removed it can cause irreparable harm to the review process and ,
> in doing so, to the author(s), Editor, reviewers and publisher. Hence,
> I will personally strongly object to release of any "confidential
> review comments" even if served a legal subpoena. I would hope T and F
> and its affiliates would hold similar views and support me and my
> position as an Editor under contract to T and F.
> I welcome your response to my
> specific question on release of comments on this specific paper.
> Moreover, I welcome your comments on the larger issue.
> Best regards,
> Roger
>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Friday, April 15, 2016 12:39 PM
To: Charles.Whalley@tandf[redacted]
Cc: roger.o.mcclellan@[redacted] mbmorgan@hargray[redacted] Didi.Peng@informa[redacted]
Subject: Fw: RE: Any legal requests to T and F or related companies
Attachments: jj trial scan 2.pdf

Charles:

Thanks for the quick response on this matter. I left a telephone message for you before I read your e-mail indicating you were working from your home today. Your message is re-assuring.

The official tile of the legal case is shown on the top of the transcript which I have attached. You can obtain additional details by goggling on key words such as hip implants, Depuy, Johnson and Johnson, etc. It is my understanding that more than 6000 cases have been filed alleging failure of the implant and/or harm to health from these particular "metal on metal" implants which have now been removed from the market.

In this specific case the court consolidated several cases. It is my understanding the Jury awarded the plaintiffs represented by Attorney Mark Lanier about $500 million. Other cases are in the "pipeline. It is my understanding that Johnson and Johnson has set aside about $2.5 billion in US dollars to cover potential losses related to these cases.

What I know about the case is derived from the transcript I have attached. The paper by Paustenbach etal (2013) was apparently introduced as evidence by the Defendants in the case just tried. The paper concludes that systemic toxicity from Cobalt reaching the blood occurs only when very high blood levels of Cobalt are encountered. As I understand it, the Plaintiff's counsel apparently tried to trash the Defendants expert, Dr Boyer, by indicating he had not considered the negative review comments (reviewer 3) on the paper thereby under-mining the credibility of Dr Boyer and the paper. Dr Boyer was obviously surprised because he had never seen the reviewers comments. The key question is how did the plaintiffs lawyer, Mark Lanier, gain access to the review comments?

As an aside, I have reviewed the process and specifics of how the paper was submitted, reviewed and accepted. I feel confident that the paper was rigorously reviewed and the authors appropriately responded to review comments which helped improve the paper resulting in its acceptance. Indeed, one could argue the Journal comes out OK in the exchange. .

My concern relative to the Journal is whether a breach occurred in the review / production process that allowed release of "confidential review comments". This could cause authors and reviewers to lose confidence in the Editor, the journal and publisher.

I appreciate what you have done to date. Moreover, I will appreciate further efforts by you, Didi and Taylor and Francis to identify any potential breaches in the confidentiality of the review and production system.

Best regards,
Roger

> From: Whalley, Charles <Charles.Whalley@tandf[redacted]
> Subject: RE: Any legal requests to T and F or related companies
> To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
> Cc: "mbmorgan@hargray[redacted]" <mbmorgan@hargray[redacted]
> Date: Friday, April 15, 2016, 4:24 AM
> Dear Roger,
>
> Further to the below, I can
> confirm that our current understanding is that Taylor & Francis has
> not disclosed any reviewer comments on this article. We're still
> investigating with the various parties who could've had access to the
> reviewer comments. I'll update you on our findings.

>
> As for your broader question,
> for now I can only refer you to mine and Didi's previous emails to you
> on T&F's policy on this issue.
> I'll get back to you on this soon. I'm still seeking further legal
> guidance.
>
> In
> return, could you let me know the nature of the litigation in which
> these reviewer comments have been raised, and your understanding of
> how this relates to the journal? I'd be grateful for whatever
> background you can give here.
>
> Best wishes,
> Charles
>
> -----Original Message-----
> From: Whalley, Charles
> Sent:
> 15 April 2016 08:14
> To: 'Roger
> McClellan'
> Cc: mbmorgan@hargray[redacted]
> Subject: RE: Any legal requests to T and F or related companies
>
> Dear
> Roger,
>
> Thanks for passing
> this on. I'm going to need to consult internally on this, I'm afraid.
> I'll get back to you as soon as I can.
>
> I'm working from
> home today, so won't be reachable via telephone, but I'm back at my
> desk next week.
>
> All best wishes as ever,
> Charles
>
> -----Original Message-----
> From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]t]
>
> Sent: 14 April 2016 22:48
> To: Whalley, Charles
> Cc: roger.o.mcclellan@[redacted];
> mbmorgan@hargray[redacted]
> Subject: Any legal requests to T and F or related companies
>
> Charles:
> I was
> very disturbed to recently learn that reference was made in US Federal
> Court to "confidential review comments"

> for a paper Paustenbach etal, A review of the health hazards of
> cobalt, CRT, 43; 316-362 (2013). Does T and F have a record of
> releasing "confidential review comments"
> for this or any other paper published by Dr Dennis Paustenbach and/or
> his associates in CRT? It is possible that the lawyers might have
> attempted to use a subpoena or merely made contact by telephone or
> e-mail. It is possible the lawyers used some means other than
> contacting T and F to obtain the "confidential review comments",
> possibly contacting a reviewer. This case is remarkable since the
> lawyers apparently had copies of multiple review comments on the
> paper.
> I am hoping
> that this does not occur again in the future. Can you provide me
> assurance that in the event T and F receives a legal or any inquiry
> for release of "confidential review comments" that T and F will
> immediately contact me before taking any action with regard to release
> of the "confidential review comments"?
>
> As you know, I have strongly held views that all transactions
> between authors, reviewers and the Editor concerning a paper are
> confidential and private. Moreover, if this curtain of confidentiality
> is removed it can cause irreparable harm to the review process and ,
> in doing so, to the author(s), Editor, reviewers and publisher. Hence,
> I will personally strongly object to release of any "confidential
> review comments" even if served a legal subpoena. I would hope T and F
> and its affiliates would hold similar views and support me and my
> position as an Editor under contract to T and F.
> I welcome your response to my
> specific question on release of comments on this specific paper.
> Moreover, I welcome your comments on the larger issue.
> Best regards,
> Roger
>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Friday, April 15, 2016 1:31 PM
To: Charles.Whalley@tandf[redacted]
Cc: roger.o.mcclellan@[redacted]; mbmorgan@[redacted]Didi.Peng@informa.c[redacted]
Subject: Re: Fw: RE: Any legal requests to T and F/ FOLLOWUP - MAJOR GOOF

Charles and Didi:

Mildred Morgan and I have gone back to the Critical Reviews In Toxicology web site and reviewed the Paustenbach etal (2013) paper available on line. Much to our dismay, under Supplemental Material, the review comments on the paper are available.

It appears that the authors attached the Review Comments as Supplemental material when the revised paper was submitted. This error was not caught by either Mildred or me. Most importantly, this error was not caught later during the production process by the Production Editor, the Production staff, me , Mildred or the authors. It is my opinion, the key final check points should be the checking of the galleys by authors and, for the Journal, the Production Editor.

With regard to this specific paper, please have the Supplemental Material removed ASAP from the CRT web site.

With regard to the Production process, Mildred will more carefully check as materials are handed off to the Production Editor to see the files are appropriate. I am also asking T and F to work with Scholar One to see that the process is as simple and straight forward as possible, I ask that because I am concerned the process has become more complex over time And see changes introduced that I have never approved. I assume the changes have been made in response to requests from others. I also strongly recommend that a specific step be added to the Production Process in which the Production Editor reviews ALL files BEFORE the material is sent to the Production staff. It is my understanding that step is not taken now. This major problem on the Paustenbach paper illustrates that past practices have not been adequate.

Please keep me posted as to actions taken by you and others. Also, let me know if you have any special insights on these matters.

Best regards,

Roger

On Fri, 4/15/16, Roger McClellan <roger.o.mcclellan@att[redacted]> wrote:

Subject: Fw: RE: Any legal requests to T and F or related companies
To: Charles.Whalley@tandf[redacted]
Cc: roger.o.mcclellan@[redacted] mbmorgan@hargray[redacted] Didi.Peng@informa[redacted]
Date: Friday, April 15, 2016, 11:39 AM

Charles:

Thanks for the quick response on this matter. I left a telephone message for you before I read your e-mail indicating you were working from your home today. Your message is re-assuring.

The official tile of the legal case is shown on the top of the transcript which I have attached. You can obtain additional details by goggling on key words such as hip implants, Depuy, Johnson and Johnson, etc. It is my understanding that more than 6000 cases have been filed alleging failure of the implant and/or harm to health from these particular "metal on metal" implants which have now been removed from the market.

In this specific case the court consolidated several cases. It is my understanding the Jury awarded the plaintiffs represented by Attorney Mark Lanier about $500 million. Other cases are in the "pipeline.

It is my understanding that Johnson and Johnson has set aside about $2.5 billion in US dollars to cover potential losses related to these cases.

What I know about the case is derived from the transcript I have attached. The paper by Paustenbach etal (2013) was apparently introduced as evidence by the Defendants in the case just tried. The paper concludes that systemic toxicity from Cobalt reaching the blood occurs only when very high blood levels of Cobalt are encountered. As I understand it, the Plaintiff's counsel apparently tried to trash the Defendants expert, Dr Boyer, by indicating he had not considered the negative review comments (reviewer 3) on the paper thereby under-mining the credibility of Dr Boyer and the paper. Dr Boyer was *obviously surprised because he had never seen the reviewers comments.*

The key question is how did the plaintiffs lawyer, Mark Lanier, gain access to the review comments?

As an aside, I have reviewed the process and specifics of how the paper was submitted, reviewed and accepted. I feel confident that the paper was rigorously reviewed and the authors appropriately responded to review comments which helped improve the paper resulting in its acceptance. Indeed, one could argue the Journal comes out OK in the exchange. .

My concern relative to the Journal is whether a breach occurred in the review / production process that allowed release of "confidential review comments". This could cause authors and reviewers to lose confidence in the Editor, the journal and publisher.

I appreciate what you have done to date. Moreover, I will appreciate further efforts by you, Didi and Taylor and Francis to identify any potential breaches in the confidentiality of the review and production system.

Best regards,
Roger

> From: Whalley, Charles <Charles.Whalley@tandf[redacted]> > Subject: RE: Any legal requests to T and F or related companies > To: "Roger McClellan" <roger.o.mcclellan@[redacted]> > Cc: "mbmorgan@hargray[redacted] <mbmorgan@hargray[redacted]>
> Date: Friday, April 15, 2016, 4:24 AM > Dear Roger, > > Further to the below, I can > confirm that our current understanding is that Taylor & > Francis has not disclosed any reviewer comments on this > article. We're still investigating with the various > parties who could've had access to the reviewer > comments. I'll update you on our findings.
>
> As for your broader question,
> for now I can only refer you to mine and Didi's previous > emails to you on T&F's policy on this issue.
> I'll get back to you on this soon. I'm still seeking > further legal guidance.
>
> In
> return, could you let me know the nature of the litigation > in which these reviewer comments have been raised, and your > understanding of how this relates to the journal? I'd be > grateful for whatever background you can give here.
>
> Best wishes,
> Charles
>
> -----Original Message-----
> From: Whalley, Charles
> Sent:
> 15 April 2016 08:14
> To: 'Roger
> McClellan'
> Cc: mbmorgan@hargray[redacted]
> Subject: RE: Any legal requests to T and F or > related companies > > Dear > Roger, > > Thanks for passing > this on. I'm going to need to consult internally on > this, I'm afraid. I'll get back to you as soon as I > can.
>

> I'm working from
> home today, so won't be reachable via telephone, but > I'm back at my desk next week.
>
> All best wishes as ever,
> Charles
>
> -----Original Message-----
> From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]
>
> Sent: 14 April 2016 22:48
> To: Whalley, Charles
> Cc: roger.o.mcclellan@[redacted]
> mbmorgan@[redacted]
> Subject: Any legal requests to T and F or > related companies > > Charles:
> I was
> very disturbed to recently learn that reference was made in > US Federal Court to "confidential review comments"
> for a paper Paustenbach etal, A review of the health hazards > of cobalt, CRT, 43; 316-362 (2013). Does T and F have a > record of releasing "confidential review comments"
> for this or any other paper published by Dr Dennis > Paustenbach and/or his associates in CRT? It is possible > that the lawyers might have attempted to use a subpoena or > merely made contact by telephone or e-mail. It is possible > the lawyers used some means other than contacting T and F to > obtain the "confidential review comments", > possibly contacting a reviewer. This case is remarkable > since the lawyers apparently had copies of multiple review > comments on the paper.
> I am hoping
> that this does not occur again in the future. Can you > provide me assurance that in the event T and F receives a > legal or any inquiry for release of "confidential > review comments" that T and F will immediately contact > me before taking any action with regard to release of the > "confidential review comments"?
>
> As you know, I have strongly held views that > all transactions between authors, reviewers and the Editor > concerning a paper are confidential and private.
Moreover,
> if this curtain of confidentiality is removed it can cause > irreparable harm to the review process and , in doing so, > to the author(s), Editor, reviewers and publisher.
Hence, I
> will personally strongly object to release of any > "confidential review comments" even if served a > legal subpoena. I would hope T and F and its affiliates > would hold similar views and support me and my position as > an Editor under contract to T and F.
> I welcome your response to my
> specific question on release of comments on this specific > paper. Moreover, I welcome your comments on the larger > issue.
> Best regards,
> Roger
>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[redacted]>
Sent: Monday, April 18, 2016 10:18 AM
To: Roger McClellan (roger.o.mcclellan@[redacted]
Cc: Mildred; Peng, Didi; Whittle, Jenna
Subject: CONFIDENTIAL -- CRT Paustenbach et al 43(4) and supplemental material

Dear Roger,

It was a pleasure to chat this afternoon, as ever, albeit unfortunately only on things that have gone wrong. Once again, please accept my apologies for the inadvertent publishing of the comments to reviewers as supplemental material for the Paustenbach article. As we've discussed before, T&F considers review comments in *CRT* to be confidential, so I do regret that this error occurred.

Based on our investigations, it would seem that this error explains how the review comments came to be cited in federal court in Texas earlier this year. To confirm, we've no record of consciously releasing any information relating to this manuscript on any request. Additionally, any 3rd party with access to review comments is bound to inform us of any request, and we've had no such notification. Whilst this is all a little academic now that we've found the problem, I hope this reassures you as to our general practice.

As I mentioned on the phone, I would stress that the Production processes in place now are much changed from those on the journal in 2012 and 2013, and that I wouldn't take this error as indicative of any serious procedural problems. However, I do think we could do with looking at how we work with supplemental material, both in ScholarOne Manuscripts and through CATS, and will discuss this with Jenna and with you and Mildred in due course.

I'll discuss some of the steps with Jenna tomorrow, as well as how supplemental material is presented in the typeset articles. I know you've some concerns here, in particular in regards to proofs for the Maronpot manuscript. Jenna and I will get to work on addressing them for you.

Finally, as agreed, I'd be grateful if you can either forward the attachments from Dr Tvermoes to me or ask the authors to send them to me directly, so that I can pursue some remaining mysteries around the Paustenbach article if possible.

All best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From: Ashley Roberts Intertek [redacted]@intertek.com>
Sent: Tuesday, May 3, 2016 2:13 PM
To: roger.o.mcclellan@[redacted]
Cc: mbmorgan@hargray[redacted]
Subject: RE: Critical Reviews in Toxicology

Dear Roger,

Hope all is going well? I was just wondering if you could give me a quick update as to where we currently stand on the review of the glyphosate manuscripts.

Thanking you in anticipation

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1[redacted]
Fax: +1[redacted]
E-mail: [redacted]intertek.com
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----
From: onbehalfof+roger.o.mcclellan[redacted]@manuscriptcentral.com
[mailto:onbehalfof+roger.o.mcclellan[redacted]@manuscriptcentral.com] On Behalf Of roger.o.mcclellan@[redacted]
Sent: April-23-16 7:14 PM
To: Ashley Roberts Intertek; Judy Vowles Intertek
Cc: roger.o.mcclellan[redacted] mbmorgan@hargray[redacted]
Subject: Critical Reviews in Toxicology

23-Apr-2016

BTXC-2016-0027 - Carcinogenicity bioassay Expert Panel review

Dear Dr Ashley Roberts:

The review comments on the five papers are starting to come in and are generally quite positive.

One issue that has been raised is access to ALL the bioassay results including material submitted for registration. Apparently, some of these results were not considered by IARC. If there is any question about such information you could include the basic data for any previously unpublished paper as Supplemental Information to one of the submitted papers. Supplemental Material is not included in the hard copy version of the papers that have been type set, rather the Supplemental Material is available electronically just as submitted.

At least one of the reviewers from Europe has made reference to a review meeting starting about May 8th. You are probably aware of the meeting. Do you intend to submit these papers to that meeting. I am not certain the reviews will be completed by then , I am certain any required revision of the papers will not be completed by then. I would be willing to have the papers submitted to such a meeting for distribution only to participants with the understanding the papers have been submitted to CRT and are still undergoing review.

Sincerely,
Dr Roger McClellan
Critical Reviews in Toxicology

Roger McClellan

From: onbehalfof+roger.o.mcclellan+[redacted]@manuscriptcentral.com on behalf of roger.o.mcclellan@[redacted]
Sent: Sunday, May 8, 2016 5:57 PM
To: ashley.roberts@intertek[redacted] judy.vowles@intertek[redacted]
Cc: roger.o.mcclellan[redacted] mbmorgan@hargray[redacted]
Subject: Critical Reviews in Toxicology

08-May-2016

BTXC-2016-0025 - Glyphosate: Carcinogenic potential – A Critical review using four Expert Panels

Dear Dr Ashley Roberts:

I have spent the afternoon re-reading the glyphosate papers and reading the comments received to date from external reviewers. I have reached several over-riding conclusions on the papers as a group that I wish to convey to you now.

First, I suggest that you start now to develop revised Declarations of Interest. These need to be as complete and transparent as possible. When reference is made to past employment by or consulting for Monsanto it will be important to note the specific years. I think you will need to critically review how authors show their affiliation. This is important since the individuals, the review process , the writing of the papers and the journal review process are likely to be intensively scrutinized. For example, many show an academic appointment. Is this appropriate as a first affiliation if they were compensated via their private consulting firm?

Second, these papers are a critique of the IARC review process and conclusions. Thus, it is critical to be very specific about the IARC review process and specific conclusions. Then it will be necessary to clearly compare and contrast the IARC conclusions and those of your Panels. This can be done most readily in some cases using direct quotes from IARC and a compare and contrast approach. The authors should not try to hide behind the argument they were conducting a scientific review and not really critiquing IARC. That will not fly with many readers.

Third. the present reviews suffer from a lack of time lines other than revealed by references. Much of this review has a historical time line. I suggest that his should be revealed in tables and or graphs. This is critically important for the carcinogenicity assays, the exposure studies and epidemiology studies. As an aside, having read the papers I am still uncertain as to when it first went on the market in the USA and other countries. Likewise, the reference to multiple past reviews was interesting but rambling. It is not clear when many were conducted. I kept looking for 'the table" I would use to present this to an interested audience. Unfortunately, it was not there.

Fourth, access to unpublished data is of paramount importance. Please make certain all unpublished data that is of key importance is available in the papers , electronic supplements or key linkages are available. For example, how does one access the various exposure reports prepared for Monsanto.

Fifth, it is time to be thinking about a more appropriate set of titles for the linked papers.

I hope these comments are useful to you now since I think it will be important that they are covered as the papers are revised. It is important that to recognize that the majority of readers do not have the same background knowledge on IARC and glyphosate as you and the Panel members. Another small group of readers know the material inside and out and will be ready to attack the panel and conclusions on every slipup.

Sincerely,
Dr Roger McClellan
Critical Reviews in Toxicology

Visit www.informapharmascience.com and sign up for free eTOC alerts to all Informa Pharmaceutical Science journals

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]
Sent: Wednesday, May 11, 2016 10:08 AM
To: Ashley Roberts
Cc: Mildred; Roger McClellan
Subject: Papers to Ashley Roberts

Ashley:

By copy of this e-mail I am asking Mildred Morgan to send you the 8 reviews we have in hand on BTXC-2016-0025 (Summary) and the 3 reviews we have in hand on BTXC-2016-0026 (Exposure). I am waiting for 2 additional sets of review comments on both papers before sending you an official decision letter. You will find these comments helpful in jump starting your revision of both papers.

As I have noted it is going to be very important to clearly state the approach used by IARC and their conclusions and the approach used by the InterTek review team and their conclusions and then compare and contrast the two processes and results. In referencing IARC it will be important to be very precise in use of language. For example, the summary paper concludes with a statement that the InterTek Panel concluded " glyphosate is not carcinogenic". In contrast, IARC for category 4 uses the descriptor -"probably not carcinogenic to humans". As I recall, IARC has only placed one chemical, caprolactam, in this category.

Best regards,

Roger

Roger McClellan

From: Roger McClellan <roger.o.mcclellan[redacted]
Sent: Wednesday, May 11, 2016 12:07 PM
To: Ashley Roberts
Cc: Roger McClellan; Mildred
Subject: Re: Reviews of Summary and Exposure Papers/ Followup

Ashley:
I urge you at some point in the process to share these comments on the Summary paper with the lead authors on all the papers (indeed, perhaps all authors) so they will appreciate the range of comments offered on the Summary. To a large extent, these comments are also highly relevant to the other papers in this constellation.
Best regards, Roger

On Wed, 5/11/16, Mildred Morgan <mbmorgan@hargray[redacted] wrote:

Subject: Reviews of Summary and Exposure Papers
To: ashley.roberts@intertek[redacted]
Cc: "Roger McClellan" <roger.o.mcclellan[redacted]
Date: Wednesday, May 11, 2016, 10:56 AM

Dear Dr. Roberts:

Dr. McClellan asked me to send you the attached 8 reviews in hand on the Summary Paper and the 3 reviews on the Exposure paper.

Mildred Morgan

Roger McClellan

From: Gunnar Johanson <[redacted]@ki.se>
Sent: Thursday, May 12, 2016 8:50 AM
To: Whalley, Charles; Roger McClellan
Cc: s.tsuda@iwate-u[redacted] dellarcov@[redacted]; david.warheit@g[redacted]; david.dorman@nscu[redacted] mbmorgan@hargray[redacted] rcc0022@auburn[redacted] f.guengerich@vanderbil[redacted] Samuel Cohen
Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Thank you Charles for your prompt answer. What you say is all well, except that it is not satisfying with the secret agreement monetary agreement between T&F and the authors/sponsors. In my view, this should not be a business secret but similar as for regular open access articles where T&F openly declares the fees. The secrecy around the supplements opens up for suspicions of economic incentives for Taylor & Francis which in turns spills over to the journal since, even if there are no extra incentives for the supplements, I assume that the Chief Editor receives a salary or honorarium for his work (as he rightly should considering the importance of the task and all the effort he puts into it).
Does anyone else have thoughts on this?
Best regards,
Gunnar

Gunnar Johanson | Ph.D | Professor

Head, Unit of Work Environment Toxicology
Institute of Environmental Medicine

Karolinska Institutet
Nobels väg 13 | P.O. Box 210 | SE-171 77 Stockholm, Sweden
[redacted] Mobile [redacted]
[redacted]@ki.se
http://ki.se/[redacted]/unit-of-work-environment-toxicology
http://www.nordicexpertgroup.org

Från: Whalley, Charles [mailto[redacted]@tandf.co.uk]
Skickat: den 10 maj 2016 18:05
Till: Gunnar Johanson; Roger McClellan
Kopia: s.tsuda@iwate-u.ac[redacted] dellarcov@gmail[redacted] david.warheit@gmail[redacted] david.dorman@nscu[redacted] mbmorgan@hargray[redacted] rcc0022@auburn[redacted] f.guengerich@vanderbilt[redacted] Samuel Cohen
Ämne: RE: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear all,

Many thanks for including me on your discussions here, as I'm grateful to hear your thoughts on this crucial issue for the journal.

As Gunnar has noted, *CRT* commonly publishes supplements funded by industry sponsorship. These allow the authors to publish as a stand-alone issue separate from the normal schedule of issues, meaning that they can

publish as soon as the articles are accepted. These supplements are commonly made free-to-view, and are promoted by Taylor & Francis. Unsurprisingly, industry groups often find this publication option attractive.

The sponsorship in no way guarantees acceptance. To reiterate Roger's comments, the commercial and editorial elements of the journal are entirely separate. Editorial policy is Roger's responsibility. We do not overrule or interfere in his decisions for commercial reasons. Similarly, these articles are subject to all the same peer review and scrutiny of their declarations of interest as any other manuscript. Additionally, to be clear, there is no financial incentive for anyone involved in the editorial process relating to sponsored supplements.

I can't comment on how much sponsors pay for these supplements, as this is commercially sensitive.

Regarding publishing a commentary alongside this proposed issue, I'd be happy to make room for such an editorial, if that's Roger's decision following this suggestion. I would suggest that the focus of such a commentary should be on the significance of these articles, as Vicki has suggested, with an additional opportunity to remind our readership of editorial policy around sponsored supplements and how it applies in this case. I will, however, leave this up to Roger.

I hope this helps clarifies matters from the publisher's perspective. Please do let me know if you have any further questions or comments on this. I'm very eager to hear them!

All best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

From: Gunnar Johanson [mailto[redacted]@ki.se]
Sent: 09 May 2016 14:44
To: Roger McClellan
Cc: s.tsuda@iwate-u[redacted] dellarcov@[redacted] david.warheit@[redacted] david.dorman@nscu[redacted] mbmorgan@hardray[redacted] rcc0022@auburn[redacted] Whalley, Charles; f.quengerich@vanderbilt[redacted] Samuel Cohen
Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Thank you Roger for clarifying. It is good with the rigorous review and detailed COIs of CRT, I have no problem with those items or, for that matter, that industry (or other vested interests) funds research and expert groups and seek to publish their results.

My remaining concern is that it may be seen as industry is paying their way into the journal ("*The authors/ sponsors of these Supplemental Issues pay a special fee negotiated between the Authors / Sponsors and Taylor and Francis. As the CRT Editor, I have nothing to do with this business transaction. My role is to assure that all papers published in any Special Supplement receive the same, high quality rigorous review as papers published in regular issues.*"). I checked the last 15 supplemental papers in CRT , all stem from industry. It is reasonable that the authors/sponsors pay for the publication costs but not a lot more, as this might bias the review and publishing processes.

So, I would appreciate a clarification how much is paid by the authors/sponsors to the publisher and how editors and reviewers are reimbursed (if at all). Maybe Charles Whalley can respond to this?

Best regards,
Gunnar

PS. I agree with Vicky about an accompanying commentary.

-----Ursprungligt meddelande-----
Från: Roger McClellan [mailto:roger.o.mcclellan@[redacted]
Skickat: den 8 maj 2016 21:42
Till: Gunnar Johanson
Kopia: s.tsuda@iwate-u.ac[redacted]; dellarcov@[redacted]; david.warheit@[redacted]; david.dorman@nscu[redacted]; mbmorgan@hargray[redacted]; roger.o.mcclellan@[redacted]; rcc0022@auburn[redacted]; Charles.Whalley@tandf[redacted]; f.guengerich@vanderbilt[redacted]; Samuel Cohen
Ämne: Re: SV: 5 Glyphosate Papers/ Comments from Gunnar

Gunnar and other members of the CRT Editorial Advisory Board

Gunnar, thank you for your e-mail concerning the publication of a Supplemental Issue including 5 papers on Glyphosate. Your e-mail was a follow up to our discussion of this matter at our Editorial Advisory Board in New Orleans and my distribution of copies of the papers.

By way of background, CRT in recent years has included 920 pages each year which have been published on line electronically and last year published at year end as a single printed copy. The authors of some papers have purchased on line access.

In addition to the regular issues, CRT has a long standing practice of publishing Special Supplements. The authors/ sponsors of these Supplemental Issues pay a special fee negotiated between the Authors / Sponsors and Taylor and Francis. As the CRT Editor, I have nothing to do with this business transaction. My role is to assure that all papers published in any Special Supplement receive the same, high quality rigorous review as papers published in regular issues. Indeed, the agreement between T and F and the Authors/ Sponsors specifically note that publication of the Special Issue is contingent upon scientific review and acceptance of the papers. It does not guarantee acceptance. . The primary reason for publishing a Special Issue of CRT is to minimize the impact on our limited page budget. Papers included in the Special Supplements do not count against the current annual 920 page limit.

As I recall, CRT has published 3 papers in the recent past on Glyphosate. All three papers were downloaded many times and have been widely cited, including by IARC. One paper by Griem etal contained extensive supplemental material (This is different than a Special Issue Supplement). It is not clear how well IARC reviewed this paper and , especially, the electronic supplement. However, I can assure you that the electronic supplement is clearly marked in the text.

After the IARC review of glyphosate I was contacted by personnel from Monsanto and InterTek, a private consulting firm, as to my interest in considering one or multiple papers on glyphosate that would be a critique of the IARC review. I responded that I would be enthusiastic about considering one or multiple papers. I indicated my preference would be to have one large paper or a collection of papers to be published in a single issue. I indicated that since it was anticipated that these papers would be comprehensive and long I thought it unlikely these papers could be published in a regular issue. I noted that I would expect the papers to have comprehensive and transparent Declarations Of Interest , as is routine for CRT. As an aside, I know of no other scientific journal that has as rigorous a Declaration of Interest policy as CRT with publication of each DOI.

Gunnar has raised the issue of the employment affiliation of the authors and the past association of some of the authors with Monsanto. I expect that to be made clear in the DOIs. As a matter of policy, I do not think where an individual author is employed (academe, government, consulting firm, private consultant, etc) should be a determinant of whether a paper should be considered for publication. I do expect all relevant material relating to potential conflicts of interest to be disclosed in the DOI. Quite frankly, I am concerned by many journals allowing self proclamations from authors --"We have no conflicts of interest to declare." That is "eye wash". Conflicts of Interest are in the eyes of the beholder not the Declarer.

I think my job as an Editor is to see that the submitted paper receive a rigorous review by outstanding experts from around the globe. In the case of the submitted glyphosate papers I think I have selected some outstanding reviewers, in some case up to 7 per paper. As an aside, how many of you have received 7 sets of external review comments on any paper, original research or review paper, you have authored? Many of you agreed to review one or more of the five papers. For that special effort I extend my thanks. I will be pleased to have you review any or all of the revised papers. I use the review comments to help guide my decision to accept, request revision or reject a paper. Most importantly, I expect the authors to use the review comments to further improve their revised paper.

The five glyphosate papers are still under review. In general, the review comments are very positive and constructive. Many reviewers noted they were pleased to have these papers published in CRT.

Gunnar has raised the issue of my publishing a commentary on the five papers as part of the Special Supplement . I have never published such a commentary for either a regular issue or Special Issue. MY basic view is that all papers published in CRT "speak for them selves'. However, I am willing to consider such a commentary for this Special Issue if you think it useful. If I were to prepare one it would include many of the points made here. Of course, I would also need to refer to the IARC process and the IARC decision on glyphosate. It is my view that the five papers published in CRT will represent the most comprehensive review of the world's literature on the potential carcinogenicity of glyphosate and be widely cited by others.

I welcome you views on this important matter.

Best regards,

Roger

On Mon, 5/2/16, Gunnar Johanson <[redacted]@ki.se> wrote:

Subject: SV: 5 Glyphosate Papers
To: "Roger McClellan" <roger.o.mcclellan@[redacted], "david.warheit@[redacted] <david.warheit@[redacted]
"david_dorman@ncsu[redacted] <david_dorman@ncsu[redacted]
Cc: "s.tsuda@iwate-u.ac[redacted] <s.tsuda@iwate-u.ac[redacted] "Mildred" <mbmorgan@hargray[redacted]
Date: Monday, May 2, 2016, 4:27 AM

Dear Roger,
How will this will be introduced in the journal, i.e. how will it be explained that the 5 papers appear in a separate volume (assuming they will be accepted for publication) ?
Nearly early all
authors are more or less connected to Monsanto. My concern is that this may be viewed as an industry input and, more important, that the integrity and independence of CRT may be questioned by the scientific community.
All the best
Gunnar

-----Ursprungligt meddelande-----
Från: Roger McClellan [mailto:roger.o.mcclellan@[redacted]

Skickat: den 14 april 2016 20:55
Till: david.warheit@[redacted]
david_dorman@ncsu[redacted]
Gunnar Johanson
Kopia: s.tsuda@iwate-u[redacted];
roger.o.mcclellan@att[redacted]
Mildred
Ämne: Fw: 5 Glyphosate Papers

--- On Thu, 4/14/16, Roger McClellan <roger.o.mcclellan@[redacted]
wrote:

> From: Roger
McClellan <roger.o.mcclellan@att[redacted]
> Subject: Fw: 5 Glyphosate Papers
> To: bolt@ifado[redacted] rcc0020@auburn.[redacted]f.guengerich@vanderbilt[redacted]

> "Samuel Cohen" <scohen@unmc[redacted]
> Cc: "Roger McClellan" <roger.o.mcclellan@[redacted] "Mildred"
> <mbmorgan@hargray[redacted]
> Date: Thursday, April 14, 2016, 11:51 AM To all:
> Attached are five papers
critiquing the IARC review of glyphosate.
> Assuming the papers are accepted after rigorous review , they will be > published in a single Special Supplement to CRT. I would be pleased if > you would agree to review the general paper and one or more of the > four detailed papers. If you are willing to review one or more paper > please linform my assistant, Mildred Morgan, mbmorgan@hargray[redacted] and > you will be formally invited.
Thanks in advance for your help. Best
>
regards, Roger
>
>
--- On Thu, 4/14/16, Mildred Morgan <mbmorgan@hargray[redacted] > wrote:
>
> > From: Mildred Morgan <mbmorgan@hargray[redacted] > > Subject: 5 Glyphosate Papers > > To: "Roger McClellan" <roger.o.mcclellan@[redacted]
> > Date: Thursday, April 14, 2016, 9:38 AM The 5 glyphosate papers > > attached.
> >
>
>
> >

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]
Sent: Thursday, May 12, 2016 10:16 AM
To: David Dorman
Subject: Fw: Re: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

--- On Thu, 5/12/16, Roger McClellan <roger.o.mcclellan@[redacted]> wrote:

> From: Roger McClellan <roger.o.mcclellan@[redacted]
> Subject: Re: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar
> To: "CharlesWhalley" <[redacted]@tandf.co.uk>, "Roger McClellan"
> <roger.o.mcclellan@[redacted]>, "Gunnar Johanson" <[redacted]@ki.se>
> Cc: mbmorgan@hargray.[redacted] "s.tsuda@iwate-u.ac[redacted]"
> <s.tsuda@iwate-u.ac[redacted] "dellarcov@[redacted]" <dellarcov@[redacted],
> "david.warheit@[redacted] <david.warheit@[redacted]>,
> "david.dorman@nscu[redacted] <david.dorman@nscu[redacted] "rcc0022@auburn.[redacted]
> <rcc0022@auburn[redacted] "f.guengerich@vanderbilt.[redacted]
> <f.guengerich@vanderbilt.[redacted] "Samuel Cohen" <scohen@unmc.[redacted]
> Date: Thursday, May 12, 2016, 9:10 AM
> Gunnar:
> Thanks for your follow up note on the Special Glyphosate
> Supplement. I will off some clarification on some of the issues you
> raise.
> First, let me address my role as the Editor of Critical Reviews
> in Toxicology. I do have a contract with Informa / Taylor and Francis
> for my services as Editor of CRT. That contract provides me a flat fee
> to cover all of my time and expenses for serving as Editor, the most
> important aspects of which are the maintenance of manuscript flow and
> the delivery of high quality , peer-reviewed manuscript to T and F. To
> assist me, I engage Mildred Morgan, who has worked effectively and
> efficiently with me for decades. The fee I receive is the same
> irrespective of the number of manuscripts moving through the system
> and whether CRT includes any Special Supplements.
> Hence, there is no financial incentive for me to promote the
> publication of Special Supplements. Indeed, every Special Supplement
> requires more effort from me and Mildred for which I receive NO
> additional reimbursement.
> It follows logically to ask why I should consider recommending
> publication of any Special Supplements. I do so as part of my
> professional responsibility as Editor. I want to see the 920 pages
> allotted each year for regular issues of CRT used to publish high
> quality , high impact papers in a timely manner. That is a difficult
> balancing act involving (a) high scientific impact, (b) high
> scientific quality and (c) timeliness.
> Impact and quality are not the same. By impact I am referring to
> scientific information that is relevant to contemporary Societal
> issues. Scientific quality is independent of whether the content is

> relevant to Societal issues. Timeliness is obviously of concern for
> all authors, they would like to have their paper published as soon as
> possible. T and F addresses that issue in part by promptly processing
> all accepted manuscripts and posting them on line at the earliest
> possible date. However, no one would like to have their paper in limbo
> as to formal publication for months and months. Hence, the dilemma of
> every Editor and ,especially Review Journal Editor. I want to have a
> modest back log but not an excessive back log. I can assure you I have
> had more then a few sleepless nights thinking about whether I have the
> right balance.
> This brings me to the five
> Glyphosate papers. This is one of the world's highest impact
> chemicals. IARC operates one of the world's most widely recognized
> cancer hazard classification schemes. CRT previously published at
> least three widely cited review papers on Glyphosates that were
> considered in the IARC review. The IARC cancer hazard classification
> of Glyphosate is one of the most controversial cancer hazard
> classifications rendered in recent years. Although let me quickly note
> that the cancer hazard classifications rendered for "outdoor air" and
> "airborne particulate material" follow close behind. When I learned
> that Monsanto was going to sponsor a critical review of the cancer
> hazard of glyphosate, including a critique of the IARC review, managed
> by InterTek , I decided it would be highly desirable to publish that
> critical review in CRT. I thought then and now that CRT was the ideal
> publication venue for this review because of the rigor of CRT's review
> process, our transparent "Declaration of Interest" process and our
> desire to provide access to all underlying data through use of
> electronic supplements and electronic linkages.
> In anticipation of the number of pages involved I quickly
> decided that it would be best to publish the new review as a Special
> Supplement. At that point I handed off to Charles Whalley, the
> Managing Editor of CRT, and the business office of T and F the
> negotiation of the details , including fees, for publishing the
> Special Supplement. As the recipients of this memo know I have 60
> years of experience as a scientist, scientific manager and science
> advisor. What may not be as well known is I have over 50 years of
> business experience running large scale research enterprises,
> including responsibility for the bottom line. That means making tough
> decisions as to when you hire and fire your scientific colleagues. To
> provide me better tools for working as a scientific business manager I
> enrolled and completed a Master of Management Science degree at the
> University of New Mexico, the equivalent of an MBA. I understand
> business - it is rough and tumble!!!
> I fully understand the T and F
> business decision to not release details, including publication fees,
> of the agreement between T and F and InterTek for publishing the
> Special Supplement containing the glyphosate papers. Indeed, I suspect
> the agreement at this stage has not yet been published because the
> number of pages to be published is not yet known.
> Wearing my "business hat" I can assure you that T and F has very
> straight forward business procedures for deciding what is a reasonable
> fee for publishing a Special Supplement containing 125, 150, 175 or

> 200 pages. It is not some arbitrary process guided by a " lets charge
> as much as possible" approach. Indeed, I suspect an examination of the
> fees typically charged by T and F for 'open access" will provide clues
> as to the cost to the sponsor of publishing the Special Supplement. As
> I hope everyone knows the "scientific publishing business" is a tough
> business today with rapidly changing practices. [As an aside, how many
> paper solicitations from fly by night journals have you received this
> month?] Bottom line, I count on T and F to run their publishing
> business in an ethical and business like manner. I am counting on that
> because I want then]m to be in business and publishing CRT
> indefinitely. I certainly do not want them to go out of business. The
> counter point is that I will continue to deliver them high scientific
> quality, high impact , rigorously peer reviewed manuscripts to fill
> the 920 pages of regular issues they have contractually agreed to
> provide to their subscribers and occasional provide papers for a
> Special Supplement.
> As an update, the five glyphosate papers are moving through an
> extraordinarily rigorous review process. The review comments meet the
> high standards of CRT and will help the authors further improve the
> final accepted version of the papers. I do anticipate preparing a
> "prelude" that will introduce the Special Supplement".
> I hope the foregoing material is helpful to all of you I welcome
> any further inquiries by e-mail or phone. ([redacted]).
> Again, thank you for your assistance with CRT and , especially,
> with the glyphosate Special Supplement.
> With best regards,
> Roger
> PS This is a "business sensitive communication". I would appreciate
> your not sharing it or communicating the contents with any individuals
> other than the recipients.
> ---
> On Thu, 5/12/16, Gunnar Johanson <[redacted]@ki.se>
> wrote:
>
> Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar
> To: "Whalley, Charles" <[redacted]@tandf.co.uk>, "Roger
> McClellan" <roger.o.mcclellan@att[redacted]
> Cc: "s.tsuda@iwate-u.a[redacted]"
> <s.tsuda@iwate-u.ac.[redacted]>,
> "dellarcov@[redacted]"
> <dellarcov@[redacted]>,
> "david.warheit@[redacted]"
> <david.warheit@[redacted]>,
> "david.dorman@nscu[redacted]"
> <david.dorman@nscu[redacted]>,
> "mbmorgan@hargray[redacted]
> <mbmorgan@hargray[redacted]
> "rcc0022@auburn[redacted]
> <rcc0022@auburn[redacted]
> "f.guengerich@vanderbilt[redacted]
> <f.guengerich@vanderbilt[redacted]
> "Samuel Cohen" <scohen@unmc[redacted]>

> Date: Thursday, May 12, 2016, 7:49 AM
>
> #yiv4818449056
> #yiv4818449056 --
>
> _filtered #yiv4818449056
> {font-family:Calibri;panose-1:2 15
> 5 2 2 2 4 3 2 4;}
> _filtered #yiv4818449056
> {font-family:Tahoma;panose-1:2 11
> 6 4 3 5 4 4 2 4;}
> #yiv4818449056
> #yiv4818449056 p.yiv4818449056MsoNormal, #yiv4818449056
> li.yiv4818449056MsoNormal, #yiv4818449056 div.yiv4818449056MsoNormal
>
> {margin:0cm;margin-bottom:.0001pt;font-size:12.0pt;}
> #yiv4818449056 a:link, #yiv4818449056 span.yiv4818449056MsoHyperlink
> {color:blue;text-decoration:underline;}
> #yiv4818449056 a:visited, #yiv4818449056
> span.yiv4818449056MsoHyperlinkFollowed
>
> {color:purple;text-decoration:underline;}
> #yiv4818449056 p.yiv4818449056MsoAcetate, #yiv4818449056
> li.yiv4818449056MsoAcetate, #yiv4818449056
> div.yiv4818449056MsoAcetate
>
> {margin:0cm;margin-bottom:.0001pt;font-size:8.0pt;}
> #yiv4818449056 span.yiv4818449056BallongtextChar
> {}
> #yiv4818449056 p.yiv4818449056emailquote, #yiv4818449056
> li.yiv4818449056emailquote, #yiv4818449056
> div.yiv4818449056emailquote
>
> {margin-right:0cm;margin-left:1.0pt;font-size:12.0pt;}
> #yiv4818449056 span.yiv4818449056E-postmail20
> {color:#1F497D;}
> #yiv4818449056 p.yiv4818449056BalloonText, #yiv4818449056
> li.yiv4818449056BalloonText, #yiv4818449056
> div.yiv4818449056BalloonText
>
> {margin:0cm;margin-bottom:.0001pt;font-size:12.0pt;}
> #yiv4818449056 span.yiv4818449056BalloonTextChar
> {}
> #yiv4818449056 span.yiv4818449056E-postmail23
> {color:#1F497D;}
> #yiv4818449056 .yiv4818449056MsoChpDefault
> {font-size:10.0pt;}
> _filtered #yiv4818449056 {margin:72.0pt 72.0pt 72.0pt 72.0pt;}
> #yiv4818449056 div.yiv4818449056WordSection1
> {}
> #yiv4818449056
>

> Thank you Charles for your prompt
> answer. What you say is all well, except that it is not satisfying
> with the secret agreement monetary agreement
> between T&F and the authors/sponsors. In my view, this should not
> be a business secret but similar as for regular open access articles
> where T&F openly declares the fees.
> The secrecy around the supplements opens up for suspicions of
> economic incentives for
> Taylor & Francis which in turns spills over to the journal since,
> even if there are no extra incentives for the supplements, I assume
> that the Chief Editor receives a salary or honorarium for his work
> (as he rightly should considering the importance of the
> task and all the effort he puts into it).
> Does anyone else have thoughts on
> this?
> Best regards,
> Gunnar
>
>
> Gunnar Johanson
> | Ph.D. |
> Professor
>
>
> Head, Unit of Work
> Environment Toxicology
>
> Institute of Environmental Medicine
>
>
>
> Karolinska Institutet
>
> Nobels väg 13 | P.O. Box 210 | SE-171 77 Stockholm, Sweden
>
> +[redacted] Mobile +4[redacted]
>
> [redacted]@ki.se
>
>
> http://ki.se/en/imm/unit-of-work-environment-toxicology
>
> http://www.nordicexpertgroup.org
>
>
> _____
> _____
>
> Karolinska Institutet is one of the
> world's leading medical universities.
> Its mission is to contribute to the
> improvement of human health through research and education.

> Karolinska Institutet accounts for
> over 40 per cent of the medical academic research conducted in
> Sweden and offers the country's broadest range of education in
> medicine and health sciences.
> Since 1901 the Nobel Assembly at
> Karolinska Institutet has selected the
>
> Nobel laureates in Physiology or
> Medicine.
>
>
>
>
>
> Från: Whalley, Charles
> [mailto[redacted]@tandf.co.uk]
>
>
> Skickat: den 10 maj 2016 18:05
>
> Till: Gunnar Johanson; Roger McClellan
>
> Kopia: s.tsuda@iwate-u.ac[redacted]
> dellarcov@[redacted]
> david.warheit@[redacted]
> david.dorman@nscu[redacted]
> mbmorgan@hargray[redacted]
> rcc0022@auburn[redacted]
> f.guengerich@vanderbilt[redacted]
> Samuel Cohen
>
> Ämne: RE: SV: 5 Glyphosate Papers/ Comments from Gunnar
>
>
>
> Dear all,
>
> Many thanks for including me on
> your discussions here, as I'm grateful to hear your thoughts on this
> crucial issue for the journal.
>
> As Gunnar has noted,
> CRT commonly publishes supplements funded by industry sponsorship.
> These allow the authors to publish as a stand-alone issue separate
> from the normal schedule of issues, meaning that they can publish as
> soon as the articles are accepted. These supplements
> are commonly made free-to-view, and are promoted by Taylor &
> Francis. Unsurprisingly, industry groups often find this publication
> option attractive.
>
> The sponsorship in no way
> guarantees acceptance. To reiterate Roger's comments, the commercial

> and editorial elements of the journal are entirely
> separate. Editorial policy is Roger's responsibility. We do not
> overrule or interfere in his decisions for commercial reasons.
> Similarly, these articles are subject to all the same peer review and
> scrutiny of their declarations of interest as any other manuscript.
> Additionally, to be clear, there is no financial incentive for
> anyone involved in the editorial process relating to sponsored
> supplements.
>
> I can't comment on how much
> sponsors pay for these supplements, as this is commercially
> sensitive.
>
> Regarding publishing a commentary
> alongside this proposed issue, I'd be happy to make room for such an
> editorial, if that's Roger's decision following
> this suggestion. I would suggest that the focus of such a
> commentary should be on the significance of these articles, as Vicki
> has suggested, with an additional opportunity to remind our
> readership of editorial policy around sponsored supplements and how
> it
> applies in this case. I will, however, leave this up to Roger.
>
> I hope this helps clarifies
> matters from the publisher's perspective. Please do let me know if
> you have any further questions or comments on this.
> I'm very eager to hear them!
>
> All best wishes,
> Charles
>
> Charles Whalley
> -
> Managing Editor, Medicine & Health Science Journals Taylor &
> Francis Group
> 4 Park Square, Milton Park,
> Abingdon, Oxon, OX14 4RN, UK
> Direct line: +[redacted]
> [redacted]
> Switchboard: +[redacted]
> [redacted]
> [redacted]@tandf.co.uk
>
> www.tandfonline.com
>
>
> Taylor & Francis is a trading
> name of Informa UK Limited,
> registered in England under no.
> 1072954
>
>

>
>
>
> From: Gunnar Johanson [mailto[redacted]@ki.se]
>
>
> Sent: 09 May 2016 14:44
>
> To: Roger McClellan
>
> Cc: s.tsuda@iwate-u.ac[redacted]
>
> dellarcov@[redacted];
> david.warheit@[redacted];
> david.dorman@nscu[redacted]
>
> mbmorgan@hargray[redacted]
> rcc0022@auburn[redacted]
> Whalley, Charles;
> f.guengerich@vanderbilt[redacted]
> Samuel Cohen
>
> Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar
>
>
>
>
>
>
> Thank you Roger for clarifying. It
> is good with the rigorous review and detailed COIs of CRT, I have no
> problem with those items or, for that matter, that
> industry (or other vested interests) funds research and expert
> groups and seek to publish their results.
>
>
>
>
>
> My remaining concern is that it
> may be seen as industry is paying their way into the journal ("The
> authors/ sponsors of these Supplemental Issues pay a special
> fee negotiated between the Authors / Sponsors and Taylor and
> Francis. As the CRT Editor, I have nothing to do with this business
> transaction. My role is to assure that all papers published in any
> Special Supplement receive the same, high quality rigorous
> review as papers published in regular issues."). I checked the last
> 15 supplemental papers in CRT , all stem from industry. It is
> reasonable that the authors/sponsors pay for the publication costs
> but not a lot more, as this might bias the review and publishing
> processes.
>
>

>
>
>
> So, I would appreciate a
> clarification how much is paid by the authors/sponsors to the
> publisher and how editors and reviewers are reimbursed (if at all).
> Maybe
> Charles Whalley can respond to this?
>
>
>
>
>
> Best regards,
>
>
> Gunnar
>
>
>
>
>
> PS. I agree with Vicky about an
> accompanying commentary.
>
>
>
>
>
>
>
>
>
> -----Ursprungligt
> meddelande-----
>
> Från: Roger McClellan [mailto:roger.o.mcclellan@att[redacted]
>
>
> Skickat: den 8 maj 2016 21:42
>
> Till: Gunnar Johanson
>
> Kopia: s.tsuda@iwate-u.ac[redacted]
>
> dellarcov@gmail[redacted];
> david.warheit@gmail.c[redacted]
> david.dorman@nsc[redacted]
>
> mbmorgan@hargray[redacted];
> roger.o.mcclellan@att[redacted]
> rcc0022@auburn[redacted]

>
> Charles.Whalley@tandf[redacted];
> f.guengerich@vanderbilt[redacted]
> Samuel Cohen
>
> Ämne: Re: SV: 5 Glyphosate Papers/ Comments from Gunnar
>
>
>
>
>
>
> Gunnar and other members of the
> CRT Editorial Advisory Board
>
>
> Gunnar, thank you
> for your e-mail concerning the publication of a Supplemental Issue
> including 5 papers on Glyphosate. Your e-mail was a follow up to
> our discussion of this matter at our Editorial Advisory Board in
> New Orleans and my distribution of copies of the papers.
>
>
> By way of background,
> CRT in recent years has included 920 pages each year which have been
> published on line electronically and last year published at
> year end as a single printed copy. The authors of some papers have
> purchased on line access.
>
>
> In addition to the
> regular issues, CRT has a long standing practice of publishing
> Special Supplements. The authors/ sponsors of these Supplemental
> Issues
> pay a special fee negotiated between the Authors / Sponsors and
> Taylor and Francis. As the CRT Editor, I have nothing to do with
> this business transaction. My role is to assure that all papers
> published in any Special Supplement receive the same, high quality
> rigorous review as papers published in regular issues.
> Indeed, the agreement between T and F and the Authors/ Sponsors
> specifically note that publication of the Special Issue is contingent
> upon scientific review and acceptance of the papers. It does not
> guarantee
> acceptance. . The primary reason for publishing a Special Issue of
> CRT is to minimize the impact on our limited page budget. Papers
> included in the Special Supplements do not count against the current
> annual 920 page limit.
>
>
> As I recall, CRT has
> published 3 papers in the recent past on Glyphosate. All three
> papers were downloaded many times and have been widely cited,
> including

> by IARC. One paper by Griem etal contained extensive supplemental
> material (This is different than a Special Issue Supplement). It is
> not clear how well IARC reviewed this paper and , especially, the
> electronic supplement.
> However, I can assure you that the
> electronic supplement is clearly marked in the text.
>
>
>
> After the IARC review
> of glyphosate I was contacted by personnel from Monsanto and
> InterTek, a private consulting firm, as to my interest in considering
> one or multiple papers on glyphosate that would be a critique of
> the IARC review. I responded that I would be enthusiastic about
> considering one or multiple papers. I indicated my preference would
> be to have one large paper or a collection of papers to be
> published in a single issue. I indicated that since it was
> anticipated that these papers would be comprehensive and long I
> thought it unlikely these papers could be published in a regular
> issue. I noted that I would expect the papers to have comprehensive
> and transparent Declarations Of Interest , as is routine for CRT.
> As an aside, I know of no other scientific journal that has as
> rigorous a Declaration of Interest policy as CRT with publication of
> each DOI.
>
>
> Gunnar has raised the
> issue of the employment affiliation of the authors and the past
> association of some of the authors with Monsanto. I expect that to
> be made clear in the DOIs. As a matter of policy, I do not think
> where an individual author is employed (academe, government,
> consulting firm, private consultant, etc) should be a determinant of
> whether a paper should be considered for publication. I do expect
> all relevant material relating to potential conflicts of interest
> to be disclosed in the DOI. Quite frankly, I am concerned by many
> journals allowing self proclamations from authors --"We have no
> conflicts of interest to declare." That is "eye wash". Conflicts
> of Interest are in the eyes of the beholder not the Declarer.
>
>
> I think my job as an
> Editor is to see that the submitted paper receive a rigorous review
> by outstanding experts from around the globe. In the case of the
> submitted glyphosate papers I think I have selected some
> outstanding reviewers, in some case up to 7 per paper. As an aside,
> how many of you have received 7 sets of external review comments on
> any paper, original research or review paper, you have authored?
> Many of you agreed to review one or more of the five papers. For
> that special effort I extend my thanks. I will be pleased to have
> you review any or all of the revised papers. I use the review
> comments to help guide my decision to accept, request revision
> or reject a paper. Most importantly, I expect the authors to use

> the review comments to further improve their revised paper.
>
>
> The five glyphosate
> papers are still under review. In general, the review comments are
> very positive and constructive. Many reviewers noted they were
> pleased
> to have these papers published in CRT.
>
>
> Gunnar has raised the issue
> of my publishing a commentary on the five papers as part of the
> Special Supplement . I have never published such a commentary
> for either a regular issue or Special Issue. MY basic view is that
> all papers published in CRT "speak for them selves'. However, I am
> willing to consider such a commentary for this Special Issue if you
> think it useful.
> If
> I were to prepare one it would include
> many of the points made here. Of course, I would also need to refer
> to the IARC process and the IARC decision on glyphosate. It is my
> view that the five papers published in CRT will represent the most
> comprehensive review of the world's literature on the
> potential carcinogenicity of glyphosate and be widely cited by
> others.
>
>
> I welcome you views on
> this important matter.
>
>
> Best
> regards,
>
>
> Roger
>
>
>
>
>
>
>
>
> ---
>
>
>
> On Mon, 5/2/16, Gunnar Johanson
> <[redacted]@ki.se>
> wrote:
>

>
>
>
>
> Subject: SV: 5 Glyphosate
> Papers
>
>
> To: "Roger McClellan"
> <roger.o.mcclellan@att[redacted]>,
> "david.warheit@[redacted]"
> <david.warheit@[redacted]>,
> "david_dorman@ncsu[redacted]
> <david_dorman@ncsu[redacted]
>
>
>
> Cc: "s.tsuda@iwate-u.ac[redacted]
> <s.tsuda@iwate-u.ac[redacted]
> "Mildred" <mbmorgan@hargray[redacted]
>
>
>
> Date: Monday, May 2, 2016, 4:27
> AM
>
>
>
>
>
>
> Dear Roger,
>
>
> How will this will be introduced
> in the journal, i.e. how will it be explained that the 5 papers
> appear in a separate volume (assuming they will be accepted
> for publication) ?
>
>
> Nearly early all
>
>
> authors are more or less connected
> to Monsanto. My concern is that this may be viewed as
> an
> industry input and, more important, that the integrity
> and independence
> of CRT may be questioned by the scientific
> community.
>
>
> All the best

>
>
> Gunnar
>
>
>
>
>
>
>
>
>
>
>
>
> -----Ursprungligt
> meddelande-----
>
>
> Från: Roger McClellan [mailto:roger.o.mcclellan@att[redacted]
>
>
>
>
>
>
>
> Skickat: den 14 april 2016
> 20:55
>
>
> Till:
> david.warheit@gmail[redacted]
>
>
>
> david_dorman@ncsu[redacted]
>
>
>
> Gunnar Johanson
>
>
> Kopia:
> s.tsuda@iwate-u.ac[redacted]
>
>
>
> roger.o.mcclellan@att[redacted]
>
>
>
> Mildred
>

>
> Ämne: Fw: 5 Glyphosate
> Papers
>
>
>
>
>
>
>
>
>
>
>
>
> --- On Thu, 4/14/16, Roger
> McClellan <roger.o.mcclellan@[redacted]>
>
>
>
> wrote:
>
>
>
>
>
>
> > From: Roger
>
>
> McClellan <roger.o.mcclellan@[redacted]>
>
>
>
> > Subject: Fw: 5 Glyphosate
> Papers
>
>
> > To:
> bolt@ifado[redacted],
> rcc0020@auburn[redacted]
> f.guengerich@vanderbilt[redacted]
>
>
>
>
>
>
>
> > "Samuel Cohen"
> <scohen@unmc[redacted]
>
>
>
> > Cc: "Roger

> McClellan" <roger.o.mcclellan@[redacted],
> "Mildred"
>
>
>
> > <mbmorgan@hargray[redacted]>
>
>
>
> > Date: Thursday, April 14,
> 2016, 11:51 AM To all:
>
>
> > Attached are five
> papers
>
>
> critiquing the IARC review of
> glyphosate.
>
>
>
> > Assuming the papers are
> accepted after rigorous review , they will be >
> published in a single Special Supplement to CRT. I would
> be pleased if > you would
> agree to review the general paper and one or more
> of
> the > four detailed papers. If you are willing to
> review one or more paper > please linform my
> assistant, Mildred Morgan,
> mbmorgan@hargray[redacted]
> and > you will be formally invited.
>
>
> Thanks in advance for your help.
> Best
>
>
> >
>
>
> regards, Roger
>
>
> >
>
>
> >
>
>
> --- On Thu, 4/14/16, Mildred

> Morgan <mbmorgan@hargray[redacted]
> > wrote:
>
>
> >
>
>
> > > From: Mildred Morgan
> <mbmorgan@hargray[redacted]
> > > Subject: 5 Glyphosate Papers > > To:
> "Roger McClellan"
>
>
> <roger.o.mcclellan@[redacted]t>
>
>
>
> > > Date: Thursday, April
> 14, 2016, 9:38 AM The 5 glyphosate papers > >
> attached.
>
>
> > >
>
>
> > >
>
>
> > >
>
>
> > >
>
>
>
>
>

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Wednesday, June 1, 2016 3:37 AM
To: Gunnar Johanson; Roger McClellan
Cc: mbmorgan@hargray[redacted]; s.tsuda@iwate-u.ac[redacted]dellarcov@gmai[redacted]; david.warheit@[redacted] david.dorman@nscu[redacted]; rcc0022@auburn[redacted] f.guengerich@vanderbilt[redacted] Samuel Cohen
Subject: RE: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear Gunnar,

I understand your point about the extent of sponsorship, but I'm afraid this will have to remain confidential. I'm glad, otherwise, that the change I suggest below makes sense. I intend to implement this with the next published supplement, likely to be that of the glyphosate papers discussed below.

Once again, I'm grateful for this discussion, as it is a particularly pertinent issue for the journal. Any other thoughts, perspectives or suggestions on this from the board are very welcome, as ever.

All best wishes,
Charles

From: Gunnar Johanson [mailto[redacted]@ki.se]
Sent: 24 May 2016 14:01
To: Whalley, Charles; Roger McClellan
Cc: mbmorgan@hargray[redacted]; s.tsuda@iwate-u.a[redacted] dellarcov@[redacted]; david.warheit@[redacted]; david.dorman@nscu[redacted] rcc0022@auburn[redacted] f.guengerich@vanderbilt[redacted]Samuel Cohen
Subject: SV: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear Charles,
Sounds good, with that I am satisfied for now (although I would be happier if the extent of sponsorship was also indicated somehow).
All the best,
Gunnar

Dear Gunnar,

A change that I am planning for any sponsored supplements published in the 2016 volume and thereafter is to include a statement appended to each article, stating the name of the sponsor. In previous years this information was included with issue preliminary information, although as most sponsored supplements are now online-only this has become redundant. I also think that it's important for those reading an individual article to see the information without having to seek it out.

Do you think this would be a helpful change?

Best wishes,
Charles

From: Gunnar Johanson [mailto[redacted]@ki.se]
Sent: 13 May 2016 14:29
To: Whalley, Charles; Roger McClellan
Cc: mbmorgan@hargray[redacted]; s.tsuda@iwate-u.ac[redacted] dellarcov@[redacted] david.warheit@[redacted]; david.dorman@nscu[redacted] rcc0022@auburn[redacted] f.quengerich@vanderbilt[redacted] Samuel Cohen
Subject: SV: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear Charles,
Thank you for the info. As far as can see, the T&F Annual Report is not helpful as it contains no information specific for CRT. I am happy to note that you are "... working to ensure ... making readers aware of which issues of the journal have been sponsored..." Can you give some more details how this will be done? By downloading and reading a random paper (Vol 45 S2 1-55), I find no information telling that T&F has been sponsored by the authors to publish the paper. If the sponsorship is not openly declared, it looks very much like "native advertising" or "embedded marketing". The elaborate peer-review and extensive DOI at the end of each paper are good but not sufficient, as the don't cover the relation between the authors and T&F.
Best regards,
Gunnar

PS. Roger, I see these mails as an internal discussion within the Editorial Board.

Från: Whalley, Charles [mailto:[redacted]tandf.co.uk]
Skickat: den 13 maj 2016 11:27
Till: Roger McClellan; Gunnar Johanson
Kopia: mbmorgan@hargray[redacted] s.tsuda@iwate-u.ac[redacted] dellarcov@[redacted]; david.warheit@[redacted] david.dorman@nscu[redacted] rcc0022@auburn[redacted] f.quengerich@vanderbilt[redacted] Samuel Cohen
Ämne: RE: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear Gunnar,

Thanks for your thoughts. I wanted to add to Roger's points below.

You're right to say that we publish the cost of publishing Open Access in *CRT*, which is $2,950 and a flat fee across the journal and indeed across the majority of the journals we publish. However, as I mentioned, the cost of sponsoring a supplement in the journal (which varies) is confidential, as a commercial matter between us and the sponsor. The owner of *CRT* and my employer, Informa, is a public company and so publishes its annual report (http://informa.com/investors/annual-reports/), but I'm afraid that's as much information about the business operations of the journal and of Taylor & Francis that I can give you.

What we are doing is working to ensure that we are making readers aware of which issues of the journal have been sponsored, on top of the extensive Declarations of Interest that Roger insists upon. This information I think has more bearing than the actual monetary amount of any sponsorship. We would hope that readers can make their own judgement.

Even so, this is a particularly pertinent issue for *CRT*, due to the area it works in, and so your thoughts here, and the thoughts of the board, are very welcome. I'd be grateful for any other comments or suggestions as to how we can ensure that the journal continues to be seen as making an impartial and critical contribution to the literature. Short of areas of commercial sensitivity, I'm open to any other areas where we can increase transparency or demonstrate fairness. I also wonder if there's anything we can do to build bridges with all sides of these debates, although I'm speculating a little here.

As ever, I'd invite you all to feel free to contact me separately at my details below if you'd like to discuss personally.

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]
Sent: 12 May 2016 17:11
To: Whalley, Charles; Roger McClellan; Gunnar Johanson
Cc: mbmorgan@hargray[redacted] s.tsuda@iwate-u.ac[redacted] dellarcov@gmail[redacted] david.warheit@[redacted];
david.dorman@nscu[redacted] rcc0022@auburn[redacted] f.quengerich@vanderbilt[redacted] Samuel Cohen
Subject: Re: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Gunnar:
Thanks for your follow up note on the Special Glyphosate Supplement. I will off some clarification on some of the issues you raise.
First, let me address my role as the Editor of Critical Reviews in Toxicology. I do have a contract with Informa / Taylor and Francis for my services as Editor of CRT. That contract provides me a flat fee to cover all of my time and expenses for serving as Editor, the most important aspects of which are the maintenance of manuscript flow and the delivery of high quality , peer-reviewed manuscript to T and F. To assist me, I engage Mildred Morgan, who has worked effectively and efficiently with me for decades. The fee I receive is the same irrespective of the number of manuscripts moving through the system and whether CRT includes any Special Supplements. Hence, there is no financial incentive for me to promote the publication of Special Supplements. Indeed, every Special Supplement requires more effort from me and Mildred for which I receive NO additional reimbursement.
It follows logically to ask why I should consider recommending publication of any Special Supplements. I do so as part of my professional responsibility as Editor. I want to see the 920 pages allotted each year for regular issues of CRT used to publish high quality , high impact papers in a timely manner. That is a difficult balancing act involving (a) high scientific impact, (b) high scientific quality and (c) timeliness. Impact and quality are not the same. By impact I am referring to scientific information that is relevant to contemporary Societal issues. Scientific quality is independent of whether the content is relevant to Societal issues. Timeliness is obviously of concern for all authors, they would like to have their paper published as soon as possible. T and F addresses that issue in part by promptly processing all accepted manuscripts and posting them on line at the earliest possible date. However, no one would like to have their paper in limbo as to formal publication for months and months. Hence, the dilemma of every Editor and ,especially Review Journal Editor. I want to have a modest back log but not an excessive back log. I can assure you I have had more then a few sleepless nights thinking about whether I have the right balance.
This brings me to the five Glyphosate papers. This is one of the world's highest impact chemicals. IARC operates one of the world's most widely recognized cancer hazard classification schemes. CRT previously published at least three widely cited review papers on Glyphosates that were considered in the IARC review. The IARC cancer hazard classification of Glyphosate is one of the most controversial cancer hazard classifications rendered in recent years. Although let me quickly note that the cancer hazard classifications rendered for "outdoor air" and "airborne particulate material" follow close behind. When I learned that Monsanto was going to sponsor a critical review of the cancer hazard of glyphosate, including a critique of the IARC review, managed by InterTek , I decided it would be highly desirable to publish that critical review in CRT. I thought then and now that CRT was the ideal publication venue for this review because of the rigor of CRT's review process, our transparent "Declaration of Interest" process and our desire to provide access to all underlying data through use of electronic supplements and electronic linkages.
In anticipation of the number of pages involved I quickly decided that it would be best to publish the new review as a Special Supplement. At that point I handed off to Charles Whalley, the Managing Editor of CRT, and the business office of T and F the negotiation of the details , including fees, for publishing the Special Supplement. As the recipients of this

memo know I have 60 years of experience as a scientist, scientific manager and science advisor. What may not be as well known is I have over 50 years of business experience running large scale research enterprises, including responsibility for the bottom line. That means making tough decisions as to when you hire and fire your scientific colleagues. To provide me better tools for working as a scientific business manager I enrolled and completed a Master of Management Science degree at the University of New Mexico, the equivalent of an MBA. I understand business - it is rough and tumble!!!
I fully understand the T and F business decision to not release details, including publication fees, of the agreement between T and F and InterTek for publishing the Special Supplement containing the glyphosate papers. Indeed, I suspect the agreement at this stage has not yet been published because the number of pages to be published is not yet known. Wearing my "business hat" I can assure you that T and F has very straight forward business procedures for deciding what is a reasonable fee for publishing a Special Supplement containing 125, 150, 175 or 200 pages. It is not some arbitrary process guided by a " lets charge as much as possible" approach. Indeed, I suspect an examination of the fees typically charged by T and F for 'open access" will provide clues as to the cost to the sponsor of publishing the Special Supplement. As I hope everyone knows the "scientific publishing business" is a tough business today with rapidly changing practices. [As an aside, how many paper solicitations from fly by night journals have you received this month?]
Bottom line, I count on T and F to run their publishing business in an ethical and business like manner. I am counting on that because I want then]m to be in business and publishing CRT indefinitely. I certainly do not want them to go out of business. The counter point is that I will continue to deliver them high scientific quality, high impact , rigorously peer reviewed manuscripts to fill the 920 pages of regular issues they have contractually agreed to provide to their subscribers and occasional provide papers for a Special Supplement.
As an update, the five glyphosate papers are moving through an extraordinarily rigorous review process. The review comments meet the high standards of CRT and will help the authors further improve the final accepted version of the papers. I do anticipate preparing a "prelude" that will introduce the Special Supplement".
I hope the foregoing material is helpful to all of you I welcome any further inquiries by e-mail or phone. (505-296-7083).
Again, thank you for your assistance with CRT and , especially, with the glyphosate Special Supplement.
With best regards,
Roger
PS This is a "business sensitive communication". I would appreciate your not sharing it or communicating the contents with any individuals other than the recipients.

On Thu, 5/12/16, Gunnar Johanson <[redacted]@ki.se> wrote:

Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar
To: "Whalley, Charles" <C[redacted]@tandf.co.uk>, "Roger McClellan" <[redacted]@att.net>
Cc: "s.tsuda@iwate-u.ac[redacted]" <s.tsuda@iwate-u.ac[redacted]>, "dellarcov@[redacted]" <dellarcov@[redacted]>, "david.warheit@[redacted]" <david.warheit@[redacted]>, "david.dorman@[redacted]" <david.dorman@[redacted]>, "mbmorgan@[redacted]" <mbmorgan@[redacted]>, "rcc0022@auburn[redacted]" <rcc0022@auburn[redacted]>, "f.guengerich@vanderbilt.edu" <f.guengerich@vanderbilt[redacted]>, "Samuel Cohen" <scohen@unmc[redacted]>
Date: Thursday, May 12, 2016, 7:49 AM

#yiv4818449056
#yiv4818449056 --

_filtered #yiv4818449056 {font-family:Calibri;panose-1:2 15
5 2 2 2 4 3 2 4;}
_filtered #yiv4818449056 {font-family:Tahoma;panose-1:2 11
6 4 3 5 4 4 2 4;}
#yiv4818449056
#yiv4818449056 p.yiv4818449056MsoNormal, #yiv4818449056
li.yiv4818449056MsoNormal, #yiv4818449056
div.yiv4818449056MsoNormal
{margin:0cm;margin-bottom:.0001pt;font-size:12.0pt;}
#yiv4818449056 a:link, #yiv4818449056

span.yiv4818449056MsoHyperlink
{color:blue;text-decoration:underline;}
#yiv4818449056 a:visited, #yiv4818449056
span.yiv4818449056MsoHyperlinkFollowed
{color:purple;text-decoration:underline;}
#yiv4818449056 p.yiv4818449056MsoAcetate, #yiv4818449056
li.yiv4818449056MsoAcetate, #yiv4818449056
div.yiv4818449056MsoAcetate
{margin:0cm;margin-bottom:.0001pt;font-size:8.0pt;}
#yiv4818449056 span.yiv4818449056BallongtextChar
{}
#yiv4818449056 p.yiv4818449056emailquote, #yiv4818449056
li.yiv4818449056emailquote, #yiv4818449056
div.yiv4818449056emailquote
{margin-right:0cm;margin-left:1.0pt;font-size:12.0pt;}
#yiv4818449056 span.yiv4818449056E-postmall20
{color:#1F497D;}
#yiv4818449056 p.yiv4818449056BalloonText, #yiv4818449056
li.yiv4818449056BalloonText, #yiv4818449056
div.yiv4818449056BalloonText
{margin:0cm;margin-bottom:.0001pt;font-size:12.0pt;}
#yiv4818449056 span.yiv4818449056BalloonTextChar
{}
#yiv4818449056 span.yiv4818449056E-postmall23
{color:#1F497D;}
#yiv4818449056 .yiv4818449056MsoChpDefault
{font-size:10.0pt;}
_filtered #yiv4818449056 {margin:72.0pt 72.0pt 72.0pt
72.0pt;}
#yiv4818449056 div.yiv4818449056WordSection1
{}
#yiv4818449056

Thank you Charles for your prompt
answer. What you say is all well, except that it is not
satisfying with the secret agreement monetary agreement
between T&F and the authors/sponsors. In my view, this
should not be a business secret but similar as for regular
open access articles where T&F openly declares the fees.
The secrecy around the supplements opens up for suspicions
of economic incentives for
Taylor & Francis which in turns spills over to the
journal since, even if there are no extra incentives for the
supplements, I assume that the Chief Editor receives a
salary or honorarium for his work (as he rightly should
considering the importance of the
task and all the effort he puts into it).
Does anyone else have thoughts on
this?
Best regards,
Gunnar

Gunnar Johanson
| Ph.D. |
Professor

Head, Unit of Work
Environment Toxicology

Institute of Environmental Medicine

Karolinska Institutet

Nobels väg 13 | P.O. Box 210 | SE-171 77 Stockholm,
Sweden

+[redacted] Mobile +4[redacted]

[redacted]@ki.se

http://ki.se/en/imm/unit-of-work-environment-toxicology

http://www.nordicexpertgroup.org

Från: Whalley, Charles
[mailto:Charles.Whalley@tandf.co.uk]

Skickat: den 10 maj 2016 18:05

Till: Gunnar Johanson; Roger McClellan

Kopia: s.tsuda@iwate-u.ac.jp; dellarcov@gmail.com; david.warheit@gmail.com; david.dorman@nscu.edu; mbmorgan@hargray.com; rcc0022@auburn.edu; f.guengerich@vanderbilt.edu; Samuel Cohen

Ämne: RE: SV: 5 Glyphosate Papers/ Comments from Gunnar

Dear all,

Many thanks for including me on your discussions here, as I'm grateful to hear your thoughts on this crucial issue for the journal.

As Gunnar has noted, CRT commonly publishes supplements funded by industry sponsorship. These allow the authors to publish as a stand-alone issue separate from the normal schedule of issues, meaning that they can publish as soon as the articles are accepted. These supplements are commonly made free-to-view, and are promoted by Taylor & Francis. Unsurprisingly, industry groups often find this publication option attractive.

The sponsorship in no way guarantees acceptance. To reiterate Roger's comments, the commercial and editorial elements of the journal are entirely separate. Editorial policy is Roger's responsibility. We do not overrule or interfere in his decisions for commercial reasons. Similarly, these articles are subject to all the same peer review and scrutiny of their declarations of interest as any other manuscript. Additionally, to be clear, there is no financial incentive for anyone involved in the editorial process relating to sponsored supplements.

I can't comment on how much sponsors pay for these supplements, as this is commercially sensitive.

Regarding publishing a commentary alongside this proposed issue, I'd be happy to make room for such an editorial, if that's Roger's decision

following
this suggestion. I would suggest that the focus of such a commentary should be on the significance of these articles, as Vicki has suggested, with an additional opportunity to remind our readership of editorial policy around sponsored supplements and how it
applies in this case. I will, however, leave this up to Roger.

I hope this helps clarifies
matters from the publisher's perspective. Please do let me know if you have any further questions or comments on this. I'm very eager to hear them!

All best wishes,
Charles

Charles Whalley
-
Managing Editor, Medicine & Health Science Journals
Taylor & Francis
Group
4 Park Square, Milton Park,
Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk

www.tandfonline.com

From: Gunnar Johanson [mailto[redacted]@ki.se]

Sent: 09 May 2016 14:44

To: Roger McClellan

Cc: s.tsuda@iwate-u.ac[redacted]

dellarcov@[redacted] david.warheit@[redacted]
david.dorman@nscu[redacted]

mbmorgan@hargray[redacted]; rcc0022@auburn[redacted]
Whalley, Charles;
f.guengerich@vanderbilt[redacted]
Samuel Cohen

Subject: SV: SV: 5 Glyphosate Papers/ Comments from Gunnar

Thank you Roger for clarifying. It
is good with the rigorous review and detailed COIs of CRT,
I have no problem with those items or, for that matter,
that
industry (or other vested interests) funds research and
expert groups and seek to publish their results.

My remaining concern is that it
may be seen as industry is paying their way into the journal
("The authors/ sponsors of these Supplemental Issues
pay a special
fee negotiated between the Authors / Sponsors and Taylor
and Francis. As the CRT Editor, I have nothing to do
with this business transaction. My role is to assure that
all papers published in any Special Supplement receive the
same, high quality rigorous
review as papers published in regular issues."). I
checked the last 15 supplemental papers in CRT , all stem
from industry. It is reasonable that the authors/sponsors
pay for the publication costs but not a lot more, as this
might bias the review and publishing
processes.

So, I would appreciate a
clarification how much is paid by the authors/sponsors to
the publisher and how editors and reviewers are reimbursed
(if at all). Maybe
Charles Whalley can respond to this?

Best regards,

Gunnar

PS. I agree with Vicky about an accompanying commentary.

-----Ursprungligt meddelande-----

Från: Roger McClellan [mailto:roger.o.mcclellan@a[redacted]

Skickat: den 8 maj 2016 21:42

Till: Gunnar Johanson

Kopia: s.tsuda@iwate-u.a[redacted]

dellarcov@[redacted] david.warheit@[redacted]
david.dorman@nscu[redacted]

mbmorgan@hargray[redacted] roger.o.mcclellan@[redacted]
rcc0022@auburn[redacted]

Charles.Whalley@tar[redacted] f.guengerich@vanderbi[redacted]
Samuel Cohen

Ämne: Re: SV: 5 Glyphosate Papers/ Comments from Gunnar

Gunnar and other members of the
CRT Editorial Advisory Board

Gunnar, thank you
for your e-mail concerning the publication of a Supplemental Issue including 5 papers on Glyphosate. Your e-mail was a follow up to
our discussion of this matter at our Editorial Advisory Board in New Orleans and my distribution of copies of the papers.

By way of background,
CRT in recent years has included 920 pages each year which have been published on line electronically and last year published at
year end as a single printed copy. The authors of some papers have purchased on line access.

In addition to the
regular issues, CRT has a long standing practice of publishing Special Supplements. The authors/ sponsors of these Supplemental Issues
pay a special fee negotiated between the Authors / Sponsors and Taylor and Francis. As the CRT Editor, I have nothing to do with this business transaction. My role is to assure that all papers published in any Special Supplement receive the same, high quality
rigorous review as papers published in regular issues. Indeed, the agreement between T and F and the Authors/ Sponsors specifically note that publication of the Special Issue is contingent upon scientific review and acceptance of the papers. It does not guarantee
acceptance. . The primary reason for publishing a Special Issue of CRT is to minimize the impact on our limited page budget. Papers included in the Special Supplements do not count against the current annual 920 page
limit.

As I recall, CRT has
published 3 papers in the recent past on Glyphosate. All three papers were downloaded many times and have been widely cited, including
by IARC. One paper by Griem etal contained extensive supplemental material (This is different than a Special Issue Supplement). It is not clear how well IARC reviewed this paper and , especially, the electronic supplement. However, I can assure you that the
electronic supplement is clearly marked in the text.

After the IARC review of glyphosate I was contacted by personnel from Monsanto and InterTek, a private consulting firm, as to my interest in considering one or multiple papers on glyphosate that would be a critique of the IARC review. I responded that I would be enthusiastic about considering one or multiple papers. I indicated my preference would be to have one large paper or a collection of papers to be published in a single issue. I indicated that since it was anticipated that these papers would be comprehensive and long I thought it unlikely these papers could be published in a regular issue. I noted that I would expect the papers to have comprehensive and transparent Declarations Of Interest , as is routine for CRT. As an aside, I know of no other scientific journal that has as rigorous a Declaration of Interest policy as CRT with publication of each DOI.

Gunnar has raised the issue of the employment affiliation of the authors and the past association of some of the authors with Monsanto. I expect that to be made clear in the DOIs. As a matter of policy, I do not think where an individual author is employed (academe, government, consulting firm, private consultant, etc) should be a determinant of whether a paper should be considered for publication. I do expect all relevant material relating to potential conflicts of interest to be disclosed in the DOI. Quite frankly, I am concerned by many journals allowing self proclamations from authors --"We have no conflicts of interest to declare." That is "eye wash". Conflicts of Interest are in the eyes of the beholder not the Declarer.

I think my job as an Editor is to see that the submitted paper receive a rigorous review by outstanding experts from around the globe. In the case of the submitted glyphosate papers I think I have selected some outstanding reviewers, in some case up to 7 per paper. As an aside, how many of you have received 7 sets of external review comments on any paper, original research or review paper, you have authored?
Many of you agreed to review one or more of the five papers. For that special effort I extend my thanks. I will

be pleased to have you review any or all of the revised papers. I use the review comments to help guide my decision to accept, request revision or reject a paper. Most importantly, I expect the authors to use the review comments to further improve their revised paper.

The five glyphosate papers are still under review. In general, the review comments are very positive and constructive. Many reviewers noted they were pleased to have these papers published in CRT.

Gunnar has raised the issue of my publishing a commentary on the five papers as part of the Special Supplement . I have never published such a commentary for either a regular issue or Special Issue. MY basic view is that all papers published in CRT "speak for them selves'. However, I am willing to consider such a commentary for this Special Issue if you think it useful. If I were to prepare one it would include many of the points made here. Of course, I would also need to refer to the IARC process and the IARC decision on glyphosate. It is my view that the five papers published in CRT will represent the most comprehensive review of the world's literature on the potential carcinogenicity of glyphosate and be widely cited by others.

I welcome you views on this important matter.

Best regards,

Roger

On Mon, 5/2/16, Gunnar Johanson
<[redacted]@ki.se>
wrote:

Subject: SV: 5 Glyphosate
Papers

To: "Roger McClellan"
<roger.o.mcclellan@[redacted]
"david.warheit@[redacted]
<david.warheit@[redacted]>,
"david_dorman@ncsu[redacted]
<david_dorman@ncsu[redacted]

Cc: "s.tsuda@iwate-u.ac[redacted]
<s.tsuda@iwate-u.ac[redacted],
"Mildred" <mbmorgan@hargray[redacted]

Date: Monday, May 2, 2016, 4:27
AM

Dear Roger,

How will this will be introduced
in the journal, i.e. how will it be explained that the 5
papers appear in a separate volume (assuming they will be
accepted
for publication) ?

Nearly early all

authors are more or less connected
to Monsanto. My concern is that this may be viewed as an
industry input and, more important, that the integrity

and independence
of CRT may be questioned by the scientific
community.

All the best

Gunnar

-----Ursprungligt
meddelande-----

Från: Roger McClellan [mailto:roger.o.mcclellan@[redacted]]

Skickat: den 14 april 2016
20:55

Till:
david.warheit@[redacted]

david_dorman@[redacted]

Gunnar Johanson

Kopia:
s.tsuda@iwate-u.ac[redacted]

roger.o.mcclellan@[redacted];

Mildred

Ämne: Fw: 5 Glyphosate
Papers

--- On Thu, 4/14/16, Roger
McClellan <roger.o.mcclellan[redacted]

wrote:

> From: Roger

McClellan <roger.o.mcclellan@[redacted]

> Subject: Fw: 5 Glyphosate
Papers

> To:
bolt@ifado[redacted]
rcc0020@auburn[redacted] f.guengerich@vanderbilt[redacted]

> "Samuel Cohen"

<scohen@unmc[redacted]>

> Cc: "Roger
McClellan" <roger.o.mcclellan@[redacted]>,
"Mildred"

> <mbmorgan@hargray[redacted]

> Date: Thursday, April 14,
2016, 11:51 AM To all:

> Attached are five
papers

critiquing the IARC review of
glyphosate.

> Assuming the papers are
accepted after rigorous review , they will be >
published in a single Special Supplement to CRT. I would
be pleased if > you would
agree to review the general paper and one or more of
the > four detailed papers. If you are willing to
review one or more paper > please linform my
assistant, Mildred Morgan,
mbmorgan@hargray[redacted]
and > you will be formally invited.

Thanks in advance for your help.
Best

>

regards, Roger

>

>

--- On Thu, 4/14/16, Mildred Morgan <mbmorgan@hargray[redacted]> > wrote:

>

> > From: Mildred Morgan <mbmorgan@hargray[redacted]
> > Subject: 5 Glyphosate Papers > > To: "Roger McClellan"

<roger.o.mcclellan@att[redacted]

> > Date: Thursday, April 14, 2016, 9:38 AM The 5 glyphosate papers > > attached.

> >

>

>

> >

Roger McClellan

From:	onbehalfof+mbmorgan+hargray.com@manuscriptcentral.com on behalf of mbmorgan@hargray[redacted]
Sent:	Friday, May 13, 2016 4:58 AM
To:	roger.o.mcclellan[redacted]
Subject:	All required reviews have been returned for Manuscript ID BTXC-2016-0026

13-May-2016

Dear Dr Roger McClellan:

All required reviews have been returned by the reviewers for Manuscript ID BTXC-2016-0026 entitled "Glyphosate in the general population and in applicators: A critical review of studies on exposures" with Dr Ashley Roberts as contact author.

Please look at the reviews and make a decision by 27-May-2016.

Sincerely,
Mildred B Morgan
Critical Reviews in Toxicology Editorial Office mbmorgan@H[redacted]

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]
Sent: Saturday, May 14, 2016 10:03 AM
To: Ashley Roberts
Cc: Mildred; Roger McClellan
Subject: Titles for Constellation of Glyphosate papers

Ashley:

As you coordinate the revision of the five glyphosate papers please give consideration to revising the titles. One option is to use a single master title like "Review of Potential Carcinogenicity of Glyphosate:" and assign the five papers sub- titles like ---- I. Overview and Summary Conclusions, II. Exposure Assessment, III. Animal Evidence , IV. Epidemiological Evidence and V. Mechanistic Evidence. This would parallel the IARC structure which is being critiqued. The current titles have been confusing to some reviewers.

As I have noted earlier, many of the reviewers of the 5 papers have called for greater clarity in presenting the approach used and conclusions drawn by IARC and then the comparison and contrasting of the approach and conclusions of the InterTek organized reviews.

Best regards,

Roger

Roger McClellan

From: John Acquavella <acquajohn@[redacted]>
Sent: Saturday, May 14, 2016 10:35 AM
To: Roger McClellan
Cc: mbmorgan@hargray[redacted] ashley.roberts@intertek[redacted]
Subject: Re: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0029

Roger:

Thank you for the note. My affiliation is with Aarhus University. Like my co-authors, we can consult as we judge appropriate and our universities are not involved. I can see that my email signature can cause confusion and have revised it.

That being said, I will make sure that our disclosure of interests statement is clear - that we were all acting as independent consultants. We realize that this is a controversial area, but we hope that fair minded people will see the scientific value in our review - as all the reviewers did.

It is nice to know about your Aarhus connection. One of the great things about my professorship is spending time in residence in Aarhus. I go approximately 3 times a year to teach, advise students, and work with colleagues. The Department of Clinical Epidemiology is a great department and they have access to unparalleled national data sources for clinical epidemiology research. They are not political at all and actually value having faculty with a background in private industry. That's refreshing.

Regards,

John

John Acquavella, PhD FACE FISPE
Professor, Dept Clinical Epidemiology
Aarhus University, Denmark
+1[redacted]
+1 9[redacted]

On 5/14/16, 9:18 AM, "Roger McClellan" <[redacted]@att.net> wrote:

>John:
> I note from your e-mail you are using a combination title and address, ie Consultant and Professor. I think this will require greater clarity in the final papers. Am I correct in assuming this work was done as an independent consultant without any involvement of Aarhus University? I raise this because I can expect the critics of this and the other papers

Roger McClellan

From: onbehalfof+roger.o.mcclellan+[redacted]@manuscriptcentral.com on behalf of roger.o.mcclellan@[redacted]
Sent: Wednesday, May 25, 2016 5:01 PM
To: roger.o.mcclellan@[redacted]
Cc: mbmorgan@hargray[redacted]
Subject: Manuscript ID BTXC-2016-0029.R1 now in your Associate Editor Center

25-May-2016

Dear Dr McClellan:

The above manuscript, entitled "Glyphosate Epidemiology Expert Panel Review A weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma" with Professor John Acquavella as contact author, has been assigned to you and is awaiting reviewer selection. Please go to your Editor-in-Chief Center at https://mc.manuscriptcentral.com/btxc and select reviewers by 27-May-2016.

Sincerely,

Roger O. McClellan
Editor-in-Chief, Critical Reviews in Toxicology roger.o.mcclellan@[redacted]

Roger McClellan

From: Ashley Roberts Intertek <ashley.roberts@intertek[redacted]
Sent: Monday, May 16, 2016 10:04 AM
To: roger.o.mcclellan@[redacted]; Judy Vowles Intertek
Cc: mbmorgan@hargray[redacted]
Subject: RE: Critical Reviews in Toxicology

Thank you Roger

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 905-542-2900
Fax: +1 905-542-1011
E-mail: ashley.roberts@intertek[redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----
From: onbehalfof+roger.o.mcclellan+[redacted]@manuscriptcentral.com
[mailto:onbehalfof+roger.o.mcclellan+[redacted]@manuscriptcentral.com] On Behalf Of roger.o.mcclellan@[redacted]
Sent: May-16-16 12:03 PM
To: Ashley Roberts Intertek; Judy Vowles Intertek
Cc: roger.o.mcclellan@[redacted]; mbmorgan@hargray[redacted]
Subject: Critical Reviews in Toxicology

16-May-2016

BTXC-2016-0025 - Glyphosate: Carcinogenic potential -- A Critical review using four Expert Panels

Dear Dr Ashley Roberts:

By copy of this e-mail I am asking Mildred to provide you an additional set of comments on the summary paper. I strongly concur with the reviewer's suggestions. As you will note there is a strong concensus that the InterTek coordinated review and critique of the IARC review and classification of glyphosate needs to be very direct in comparing and contrasting the approach and results fof IARC and the InterTek panels. I strongly support the inclusion in the summary paper of a table listing the participants in each InteTek Panel and a summary table comparing and contrasting key findings and conclusions of the IARC Panels and the InterTek panels with linkages to each of the detailed papers.

There may be one more set of comments on this paper. I will keep you posted.

Sincerely,
Dr Roger McClellan
Critical Reviews in Toxicology

Valued Quality. Delivered.

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[redacted]
Sent: Friday, May 20, 2016 8:16 AM
To: Mildred Morgan; 'Roger McClellan'
Subject: RE: Glyphosate manuscripts in ScholarOne

Dear Mildred,

I see! I didn't realise they'd already had a decision, which is why I couldn't find them. I'm a little behind.

I am sorry that you're still having to work with your left hand, so I'm especially grateful for your response here. I do hope you are back to both hands soon.

Very best wishes,
Charles

From: Mildred Morgan [mailto:mbmorgan@hargray[redacted]
Sent: 20 May 2016 15:07
To: Whalley, Charles; 'Roger McClellan'
Subject: RE: Glyphosate manuscripts in ScholarOne

Dear Charles:

All of the Glyphosate papers are loaded into Scholar One , they have all been reviewed and the comments sent back to authors for revision of the papers. Dr. Ashley Roberts has also received all of the comments.

I am still typing with only my left hand so it is a slow process. I am going to therapy 3 times a week. I will be so happy to be able to use both hands. Just going to take and patience.

Mildred

From: Whalley, Charles [mailto:Charles.Whalley@tandf[redacted]
Sent: Friday, May 20, 2016 9:49 AM
To: Roger McClellan (roger.o.mcclellan@[redacted])
Cc: mbmorgan@hargray[redacted]
Subject: Glyphosate manuscripts in ScholarOne

Dear Roger and Mildred,

Am I right in thinking that the Glyphosate manuscripts from Dr Roberts' group are not currently loaded into the ScholarOne system?

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: [redacted]
[redacted]@tandf.co.uk

www.tandfonline.com

Taylor & Francis is a trading name of Informa UK Limited,
registered in England under no. 1072954

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[redacted]>
Sent: Friday, May 20, 2016 9:00 AM
To: Roger McClellan
Cc: mbmorgan@hargray[redacted]
Subject: RE: Glyphosate manuscripts in ScholarOne

Dear Roger,

Many thanks for confirmation. I wasn't aware that a decision had already been returned on these manuscripts. I've got what I need to start preparing a quote for a possible supplement.

All best wishes as ever,
Charles

From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]
Sent: 20 May 2016 15:41
To: Whalley, Charles
Cc: mbmorgan@hargray[redacted]; Roger McClellan
Subject: Re: Glyphosate manuscripts in ScholarOne

Charles:
All five manuscripts have gone through a rigorous initial round of review including 10 reviewers on the Introduction and Summary paper. The comments have been positive and will help the authors further improve the constellation of five papers. Making revisions and ensuring the papers are appropriately crossed linked and that references and Supplemental material are in order is going to be challenging for Ashley and his colleagues and will take some time.
I suspect the reference to Sponsor should note InterTek with reimbursement by Monsanto.
Best regards,
Roger

On Fri, 5/20/16, Whalley, Charles <[redacted]@tandf.co.uk> wrote:

Subject: Glyphosate manuscripts in ScholarOne
To: "Roger McClellan (roger.o.mcclellan@[redacted]" <roger.o.mcclellan@[redacted]>
Cc: "mbmorgan@hargray[redacted] <mbmorgan@hargray[redacted]>
Date: Friday, May 20, 2016, 6:49 AM

Dear Roger
and Mildred,

Am I right
in thinking that the Glyphosate manuscripts from Dr Roberts' group are not currently loaded into the ScholarOne system?

Best
wishes,
Charles

Charles Whalley
-
Managing Editor, Medicine & Health Science Journals
Taylor & Francis
Group
4 Park Square, Milton
Park, Abingdon, Oxon, OX14 4RN, UK
Direct line:
+[redacted]
Switchboard:
+[redacted]
[redacted]@tandf.co.uk

www.tandfonline.com

Roger McClellan

From: Ashley Roberts intertek <[redacted]@intertek.com>
Sent: Thursday, May 26, 2016 8:33 AM
To: roger.o.mcclellan@[redacted]
Cc: mbmorgan@hargray[redacted]
Subject: RE: Critical Reviews in Toxicology

Hi Roger,

I will call later today to discuss.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1[redacted]
Fax: +1[redacted]
E-mail:[redacted]@intertek.com
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----
From: onbehalfof+roger.o.mcclellan+[redacted]@manuscriptcentral.com
[mailto:onbehalfof+roger.o.mcclellan[redacted]t@manuscriptcentral.com] On Behalf Of roger.o.mcclellan[redacted]
Sent: May-25-16 6:58 PM
To: Ashley Roberts Intertek; Judy Vowles Intertek
Cc: roger.o.mcclellan@[redacted] mbmorgan@hargray[redacted]
Subject: Critical Reviews in Toxicology

25-May-2016

BTXC-2016-0026.R1 - Glyphosate in the general population and in applicators: A critical review of studies on exposures

Dear Dr Ashley Roberts:

Let's discuss how to better identify the Supplemental Material so it will stand alone and be informative to the reader. A brief paragraph to introduce it would be helpful to the reader.

A one or two sentence descriptor for each set of Supplemental Material that could be used at the end of the text would be useful.

Sincerely,
Dr Roger McClellan

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@a[redacted]>
Sent: Tuesday, July 5, 2016 3:31 PM
To: Roger McClellan; Ashley Roberts Intertek
Cc: Roger McClellan; Mildred
Subject: Re: Need for telephone conversation/ Followup

Ashley:
It is shown below -[redacted] Or you can reach me at my desk at[redacted] if I am at my desk, it is my fax line. Or call my cell phone at[redacted] I hope your having a great time in Nova Scotia, one of my favorite spots. I found a lot of McClellans and MacLellans there, almost all were six feet under.
Roger

On Tue, 7/5/16, Ashley Roberts Intertek <[redacted]@intertek.com> wrote:

Subject: Re: Need for telephone conversation/ Followup
To: "Roger McClellan" <roger.o.mcclellan@[redacted]
Cc: "Roger McClellan" <roger.o.mcclellan@[redacted]>, "Mildred" <mbmorgan@hargray[redacted]>
Date: Tuesday, July 5, 2016, 2:17 PM

Hi Roger,

As I am on vacation, please
could you send me your telephone number so I can call you?

Thanks

Ashley

Sent from my BlackBerry 10 smartphone on the Bell network.
Original Message
From: Roger McClellan
Sent:
Tuesday, July 5, 2016 5:37 PM
To: Ashley
Roberts Intertek
Reply To: Roger
McClellan
Cc: Roger McClellan; Mildred
Subject: Re: Need for telephone conversation/ Followup

Ashley:
I am also
eager to get these papers wrapped up. I was hoping I could deal with one individual, you, rather than multiple authors. However, I understand you are away from your office for some time. There are several issues that need to be addressed.
First, the Acknowledgements

section and Declaration of Interest sections in all the papers need further attention. I want them to be as clear and transparent as possible. At the end of the day I want the most aggressive critics of Monsanto, your organization and each of the authors to read them and say - Damm, they covered all the points we intended to raise.

I was anticipating that each paper would include an Acknowledgements section that would read something like —"The authors gratefully acknowledge the extensive comments received from xx reviewers selected by the Editor and anonymous to the authors. These comments were very helpful in revising the paper." I am proud of the rigorous review given these papers and want to make certain that review is clear to all readers. The Acknowledgements sections should also identify any other reviewers of the paper and any editorial assistance.

The DOIs should start something like --" The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer. The remainder of the DOI should make clear how individuals were engaged, ie by Intertek. If you can say without consultation with Monsanto that would be great. If there was any review of the reports by Monsanto or their legal representatives that needs to be disclosed. Any previous appearances by individuals before regulatory agencies in the USA or abroad needs to be disclosed. The wording concerning involvement of employees of your firm and Can-Tox is not very clear and invites criticism, let it all hang out. Identify the individuals by name and note the nature of work done by the organization for Monsanto.

I want to be assured that all of the references in all the papers are clearly identified and can be made available to any interested person. Can your firm fill that role. I am concerned that in the summary paper key information is not directly referenced , rather reference is made to EPA documents. It is important to be as clear and transparent as possible. As I recall one paper refers to a "Confidential Document". Can that document be made available now?

As a summary point, did the review you conducted use ANY papers not referenced by IARC? If so, should that point be addressed in the summary paper and , perhaps, other papers as appropriate.

On a personal note I think the papers to a varying degree would benefit from very careful editing to minimize language that is combative. I had assumed that at a final stage all the papers would have been carefully edited by a professional editor.

Please give me a call at [redacted] to discuss how best to move forward.

Best regards, Roger

On Tue, 7/5/16, Ashley Roberts Intertek [redacted]intertek.com> wrote:

Subject: Re: Need for telephone conversation
To: "Roger McClellan" <[redacted]@att.net>
Date: Tuesday, July 5, 2016, 4:06 AM

Hi Roger

I am messaging you from a few days vacation I am taking in Nova Scotia.

I am getting a lot of pressure to publish the papers for a lot of reasons as you can imagine. Please could you let me know the changes you require that we spoke of while I was in China. Sorry to rush you on

this matter but these papers
will also
be useful for ECHA which is a European Agency
that is reviewing the safety of glyphosate. We would very
much like to share our
manuscripts with them to aid in their

deliberations.

I look
forward to receiving your reply.

Best Wishes

Ashley

Sent from my
BlackBerry 10 smartphone on the Bell network.
Original Message

From: Roger McClellan
Sent: Sunday, June
19, 2016 8:41 PM
To: Ashley Roberts
Intertek
Reply To: Roger McClellan
Cc: Mildred; Roger McClellan

Subject: Need for telephone conversation

Ashley:
I think it would be
useful if you and I were to have a

telephone conversation with regard to the glyphosate papers.
What is your schedule on Monday or
Wednesday and your
availability for a
call?
Do you have a professional editor
assisting with finalizing
these papers? You
reference in the DOIs that employees of

your firm previously did work for Monsanto. Can you provide
details, ie individuals and areas
of work and time period? I
note at least
one reference to a confidential report. Has

that now been disclosed. Is there any work that the Panels

used in drawing their conclusions
that is not now available?
I would have
been happier if all the paper had noted the

number of external reviewers and the value of the comments.
I am concerned that the authors
have chosen to not comply
with requests to
make it easier fro the readers of identify

ALL the relevant literature. Why not bend over backwards to
address concerns? I am still concerned about the tone in
some places. Why
antagonize the readers? I am still not

clear as to the process used by all of the Panels. These
reports are essentially a rebuttal of IARCs process and
conclusions. There appears to
be a reluctance to be
absolutely clear in
presenting exactly what IARC concluded ,

the Panels conclusions and how they differ. Am I missing
something?
I look forward to
speaking with you.
Best regards,
Roger

Valued
Quality. Delivered.

Valued Quality. Delivered.

Subject: Re: Need for telephone conversation
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
Date: Tuesday, July 5, 2016, 4:06 AM

Hi Roger

I am messaging you from a few days vacation I am taking in Nova Scotia.

I am getting a lot of pressure to publish the papers for a lot of reasons as you can imagine. Please could you let me know the changes you require that we spoke of while I was in China. Sorry to rush you on this matter but these papers will also be useful for ECHA which is a European Agency that is reviewing the safety of glyphosate. We would very much like to share our manuscripts with them to aid in their deliberations.

I look forward to receiving your reply.

Best Wishes

Ashley

Sent from my BlackBerry 10 smartphone on the Bell network.
Original Message
From: Roger McClellan
Sent: Sunday, June 19, 2016 8:41 PM
To: Ashley Roberts Intertek
Reply To: Roger McClellan
Cc: Mildred; Roger McClellan
Subject: Need for telephone conversation

Ashley:
I think it would be useful if you and I were to have a telephone conversation with regard to the glyphosate papers.
What is your schedule on Monday or Wednesday and your availability for a call?
Do you have a professional editor assisting with finalizing these papers? You reference in the DOIs that employees of your firm previously did work for Monsanto. Can you provide details, ie individuals and areas of work and time period? I note at least one reference to a confidential report. Has that now been disclosed. Is there any work that the Panels used in drawing their conclusions that is not now available?
I would have been happier if all the paper had noted the number of external reviewers and the value of the comments.
I am concerned that the authors have chosen to not comply with requests to make it easier fro the readers of identify ALL the relevant literature. Why not bend over backwards to address concerns? I am still concerned about the tone in some places. Why antagonize the readers? I am still not clear as to the process used by all of the Panels. These reports are essentially a rebuttal of IARCs process and conclusions. There appears to be a reluctance to be absolutely clear in presenting exactly what IARC concluded , the Panels conclusions and how they differ. Am I missing something?
I look forward to speaking with you.
Best regards,
Roger

Valued Quality. Delivered.

CONFIDENTIALITY NOTICE

This email may contain confidential or privileged information, if you are not the intended recipient, or the person responsible for delivering the message to the intended recipient then please notify us by return email immediately. Should you have received this email in error then you should not copy this for any purpose nor disclose its contents to any other person.

http://www.intertek.com

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Thursday, July 7, 2016 9:09 AM
To: Ashley Roberts Intertek
Cc: Mildred; Roger McClellan
Subject: Re: Final Revisions

Ashley:
Thanks for the revised papers. I have started to review them. In the summary paper key information is presented in a paragraph beginning at line 127. This is now supported by a reference to a secondary document, ie EPA. Can you provide the primary references. I would personally like to know the reviewing pathologist and have a reference to that report, the other 3 pathologists and a reference to their report and the Pathology Working Group and a reference to their report. Can these be provided?
In the DOI reference is made to a key report Can-Tox was involved in preparing along with Gary Williams. Can that report be referenced? Perhaps it s already referenced in the text. Even if it is reference it again in the DOI.
I will be working through the others and will no doubt have additional comments.
Best regards, Roger

On Wed, 7/6/16, Ashley Roberts Intertek <[redacted]@intertek.com> wrote:

Subject: Final Revisions
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
Cc: "Mildred" <mbmorgan@hargray[redacted]>
Date: Wednesday, July 6, 2016, 5:16 PM

Dear Roger,

Please find attached the revised manuscripts as per your request below.

The changes can be seen as tracked changes for the sake of easy review. We have changed the DOI and made some slight editorial changes to the animal carcinogenicity paper.

I hope these address your concerns? I am currently on my way to Brussels so if these changes are acceptable, please could you confirm and provide me with a letter regarding our sharing these papers with ECHA.

Thanking you in anticipation.

Best Wishes

Ashley

PS. I noted that there was a McClellan street just outside of the town of Baddeck today. I am presuming some of your ancestors migrated to that part of Nova Scotia!!!

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy

Tel: +1[redacted]
Fax: +[redacted]
E-mail: [redacted]@intertek.com
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----
From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]
Sent: July-05-16 4:35 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred
Subject: Re: Need for telephone conversation/ Followup

Ashley:

I am also eager to get these papers wrapped up. I was hoping I could deal with one individual, you, rather than multiple authors. However, I understand you are away from your office for some time.

There are several issues that need to be addressed.

First, the Acknowledgements section and Declaration of Interest sections in all the papers need further attention. I want them to be as clear and transparent as possible. At the end of the day I want the most aggressive critics of Monsanto, your organization and each of the authors to read them and say - Damm, they covered all the points we intended to raise.

I was anticipating that each paper would include an Acknowledgements section that would read something like —"The authors gratefully acknowledge the extensive comments received from xx reviewers selected by the Editor and anonymous to the authors. These comments were very helpful in revising the paper." I am proud of the rigorous review given these papers and want to make certain that review is clear to all readers. The Acknowledgements sections should also identify any other reviewers of the paper and any editorial assistance.

The DOIs should start something like --" The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and preparation of this paper as an independent professional and not as a representative of their employer. The remainder of the DOI should make clear how individuals were engaged, ie by Intertek. If you can say without consultation with Monsanto that would be great. If there was any review of the reports by Monsanto or their legal representatives that needs to be disclosed. Any previous appearances by individuals before regulatory agencies in the USA or abroad needs to be disclosed. The wording concerning involvement of employees of your firm and Can-Tox is not very clear and invites criticism, let it all hang out. Identify the individuals by name and note the nature of work done by the organization for Monsanto.

I want to be assured that all of the references in all the papers are clearly identified and can be made available to any interested person. Can your firm fill that role. I am concerned that in the summary paper key information is not directly referenced , rather reference is made to EPA documents. It is important to be as clear and transparent as possible. As I recall one paper refers to a "Confidential Document". Can that document be made available now?

As a summary point, did the review you conducted use ANY papers not referenced by IARC? If so, should that point be addressed in the summary paper and , perhaps, other papers as appropriate.

On a personal note I think the papers to a varying degree would benefit from very careful editing to minimize language that is combative. I had assumed that at a final stage all the papers would have been carefully edited by a professional editor.

Please give me a call at [redacted] to discuss how best to move forward.

Best regards, Roger

On Tue, 7/5/16, Ashley Roberts Intertek <[redacted]@intertek.com>
wrote:

Subject: Critical Reviews in Toxicology standing matter
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
Cc: "Mildred" <mbmorgan@hargray[redacted] "Whalley, Charles" <Charles.Whalley@tandf[redacted]
Date: Friday, July 8, 2016, 7:13 AM

Dear Roger and Mildred

Thank you for the phone call yesterday. It was lovely to speak to you both. After our conversation, I instructed the typesetter to follow the new guidelines for the presentation of supplemental material so we should soon start to see articles containing a 'Supplemental material' section, as shown in the sample Charles sent you.

I also wanted to follow up my message yesterday with some further information about the changes to journal standing matter I mentioned. These would be beneficial as we could potentially reduce the number of preliminary pages from four to two, freeing up a couple more pages in the journal budget for articles. The information on the standing matter has also been better organised and made clearer and more concise for readers.

I've attached descriptions of the two different templates and also explained a bit more about them below. If either of these appeal to you, I can ask the typesetter to create a journal-specific sample, which I can send to you for your review.

Please do let me know if you have any questions. I look forward to hearing your thoughts once you've had time to consider the various options.

Many thanks
and best wishes

Jenna

Option A

-
The subscriptions information page is removed.
Subscriptions information is merged with the text on the inside covers. The journal's aims and scope appear on the back cover.
-
We would have two preliminary pages if we were to adopt this option: the two table of contents pages.

Option B

-
The table of contents appears on the outside back cover of the journal and is continued onto the inside back cover.
The internal table of contents pages would therefore be removed.
-

Subscription information and typesetting and printing information would be added on page i of the journal.

We would have two preliminary pages: the subscriptions information page (p. i) and a blank page on the reverse of this (p. ii).

Jenna
Whittle
Production Editor,
Journals
Taylor & Francis

4 Park Square, Milton
Park, Abingdon, Oxon, OX14 4RN, UK

jenna.whittle@tandf[redacted]

www.tandfonline.com

Roger McClellan

From: Ashley Roberts Intertek <[redacted]@intertek.com>
Sent: Tuesday, July 12, 2016 3:50 AM
To: Roger McClellan
Subject: RE: Glyposate papers -Frustration
Attachments: Genotoxicity Paper _Supplemental Info_Refs expanded_App B FINAL 2-25-16.....docx

Hi Roger,

Please find attached the changes requested to the genetox manuscript. Please let me know if this is now okay?

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1[redacted]
Fax: +1[redacted]
E-mail:[redacted]@intertek.com
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

-----Original Message-----
From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]]
Sent: July-08-16 2:34 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan
Subject: Glyposate papers -Frustration

Ashley:
When can you and I speak again about these papers. I have spent substantial time working on these papers and I am becoming increasingly frustrated. As an example --read the "revised" carcinogenicity paper. This paper is intended to critique the "animal evidence" that feeds in to the IARC classification. The IARC position should be clearly stated, indeed quoted, as a basis for the review. It is NOT.
Have you read the genotoxicity "revised" paper and the response to reviewers comments. Reviewer 1 calls for more details in Appendix B on identity of studies. The authors argue that was not requested in the earlier publication , why do we need to give it now? Do you agree with this approach to"stiffing" the reviewer?
These are just a couple of examples that heighten my frustration.
When can we speak about these matters?
Roger

Valued Quality. Delivered.

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]t>
Sent: Thursday, July 14, 2016 1:12 PM
To: Mildred
Subject: Fw: RE: Glyposate papers -Frustration
Attachments: Genotoxicity Paper _Supplemental Info_Refs expanded_App B FINAL 2-25-16.....docx

--- On Tue, 7/12/16, Ashley Roberts Intertek <ashley.roberts@intertek[redacted] wrote:

> From: Ashley Roberts Intertek[redacted]intertek.com>
> Subject: RE: Glyposate papers -Frustration
> To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
> Date: Tuesday, July 12, 2016, 2:49 AM
> Hi Roger,
>
> Please find attached the
> changes requested to the genetox manuscript. Please let me know if
> this is now okay?
>
> Best Wishes
>
> Ashley
>
> Ashley
> Roberts, Ph.D.
> Senior Vice President
> *Food & Nutrition Group*
> Intertek Scientific & Regulatory
> Consultancy
> Tel: +1[redacted]
> Fax: +1[redacted]
> E-mail:[redacted]@intertek.com
> 2233 Argentia Road, Suite 201
> Mississauga, Ontario Canada L5N 2X7
>
>
> -----Original
> Message-----
> From: Roger McClellan
> [mailto:roger.o.mcclellan@[redacted]]
> Sent: July-08-16 2:34 PM
> To:
> Ashley Roberts Intertek
> Cc: Roger
> McClellan
> Subject: Glyposate papers
> -Frustration

>
> Ashley:
> When can you and I speak again about these papers. I have spent
> substantial time working on these papers and I am becoming
> increasingly frustrated. As an example --read the "revised"
> carcinogenicity paper. This paper is intended to critique the "animal
> evidence" that feeds in to the IARC classification. The IARC position
> should be clearly stated, indeed quoted, as a basis for the review. It
> is NOT.
> Have you read the genotoxicity
> "revised" paper and the response to reviewers comments. Reviewer 1
> calls for more details in Appendix B on identity of studies. The
> authors argue that was not requested in the earlier publication , why
> do we need to give it now? Do you agree with this approach
> to"stiffing" the reviewer?
> These are just a couple of
> examples that heighten my frustration.
> When can we speak about these
> matters?
> Roger
>
> Valued Quality. Delivered.
> _____
> CONFIDENTIALITY NOTICE
>
> This email may contain confidential or privileged information, if you
> are not the intended recipient, or the person responsible for
> delivering the message to the intended recipient then please notify us
> by return email immediately. Should you have received this email in
> error then you should not copy this for any purpose nor disclose its
> contents to any other person.
>
> http://www.intertek.com
>

Roger McClellan

From: Ashley Roberts Intertek <[redacted]@intertek.com>
Sent: Saturday, July 16, 2016 8:26 AM
To: Roger McClellan
Subject: FW: Manuscript

Hi Roger,

I know you are off for a few days but I have had a question from one of the manuscript leaders and so I thought I better confirm with you.

The question is 1. Should I complete the copyright release form or does that go with the set of all publications?

I believe each person assigned the lead on the manuscript should do this but just thought I should get confirmation.

Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [redacted]
Fax: +1 [redacted]
E-mail: [redacted]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

1. Should I complete the copyright release form or does that go with the set of all publications?
2. When the proofs arrive, the journal wants them returned in 48 hours. Knowing that our group never does anything in 48 hours, is there a standard method you suggest?

David

Roger McClellan

From: John Acquavella <acquajohn@[redacted]>
Sent: Monday, July 18, 2016 1:56 PM
To: roger.o.mcclellan@[redacted]; ashley.roberts@intertek[redacted] judy.vowles@intertek[redacted]
Cc: mbmorgan@hargray[redacted]
Subject: Re: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0029.R1

Dr. McClellan:

I will be speaking at the Toxicology Forum on Tuesday, July 26. My topic is: Implications of the Use of Epidemiologic Data in Risk Analysis. Can I assume that I have your permission to mention some of the key thoughts from our recently accepted glyphosate epidemiology article and to cite it on my slides as: Acquavella et al. A weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma. Crit Rev Toxicol DOI 10.1080/10408444.2016.1214681.

Thank you for your consideration of this request.

Regards,

John

John Acquavella, PhD FACE FISPE
Professor, Dept Clinical Epidemiology
Aarhus University, Denmark
+1[redacted]
+1[redacted]

On 7/15/16, 1:30 PM, "Critical Reviews in Toxicology" <onbehalfof+roger.o.mcclellan[redacted]@manuscriptcentral.com> wrote:

15-Jul-2016

Dear Professor Acquavella:

Ref: Glyphosate Epidemiology Expert Panel Review
A weight of evidence systematic review of the relationship between glyphosate exposure and non-Hodgkin's lymphoma or multiple myeloma

It was a pleasure to receive your revised manuscript and, especially, to note the careful attention you gave to the reviewers comments. In my opinion, the paper is now clearer and will be a valuable contribution to the literature on this widely used chemical. Hence, I am pleased to accept your paper in its current form which will now be forwarded to the publisher for copy editing and typesetting. This paper will be published in a Special Supplement of Critical Reviews in Toxicology along with four related papers.

In a letter to Ashley Roberts I have detailed the circumstances under which this and the other four papers in the Special Issue can be shared with regulatory authorities. Please be certain you adhere to that guidance.

You will receive proofs for checking, and instructions for transfer of copyright in due course.

The publisher also requests that proofs are checked and returned within 48 hours of receipt.

Thank you for your contribution to Critical Reviews in Toxicology and we look forward to receiving further submissions from you.

Sincerely,

Roger O. McClellan
Editor-in-Chief, Critical Reviews in Toxicology
roger.o.mcclellan@[redacted]

Roger McClellan

From:	Whittle, Jenna <[redacted]@informa.com>
Sent:	Monday, July 18, 2016 7:38 AM
To:	Roger McClellan; Whalley, Charles
Cc:	Mildred
Subject:	RE: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0025.R1

Thanks for your messages, Roger. I confirm that the papers have arrived in production and I'll be in touch if I have any questions about them.
The publication date largely depends on how quickly authors can return corrections, assuming all the contractual arrangements are finalised shortly. However, all going well, I would estimate that mid-September seems likely and we will do our best to move things along as quickly as possible. Initial proofs of each article should be ready next week.
Please do let me know if you have any questions.
Many thanks again and best wishes
Jenna

From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]
Sent: 16 July 2016 03:50
To: Whalley, Charles
Cc: Whittle, Jenna; Mildred; Roger McClellan
Subject: Fw: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0025.R1

Charles and Jenna:
Attached is the first of five letters accepting papers on the review of the potential carcinogenic hazard of Glyphosate (Roundup) to be published in a special supplement to Critical Reviews in Toxicology.
Charles, I anticipate that you will finalize any necessary arrangements for publication of these five papers with any fees paid by Intertek or by Monsanto. I am assuming they will want open access to maximize the readership.
Jenna, please notify me as to the most likely production and publication schedule. The authors and sponsor are very eager to have these available on line at the earliest possible date.
I will be preparing a brief Editors note that will be placed in front of the five papers. I will try to get the piece to you at the earliest possible date.
As an aside, a total of 27 reviewers reviewed these papers with one paper reviewed by 5 individuals, three papers reviewed by 7 individuals and one paper reviewed by 10 individuals. Some individuals reviewed several papers and one individual reviewed all five papers. I doubt tht collectively any other pset of papers has been extensively reviewed.
Please let me know if you have any questions.
As a favor could one of you do a quick literature search using search terms like -- glyphosate, Roundup, cancer, carcinogenesis, genotoxicity, mechanisms of action, epidemiology, hazard and risk to see how many papers on these subjects have been published in last 10 years or 20 years.
How readily can you determine how many different references have been cited collectively in the 5 papers?
Thanks for your help on publishing what I think will be a highly cited collection of papers.
Best regards, Roger

--- On Fri, 7/15/16, Critical Reviews in Toxicology
<onbehalfof+roger.o.mcclellan=[redacted]manuscriptcentral.com> wrote:

> From: Critical Reviews in Toxicology <onbehalfof+roger.o.mcclellan+[redacted]@manuscriptcentral.com>
> Subject: Critical Reviews in Toxicology - Decision on Manuscript ID BTXC-2016-0025.R1
> To: ashley.roberts@intertek[redacted], judy.vowles@intertek[redacted]
> Cc: mbmorgan@hargray[redacted]
> Date: Friday, July 15, 2016, 1:07 PM
> 15-Jul-2016
>
> Dear Dr Roberts:
>
> Ref: A Review of the Carcinogenic Potential of Glyphosate by
> Four Independent Expert Panels and Comparison to the IARC
> Assessment
>
> It was a pleasure to receive the revised manuscript and to
> note the careful attention given to the reviewers comments.
> In my opinion, the revisions were helpful in clarifying key
> points. This paper should be a valuable contribution to the
> literature on this widely used chemical. Hence, I am
> pleased to accept your paper in its current form which will
> now be forwarded to the publisher for copy editing and
> typesetting. It is understood that this paper will be
> published with four related papers in a Special Supplement
> to Critical Reviews in Toxicology.
>
> Recognizing the great interest of regulatory authorities in
> this and the related papers, I am extending permission to
> you to provide pre-publication copies of this and the four
> other papers to regulatory authorities and their advisors.
> It is understood these individuals will not reproduce or
> distribute these draft papers beyond the individuals who
> have need to review and cite the papers. Taylor and Francis
> will hold the copy right to the published papers. The papers
> should not be distributed further until you receive specific
> authorization from Mr Charles Whalley, the Managing Editor
> for CRT at T and F.
>
> You will receive proofs for checking, and instructions for
> transfer of copyright in due course.
>
> The publisher also requests that proofs are checked and
> returned within 48 hours of receipt.
>
> Thank you for your contribution to Critical Reviews in
> Toxicology and we look forward to receiving further
> submissions from you.
>
>
> Sincerely,
>
> Roger O. McClellan

> Editor-in-Chief, Critical Reviews in Toxicology
> roger.o.mcclellan@[redacted]
>
>
>
>
> Visit www.informapharmascience.com and sign up for free eTOC
> alerts to all Informa Pharmaceutical Science journals
>

Roger McClellan

From: Ashley Roberts Intertek <ashley.roberts@intertek[redacted]>
Sent: Tuesday, July 19, 2016 1:47 PM
To: Roger McClellan
Subject: Re: Five Glyphosate Manuscripts

Hi Roger,

I have been actioned to ask you how much it would cost in addition to the cost of the publication of the journal, to have free access to the individual manuscripts? I think this service was provided previously for the Greim paper.

Please could you let me know what the additional cost for this service would be?

Thanking you in anticipation

Ashley

Sent from my BlackBerry 10 smartphone on the Bell network.
Original Message
From: Roger McClellan
Sent: Sunday, July 17, 2016 10:59 AM
To: Ashley Roberts Intertek
Reply To: Roger McClellan
Cc: Charles.Whalley@tandf[redacted] Jenna.Whittle@informa[redacted]; Mildred; Roger McClellan
Subject: Re: FW:Five Glyphosate Manuscripts

Ashley:
I suggest the lead author for each of the Glyphosate papers complete the copyright assignment form for their paper and return them as requested. If this is not adequate I am sure you will hear from Jenna Whittle, the Production Editor for CRT, and/or Charles Whalley, the Managing Editor for CRT. Both are copied on this e-mail.
By copy of this e-mail I am asking Jenna to give the authors a week to approve the galleys for their paper. I encourage you to ask the lead author of each paper to take responsibility for review of the galley proofs for their paper. You may also want to ask that some one from the Intertek Editorial staff review all the galleys in view of the importance of these papers.
You should be aware that Charles is now on business travel and in the USA. Thus, you may not hear from him for a few days. You may want to alert Charles to your travel schedule to facilitate the two of you making contact on the Special Issue. In the meantime I am confident that Jenna will be moving the production forward in an expeditious manner.
Best regards,
Roger

On Sat, 7/16/16, Ashley Roberts Intertek <ashley.roberts@intertek[redacted]wrote:

Subject: FW: Manuscript
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
Date: Saturday, July 16, 2016, 7:25 AM

Hi Roger,

I know you are off
for a few days but I have had a question from one of the manuscript leaders and so I thought I better confirm with you.

The question is 1.
Should I complete the copyright release form or does that go with the set of all publications?

I believe each
person assigned the lead on the manuscript should do this but just thought I should get confirmation.

Thanks

Ashley

Ashley Roberts,
Ph.D.

Senior Vice President

Food & Nutrition Group

Intertek Scientific
& Regulatory Consultancy

Tel: +1
[redacted]

Fax: +1[redacted]

E-mail: ashley.roberts@intertek[redacted]

2233 Argentia Road,
Suite 201

Mississauga, Ontario Canada L5N 2X7

1. Should I complete
the copyright release form or does that go with the set of all publications?

2. When the proofs
arrive, the journal wants them returned in 48 hours.
Knowing that our group never does anything in 48 hours, is there a standard method you
suggest?

David

Valued Quality. Delivered.

Valued Quality. Delivered.

CONFIDENTIALITY NOTICE

This email may contain confidential or privileged information, if you are not the intended recipient, or the person responsible for delivering the message to the intended recipient then please notify us by return email immediately. Should you have received this email in error then you should not copy this for any purpose nor disclose its contents to any other person.

http://www.intertek.com

>
> From: Ashley Roberts
> Intertek
> Sent: Tuesday, July 19, 2016 3:47
> PM
> To: Roger McClellan
> Subject: Re: Five Glyphosate Manuscripts
>
>
> Hi Roger,
>
> I have been actioned to
> ask
> you how much it would cost in addition to the cost of the
> publication of the journal, to have free access to the individual
> manuscripts? I think this service was provided previously for the
> Greim paper.
>
> Please could you let me know
> what the
> additional cost for this service
> would be?
>
> Thanking you
> in
> anticipation
>
> Ashley
>
> Sent
> from my BlackBerry 10
> smartphone on the
> Bell network.
> Original
> Message
> From: Roger
> McClellan
> Sent: Sunday, July 17, 2016 10:59
> AM
> To: Ashley Roberts Intertek
> Reply To: Roger McClellan
>
> Cc:
> Charles.Whalley@tandf[redacted]
> Jenna.Whittle@informa[redacted]
> Mildred; Roger McClellan
>
> Subject: Re:
> FW:Five Glyphosate
> Manuscripts
>
>

> Ashley:
>
> I
> suggest the lead author for each of the Glyphosate papers complete the
> copyright assignment form for their paper and return them as
> requested. If this is not adequate I am sure you will hear from Jenna
> Whittle, the Production Editor for CRT, and/or Charles Whalley, the
> Managing Editor for CRT.
> Both are copied on this
> e-mail.
> By
>
> copy of this e-mail I am asking Jenna to give the authors a week to
> approve the galleys for their paper. I encourage you to ask the lead
> author of each paper to take responsibility for review of the galley
> proofs for their paper. You may also want to ask that some one from
> the Intertek Editorial staff review all the galleys in view of the
> importance of these papers.
>
> You should be
> aware that Charles is
> now on business travel and in the USA.
>
> Thus, you may not hear from him for a few days. You may want to alert
> Charles to your travel schedule to facilitate the two of you making
> contact on the Special Issue. In the meantime I am confident that
> Jenna will be moving the production forward in an expeditious manner.
> Best regards,
>
> Roger
>
> ----------
> On Sat, 7/16/16, Ashley Roberts Intertek
> <ashley.roberts@intertek[redacted]>
> wrote:
>
>
> Subject: FW:
> Manuscript
>
> To: "Roger McClellan"
> <roger.o.mcclellan@[redacted]>
> Date: Saturday, July 16, 2016, 7:25 AM
>
>
>
>
>
>
>
>
>
>

> Hi Roger,
>
>
> I know you are off
> for a few
> days but I have
> had a question from one of the
> manuscript
> leaders and so I thought I better confirm with
> you.
>
> The
> question is 1.
> Should I
>
> complete the copyright release form or does that go
> with the set of all publications?
>
> I believe each
> person assigned the lead on the manuscript should do this
> but just thought I
> should
> get confirmation.
>
>
> Thanks
>
> Ashley
>
>
> Ashley
>
> Roberts,
> Ph.D.
>
> Senior Vice President
>
> Food & Nutrition Group
>
> Intertek Scientific
> &
> Regulatory
> Consultancy
>
>
> Tel: +1
> [redacted]
>
>
> Fax: +1
> [redacted]
>

> E-mail: [redacted]@intertek.com
>
> 2233 Argentia Road,
> Suite 201
>
>
> Mississauga, Ontario Canada
> L5N 2X7
>
>
>
>
> .
>
>
>
>
>
> 1. Should
> I complete
> the
> copyright
> release form or does that go with the set of
> all publications?
>
>
> 2. When the proofs
> arrive, the journal wants them returned in
> 48 hours.
> Knowing that our
> group never does
> anything in 48
> hours, is there a standard
>
> method you
> suggest?
>
>
>
>
>
> David
>
>
>
>
> Valued Quality.
> Delivered.
>
>
>
>

>
> CONFIDENTIALITY NOTICE
> This email may
> contain
> confidential or
> privileged
> information, if you are not
> the
> intended
> recipient,
> or the person responsible for delivering
>
> the message to the intended recipient then please
> notify us by return email
> immediately. Should you have
> received this
> email in
> error then you should not copy this
> for
> any purpose nor disclose its contents to any other
> person.
> http://www.intertek.com
>
>
>
>
>
>
>
> Valued Quality. Delivered.
>
> _____
>
> CONFIDENTIALITY NOTICE
>
>
> This email may contain confidential or
>
> privileged information, if you are not the intended
> recipient, or the person responsible for delivering the
> message to the intended recipient then please notify us by
> return email immediately. Should you have received this
> email in error then you should not copy this for any
> purpose nor disclose its contents to any other person.
>
> http://www.intertek.com
>
> Valued Quality. Delivered.
> _____
> CONFIDENTIALITY NOTICE
>
> This email may contain confidential or

> privileged information, if you are not the intended
> recipient, or the person responsible for delivering the
> message to the intended recipient then please notify us by
> return email immediately. Should you have received this
> email in error then you should not copy this for any purpose
> nor disclose its contents to any other person.
>
> http://www.intertek.com
>

Mississauga, Ontario, ON L5N 2X7
Canada

Many thanks,

Keith

On 2016-07-19 11:35 AM, Jenna.Whittle@informa[redacted] wrote:

> 19 Jul 2016
>
> Keith Solomon,
>
> Re: Glyphosate in the general population and in applicators: A critical review of studies on exposures
>
> Production tracking number: ITXC 1214678
>
> Thank you for submitting your paper, which has now been received by the Taylor & Francis production department. As production editor I will work with you to oversee the production of your article from manuscript to publication. My contact details are given at the end of this email.
>
> If your article contains colour figures, reproduction in colour in the online edition of the journal is free of charge. If it is necessary for any figures to be reproduced in colour in the printed journal, please let me know as a charge will apply. Charges for colour in print are £250 per figure for the first four figures ($395 US Dollars; $385 Australian Dollars; 315 Euros). Figures 5 and above will be charged at £50 per figure ($80 US Dollars; $75 Australian Dollars; 63 Euros). If you plan to order colour reprints, please order colour now before you order reprints.
>
> • Please print and sign the attached Author Publishing Agreement. Then return the completed agreement to Taylor & Francis, by uploading to CATS (see below), or post it to the address below.
>
> Proofs will be ready for you to check in approximately 6 working days and we would like you to return your corrections within 3 days. Please let me know if there will be any difficulty in meeting this schedule.
>
> We will be sending proofs to you through our workflow system, CATS (Central Article Tracking System).
>
> • The DOI of your paper is: 10.1080/10408444.2016.1214678. Once your article has published online, it will be available at the following permanent link: http://dx.doi.org/10.1080/10408444.2016.1214678 .
>
> • You can check the status of your paper online through the CATS system at: https://cats.informa.com/PTS/in
>
> • Your User Name is: SLMNK6

• If you do not know your password, you may reset it here:
http://cats.informa.com/PTS/forgottenPassword.do

Yours sincerely,

Jenna Whittle

Taylor & Francis
4 Park Square
Milton Park
Abingdon
Oxfordshire
OX14 4RN
UNITED KINGDOM
Email:Jenna.Whittle@informa[redacted]

--

Keith R Solomon, Fellow ATS, Fellow SETAC, Prof. Emeritus (U of G)
Centre for Toxicology, School of Environmental Sciences
University of Guelph, 2120 Bovey Building
Gordon Street, Guelph, ON, N1G 2W1, Canada
[redacted] x [redacted]
Skype - [redacted]n
Fax: [redacted]
[redacted]@uoguelph.ca

Centre for Toxicology
University of Guelph

SCC Recognized GLP

Protecting health of humans and the environment with quality science

Valued Quality. Delivered.

>
> -----Original
> Message-----
> From: Roger McClellan
> [mailto:roger.o.mcclellan@[redacted]]
> Sent: July-26-16 3:52 PM
> To:
> Ashley Roberts Intertek; Charles.Whalley@tandf[redacted]
> Cc: Roger McClellan; Mildred
> Subject: Re: Five Glyphosate Manuscripts/ Need to Negotiate with
> Charles Whalley
>
> Ashley:
> I am
> traveling so I do not have access to all my records. I thought I had
> responded. You need to cover all business aspects of relationships
> with Critical Reviews in Toxicology with the journal's Managing
> Editor, Charles Whalley. I cover the science and he covers the
> business aspects of the journal. This should be covered in the
> contract for publishing the Special Issue. Charles, please let me know
> the status of the agreement between Taylor and Francis and/ Intertek
> and or Monsanto.
>
> Production is moving forward rapidly.
> Best regards, Roger
> ---
> On Tue, 7/26/16, Ashley Roberts Intertek <[redacted]@intertek.com>
> wrote:
>
> Subject: Re: Five
> Glyphosate Manuscripts
> To: "Roger
> McClellan" <roger.o.mcclellan@[redacted]
> Date: Tuesday, July 26, 2016, 9:29 AM
>
> Hi Roger,
>
> I hope you had a good break? I
> was wondering if you have had a chance to consider my message below?
>
> I look
> forward to receiving
> your reply.
>
> Best Wishes
>
> Ashley
>
> Sent
> from my BlackBerry 10
> smartphone on the Bell network.
> Original Message

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Wednesday, August 3, 2016 3:24 PM
To: Charles.Whalley@tandf[redacted]
Cc: Roger McClellan
Subject: Fw: RE: Five Glyphosate Manuscripts/ Need to Negotiate with Charles Whalley

Charles:
Does T and F have a signed contract with Intertek/ Monsanto for the glyphosate Supplement?
Best regards, Roger

--- On Wed, 8/3/16, Ashley Roberts Intertek <[redacted]@intertek.com> wrote:

> From: Ashley Roberts Intertek <a[redacted]@intertek.com>
> Subject: RE: Five Glyphosate Manuscripts/ Need to Negotiate with
> Charles Whalley
> To: "Roger McClellan" <roger.o.mcclellan@[redacted]>,
> "Charles.Whalley@tandf[redacted]<Charles.Whalley@tandf[redacted]
> Cc: "Mildred" <mbmorgan@hargray[redacted]
> Date: Wednesday, August 3, 2016, 11:18 AM Dear Roger/Charles,
>
> Please could you give me an
> update as to where we stand regarding the publications? I believe we
> have finalised all of the papers so are just awaiting to see the
> galley proofs. If you need me to pay for the printing of the journal
> etc, please send me the invoice as soon as you can. Regarding the
> free access to the manuscripts, please just add on what the additional
> cost for this function would be.
>
> I look forward to receiving an update as to next steps.
>
> Many Best
> Wishes
>
> Ashley
>
> Ashley Roberts, Ph.D.
> Senior Vice President
> Food
> & Nutrition Group
> Intertek Scientific
> & Regulatory Consultancy
> Tel: +1
> [redacted]
> Fax: +1[redacted]
> E-mail: [redacted]s@intertek.com
> 2233 Argentia Road, Suite 201
> Mississauga, Ontario Canada L5N 2X7
>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tand[redacted]>
Sent: Friday, August 5, 2016 6:02 AM
To: Ashley Roberts Intertek; Roger McClellan
Subject: RE: Welcome to Taylor & Francis Production: Critical Reviews in Toxicology 1214678

Dear Ashley.

Thanks for your email. As per our prior conversations, we had initially agreed with an online-only supplement, as this would be cheaper. The great majority of our readers and subscribers read the journal online, where they benefit from, amongst other things, supplemental material. The journal is only printed once a year, at the end of each volume, with print copies being sent to a relatively small proportion of our subscribers. Our current proposal assumes that the supplement issue would not be included in that end-of-year print volume; subscribers would be directed to the website. My apologies if this wasn't made clear, although I appreciate it's been a few months since we discussed these details.

I would, of course, be happy to include print for you, although this would be further additional cost, on top of the price sent to you recently to include Open Access. All that would entail would be inclusion in the print volume at the end of the year.

Let me know if you have any questions. I'm out of the office today and Monday but could call you on Tuesday.

Best wishes
Charles

From: Ashley Roberts Intertek [mailto[redacted]@intertek.com]
Sent: 05 August 2016 12:32
To: Whalley, Charles; Roger McClellan
Subject: Fw: Welcome to Taylor & Francis Production: Critical Reviews in Toxicology 1214678

Dear Roger/Charles,

May be this is my misunderstanding but it was my impression that the articles were to be published in a stand alone paper back copy. Is this not the position?

Thanking you for your reply.

Best Wishes

Ashley

Sent from my BlackBerry 10 smartphone on the Bell network.

From: Whittle, Jenna <Jenna.Whittle@informa[redacted]
Sent: Friday, August 5, 2016 8:15 AM
To: Keith Solomon
Cc: Ashley Roberts Intertek
Subject: RE: Welcome to Taylor & Francis Production: Critical Reviews in Toxicology 1214678

Dear Keith

Many thanks for your message and apologies for the delay in responding to your request to publish Figure 3 in colour.

Color figures will be reproduced in color in your online article free of charge. Although printing figures in color incurs a charge, your article is assigned for publication in a supplement that we believe will be published online only and not in print.

Please do let me know if you have any questions.

Best wishes

Jenna

Jenna Whittle
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group
an informa business

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

[redacted]e@tandf.co.uk
www.tandfonline.com

From: Keith Solomon [mailto:[redacted]@uoguelph.ca]
Sent: 20 July 2016 13:15
To: Whittle, Jenna
Cc: Ashley Roberts Intertek
Subject: Re: Welcome to Taylor & Francis Production: Critical Reviews in Toxicology 1214678

Jenna,

As requested, I attach the signed copyright form.

I will be fine with the proposed schedule.

I have spoken with the supporter of the research and we would like Fig 3 (only) to be printed in color. The invoice for this should be directed to:

Dr Ashley Roberts
Senior Vice President
Intertek Scientific & Regulatory Consultancy
E-Mail [redacted]@intertek.com
Work Address
2233 Argentia Road, Suite 201

Roger McClellan

From: Roger McClellan <[redacted]@att.net>
Sent: Friday, August 12, 2016 12:23 PM
To: Jenna.Whittle@informa[redacted]
Cc: roger.o.mcclellan[redacted] Mildred; Charles.Whalley@tandf[redacted]
Subject: Re: Trivia versus substance: CRT standing matter

Jenna,

Please provide me an example of the type set version A for Volume 46. As the T and F staff consider changes for Critical Reviews in Toxicology I urge them to recognize the unique nature of the Journal.

Specifically, it is important to recognize that each annual issue, exclusive of Special Supplements, consists of 10 issues and a target of 920 pages. As I will note later, do the front and back cover count against the 920 page target. (I CAN NOT BELIEVE WE ARE WASTING TIME ON THIS KIND OF TRIVIA!!!!!!) The 10 issues in a sense become a legacy issue since all papers are published on-line when the final galley proofs are accepted. I am uncertain if a Table of Contents is created for each issue. Indeed, as I think about the matter it may be appropriate to consider creating a virtual Table of Contents that is 'built out' as new papers are accepted and published on line during the year.. For example, issues 1 through 9 contain 27 papers. As issue 10 is completed the number of papers in the regular issues of Volume 46 will increase to 29 or 30.

The only hard copies of Critical Reviews in Toxicology are now prepared and printed at year end. This started with Volume 44 in 2014. I note that Volume 44 did not have a Table of Contents. I now recall that being very inconvenient when I returned on several occasions to use the hard copy. Volume 45 (2015) has a Table of Contents at the front of the hard copy. This is convenient to use since the two pages are in consecutive order. By writing this memo I have answered one question. I am strongly opposed to placing the Table of Contents on the back cover (and presumably continuing it on the inside of the back cover) for a single annual hard copy of CRT. The approach of using the back cover for a Table of Contents may make sense for a multi-issue journal , it makes no sense for CRT. I question if the proposer of this approach is a scientific editor or author or user of journals. AS a scientist when I pick up a bound volume it is natural for me to go to the front to search for the Table of Contents.

As I write this e-mail I recall my anger a year ago at doing battle over a couple of pages of print in the journal. As a MANAGER, I have always viewed quantitative goals as targets that should be interpreted with the abundant use of common sense. I doubt that the financial success of T and F will turn on this issue. I urge that all of us focus on what makes sense.

Charles and Jenna, in the world of "bean counters" at T and F do the cover (front and back) and the back cover (front and back) count as part of the 920 pages assigned to CRT for 2016? If we collectively deliver less pages does some one get a BONUS or brownie points? What is your current production system for CRT? In printing hard copies does the press print 8 , 16 or 32 pages to the sheet or does the printing system work differently today? I note that the front and back cover are different weight paper than the rest of the Journal so they have to be printed separately.

Thanks for hearing me out.

Roger

PS I. In my opinion, the inability to focus on what is really important as opposed to trivia is a world wide phenomena. We need to return our focus to what will improve the scientific quality of CRT and it's profitability to T and F.

PS II. I do think it is important to list the membership of the Editorial Advisory Board at the front of the hard copy for historical reasons. Quite frankly, it probably does not make much difference what else is printed on the inside of the front cover or on either side of the back cover. Whatever is printed will soon be out dated and is not likely to be a primary reference source, ie folks will go elsewhere to obtain current information on subscriptions, instructions to authors, etc. The publication world is changing. Hard copies will probably be a thing of the past within a decade.

On Fri, 7/8/16, Whittle, Jenna <Jenna.Whittle@informa.com> wrote:

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[redacted]>
Sent: Thursday, August 18, 2016 8:21 AM
To: Roger McClellan
Subject: Glyphosate editorial

Dear Roger,

There's one more colleague I'd like to have a look at your editorial, but I wanted to raise something with you now. One of my colleagues has mentioned that, in the spirit of the editorial, it would be appropriate for us to include a Declaration of Interest statement from you. What do you think?

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

>

> From: Whalley,

> Charles

>

> Sent: 22 August 2016 15:55

>

> To: 'Ashley Roberts Intertek'

>

> Cc: Vasili, Temis

>

> Subject: Glyphosate supplement contract

>

>

>

>

> Dear Ashley,

>

> Please find attached a draft contract for your

> review. To summarise, this covers an Open Access online-only

> supplement in

> CRT, with 200 additional print copies of the

> supplement issue despatched in bulk to a single address

> (assuming St Louis, Missouri). (These print copies will not

> be sent to subscribers). The cost will be

> $29,339 for the supplement plus $1,306 for the

> print and delivery of the print issues, so

> $30,645. We will issue a single invoice once the

> contract is signed.

>

> Please let me know if you have any questions

> regarding the contract. Once I hear you're happy, we

> will arrange for 2 print copies to be couriered to you for

> signature. These will

> need to be sent back to us for counter-signature, and then

> we will send one to you for your records.

>

> With that in mind, I will need to know from

> you:

>

> ·

> The name

> and address to send the contracts

> ·

> A contact

> number for the courier for this address

> ·

> The name

> and address for the invoice

>

> I look forward to hearing from you on the

> above.

>

> Please be advised that I am out of the office,

> without an internet connection,

> 24th-30th Aug inclusive. I CC my

> Editorial Assistant, Temis Vasili, who will

> be able to cover for me in my absence. I don't

> anticipate my holiday to cause any delays here.

>

> Best wishes,

> Charles

>

> Charles Whalley

> -

> Managing Editor, Medicine & Health Science

> Journals

> Taylor & Francis

> Group

> 4 Park Square, Milton

> Park, Abingdon, Oxon, OX14 4RN, UK

> Direct line:

> +[redacted]

> Switchboard:

> +[redacted]

> charles.whalley@tandf[redacted]

>

> www.tandfonline.com

>

>

> Taylor & Francis

> is a trading name of Informa UK Limited,

> registered in England

> under no. 1072954

>

>

>

>

>

> Valued Quality. Delivered.

>

>

>

> CONFIDENTIALITY NOTICE

>

> This email may contain

> confidential or privileged information, if you are not the

> intended recipient, or the person responsible for delivering

> the message to the intended recipient then please

> notify us by return email immediately. Should you have

> received this email in error then you should not copy this

> for any purpose nor disclose its contents to any other

> person.

>

http://www.intertek.com

>

>

>

>

>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tand[redacted]
Sent: Wednesday, September 14, 2016 6:33 AM
To: Ashley Roberts Intertek
Cc: Vasili, Temis; Roger McClellan
Subject: RE: Glyphosate supplement

Dear Ashley,

Many thanks for this, which is very helpful. In advance of the final publication of these review papers, the authors are welcome to share their original accepted version of their manuscripts with the reporter you mention below, for the purposes of preparing their interview. We'd be pleased for any statement to link directly to the journal's website. I can send you the direct link to the articles once published, if that helps. They will, of course, be Open Access, so direct links will take readers straight to the full text.

Thanks also for sharing the wording of Monsanto's statement. Can I ask if we can see in advance any other statement, press release or promotional copy with references Taylor & Francis and/or *CRT*?

Finally, you've not mentioned anything on this front, but my colleagues in Marketing are eager to know of any social media plans, if any exist.

Best wishes,
Charles

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek[redacted]
Sent: 13 September 2016 16:03
To: Whalley, Charles
Cc: Vasili, Temis; Roger McClellan
Subject: RE: Glyphosate supplement

Dear Charles/Roger,

In addition to the previous information that I sent to you regarding the promotion of the glyphosate publications, Monsanto has now updated this to include the following and they want to be transparent on what they are doing and to keep you in the loop on these matters.

For your information, they plan to help amplify the lack of carcinogenicity potential thorough, science-based review by: 1) helping coordinate an exclusive interview with Sir Colin Berry and a science reporter in advance of publication, 2) providing any inquiring media after publication with a Monsanto statement, and 3) directing interested media to the Critical Reviews in Toxicology website after publication. More details below.

1. The Sir Colin Berry exclusive interview will be with a science reporter from a mainstream media outlet in Europe. The reporter's story will be embargoed until after publication and the expert panels findings are publically available online. As part of this exclusive interview, we also think it would be beneficial to provide the reporter with an early version of the expert panel's report so the reporter has the information needed to write a detailed article. Please let us know if CRT supports this approach? if this is okay, Monsanto will suggest to Sir Colin that he share the early version of the report with the reporter during the interview.

2. For your reference, below is the Monsanto statement they plan to share on a reactive basis if they receive media inquiries after publication.

At Monsanto, we're fully confident in the safety profile of our products. Our confidence is based on rigorous internal safety assessments in addition to safety assessments by regulatory authorities, independent researchers and other experts around the world. In July 2015, Monsanto retained a scientific consultant to convene an expert panel to review the International Agency for Research on Cancer (IARC) monograph on glyphosate once it published. The charge to the experts was to take a thorough look at the data in the monograph, assess the scope of the research included or excluded, and publish their conclusions to allow for external review. The experts that make up the panel include medical doctors, cancer experts, and individuals who hold doctoral degrees and who are experts in public health. The experts have spent their careers as researchers at major universities and medical schools, at research institutions and as consultants. The panel's peer-reviewed findings recently were published in the journal Critical Reviews in Toxicology and are available here: [Monsanto will insert direct link here]. These findings by the panel come at an important time, after so much unnecessary confusion and concern has been caused by IARC's classification of glyphosate. The panel's findings are consistent with the conclusions of regulatory authorities around the world. In fact, since IARC classified glyphosate, regulatory authorities in Europe, Canada, Japan, New Zealand and Australia have publicly reaffirmed that glyphosate does not cause cancer. Additionally, in May 2016, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) concluded that "glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet."

3. Lastly, after publication, Monsanto plan to proactively inform some reporters who have previously covered IARC's glyphosate monograph about the publication of the expert panel's findings. As such Monsanto plans to share a direct link to the Critical Reviews in Toxicology's website.

Please let me know if this is acceptable to the journal.

Many best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [redacted]
Fax: +1 [redacted]
E-mail: a[redacted]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whalley, Charles [mailto:Charles.Whalley@tandf[redacted]
Sent: September-06-16 8:35 AM
To: Ashley Roberts Intertek
Cc: Vasili, Temis
Subject: RE: Glyphosate supplement contract

Dear Ashley,

Thanks for coordinating signature and return of contracts with Temis. I hope you've had a pleasant holiday.

Further to your response re promotion, I'd be grateful if Monsanto could provide:

- A draft of the press release before publication
- The names of the journalists who would receive the press release
- The names of the panellists who would be provided to these journalists for follow-up discussion
- Information on any social media promotion

Apologies for the quizzing, but we're anticipating a lot of interest in this supplement and so I'm eager that we're aware of any marketing in advance.

As for our promotion, I'll be able to confirm our plans after hearing from you on the above.

I'd be happy to discuss this with the appropriate person at Monsanto directly if that's easier for you.

All best wishes,
Charles

From: Ashley Roberts Intertek [mailto:[redacted]@intertek.com]
Sent: 23 August 2016 21:28
To: Whalley, Charles
Cc: Vasili, Temis
Subject: RE: Glyphosate supplement contract

Dear Charles,

Regarding the contract, I will respond to you tomorrow morning my time.

On the topic of promotion, I have spoken to Monsanto and they have indicated that if you are in agreement they would like to promote the publications. While nothing definite has been planned they were contemplating making a press release to some "friendly" journalists indicating when the report will be released with the time estimation for publication as well as provide some names of the panelists who they could contact for follow-up discussion. Beyond this initial action, no further thought has gone in to this and they were wondering if the Journal does any of their own kind of promotion.

If you could let me know if the above is acceptable, that would be great.

Many Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President
Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Tel: +1 [redacted]
Fax: +1 [redacted]
E-mail: [redacted]@intertek.com

2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whalley, Charles [mailto:Charles.Whalley@tandf[redacted]
Sent: August-23-16 10:52 AM
To: Ashley Roberts Intertek
Cc: Vasili, Temis
Subject: RE: Glyphosate supplement contract

Dear Ashley,

Further to the below, it occurs to me that it would helpful and much appreciated if you could let me know on Intertek's and Monsanto's plans for promoting the supplement, if any, both with the print copies which we will

be producing and in any electronic or other communications/promotion. I look forward to hearing from you on this and the below.

Best wishes as ever,
Charles

From: Whalley, Charles
Sent: 22 August 2016 15:55
To: 'Ashley Roberts Intertek'
Cc: Vasili, Temis
Subject: Glyphosate supplement contract

Dear Ashley,

Please find attached a draft contract for your review. To summarise, this covers an Open Access online-only supplement in *CRT*, with 200 additional print copies of the supplement issue despatched in bulk to a single address (assuming St Louis, Missouri). (These print copies will not be sent to subscribers). The cost will be **$29,339** for the supplement plus **$1,306** for the print and delivery of the print issues, so **$30,645.** We will issue a single invoice once the contract is signed.

Please let me know if you have any questions regarding the contract. Once I hear you're happy, we will arrange for 2 print copies to be couriered to you for signature. These will need to be sent back to us for counter-signature, and then we will send one to you for your records.

With that in mind, I will need to know from you:

- The name and address to send the contracts
- A contact number for the courier for this address
- The name and address for the invoice

I look forward to hearing from you on the above.

Please be advised that I am out of the office, without an internet connection, 24th-30th Aug inclusive. I CC my Editorial Assistant, Temis Vasili, who will be able to cover for me in my absence. I don't anticipate my holiday to cause any delays here.

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Tuesday, August 23, 2016 2:33 AM
To: Roger McClellan
Cc: mbmorgan@hargray[redacted]
Subject: Editorial for special issue
Attachments: Special Supplemental Issue on Glyphosates Document for CRT_TF edits.docx

Dear Roger,

Please find attached your editorial for the glyphosate special issue, having been reviewed here. The only changes I've made are to the penultimate paragraph relating to the negotiations around the supplement.

I also note that the title for the supplement is 'An Independent Review of the Carcinogenic Potential of Glyphosate'

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Science Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: [redacted]
Switchboard: [redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]t>
Sent: Wednesday, August 31, 2016 1:37 PM
To: Jenna.Whittle@informa[redacted]; Charles.Whalley@tand[redacted]
Cc: Roger McClellan; Mildred
Subject: Fw:Foreword for Special Glyphosates Supplement
Attachments: Special Supplemental Issue on Glyphosates 8 31 16 ROM.docx

Jenna and Charles:

Attached is the penultimate version of the Foreword for the Special Supplement. You will note it contains a Declaration of Interest. I welcome your comments on the DOI. I am uncertain if I have seen the Galleys on the two Williams etal papers. Can you send me the latest version. I assume they have been returned by Gary Williams. What is your current view of when the Supplement will be posted on line. I would prefer that it all be posted at the same time. A related question is how much space will be required to print the Abstracts in the hard copy issue of Volume 46.

Thanks for all your help on this special project.

Regards, Roger

--- On Wed, 8/31/16, Mildred Morgan <mbmorgan@hargray[redacted] wrote:

> From: Mildred Morgan <mbmorgan@hargray[redacted]
> Subject: Special Glyphosates Supplement
> To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
> Date: Wednesday, August 31, 2016, 12:01 PM Attached.
>

Roger McClellan

From: Mildred Morgan <mbmorgan@hargray[redacted]
Sent: Wednesday, August 31, 2016 5:39 AM
To: Roger McClellan
Subject: FW: CRT, sample cover

FYI. I don't know what affiliation you want to show for Vicki. Let me and Jenna know. She also asked whether you had any corrections.

MM

From: Whittle, Jenna [mailto:Jenna.Whittle@informa[redacted]
Sent: Wednesday, August 31, 2016 3:53 AM
To: Mildred Morgan
Subject: RE: CRT, sample cover

Thanks for letting me know, Mildred. Please can you tell me what her affiliation is and I'll ensure that change is made?
Do you know if Roger had any corrections?
Many thanks and best wishes
Jenna

Jenna Whittle
Production Editor
Taylor & Francis

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

From: Mildred Morgan
Sent: 30 August 2016 23:26
To: Whittle, Jenna
Subject: RE: CRT, sample cover

Hi Jenna,

On the CRT Sample cover you sent, be sure and include Vicki Deliarco to the list of CRT Board Members.

Mildred

From: Whittle, Jenna [mailto[redacted]@informa.com]
Sent: Friday, August 19, 2016 1:15 PM
To: Roger McClellan
Cc: Mildred; Whalley, Charles
Subject: CRT, sample cover

Dear Roger, Mildred and Charles

Please find attached a sample cover with the layout changes discussed for your review. The subscriptions information has been reduced and added to the inside back cover, meaning that we no longer need a separate internal subscriptions page.

The print issue will feature a table of contents on pages i and ii. To give an idea of what this will look like, I've attached the table of contents from last year's volume – we can follow the same layout as this in the upcoming print issue.

Please do let me know if you have any feedback on this cover or, indeed, the style of the contents page and I can ask the typesetter to make adjustments.

Thanks and best wishes

Jenna

From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]]
Sent: 12 August 2016 19:23
To: Whittle, Jenna
Cc: roger.o.mcclellan@[redacted]; Mildred; Whalley, Charles
Subject: Re: Trivia versus substance; CRT standing matter

Jenna,
Please provide me an example of the type set version A for Volume 46. As the T and F staff consider changes for Critical Reviews in Toxicology I urge them to recognize the unique nature of the Journal.
Specifically, it is important to recognize that each annual issue, exclusive of Special Supplements, consists of 10 issues and a target of 920 pages. As I will note later, do the front and back cover count against the 920 page target. (I CAN NOT BELIEVE WE ARE WASTING TIME ON THIS KIND OF TRIVIA!!!!!!) The 10 issues in a sense become a legacy issue since all papers are published on-line when the final galley proofs are accepted. I am uncertain if a Table of Contents is created for each issue. Indeed, as I think about the matter it may be appropriate to consider creating a virtual Table of Contents that is 'built out' as new papers are accepted and published on line during the year.. For example, issues 1 through 9 contain 27 papers. As issue 10 is completed the number of papers in the regular issues of Volume 46 will increase to 29 or 30.
The only hard copies of Critical Reviews in Toxicology are now prepared and printed at year end. This started with Volume 44 in 2014. I note that Volume 44 did not have a Table of Contents. I now recall that being very inconvenient when I returned on several occasions to use the hard copy. Volume 45 (2015) has a Table of Contents at the front of the hard copy. This is convenient to use since the two pages are in consecutive order. By writing this memo I have answered one question. I am strongly opposed to placing the Table of Contents on the back cover (and presumably continuing it on the inside of the back cover) for a single annual hard copy of CRT. The approach of using the back cover for a Table of Contents may make sense for a multi-issue journal , it makes no sense for CRT. I question if the proposer of this approach is a scientific editor or author or user of journals. AS a scientist when I pick up a bound volume it is natural for me to go to the front to search for the Table of Contents.

As I write this e-mail I recall my anger a year ago at doing battle over a couple of pages of print in the journal. As a MANAGER, I have always viewed quantitative goals as targets that should be interpreted with the abundant use of common sense. I doubt that the financial success of T and F will turn on this issue. I urge that all of us focus on what makes sense.
Charles and Jenna, in the world of "bean counters" at T and F do the cover (front and back) and the back cover (front and back) count as part of the 920 pages assigned to CRT for 2016? If we collectively deliver less pages does some one get a BONUS or brownie points? What is your current production system for CRT? In printing hard copies does the press print 8 , 16 or 32 pages to the sheet or does the printing system work differently today? I note that the front and back cover are different weight paper than the rest of the Journal so they have to be printed separately.
Thanks for hearing me out.
Roger

PS I. In my opinion, the inability to focus on what is really important as opposed to trivia is a world wide phenomena. We need to return our focus to what will improve the scientific quality of CRT and it's profitability to T and F.
PS II. I do think it is important to list the membership of the Editorial Advisory Board at the front of the hard copy for historical reasons. Quite frankly, it probably does not make much difference what else is printed on the inside of the front cover or on either side of the back cover. Whatever is printed will soon be out dated and is not likely to be a primary reference source, ie folks will go elsewhere to obtain current information on subscriptions, instructions to authors, etc. The publication world is changing. Hard copies will probably be a thing of the past within a decade.

On Fri, 7/8/16, Whittle, Jenna <Jenna.Whittle@informa[redacted]> wrote:

Subject: Critical Reviews in Toxicology standing matter
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
Cc: "Mildred" <mbmorgan@hargray.[redacted]>, "Whalley, Charles" <Charles.Whalley@tandf[redacted]>
Date: Friday, July 8, 2016, 7:13 AM

Dear Roger and Mildred

Thank you for the phone
call yesterday. It was lovely to speak to you both. After
our conversation, I instructed the typesetter to follow the
new guidelines for the presentation of supplemental material
so we should soon start to see articles
containing a 'Supplemental material' section,
as shown in the sample Charles sent you.

I also wanted to follow up
my message yesterday with some further information about the
changes to journal standing matter I mentioned. These would
be beneficial as we could potentially reduce the number of
preliminary pages from four to
two, freeing up a couple more pages in the journal budget
for articles. The information on the standing matter has
also been better organised and made clearer and more concise
for readers.

I've attached
descriptions of the two different templates and also
explained a bit more about them below. If either of these
appeal to you, I can ask the typesetter to create a
journal-specific sample, which I can send to you for your
review.

Please do
let me know if you have any questions. I look forward to
hearing your thoughts once you've had time to consider
the various options.

Many thanks
and best wishes

Jenna

Option A

-
The subscriptions information page is removed. Subscriptions information is merged with the text on the inside covers. The journal's aims and scope appear on the back cover.
-
We would have two preliminary pages if we were to adopt this option: the two table of contents pages.

Option B

-
The table of contents appears on the outside back cover of the journal and is continued onto the inside back cover. The internal table of contents pages would therefore be removed.
-
Subscription information and typesetting and printing information would be added on page i of the journal.

-
We would have two preliminary pages: the subscriptions information page (p. i) and a blank page on the reverse of this (p. ii).

Jenna
Whittle
Production Editor,
Journals
Taylor & Francis

4 Park Square, Milton
Park, Abingdon, Oxon, OX14 4RN, UK

jenna.whittle@tandf[redacted]

www.tandfonline.com

Roger McClellan

From: Whittle, Jenna <Jenna.Whittle@informa[redacted]
Sent: Thursday, September 1, 2016 9:48 AM
To: Roger McClellan; Whalley, Charles
Cc: Roger McClellan; Mildred
Subject: RE: Foreword for Special Glyphosates Supplement

Dear Roger
I'll respond in more detail to your queries soon, but I wanted to let you know in the meantime that I've just sent you one of the Williams papers (Glyphosate rodent carcinogenicity bioassay expert panel review) after receiving it from the typesetter. Please let me know if you haven't received it. The other Williams proof is with the typesetter for amendment as we only received the author's corrections earlier this week. I'll send you the revised proof as soon as it is ready.
Best wishes
Jenna

Jenna Whittle
Production Editor
Taylor & Francis

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

From: Roger McClellan
Sent: 31 August 2016 20:37
To: Whittle, Jenna; Whalley, Charles
Cc: Roger McClellan; Mildred
Subject: Fw:Foreword for Special Glyphosates Supplement

Jenna and Charles:
Attached is the penultimate version of the Foreword for the Special Supplement. You will note it contains a Declaration of Interest. I welcome your comments on the DOI. I am uncertain if I have seen the Galleys on the two Williams etal papers. Can you send me the latest version. I assume they have been returned by Gary Williams. What is your current view of when the Supplement will be posted on line. I would prefer that it all be posted at the same time. A related question is how much space will be required to print the Abstracts in the hard copy issue of Volume 46.
Thanks for all your help on this special project.
Regards, Roger

--- On Wed, 8/31/16, Mildred Morgan <mbmorgan@hargray[redacted] wrote:

> From: Mildred Morgan <mbmorgan@hargray[redacted]>
> Subject: Special Glyphosates Supplement
> To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
> Date: Wednesday, August 31, 2016, 12:01 PM
> Attached.
>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Wednesday, September 7, 2016 12:48 PM
To: Charles.Whalley@tandf[redacted]Jenna.Whittle@informa[redacted]
Cc: Mildred; Roger McClellan
Subject: Re: Automatic reply: Proofs for Williams etal --FUNDING ?????/URGENT ATTENTION

Charles and Jenna:
As you are both aware, it is highly desirable that the five papers and my Foreword in the Glyphosate Special Supplemental Issue be posted on line at the earliest possible date. I note that Charles is out through September 22nd. Hence, it will not be possible to have a telephone conference call on September 8th to resolve the Funding entry issue.
My strong preference would be to publish the five papers and Foreword with the Declaration of Interest statements originally submitted. This approach is consistent with the other papers published in Volume 46. Is this approach acceptable to both of you and your supervisors?
Regards, Roger

On Wed, 9/7/16, Whalley, Charles <Charles.Whalley@tandf[redacted]> wrote:

Subject: Automatic reply: Proofs for Williams etal --FUNDING ?????/URGENT
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
Date: Wednesday, September 7, 2016, 10:56 AM

#yiv5685896198
#yiv5685896198 --

_filtered #yiv5685896198 {font-family:Calibri;panose-1:2 15 5 2 2 2 4 3 2 4;}
_filtered #yiv5685896198 {font-family:Tahoma;panose-1:2 11 6 4 3 5 4 4 2 4;}
_filtered #yiv5685896198 {font-family:Verdana;panose-1:2 11 6 4 3 5 4 4 2 4;}
#yiv5685896198
#yiv5685896198 p.yiv5685896198MsoNormal, #yiv5685896198 li.yiv5685896198MsoNormal, #yiv5685896198 div.yiv5685896198MsoNormal
{margin:0cm;margin-bottom:.0001pt;font-size:11.0pt;}
#yiv5685896198 a:link, #yiv5685896198 span.yiv5685896198MsoHyperlink
{color:blue;text-decoration:underline;}
#yiv5685896198 a:visited, #yiv5685896198 span.yiv5685896198MsoHyperlinkFollowed
{color:purple;text-decoration:underline;}
#yiv5685896198 span.yiv5685896198EmailStyle17
{}
#yiv5685896198 .yiv5685896198MsoChpDefault
{}
_filtered #yiv5685896198 {margin:72.0pt 72.0pt 72.0pt 72.0pt;}
#yiv5685896198 div.yiv5685896198WordSection1
{}
#yiv5685896198

Thank you for your email. I'm currently out of the office with intermittent email access, returning 22nd September.

Best wishes,
Charles

Charles Whalley
-
Managing Editor, Medicine & Health Science Journals Taylor & Francis Group
4 Park Square, Milton Park,
Abingdon, Oxon, OX14 4RN, UK
Direct line: [redacted]
Switchboard: [redacted]
charles.whalley@tandf[redacted]

www.tandfonline.com

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]
Sent: Wednesday, September 7, 2016 3:10 PM
To: Charles.Whalley@tandf[redacted] JennaWhittle
Cc: Mildred; Roger McClellan
Subject: RE: Special Glyphosates Supplement--Need to resolveDOI versus DOI plus Funding

Jenna and Charles:
As I have noted in other e-mails the issue of potentially publishing separate "Funding" entries for each paper caught me totally by surprise. As I noted it is not necessary since funding of the management of the advisory committees and preparation of these five paper is clearly described in the papers and the DOIs. Let's get that matter settled soon!!!!
Regards, Roger

On Tue, 9/6/16, Whittle, Jenna <[redacted]@informa.com> wrote:

Subject: RE: Fw:Foreword for Special Glyphosates Supplement
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>, "Whalley, Charles" <Charles.Whalley@tandf[redacted]
Cc: "Mildred" <mbmorgan@hargray[redacted]
Date: Tuesday, September 6, 2016, 2:12 AM

Dear Roger

I understand from Charles that
this is the final version of the foreword, so I will send it off for copyediting and typesetting. You'll be sent the proofs for review/any corrections as soon as they're ready.

I've just
received the corrected Williams proof from the typesetter so I will send it to you and the author shortly. Once the foreword is at revised proof stage, I can compile the issue.
It should be fine to publish all the papers online at the same time. I can send you and Ashley the issue proofs for approval before we go to press.

We can probably expect each abstract to take up approximately half a page so we should allow around 3 pages for the supplement abstracts in the printed volume.

Please do let me know if you
have any further questions.

Best wishes

Jenna

-----Original Message-----
From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]

Sent: 31 August 2016 20:37
To: Whittle, Jenna; Whalley, Charles
Cc: Roger McClellan; Mildred
Subject: Fw:Foreword for Special Glyphosates Supplement

Jenna and
Charles:
Attached is the
penultimate version of the Foreword for the Special Supplement. You will note it contains a Declaration of Interest. I welcome your comments on the DOI. I am uncertain if I have seen the Galleys on the two Williams etal papers.
Can you send me the latest version. I assume they have been returned by Gary Williams. What is your current view of when the Supplement will be posted on line. I would prefer that it all be posted at the same time. A related question is how much space will be required to print the Abstracts in the hard copy issue of Volume 46.
Thanks for all your help on this
special project.
Regards, Roger

--- On Wed, 8/31/16, Mildred
Morgan <mbmorgan@hargray[redacted]
wrote:

> From: Mildred
Morgan <mbmorgan@hargray[redacted]>
> Subject: Special Glyphosates Supplement > To: "Roger McClellan" <roger.o.mcclellan@a[redacted]> > Date: Wednesday, August 31, 2016, 12:01 PM Attached.
>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[redacted]
Sent: Friday, September 9, 2016 3:28 AM
To: Roger McClellan
Cc: Vasili, Temis
Subject: Previous highly cited glyphosate toxicity papers
Attachments: Glyphosate toxicity.docx

Dear Roger,

A month or so ago you asked if we could do some research on the citations to previously published articles on glyphosate. I attach the details that Temis has put together on this. It seems most of the highly cited articles on environmental/aquatic toxicity, and that there has been a steady increase in publications on this topic, peaking a few years ago.

Let me know if you've any questions.

Best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[redacted]
Sent: Monday, September 12, 2016 5:24 PM
To: Roger McClellan; Whittle, Jenna
Cc: Mildred B. Morgan
Subject: RE: Funding Entry

Dear Roger,

Thanks for this. Jenna is going to check in with her manager and the typesetter on this, but we should be able to take that section out from the template for CRT. It's popped in at a bad time, as we're so close to finishing this supplement, but won't be difficult to resolve. Our policy on Declarations of Interest hasn't changed.

I'd be happy to discuss this over the phone once I'm back. As you've seen, I'm travelling until Thursday 22nd, at a clinical toxicology meeting in Boston, but will see emails.

Best wishes as ever,
Charles

From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]
Sent: 08 September 2016 00:29
To: Whittle, Jenna
Cc: Whalley, Charles; Roger McClellan; Mildred B. Morgan
Subject: Funding Entry

Charles and Jenna:

Jenna, I appreciate being given some background on the use of a "Funding" entry on papers published by T&F. This is the first time I have heard anything about the use of a "Funding" entry. Thus, I was surprised when it first showed up in galleys.

Perhaps you can provide me some additional details about this entry. I am confident that many authors publishing in CRT will be confused since funding sources have routinely been included in the mandatory Declaration of Interest (DOI) statements that CRT has been using for several years.

As you know, CRT has been a leader in championing a mandatory DOI. The DOI was created since it was apparent that the usual statements about "Conflicts of Interest" were not adequate. It is my personal opinion that statements such as "The authors have no conflict of interest to declare" are virtually useless. That is the case since conflicts of interest are in the eye of the beholder, not the declarer.

As you are aware, the typical DOI for a CRT review paper covers funding. However, the typical DOI includes substantially more information that allows a reader to form an opinion as to potential conflicts of interest. In short, statements about funding are a useful step in the right direction but are not adequate for CRT.

In my opinion, the issue of funding for a paper reporting original research findings is very different than for review papers such as those published in CRT. I suspect the T&F procedures on creating the "Funding" entry are oriented primarily to papers reporting original research findings. Perhaps you

can share with me the internal T&F procedures used to create "Funding" entries. From the several funding entries I have read, it appears T&F uses information provided by authors and some independent data bases. What are these data bases?

As you know, the funding of preparation of review papers can be very complex along with their authorship. Some authors are from academic institutions while other authors are employed by industrial firms, government agencies or consulting firms. Many papers have authors from all of the above sectors. Preparation of reviews may be self-funded by the author's employer or sponsorship by government or private sector grants or contracts. In some cases a consulting firm or trade association may be involved. I suggest that the T&F personnel involved in creating "Funding" entries review the DOIs for all of the papers published in CRT in 2016. This will give them an appreciation of the complexity of these matters. In particular, it will become apparent from this review that "funding" must be considered in the context of other elements of a DOI.

For now, I suggest that CRT continues to use DOIs of the kind used in 2016. In addition, I would welcome in the future, T&F personnel reviewing prospective DOIs to verify that funding has been adequately addressed within the DOI. This approach may help us improve the DOIs in CRT review papers and avoid the confusion of introducing a separate "Funding" entry for each paper.

I look forward to your feedback on this important issue.

Best Regards,

Roger

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[redacted]
Sent: Monday, September 12, 2016 5:26 PM
To: Roger McClellan; Whittle, Jenna
Cc: Mildred
Subject: RE: Publication Options for your Article

Dear Roger,

Thanks for this. It is indeed an automated email. We will make the article free-to-view at no cost.

Best wishes,
Charles

From: Roger McClellan [*mailto:roger.o.mcclellan@*[redacted]
Sent: 09 September 2016 16:19
To: Whittle, Jenna; Whalley, Charles
Cc: *Mildred; Roger McClellan*
Subject: Re: Publication Options for your Article

Jenna anCharles:
I recognize this is a form letter. Please coordinate the handling of details related to publishing this Foreword to the Special Glyphosate Issue. I assume any costs are covered within the agreement between T and F and Intertek or as an internal T and F cost.
Regards, Roger

On Fri, 9/9/16, Jenna.Whittle@informa[redacted]<cats@taylorandfrancis.com> wrote:

Subject: Publication Options for your Article
To: roger.o.mcclellan@[redacted]
Date: Friday, September 9, 2016, 2:33 AM

Roger McClellan

roger.o.mcclellan@att.net

06 Sep 2016

Your article listed below is currently in production
with Taylor & Francis.
Journal: ITXC, Critical Reviews in Toxicology
Manuscript ID: 1234117
Manuscript Title: Evaluating the Potential Carcinogenic
Hazard of Glyphosate
By: McClellan
We are delighted that you have chosen to publish your

paper in Critical Reviews in Toxicology. This email is to inform you of the publication options available to you.

Standard publication route

Your paper will be published in the journal, and made available online permanently for subscribers and licensed institutions throughout the world, including provision of online access through developing world initiatives. You will also receive a link via email that you can send on to 50 colleagues who can download the paper free of charge. After the appropriate publisher embargo period, you may deposit the Accepted Manuscript into an institutional or subject repository (Green Open Access). (See http://journalauthors.tandf.co.uk/publication/rapidonlinepublication.asp for further information.) If we do not hear from you, your article will be published on this basis.

Gold Open Access publication

You have the option to pay a charge to make the final version of your article freely available online at the point of publication, permanently, for anyone to read (Gold Open Access). This requires payment of an article publishing charge (APC). Please note that this option is strictly your choice, and is not required for publication in the journal. It is not available for research articles of less than two printed pages in length.

If you would like to publish your article via the Gold Open Access route please read the notes below:

• You will retain the rights in your article but will be asked to sign an appropriate article publishing agreement to enable us to publish the article.

• If you are affiliated with an institution that has a prepayment or Open Access partner scheme membership (see http://www.tandfonline.com/page/openaccess/funders for further information), please email apc@tandf.co.uk, providing your full name, article title, journal title and details of any funding.

• Find out more information on Open Access licence options and APCs by journal here: http://journalauthors.tandf.co.uk/permissions/Green-OA-AAM-embargo-periods.xlsx

• Otherwise, please contact apc@tandf.co.uk to arrange payment of the article publishing charge.

If you have questions about Open Access please contact openaccess@tandf.co.uk or visit http://journalauthors.tandf.co.uk/preparation/OpenAccess.asp for further information.

Yours sincerely,

Jenna Whittle
Taylor & Francis
4 Park Square
Milton Park
Abingdon
Oxfordshire

OX14 4RN
UNITED KINGDOM
Email:[redacted]informa.com

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Tuesday, September 13, 2016 9:12 AM
To: Charles.Whalley@tandf[redacted]
Cc: Roger McClellan; Mildred
Subject: Fw: RE: Glyphosate supplement

Charles:
Are you available to discuss by telephone later today. Are you in the USA today? Do you have the tel # for Vasili? What is his position at T and F?
Regards, Roger

--- On Tue, 9/13/16, Ashley Roberts Intertek <ashley.roberts@intertek[redacted] wrote:

> From: Ashley Roberts Intertek <ashley.roberts@intertek[redacted]
> Subject: RE: Glyphosate supplement
> To: "Whalley, Charles" <Charles.Whalley@tandf[redacted]
> Cc: "Vasili, Temis" <Temis.Vasili@informa[redacted], "Roger McClellan"
> <roger.o.mcclellan@[redacted]t>
> Date: Tuesday, September 13, 2016, 8:03 AM
>
>
>
>
>
>
>
>
> Dear Charles/Roger,
>
> In addition to the previous
> information that I sent to you regarding the promotion of the
> glyphosate publications, Monsanto has now updated this to include the
> following and they want to be transparent on what they are doing and
> to keep you in the loop on these matters.
>
> For your information, they plan to
> help amplify the lack of carcinogenicity potential thorough,
> science-based review by: 1) helping coordinate an exclusive interview
> with Sir Colin Berry and a science reporter in advance of
> publication, 2) providing any inquiring media after publication with a
> Monsanto statement, and 3) directing interested media to the Critical
> Reviews in Toxicology website after publication. More details below.
>
>
> 1.
> The Sir Colin Berry exclusive interview will be with a science
> reporter from a mainstream media outlet in Europe.
> The reporter's story will be embargoed until after publication and the

> expert panels findings are publically available online. As part of
> this exclusive interview, we also think it would be beneficial to
> provide the reporter with an early version of the expert panel's
> report so the reporter has the information needed to write a detailed
> article.
> Please let us know if CRT supports this approach? if this is okay,
> Monsanto will suggest to Sir Colin that he share the early version of
> the report with the reporter during the interview.
>
>
> 2.
> For your reference, below is the Monsanto statement they plan to share
> on a reactive basis if they receive media inquiries after publication.
>
> At Monsanto, we're fully
> confident in the safety profile of our products. Our confidence is
> based on rigorous internal safety assessments in addition to safety
> assessments by regulatory authorities, independent researchers and
> other experts around the world. In July 2015, Monsanto retained a
> scientific consultant to convene an expert panel to review the
> International Agency for Research on Cancer (IARC) monograph on
> glyphosate once it published. The charge to the experts was to take a
> thorough look at the data in the monograph, assess the scope of the
> research included or excluded, and publish their conclusions to allow
> for external review. The experts that make up the panel include
> medical doctors, cancer experts, and individuals who hold doctoral
> degrees and who are experts in public health. The experts have spent
> their careers as researchers at major universities and medical
> schools, at research institutions and as consultants. The panel's
> peer-reviewed findings recently were published in the journal
> Critical Reviews in Toxicology and are available here: [Monsanto will
> insert direct link here]. These findings by the panel come at an
> important time, after so much unnecessary confusion and concern has
> been caused by IARC's classification of glyphosate. The panel's
> findings are consistent with the conclusions of regulatory authorities
> around the world. In fact, since IARC classified glyphosate,
> regulatory authorities in Europe, Canada, Japan, New Zealand and
> Australia have publicly reaffirmed that glyphosate does not cause
> cancer. Additionally, in May 2016, the Joint FAO/WHO Meeting on
> Pesticide Residues (JMPR) concluded that "glyphosate is unlikely to
> pose a carcinogenic risk to humans from exposure through the diet."
>
> 3.
> Lastly, after publication, Monsanto plan to proactively inform some
> reporters who have previously covered IARC's glyphosate monograph
> about the publication of the expert panel's findings. As such Monsanto
> plans to share a direct link to the Critical Reviews in Toxicology's
> website.
>
> Please let me know if this is
> acceptable to the journal.
>

> Many best Wishes
>
> Ashley
>
>
> Ashley Roberts,
> Ph.D.
>
> Senior Vice President
>
> Food & Nutrition Group
>
> Intertek Scientific
> & Regulatory Consultancy
>
> Tel: +1
> [redacted]
>
>
> Fax: +1[redacted]
>
> E-mail: ashley.roberts@intertek[redacted]
>
> 2233 Argentia Road,
> Suite 201
>
> Mississauga, Ontario Canada L5N 2X7
>
>
>
>
> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf[redacted]
>
> Sent: September-06-16 8:35 AM
>
> To: Ashley Roberts Intertek
>
> Cc: Vasili, Temis
>
> Subject: RE: Glyphosate supplement
> contract
>
>
>
> Dear Ashley,
>
> Thanks for coordinating signature and
> return of contracts with Temis. I hope you've had a pleasant holiday.
>
> Further to your response re
> promotion, I'd be grateful if Monsanto could

> provide:
> ·
> A draft of the press release before
> publication
> ·
> The names of the journalists who
> would receive the press release
> ·
> The names of the panellists who would
> be provided to these journalists for follow-up discussion ·
> Information on any social media promotion
>
> Apologies for the quizzing, but
> we're anticipating a lot of interest in this supplement and so I'm
> eager that we're aware of any marketing in advance.
>
> As for our promotion, I'll be
> able to confirm our plans after hearing from you on the above.
>
> I'd be happy to discuss this
> with the appropriate person at Monsanto directly if that's easier for
> you.
>
> All best wishes,
> Charles
>
>
>
>
> From: Ashley
> Roberts Intertek [mailto:ashley.roberts@intertek[redacted]]
>
>
> Sent: 23 August 2016 21:28
>
> To: Whalley, Charles
>
> Cc: Vasili, Temis
>
> Subject: RE: Glyphosate supplement
> contract
>
>
>
>
> Dear Charles,
>
> Regarding the contract, I will
> respond to you tomorrow morning my time.
>
> On the topic of promotion, I have
> spoken to Monsanto and they have indicated that if you are in

> agreement they would like to promote the publications. While nothing
> definite has been planned they were contemplating making a press
> release to some "friendly"
> journalists indicating when the report will be released with the time
> estimation for publication as well as provide some names of the
> panelists who they could contact for follow-up discussion. Beyond
> this initial action, no further thought has gone in to this and they
> were wondering if the Journal does any of their own kind of promotion.
>
> If you could let me know if the above
> is acceptable, that would be great.
>
> Many Thanks
>
> Ashley
>
>
> Ashley Roberts,
> Ph.D.
>
> Senior Vice President
>
> Food & Nutrition Group
>
> Intertek Scientific
> & Regulatory Consultancy
>
> Tel: +1
> [redacted]
>
>
> Fax: +1 [redacted]
>
> E-mail: ashley.roberts@intertek[redacted]
>
> 2233 Argentia Road,
> Suite 201
>
> Mississauga, Ontario Canada L5N 2X7
>
>
>
>
> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf[redacted]
>
>
> Sent: August-23-16 10:52 AM
>
> To: Ashley Roberts Intertek
>
> Cc: Vasili, Temis

>
> Subject: RE: Glyphosate supplement
> contract
>
>
>
> Dear Ashley,
>
> Further to the below, it occurs to me
> that it would helpful and much appreciated if you could let me know on
> Intertek's and Monsanto's plans for promoting the supplement, if any,
> both with the print copies which we will be producing and in any
> electronic or other communications/promotion. I look forward to
> hearing from you on this and the below.
>
> Best wishes as ever,
> Charles
>
>
>
> From: Whalley,
> Charles
>
> Sent: 22 August 2016 15:55
>
> To: 'Ashley Roberts Intertek'
>
> Cc: Vasili, Temis
>
> Subject: Glyphosate supplement contract
>
>
>
>
> Dear Ashley,
>
> Please find attached a draft contract for your review. To summarise,
> this covers an Open Access online-only supplement in CRT, with 200
> additional print copies of the supplement issue despatched in bulk to
> a single address (assuming St Louis, Missouri). (These print copies
> will not be sent to subscribers). The cost will be
> $29,339 for the supplement plus $1,306 for the print and delivery of
> the print issues, so $30,645. We will issue a single invoice once the
> contract is signed.
>
> Please let me know if you have any questions regarding the contract.
> Once I hear you're happy, we will arrange for 2 print copies to be
> couriered to you for signature. These will need to be sent back to us
> for counter-signature, and then we will send one to you for your
> records.
>
> With that in mind, I will need to know from

> you:
>
> .
> The name
> and address to send the contracts
> .
> A contact
> number for the courier for this address · The name and address for the
> invoice
>
> I look forward to hearing from you on the above.
>
> Please be advised that I am out of the office, without an internet
> connection, 24th-30th Aug inclusive. I CC my Editorial Assistant,
> Temis Vasili, who will be able to cover for me in my absence. I don't
> anticipate my holiday to cause any delays here.
>
> Best wishes,
> Charles
>
> Charles Whalley
> -
> Managing Editor, Medicine & Health Science Journals Taylor & Francis
> Group
> 4 Park Square, Milton
> Park, Abingdon, Oxon, OX14 4RN, UK
> Direct line:
> +[redacted]
> Switchboard:
> +[redacted]
> charles.whalley@tandf[redacted]
>
> www.tandfonline.com
>
>
> Taylor & Francis
> is a trading name of Informa UK Limited, registered in England under
> no. 1072954
>
>
>
>
>
> Valued Quality. Delivered.
>
>
>
> CONFIDENTIALITY NOTICE
>
> This email may contain
> confidential or privileged information, if you are not the intended
> recipient, or the person responsible for delivering the message to the

> intended recipient then please notify us by return email immediately.
> Should you have received this email in error then you should not copy
> this for any purpose nor disclose its contents to any other person.
> http://www.intertek.com
>
>
>
>
>

Roger McClellan

From: Whalley, Charles <Charles.Whalley@tandf[redacted]
Sent: Tuesday, September 13, 2016 9:29 AM
To: Roger McClellan
Cc: Mildred
Subject: RE: RE: Glyphosate supplement

Dear Roger,

I'm currently in Boston, and will be heading off to set up my booth for the conference in a moment. T&F does not provide me with a mobile phone, so we'll have to continue by email until I return to the office on 22nd Sept. Did you have any concerns with Monsanto's Marketing plans, or just questions about timelines?

For your reference, Temis' number for her desk is +[redacted] (Vasili is her surname; our email addresses show as 'surname, first name'.) She is an Editorial Assistant, and helps me in the management and administration of all of my journals, as well as supporting some other members of my team. Editorial Assistant is the entry-level role in our department, although Temis is more experienced than most, having previously worked at another publisher and with a background in neuroscience.

Best wishes as ever,
Charles

From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]]
Sent: 13 September 2016 16:12
To: Whalley, Charles
Cc: Roger McClellan; Mildred
Subject: Fw: RE: Glyphosate supplement

Charles:
Are you available to discuss by telephone later today. Are you in the USA today? Do you have the tel # for Vasili? What is his position at T and F?
Regards, Roger

--- On Tue, 9/13/16, Ashley Roberts Intertek <[redacted]@intertek.com> wrote:

> From: Ashley Roberts Intertek <ashley.roberts@intertek.com>
> Subject: RE: Glyphosate supplement
> To: "Whalley, Charles" <Charles.Whalley@tandf[redacted]
> Cc: "Vasili, Temis" <[redacted]@informa.com>, "Roger McClellan" <roger.o.mcclellan@[redacted]
> Date: Tuesday, September 13, 2016, 8:03 AM
>
>
>
>
>
>
>
>
> Dear Charles/Roger,
>

> In addition to the previous
> information that I sent to you regarding the promotion of
> the glyphosate publications, Monsanto has now updated this
> to include the following and they want to be transparent on
> what
> they are doing and to keep you in the loop on these
> matters.
>
> For your information, they plan to
> help amplify the lack of carcinogenicity potential thorough,
> science-based review by: 1) helping coordinate an exclusive
> interview with Sir Colin Berry and a science reporter
> in advance of publication, 2) providing any inquiring media
> after publication with a Monsanto statement, and 3)
> directing interested media to the Critical Reviews in
> Toxicology website after publication. More details below.
>
>
> 1.
> The Sir Colin Berry exclusive interview will be with a
> science reporter from a mainstream media outlet in Europe.
> The reporter's story will be embargoed until after
> publication and the expert panels
> findings are publically available online. As part of this
> exclusive interview, we also think it would be beneficial to
> provide the reporter with an early version of the expert
> panel's report so the reporter has the information
> needed to write a detailed article.
> Please let us know if CRT supports this approach? if this
> is okay, Monsanto will suggest to Sir Colin that he share
> the early version of the report with the reporter during the
> interview.
>
>
> 2.
> For your reference, below is the Monsanto statement they
> plan to share on a reactive basis if they receive media
> inquiries after publication.
>
> At Monsanto, we're fully
> confident in the safety profile of our products. Our
> confidence is based on rigorous internal safety assessments
> in addition to safety assessments by regulatory authorities,
> independent
> researchers and other experts around the world. In July
> 2015, Monsanto retained a scientific consultant to convene
> an expert panel to review the International Agency for
> Research on Cancer (IARC) monograph on glyphosate once it
> published. The charge to the
> experts was to take a thorough look at the data in the
> monograph, assess the scope of the research included or

> excluded, and publish their conclusions to allow for
> external review. The experts that make up the panel include
> medical doctors, cancer experts,
> and individuals who hold doctoral degrees and who are
> experts in public health. The experts have spent their
> careers as researchers at major universities and medical
> schools, at research institutions and as consultants. The
> panel's peer-reviewed findings recently
> were published in the journal Critical Reviews in
> Toxicology and are available here: [Monsanto will insert
> direct link here]. These findings by the panel come at an
> important time, after so much unnecessary confusion and
> concern has been caused by IARC's classification
> of glyphosate. The panel's findings are consistent
> with the conclusions of regulatory authorities around the
> world. In fact, since IARC classified glyphosate, regulatory
> authorities in Europe, Canada, Japan, New Zealand and
> Australia have publicly reaffirmed
> that glyphosate does not cause cancer. Additionally, in May
> 2016, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR)
> concluded that "glyphosate is unlikely to pose a
> carcinogenic risk to humans from exposure through the
> diet."
>
> 3.
> Lastly, after publication, Monsanto plan to proactively
> inform some reporters who have previously covered
> IARC's glyphosate monograph about the publication of
> the expert panel's findings. As such Monsanto
> plans to share a direct link to the Critical Reviews in
> Toxicology's website.
>
> Please let me know if this is
> acceptable to the journal.
>
> Many best Wishes
>
> Ashley
>
>
> Ashley Roberts,
> Ph.D.
>
> Senior Vice President
>
> Food & Nutrition Group
>
> Intertek Scientific
> & Regulatory Consultancy
>
> Tel: +1

[redacted]
>
>
> Fax: +1 [redacted]
>
> E-mail: [redacted]@intertek.com
>
> 2233 Argentia Road,
> Suite 201
>
> Mississauga, Ontario Canada L5N 2X7
>
>
>
>
> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf[redacted]
>
> Sent: September-06-16 8:35 AM
>
> To: Ashley Roberts Intertek
>
> Cc: Vasili, Temis
>
> Subject: RE: Glyphosate supplement
> contract
>
>
>
> Dear Ashley,
>
> Thanks for coordinating signature and
> return of contracts with Temis. I hope you've had a
> pleasant holiday.
>
> Further to your response re
> promotion, I'd be grateful if Monsanto could
> provide:
> ·
> A draft of the press release before
> publication
> ·
> The names of the journalists who
> would receive the press release
> ·
> The names of the panellists who would
> be provided to these journalists for follow-up
> discussion
> ·
> Information on any social media
> promotion

>
> Apologies for the quizzing, but
> we're anticipating a lot of interest in this
> supplement and so I'm eager that we're aware of
> any marketing in advance.
>
> As for our promotion, I'll be
> able to confirm our plans after hearing from you on the
> above.
>
> I'd be happy to discuss this
> with the appropriate person at Monsanto directly if
> that's easier for you.
>
> All best wishes,
> Charles
>
>
>
>
> From: Ashley
> Roberts Intertek [mailto:[redacted]@intertek.com]
>
>
> Sent: 23 August 2016 21:28
>
> To: Whalley, Charles
>
> Cc: Vasili, Temis
>
> Subject: RE: Glyphosate supplement
> contract
>
>
>
>
> Dear Charles,
>
> Regarding the contract, I will
> respond to you tomorrow morning my time.
>
> On the topic of promotion, I have
> spoken to Monsanto and they have indicated that if you are
> in agreement they would like to promote the
> publications. While nothing definite has been planned
> they were contemplating
> making a press release to some "friendly"
> journalists indicating when the report will be released with
> the time estimation for publication as well as provide some
> names of the panelists who they could contact for follow-up
> discussion. Beyond this initial

> action, no further thought has gone in to this and they
> were wondering if the Journal does any of their own kind of
> promotion.
>
> If you could let me know if the above
> is acceptable, that would be great.
>
> Many Thanks
>
> Ashley
>
>
> Ashley Roberts,
> Ph.D.
>
> Senior Vice President
>
> Food & Nutrition Group
>
> Intertek Scientific
> & Regulatory Consultancy
>
> Tel: +1
> [redacted]
>
>
> Fax: +1[redacted]
>
> E-mail: [redacted]@intertek.com
>
> 2233 Argentia Road,
> Suite 201
>
> Mississauga, Ontario Canada L5N 2X7
>
>
>
>
> From: Whalley,
> Charles [mailto:Charles.Whalley@tandf[redacted]
>
>
> Sent: August-23-16 10:52 AM
>
> To: Ashley Roberts Intertek
>
> Cc: Vasili, Temis
>
> Subject: RE: Glyphosate supplement
> contract
>

>
>
> Dear Ashley,
>
> Further to the below, it occurs to me
> that it would helpful and much appreciated if you could let
> me know on Intertek's and Monsanto's plans for
> promoting the supplement,
> if any, both with the print copies which we will be
> producing and in any electronic or other
> communications/promotion. I look forward to hearing from you
> on this and the below.
>
> Best wishes as ever,
> Charles
>
>
>
> From: Whalley,
> Charles
>
> Sent: 22 August 2016 15:55
>
> To: 'Ashley Roberts Intertek'
>
> Cc: Vasili, Temis
>
> Subject: Glyphosate supplement contract
>
>
>
>
>
> Dear Ashley,
>
> Please find attached a draft contract for your
> review. To summarise, this covers an Open Access online-only
> supplement in
> CRT, with 200 additional print copies of the
> supplement issue despatched in bulk to a single address
> (assuming St Louis, Missouri). (These print copies will not
> be sent to subscribers). The cost will be
> $29,339 for the supplement plus $1,306 for the
> print and delivery of the print issues, so
> $30,645. We will issue a single invoice once the
> contract is signed.
>
> Please let me know if you have any questions
> regarding the contract. Once I hear you're happy, we
> will arrange for 2 print copies to be couriered to you for
> signature. These will
> need to be sent back to us for counter-signature, and then

> we will send one to you for your records.
>
> With that in mind, I will need to know from
> you:
>
> ·
> The name
> and address to send the contracts
> ·
> A contact
> number for the courier for this address
> ·
> The name
> and address for the invoice
>
> I look forward to hearing from you on the
> above.
>
> Please be advised that I am out of the office,
> without an internet connection,
> 24th-30th Aug inclusive. I CC my
> Editorial Assistant, Temis Vasili, who will
> be able to cover for me in my absence. I don't
> anticipate my holiday to cause any delays here.
>
> Best wishes,
> Charles
>
> Charles Whalley
> -
> Managing Editor, Medicine & Health Science
> Journals
> Taylor & Francis
> Group
> 4 Park Square, Milton
> Park, Abingdon, Oxon, OX14 4RN, UK
> Direct line:
> +[redacted]
> Switchboard:
> +[redacted]
> charles.whalley@tandf[redacted]
>
> www.tandfonline.com
>
>
> Taylor & Francis
> is a trading name of Informa UK Limited,
> registered in England
> under no. 1072954
>
>

>
>
>
> Valued Quality. Delivered.
>
>
>
> CONFIDENTIALITY NOTICE
>
> This email may contain
> confidential or privileged information, if you are not the
> intended recipient, or the person responsible for delivering
> the message to the intended recipient then please
> notify us by return email immediately. Should you have
> received this email in error then you should not copy this
> for any purpose nor disclose its contents to any other
> person.
> http://www.intertek.com
>
>
>
>
>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]
Sent: Tuesday, September 13, 2016 9:50 AM
To: Charles.Whalley@tandf[redacted]
Cc: mbmorgan@hargray[redacted]; roger.o.mcclellan[redacted]; Jenna.Whittle@informa[redacted]
Subject: RE: RE: Glyphosate supplement/ Followup

Charles:
I have no problems with the Monsanto Proposal. My concern is with removal of the special entry for Funding and the inter-related issue of schedule. . I want this Special Supplement Issue to be identical in format to earlier regular issues in Vol 46. I see no need to change horses in mid stream since the DOI of the accepted papers covered funding.
Later we can discuss why the T and F folks got a "bee in their bonnet" over funding , especially since CRT had been a leader on the disclosure issue.
Roger

On Tue, 9/13/16, Whalley, Charles <Charles.Whalley@tandf[redacted]> wrote:

Subject: RE: RE: Glyphosate supplement
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>
Cc: "Mildred" <mbmorgan@hargray[redacted]>
Date: Tuesday, September 13, 2016, 8:29 AM

#yiv1006742520
#yiv1006742520 --

_filtered #yiv1006742520 {font-family:Calibri;panose-1:2 15
5 2 2 2 4 3 2 4;}
_filtered #yiv1006742520 {font-family:Tahoma;panose-1:2 11
6 4 3 5 4 4 2 4;}
#yiv1006742520
#yiv1006742520 p.yiv1006742520MsoNormal, #yiv1006742520 li.yiv1006742520MsoNormal, #yiv1006742520
div.yiv1006742520MsoNormal
{margin:0cm;margin-bottom:.0001pt;font-size:12.0pt;}
#yiv1006742520 a:link, #yiv1006742520
span.yiv1006742520MsoHyperlink
{color:blue;text-decoration:underline;}
#yiv1006742520 a:visited, #yiv1006742520 span.yiv1006742520MsoHyperlinkFollowed
{color:purple;text-decoration:underline;}
#yiv1006742520 span.yiv1006742520EmailStyle17
{color:#1F497D;}
#yiv1006742520 .yiv1006742520MsoChpDefault
{font-size:10.0pt;}
_filtered #yiv1006742520 {margin:72.0pt 72.0pt 72.0pt 72.0pt;}
#yiv1006742520 div.yiv1006742520WordSection1
{}
#yiv1006742520

Dear Roger,

I'm currently in Boston, and
will be heading off to set up my booth for the conference in a moment. T&F does not provide me with a mobile phone, so we'll have
to continue by email until I return to the office on 22nd Sept. Did you have any concerns with Monsanto's Marketing plans, or just questions about timelines?

For your reference, Temis'
number for her desk is +[redacted] (Vasili is her surname; our email addresses show as 'surname, first name'.) She is an Editorial
Assistant, and helps me in the management and administration of all of my journals, as well as supporting some other members of my team. Editorial Assistant is the entry-level role in our department, although Temis is more experienced than most, having previously
worked at another publisher and with a background in neuroscience.

Best wishes as ever,
Charles

From: Roger McClellan
[mailto:roger.o.mcclellan@[redacted]

Sent: 13 September 2016 16:12

To: Whalley, Charles

Cc: Roger McClellan; Mildred

Subject: Fw: RE: Glyphosate supplement

Charles:

Are you available to discuss by telephone later today. Are you in the USA today? Do you have the tel # for Vasili? What is his position at T and F?

Regards, Roger

--- On Tue, 9/13/16, Ashley Roberts Intertek <ashley.roberts@intertek[redacted]>
wrote:

> From: Ashley Roberts Intertek <ashley.roberts@intertek[redacted]

> Subject: RE: Glyphosate supplement

> To: "Whalley, Charles" <Charles.Whalley@tandf[redacted]>

> Cc: "Vasili, Temis" <Temis.Vasili@informa[redacted] "Roger McClellan" <roger.o.mcclellan[redacted]

> Date: Tuesday, September 13, 2016, 8:03 AM

>

>

>

>

>

>

>

>

> Dear Charles/Roger,

>

> In addition to the previous

> information that I sent to you regarding the promotion of

> the glyphosate publications, Monsanto has now updated this

> to include the following and they want to be transparent on

> what

> they are doing and to keep you in the loop on these

> matters.

>

> For your information, they plan to

> help amplify the lack of carcinogenicity potential thorough,

> science-based review by: 1) helping coordinate an exclusive

> interview with Sir Colin Berry and a science reporter

> in advance of publication, 2) providing any inquiring media

> after publication with a Monsanto statement, and 3)

> directing interested media to the Critical Reviews in

> Toxicology website after publication. More details below.

>

>

> 1.

> The Sir Colin Berry exclusive interview will be with a

> science reporter from a mainstream media outlet in Europe.

> The reporter's story will be embargoed until after

> publication and the expert panels

> findings are publically available online. As part of this

> exclusive interview, we also think it would be beneficial to

> provide the reporter with an early version of the expert

> panel's report so the reporter has the information

> needed to write a detailed article.

> Please let us know if CRT supports this approach? if this

> is okay, Monsanto will suggest to Sir Colin that he share

> the early version of the report with the reporter during the

> interview.

>

>

> 2.

> For your reference, below is the Monsanto statement they

> plan to share on a reactive basis if they receive media

> inquiries after publication.

>

> At Monsanto, we're fully

> confident in the safety profile of our products. Our

> confidence is based on rigorous internal safety assessments

> in addition to safety assessments by regulatory authorities,

> independent

> researchers and other experts around the world. In July

> 2015, Monsanto retained a scientific consultant to convene

> an expert panel to review the International Agency for

> Research on Cancer (IARC) monograph on glyphosate once it

> published. The charge to the

> experts was to take a thorough look at the data in the

> monograph, assess the scope of the research included or

> excluded, and publish their conclusions to allow for

> external review. The experts that make up the panel include

> medical doctors, cancer experts,

> and individuals who hold doctoral degrees and who are

> experts in public health. The experts have spent their

> careers as researchers at major universities and medical

> schools, at research institutions and as consultants.
The

> panel's peer-reviewed findings recently

> were published in the journal Critical Reviews in

> Toxicology and are available here: [Monsanto will insert

> direct link here]. These findings by the panel come at an

> important time, after so much unnecessary confusion and

> concern has been caused by IARC's classification

> of glyphosate. The panel's findings are consistent

> with the conclusions of regulatory authorities around the

> world. In fact, since IARC classified glyphosate, regulatory

> authorities in Europe, Canada, Japan, New Zealand and

> Australia have publicly reaffirmed

> that glyphosate does not cause cancer. Additionally, in May

> 2016, the Joint FAO/WHO Meeting on Pesticide Residues (JMPR)

> concluded that "glyphosate is unlikely to pose a

> carcinogenic risk to humans from exposure through the

> diet."

>

> 3.

> Lastly, after publication, Monsanto plan to proactively

> inform some reporters who have previously covered

> IARC's glyphosate monograph about the publication of

> the expert panel's findings. As such Monsanto

> plans to share a direct link to the Critical Reviews in

> Toxicology's website.

>

> Please let me know if this is

> acceptable to the journal.

>

> Many best Wishes

>

> Ashley

>

>

> Ashley Roberts,

> Ph.D.

>

> Senior Vice President

>

> Food & Nutrition Group

>

> Intertek Scientific

> & Regulatory Consultancy

>

> Tel: +1

> [redacted]

>

>

> Fax: +1 [redacted]

>

> E-mail: [redacted]@intertek[redacted]

>

> 2233 Argentia Road,

> Suite 201

>

> Mississauga, Ontario Canada L5N 2X7

>

>

>

>

> From: Whalley,

> Charles [mailto:Charles.Whalley@tandf[redacted]]

>

> Sent: September-06-16 8:35 AM

>

> To: Ashley Roberts Intertek

>

> Cc: Vasili, Temis

>

> Subject: RE: Glyphosate supplement

> contract

>

>

>

> Dear Ashley,

>

> Thanks for coordinating signature and

> return of contracts with Temis. I hope you've had a

> pleasant holiday.

>

> Further to your response re

> promotion, I'd be grateful if Monsanto could

> provide:

> ·

> A draft of the press release before

> publication

> ·

> The names of the journalists who

> would receive the press release

> ·

> The names of the panellists who would

> be provided to these journalists for follow-up

> discussion

> ·

> Information on any social media

> promotion

>

> Apologies for the quizzing, but

> we're anticipating a lot of interest in this

> supplement and so I'm eager that we're aware of

> any marketing in advance.

>

> As for our promotion, I'll be

> able to confirm our plans after hearing from you on the

> above.

>

> I'd be happy to discuss this

> with the appropriate person at Monsanto directly if

> that's easier for you.

>

> All best wishes,

> Charles

>

>

>

>

> From: Ashley

> Roberts Intertek [mailto:ashley.roberts@intertek[redacted]

>

>

> Sent: 23 August 2016 21:28

>

> To: Whalley, Charles

>

> Cc: Vasili, Temis

>

> Subject: RE: Glyphosate supplement

> contract

>

>

>

>

> Dear Charles,

>

> Regarding the contract, I will

> respond to you tomorrow morning my time.

>

> On the topic of promotion, I have

> spoken to Monsanto and they have indicated that if you are

> in agreement they would like to promote the

> publications. While nothing definite has been planned

> they were contemplating

> making a press release to some "friendly"

> journalists indicating when the report will be released with

> the time estimation for publication as well as provide some

> names of the panelists who they could contact for follow-up

> discussion. Beyond this initial

> action, no further thought has gone in to this and they

> were wondering if the Journal does any of their own kind of

> promotion.

>

> If you could let me know if the above

> is acceptable, that would be great.

>

> Many Thanks

>

> Ashley

>

>

> Ashley Roberts,

> Ph.D.

>

> Senior Vice President

>

> Food & Nutrition Group

>

> Intertek Scientific

> & Regulatory Consultancy

>

> Tel: +1

> [redacted]

>

>

> Fax: +1[redacted]

>

> E-mail:[redacted]@intertek.com

>

> 2233 Argentia Road,

> Suite 201

>

> Mississauga, Ontario Canada L5N 2X7

>

>

>

>

> From: Whalley,

> Charles [mailto:Charles.Whalley@tandf[redacted]

>

>

> Sent: August-23-16 10:52 AM

>

> To: Ashley Roberts Intertek

>

> Cc: Vasili, Temis

>

> Subject: RE: Glyphosate supplement

> contract

>

>

>

> Dear Ashley,

>

> Further to the below, it occurs to me

> that it would helpful and much appreciated if you could let

> me know on Intertek's and Monsanto's plans for

> promoting the supplement,

> if any, both with the print copies which we will be

> producing and in any electronic or other

> communications/promotion. I look forward to hearing from you

> on this and the below.

>

> Best wishes as ever,

> Charles

>

>

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Tuesday, September 20, 2016 2:21 PM
To: ashley.roberts@intertek[redacted] roger.o.mcclellan@[redacted] JennaWhittle
Cc: Charles.Whalley@tandf[redacted] Mildred Morgan; judy.vowles@intertek[redacted]
Subject: Re: CRT supplement 1, final files for approval/ Changes to 3 DOIs

Jenna:
To provide consistency across all five papers the DOIs on 3 papers need to be expanded.
Solomon: Add at beginning of DOI --"The employment affiliation of the author is shown on the cover page. However, it should be recognized that the author participated in there view process and preparation of this paper as an independent professional and not as a representative of his employer."
Brusick etal.: Add 2 sentences to beginning of DOI identical to the Williams etal papers.
Acquavella etal: Add 2 sentences to beginning of DOI identical to first 2 sentences of Williams etal papers.
In my opinion, with these changes, the papers are now ready for on-line posting. I assume that Dr Roberts concurs.
Please acknowledge receipt and note when papers will be posted.
Thnaks for your help on this special issue.
Roger

On Tue, 9/20/16, Whittle, Jenna <Jenna.Whittle@informa[redacted] wrote:

Subject: CRT supplement 1, final files for approval
To: "Ashley Roberts Intertek" <ashley.roberts@intertek[redacted] "Roger McClellan" <roger.o.mcclellan@a[redacted]
Cc: "Whalley, Charles" <Charles.Whalley@tandf[redacted], "Mildred Morgan" <mbmorgan@hargray[redacted]
"judy.vowles@intertek[redacted] <judy.vowles@intertek[redacted]
Date: Tuesday, September 20, 2016, 9:51 AM

Dear Roger and Ashley

As discussed, please find
attached the final print files for the supplement. Please could you review these files and let me know if they have your approval for publication.

In addition, as a number
of changes had to be made to the Declaration of interest sections, I would be grateful if you could check these in particular to ensure that they are correct and complete.

Many thanks for all your
help with this. Please do let me know if you have any questions.

Best wishes

Jenna

Jenna
Whittle
Production Editor,
Journals
Taylor & Francis

4 Park Square, Milton
Park, Abingdon, Oxon, OX14 4RN, UK

jenna.whittle@tandf[redacted]

www.tandfonline.com

Roger McClellan

From: Larry Kier <ldkier@[redacted]>
Sent: Tuesday, September 20, 2016 1:26 PM
To: Roger O. McClellan
Subject: Quotes in SAP Letter

Dear Roger:

It's been a while and I hope you are doing well.

As you are probably aware the EPA will be convening a FIFRA SAP in October to review glyphosate carcinogenicity.

I am preparing a letter for submission to the SAP which briefly presents the conclusions of the glyphosate genotoxicity Expert Panel report and provides relevant material from the report to comment on the Charge Questions relevant to genotoxicity evaluation submitted to the SAP.

I would like to use brief (one or two sentences each) direct quotes from the report in this letter to make sure there is as accurate a representation as possible.

It's my understanding that the report will be published online this week and will be open access but I wanted to check with you to make sure it's ok to use direct quotes from the publication in the letter.

Thanks and best regards,

Larry Kier

Roger McClellan

From: Roger McClellan <roger.o.mcclellan@[redacted]>
Sent: Tuesday, September 20, 2016 2:50 PM
To: Larry Kier
Cc: ashley.roberts@intertek[redacted] mbmorgan@hargray[redacted]Roger McClellan
Subject: Re: Quotes in SAP Letter/ Yes

Larry
Great to her from you. Yes, the Special Glyphosate Issue should be posted on line in a matter of days. You are certainly free to make direct quotes , with appropriate attribution, from the paper in your letter and oral presentation, if you make one. . In some cases you may even want to make direct quotes from your earlier papers which were provided to IARC prior to their review. To cover all the options you may wish to make direct quotes from the original papers published by you and others.

You should be aware that in the past some EPA Offices have raised issues about citing review papers. If you want more details I suggest you contact Barbara Beck and/or Sam Cohen.
Best regards,
Roger

On Tue, 9/20/16, Larry Kier <ldkier@[redacted] wrote:

Subject: Quotes in SAP Letter
To: "Roger O. McClellan" <roger.o.mcclellan@[redacted]>
Date: Tuesday, September 20, 2016, 12:25 PM

Dear Roger: It's been a while and I
hope you are doing well. As you are probably aware the EPA will be convening a FIFRA SAP in October to review glyphosate carcinogenicity. I am preparing a letter for submission to the SAP which briefly presents the conclusions of the glyphosate genotoxicity Expert Panel report and provides relevant material from the report to comment on the Charge Questions relevant to genotoxicity evaluation submitted to the SAP.
I would like to
use brief (one or two sentences each) direct quotes from the report in this letter to make sure there is as accurate a representation as possible. It's my understanding that the report will be published online this week and will be open access but I wanted to check with you to make sure it's ok to use direct quotes from the publication in the letter.
Thanks and best
regards, Larry Kier ---------- This e-mail message may contain privileged and/or confidential information, and is intended to be received only by persons entitledto receive such information. If you have received this e-mail in error, please notify the sender immediately. Please delete it andall attachments from any servers, hard drives or any other media. Other use of this e-mail by you is strictly prohibited.

Roger McClellan

From: Ashley Roberts Intertek <[redacted]@intertek.com>
Sent: Thursday, September 22, 2016 10:41 AM
To: Whittle, Jenna
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Many Thanks Jenna.

Ashley Roberts, Ph.D.
Senior Vice President. Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Health. Environmental and Regulatory Services
www.intertek.com

E-mail: [redacted]s@intertek.com
Tel: +1 [redacted]; Fax: +1 [redacted]
Skype: [redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:Jenna.Whittle@informa[redacted]
Sent: September-22-16 12:37 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Hi Ashley
I unfortunately can't give a specific date for publication as this depends on whether further corrections will be required to the next set of final files. The corrected files should hopefully arrive by the end of the day UK time on Monday if the typesetter doesn't have any difficulty incorporating the corrections. We also need to allow time for you to check the final files and for all the quality control checks here to take place so I'm afraid publication on Monday is unlikely. Hopefully it shouldn't be too much later in the week if no further corrections are required.
Best wishes
Jenna

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek[redacted]
Sent: 22 September 2016 16:48
To: Whittle, Jenna
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes
Importance: High

Hi Jenna,

Could you let me know with the changes we made if we are still aiming for a Monday publication?

Many Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Health, Environmental and Regulatory Services
www.intertek.com

E-mail: ashley.roberts@intertek[redacted]
Tel: +1[redacted] Fax: +1[redacted]
Skype: [redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:Jenna.Whittle@informa[redacted]
Sent: September-21-16 12:12 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Thank you for sending me your final amendments, Ashley. I'll arrange for them to be incorporated and I will let you know if I have any questions. For Roger's reference, I've attached your other emails detailing the other corrections.

These are more extensive changes than we would normally expect at this stage in the production process (reorganising the order of various sections, etc.) and so the typesetter will need more time to incorporate them accurately. I'm concerned that errors could be accidentally introduced while they make these amendments, despite their best efforts, so I will send you another final file for approval before we go to press. This should hopefully be on or by Monday 26th. Please note that only major errors that would otherwise result in an erratum or corrigendum should be corrected at that stage to avoid delays.

If you have any questions, please do not hesitate to contact me.

Best wishes

Jenna

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek[redacted]
Sent: 21 September 2016 16:57
To: Whittle, Jenna
Subject: Final changes

Hi Jenna,

These are the last of the typos changes we found in the manuscripts as outlined on the various page numbers

1. Need to reorder within the summary document so the sections follow the same sequence as the chapters - Introduction, Exposure, Epidemiology, Rodent bioassay, and Genotoxicity

2. *Page 8, second column, bullet point* "c.", "(positive trend p<0.05)" should be "positive trend (p<0.05)"

3. Page 47, second column, second complete paragraph beginning " In the first two-year bioassay.....", ".... [157/190, low-dose (LD) group), 5000 (814/955, mid-dose (MD) group) or 30,000 (4841/5874 mg/kg/d, high-dose (HD) group]", should be " ....[157/190, low-dose (LD) group], 5000 [814/955, mid-dose (MD) group] or 30,000 [4841/5874 mg/kg/d, high-dose (HD) group]" (just making the bracket sequence line up).

4. Page 48, last line of first column, "....low observed adverse effect..." should be "lowest observed adverse effect"

5. Page 49, second column, third complete paragraph, "IARC did not comment on the absence of hemangiosarcomas in the Nufarm (2009)...." should be "IARC did not comment on the absence of hemangiosarcomas in Nufarm (2009)" (delete "the" from original text)

6. Page 59, second column, 4 lines up from bottom, "high degree of and standard for detailed" should be "high degree of, and standard for, detailed" (added commas)

7. Page 63, first column, second complete paragraph "25.0 µM" should be "25.0 µm" (small "m" for micrometer)

8. Page 65, the "in vivo" in the title heading "Chromosomal effects in vivo" needs to be italicized.

9. Page 65 second column, 17 lines up from the bottom "Another positive publication Amer et al. (2006)" should be "Another positive publication (Amer et al. 2006)" (change position of bracket)

If you have any questions, please let me know.

Best Wishes

Ashley

From: Whittle, Jenna [mailto:Jenna.Whittle@informa[redacted]
Sent: September-21-16 10:38 AM
To: Ashley Roberts Intertek
Subject: RE: A few changes

Thanks for these, Ashley. Just to confirm the changes to pp. 49 and 50, please can you check that this is correct:

In the first study, SD rats received 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/d) ppm ad libitum in diet for 26 months. No pancreatic islet carcinomas were observed. The incidence of adenoma was found to have a positive trend ($p<.05$) in the study. Here, again the level of significance in common tumors is $p<.005$. The following islet cell adenoma incidences were observed for controls, low, mid and high doses respectively in males: 0/50, 5/49 (10%), 2/50 (4%), 2/50 (4%). This incidence data shows no dose-response patterns and preneoplastic effects are absent. In addition, in the first study in males, the adenomas also did not progress to carcinomas. Thus, the pancreatic islet cell adenomas were not compound-related. In females, the corresponding values were: 2/50 (4%), 1/50 (2%), 1/50 (2%), and 0/50.

In the second study, male and female Sprague–Dawley (SD) rats were fed 0, 2000 (89/113), 8000 (362/457), or 20,000 (940/1183 mg/kg bw/d) ppm glyphosate (96.5% pure) ad libitum in diet for 24 months. The following islet cell tumor incidences were observed in males: adenomas – 1/58 (2%), 8/57 (14%), 5/60 (8%), 7/59 (12%); carcinomas – 1/58 (25%), 0/57, 0/60, 0/59. In females, the corresponding incidences were: adenomas – 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59; carcinomas – 0/60, 0/60, 0/60, 0/59. The historical control rates for pancreatic islet cell tumors at the testing laboratory were in the range 1.8–8.5%. The panel disagrees with the conclusion of IARC that there is a significant positive trend ($p<.05$) in the incidence of pancreatic adenomas in males, since the level of significance for trend should be $p<.005$ (US FDA 2001; Williams et al. 2014). Moreover, there was no progression of adenomas to carcinomas.

Thanks and best wishes

Jenna

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek[redacted]
Sent: 21 September 2016 14:25
To: Whittle, Jenna
Subject: A few changes

Hi Jenna,

The following typos and changes need to be made to the following papers

- Page 2, lines 19 and 24 – change "glyphosate**s**" (plural) to "glyphosate" (singular) paper #1 Rogers Foreword
- Page 32, Table 4 Title – should be "Validity considerations **for** glyphosate studies (add the word "for") Paper #3 Epidemiology

For the summary paper #2 and the animal bioassay paper #4 the following error was picked up.

As outlined below the study identified as "the first study" is actually "the second study" and vice-versa in the discussion of "Pancreatic tumors in rats", here is how the text should read on the bottom of page 9/top of page 10. I highlighted words which need to change:

In the ~~second~~ first study Sprague-Dawley rats received doses of 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/day) ppm in the diet for 26 months. No pancreatic islet carcinomas were observed. Adenomas were found having a positive trend ($p<.05$) in the study. ~~Here again t~~ The level of significance for an increase in common tumors in the trend test should be $p<.005$. The tumor incidences for controls, low, mid, and high doses respectively were: males – 0/50, 5/49 (10%), 2/50 (4%), 2/50 (4%), and females – 2/50 (4%), 1/50 (2%), 1/50 (2%) 0/50. This incidence demonstrates no dose-response pattern, and an absence of pre-neoplastic effects. In addition, in the second study in males, the adenomas did not progress to carcinomas.

In the ~~first~~ second study Sprague-Dawley rats received 0, 2000, 8000, and 20,000ppm glyphosate (96.5% purity) in the diet, fed ad libitum for 24 months. In males, the following pancreatic islet cell tumor incidences were observed in the controls and three dose groups (low to high): adenoma: 1/58 (2%), 8/57 (14%), 5/60 (8%), 7/59 (12%); carcinoma: 1/58 (2), 0/57, 0/60, 0/59. Corresponding incidence values in females were: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59, and 0/60, 0/60, 0/60, 0/59. The historical control rates for pancreatic islet cell tumors at the testing laboratory were in the range 1.8–8.5%. The Panel disagrees with the conclusion of IARC that there is a significant positive trend ($p<.05$) in the incidence of pancreatic adenomas in males, since here again the level of significance should be $p<.005$ (US FDA, 2001; Williams et al. 2014). Moreover, there was no progression of adenomas to carcinomas.
Four additional studies in rats, described by Greim et al. (2015) not evaluated by IARC, similarly did not show pancreatic islet cell tumors. Based on this information the Expert Panel concludes that there is no evidence that glyphosate induces islet cell tumors in the pancreas.

The same changes will need to be done on the bottom of page 49 and top of page 50 of the animal bioassay paper #4. Here the changes are slightly simpler – the text needs to be moved as shown above, and the only word-changing is "first" to "second" and "second" to "first" (2 times in that paragraph).

Please let me know if you need clarification on any of the above?

Best Wishes

Ashley
Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Health, Environmental and Regulatory Services
www.intertek.com

E-mail: a[redacted]@intertek.com
Tel: +1[redacted]; Fax: +[redacted]
Skype: [redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:Jenna.Whittle@informa[redacted]]
Sent: September-20-16 12:52 PM

To: Ashley Roberts Intertek; Roger McClellan
Cc: Whalley, Charles; Mildred Morgan; Judy Vowles Intertek
Subject: CRT supplement 1, final files for approval

Dear Roger and Ashley

As discussed, please find attached the final print files for the supplement. Please could you review these files and let me know if they have your approval for publication.

In addition, as a number of changes had to be made to the Declaration of interest sections, I would be grateful if you could check these in particular to ensure that they are correct and complete.

Many thanks for all your help with this. Please do let me know if you have any questions.

Best wishes

Jenna

Jenna Whittle
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group
an informa business

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From: Whittle, Jenna <[redacted]@informa.com>
Sent: Monday, September 26, 2016 8:07 AM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: Supplement proofs - update

Dear all
I have just received the final proofs from the typesetter, but the tables in the Williams et al. paper haven't been renumbered and repositioned following the changes requested to the article structure, so I will need to request another updated proof from the typesetter. I'm afraid this means that there will be a delay in sending you the final proof for approval – please accept my apologies for this. I will be in touch again as soon as I can.
Best wishes
Jenna

From: Ashley Roberts Intertek [mailto:ashley.roberts@intertek[redacted]
Sent: 22 September 2016 17:41
To: Whittle, Jenna
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Many Thanks Jenna.

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Health, Environmental and Regulatory Services
www.intertek.com

E-mail: [redacted]@intertek.com
Tel: +1 [redacted]2900; Fax: +1 [redacted]
Skype: [redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:[redacted]@informa.com]
Sent: September-22-16 12:37 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Hi Ashley
I unfortunately can't give a specific date for publication as this depends on whether further corrections will be required to the next set of final files. The corrected files should hopefully arrive by the end of the day UK time on Monday if the typesetter doesn't have any difficulty incorporating the corrections. We also need to allow time for you to check the final files and for all the quality control checks here to take place so I'm afraid publication on Monday is unlikely. Hopefully it shouldn't be too much later in the week if no further corrections are required.
Best wishes
Jenna

From: Ashley Roberts Intertek [mailto:[redacted]@intertek.com]
Sent: 22 September 2016 16:48
To: Whittle, Jenna
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes
Importance: High

Hi Jenna,

Could you let me know with the changes we made if we are still aiming for a Monday publication?

Many Thanks

Ashley

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Health, Environmental and Regulatory Services
www.intertek.com

E-mail: [redacted]@intertek.com
Tel: +1 [redacted] Fax: +1 [redacted]
Skype: [redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:[redacted]@informa.com]
Sent: September-21-16 12:12 PM
To: Ashley Roberts Intertek
Cc: Roger McClellan; Mildred Morgan; Whalley, Charles
Subject: RE: Final changes

Thank you for sending me your final amendments, Ashley. I'll arrange for them to be incorporated and I will let you know if I have any questions. For Roger's reference, I've attached your other emails detailing the other corrections.

These are more extensive changes than we would normally expect at this stage in the production process (reorganising the order of various sections, etc.) and so the typesetter will need more time to incorporate them accurately. I'm concerned that errors could be accidentally introduced while they make these amendments, despite their best efforts, so I will send you another final file for approval before we go to press. This should hopefully be on or by Monday 26th. Please note that only major errors that would otherwise result in an erratum or corrigendum should be corrected at that stage to avoid delays.

If you have any questions, please do not hesitate to contact me.

Best wishes

Jenna

From: Ashley Roberts Intertek [mailto:[redacted]@intertek.com]
Sent: 21 September 2016 16:57
To: Whittle, Jenna
Subject: Final changes

Hi Jenna,

These are the last of the typos changes we found in the manuscripts as outlined on the various page numbers

1. Need to reorder within the summary document so the sections follow the same sequence as the chapters - Introduction, Exposure, Epidemiology, Rodent bioassay, and Genotoxicity

2. Page 8, second column, bullet point "c.", "(positive trend p<0.05)" should be "positive trend (p<0.05)"

3. Page 47, second column, second complete paragraph beginning " In the first two-year bioassay.....", ".... [157/190, low-dose (LD) group), 5000 (814/955, mid-dose (MD) group) or 30,000 (4841/5874 mg/kg/d, high-dose (HD) group]", should be " ....[157/190, low-dose (LD) group], 5000 [814/955, mid-dose (MD) group] or 30,000 [4841/5874 mg/kg/d, high-dose (HD) group]" (just making the bracket sequence line up).

4. Page 48, last line of first column, "....low observed adverse effect..." should be "lowest observed adverse effect"

5. Page 49, second column, third complete paragraph, "IARC did not comment on the absence of hemangiosarcomas in the Nufarm (2009)...." should be "IARC did not comment on the absence of hemangiosarcomas in Nufarm (2009)" (delete "the" from original text)

6. Page 59, second column, 4 lines up from bottom, "high degree of and standard for detailed" should be "high degree of, and standard for, detailed" (added commas)

7. Page 63, first column, second complete paragraph "25.0 µM" should be "25.0 µm" (small "m" for micrometer)

8. Page 65, the "in vivo" in the title heading "Chromosomal effects in vivo" needs to be italicized.

9. Page 65 second column, 17 lines up from the bottom "Another positive publication Amer et al. (2006)" should be "Another positive publication (Amer et al. 2006)" (change position of bracket)

If you have any questions, please let me know.

Best Wishes

Ashley

From: Whittle, Jenna [mailto[redacted]@informa.com]
Sent: September-21-16 10:38 AM
To: Ashley Roberts Intertek
Subject: RE: A few changes

Thanks for these, Ashley. Just to confirm the changes to pp. 49 and 50, please can you check that this is correct:

In the first study, SD rats received 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/d) ppm ad libitum in diet for 26 months. No pancreatic islet carcinomas were observed. The incidence of adenoma was found to have a positive trend ($p<.05$) in the study. Here, again the level of significance in common tumors is $p<.005$. The following islet cell adenoma incidences were observed for controls, low, mid and high doses respectively in males: 0/50, 5/49 (10%), 2/50 (4%), 2/50 (4%). This incidence data shows no dose-response patterns and preneoplastic effects are absent. In addition, in the first study in males, the adenomas also did not progress to carcinomas. Thus, the pancreatic islet cell adenomas were not compound-related. In females, the corresponding values were: 2/50 (4%), 1/50 (2%), 1/50 (2%), and 0/50.

In the second study, male and female Sprague–Dawley (SD) rats were fed 0, 2000 (89/113), 8000 (362/457), or 20,000 (940/1183 mg/kg bw/d) ppm glyphosate (96.5% pure) ad libitum in diet for 24 months. The following islet cell tumor incidences were observed in males: adenomas – 1/58 (2%), 8/57 (14%), 5/60 (8%), 7/59 (12%); carcinomas – 1/58 (25%), 0/57, 0/60, 0/59. In females, the corresponding incidences were: adenomas – 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59; carcinomas – 0/60, 0/60, 0/60, 0/59. The historical control rates for pancreatic islet cell tumors at the testing laboratory were in the range 1.8–8.5%. The panel disagrees with the conclusion of IARC that there is a significant positive trend ($p<.05$) in the incidence of pancreatic adenomas in males, since the level of significance for trend should be $p<.005$ (US FDA 2001; Williams et al. 2014). Moreover, there was no progression of adenomas to carcinomas.

Thanks and best wishes

Jenna

From: Ashley Roberts Intertek [mailto[redacted]@intertek.com]
Sent: 21 September 2016 14:25
To: Whittle, Jenna
Subject: A few changes

Hi Jenna,

The following typos and changes need to be made to the following papers

- Page 2, lines 19 and 24 – change "glyphosates" (plural) to "glyphosate" (singular) paper #1 Rogers Foreword
- Page 32, Table 4 Title – should be "Validity considerations for glyphosate studies (add the word "for") Paper #3 Epidemiology

For the summary paper #2 and the animal bioassay paper #4 the following error was picked up.

As outlined below the study identified as "the first study" is actually "the second study" and vice-versa in the discussion of "Pancreatic tumors in rats", here is how the text should read on the bottom of page 9/top of page 10. I highlighted words which need to change:

In the ~~second~~ first study Sprague-Dawley rats received doses of 0, 30 (3), 100 (10), and 300 (31 mg/kg bw/day) ppm in the diet for 26 months. No pancreatic islet carcinomas were observed. Adenomas were found having a positive trend ($p<.05$) in the study. ~~Here again t~~ The level of significance for an increase in common tumors in the trend test should be $p<.005$. The tumor incidences for controls, low, mid, and high doses respectively were: males – 0/50, 5/49 (10%), 2/50 (4%), 2/50 (4%), and females – 2/50 (4%), 1/50 (2%), 1/50 (2%) 0/50. This incidence demonstrates no dose-response pattern, and an absence of pre-neoplastic effects. In addition, in the second study in males, the adenomas did not progress to carcinomas.

In the ~~first~~ second study Sprague-Dawley rats received 0, 2000, 8000, and 20,000ppm glyphosate (96.5% purity) in the diet, fed ad libitum for 24 months. In males, the following pancreatic islet cell tumor incidences were observed in the controls and three dose groups (low to high): adenoma: 1/58 (2%), 8/57 (14%), 5/60 (8%), 7/59 (12%); carcinoma: 1/58 (2), 0/57, 0/60, 0/59. Corresponding incidence values in females were: 5/60 (8%), 1/60 (2%), 4/60 (7%), 0/59, and 0/60, 0/60, 0/60, 0/59. The historical control rates for pancreatic islet cell tumors at the testing laboratory were in the range 1.8–8.5%. The Panel disagrees with the conclusion of IARC that there is a significant positive trend ($p<.05$) in the incidence of pancreatic adenomas in males, since here again the level of significance should be $p<.005$ (US FDA, 2001; Williams et al. 2014). Moreover, there was no progression of adenomas to carcinomas.
Four additional studies in rats, described by Greim et al. (2015) not evaluated by IARC, similarly did not show pancreatic islet cell tumors. Based on this information the Expert Panel concludes that there is no evidence that glyphosate induces islet cell tumors in the pancreas.

The same changes will need to be done on the bottom of page 49 and top of page 50 of the animal bioassay paper #4. Here the changes are slightly simpler – the text needs to be moved as shown above, and the only word-changing is "first" to "second" and "second" to "first" (2 times in that paragraph).

Please let me know if you need clarification on any of the above?

Best Wishes

Ashley
Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
Health, Environmental and Regulatory Services
www.intertek.com

E-mail: [redacted]Intertek.com
Tel: +1 [redacted] Fax: +1 [redacted]
Skype: [redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:[redacted]@informa.com]
Sent: September-20-16 12:52 PM
To: Ashley Roberts Intertek; Roger McClellan
Cc: Whalley, Charles; Mildred Morgan; Judy Vowles Intertek
Subject: CRT supplement 1, final files for approval

Dear Roger and Ashley

As discussed, please find attached the final print files for the supplement. Please could you review these files and let me know if they have your approval for publication.

In addition, as a number of changes had to be made to the Declaration of interest sections, I would be grateful if you could check these in particular to ensure that they are correct and complete.

Many thanks for all your help with this. Please do let me know if you have any questions.

Best wishes

Jenna

Jenna Whittle
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group
an informa business

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From: Whittle, Jenna <[redacted]@informa.com>
Sent: Tuesday, September 27, 2016 10:34 AM
To: Roger McClellan
Subject: RE: CRT supplement (46.S1) - final files for approval/ Approved

Thanks Roger. I will do.

From: Roger McClellan [mailto:roger.o.mcclellan@[redacted]]
Sent: 27 September 2016 16:34
To: ashley.roberts@intertek[redacted] Whittle, Jenna <[redacted]@informa.com>
Cc: ashley.roberts@intertek[redacted] roger.o.mcclellan@at[redacted] Whalley, Charles <Charles.Whalley@tandf[redacted]; Mildred Morgan <mbmorgan@hargray.c[redacted]
Subject: Re: CRT supplement (46.S1) - final files for approval/ Approved

Jenna
The final files look great!!! Please proceed with posting on-line as soon as you have approval from Charles. I note that Ashley has approved the files. Please send an electronic linkage to the Special Issue , a linkage I can share with others. Thanks for your assistance with this major project.
Regards, Roger

On Tue, 9/27/16, Whittle, Jenna <[redacted]@informa.com> wrote:

Subject: CRT supplement (46.S1) - final files for approval
To: "Roger McClellan" <roger.o.mcclellan@[redacted]>, "Ashley Roberts Intertek" <[redacted]@intertek.com>
Cc: "Whalley, Charles" <Charles.Whalley@tandf[redacted]>, "Mildred Morgan" <mbmorgan@[redacted]>
Date: Tuesday, September 27, 2016, 6:41 AM

Dear Ashley and Roger
Please find attached the
final files for the supplement. Apologies again for the
delay.

Please could you review
these files and let me know if they have your approval for
publication.
Thanks and best wishes

Jenna

Jenna
Whittle
Production Editor,
Journals
Taylor & Francis

4 Park Square, Milton
Park, Abingdon, Oxon, OX14 4RN, UK

[redacted]@tandf.co.uk

www.tandfonline.com

Roger McClellan

From: Ashley Roberts Intertek <ashley.roberts@intertek[redacted]
Sent: Tuesday, September 27, 2016 10:36 AM
To: Whittle, Jenna; Roger McClellan
Cc: Whalley, Charles; Mildred Morgan
Subject: RE: CRT supplement (46.S1) - final files for approval

Thank you Jenna

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
www.intertek.com

E-mail: [redacted]@intertek.com
Tel: +1 [redacted]; Fax: +1 [redacted]
Skype: [redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:J[redacted]@informa.com]
Sent: September-27-16 12:33 PM
To: Ashley Roberts Intertek; Roger McClellan
Cc: Whalley, Charles; Mildred Morgan
Subject: RE: CRT supplement (46.S1) - final files for approval

Thanks for checking the files, Ashley. After Charles has confirmed we can proceed with publication, I'll send the issue to press. It should appear on the journal website approximately 24 hours after this.
Best wishes
Jenna

From: Ashley Roberts Intertek [mailto[redacted]@intertek.com]
Sent: 27 September 2016 15:55
To: Whittle, Jenna <J[redacted]nforma.com>; Roger McClellan <roger.o.mcclellan@[redacted]>
Cc: Whalley, Charles <Charles.Whalley@tandf[redacted]; Mildred Morgan <mbmorgan@hargray[redacted]
Subject: RE: CRT supplement (46.S1) - final files for approval

Hi Jenna,

We have checked the final files and we are good to go.

So, please take this as an approval for publication. As a result, could you let me know when they will go on line?

Many Thanks for your hard work on this matter.

Best Wishes

Ashley

Ashley Roberts, Ph.D.
Senior Vice President, Food & Nutrition Group
Intertek Scientific & Regulatory Consultancy
www.intertek.com

E-mail: [redacted]@intertek.com
Tel: +1 [redacted] Fax: +1 [redacted]
Skype: a[redacted]
2233 Argentia Road, Suite 201
Mississauga, Ontario Canada L5N 2X7

From: Whittle, Jenna [mailto:[redacted]@informa.com]
Sent: September-27-16 9:41 AM
To: Roger McClellan; Ashley Roberts Intertek
Cc: Whalley, Charles; Mildred Morgan
Subject: CRT supplement (46.S1) - final files for approval
Importance: High

Dear Ashley and Roger
Please find attached the final files for the supplement. Apologies again for the delay.
Please could you review these files and let me know if they have your approval for publication.
Thanks and best wishes
Jenna

Jenna Whittle
Production Editor, Journals
Taylor & Francis

Taylor & Francis Group

4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK

[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From: Whalley, Charles <[redacted]@tandf.co.uk>
Sent: Thursday, September 29, 2016 1:45 AM
To: Roger McClellan
Cc: mbmorgan@hargray[redacted] Whittle, Jenna; Vasili, Temis
Subject: CRT Supplement now published

Dear Roger,

I note that the glyphosate supplement is now published online and all showing as Open Access. The full table of contents is accessible at the following link: http://tandfonline.com/toc/itxc20/46/sup1?nav=tocList This has been a considerable amount of work on all sides so I'm delighted to see it come to fruition

I'm in the office today if you wanted to follow up on this by phone. Between 3:30 and 4pm UK time I shall be on the phone (incidentally to a toxicologist at the University of New Mexico), but otherwise I should be available and at my desk.

Very best wishes,
Charles

Charles Whalley - Managing Editor, Medicine & Health Journals
Taylor & Francis Group
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK
Direct line: +[redacted]
Switchboard: +[redacted]
[redacted]@tandf.co.uk
www.tandfonline.com

Roger McClellan

From:	Roger McClellan <roger.o.mcclellan@[redacted]>
Sent:	Thursday, September 29, 2016 12:34 PM
To:	bolt@ifado[redacted] rcc0022@auburn[redacted] scohen@unmc[redacted] dellarcov@gmail[redacted] david_dorman@ncsu[redacted] f.guengerich@vanderbilt[redacted] gunnar.johanson@[redacted] s.tsuda@iwate-u.ac[redacted] david.warheit@gmail[redacted]
Cc:	Charles Whalley; Roger McClellan; Mildred B. Morgan
Subject:	SPECIAL ISSUE: GLYPHOSATE

CRT Board of Directors

The Special Issue of Critical Reviews in Toxicology (CRT), Vol. 46, entitled "An Independent Review of the Carcinogenic Potential of Glyphosate" has been published on-line and can be accessed via the following link: http://tandfonline.com/toc/itxc20/46/sup1?nav=tocList. As you will note, the issue includes a brief foreword I prepared and five papers prepared by the Panel. I call your attention to the comprehensive "Declaration of Interests" statement for each of the papers. Such DOI statements routinely accompany each article published in CRT. In my opinion, these statements are among the most comprehensive published today in scientific journals.

You will also note the papers were extensively reviewed by a total of 27 independent reviewers, including a number of you serving on the CRT Editorial Advisory Board. Several of you reviewed all five papers. The review comments proved very useful to the authors and contributed to the overall quality of the published papers.

I expect the papers in the Special Issue will be widely read and cited. As you will note, the papers are available on open access which should encourage readership.

I extend a special note of thanks to you for your valuable advice concerning these papers and the Special Issue. Your advice contributed to the quality of the rigorous review process used and the scientific quality of the Issue.

If you know of individuals who would like to prepare a set of papers on a single lengthy paper for publication as a Special Issue of CRT, please have them contact me with regard to scientific details concerned with publication of such issues. If the material is deemed scientifically appropriate for a Special Issue, I will refer the individual to Charles Whalley, the Managing Editor for CRT to discuss costs and business details associated with publication of a Special Issue.

Roger

--- On Sat, 10/15/16, Nebert, Daniel (nebertdw) <NEBERTDW@UCMAIL.UC[redacted] wrote:

> From: Nebert, Daniel (nebertdw) <NEBERTDW@UCMAIL.UC[redacted]
> Subject: An Independent Review of the Carcinogenic Potential of
> Glyphosate
> To: "Abdel-Malek, Zalfa (abdelmza)" <ABDELMZA@UCMAIL.UC[redacted]
> "Bernstein, Jonathan (bernstja)" <BERNSTJA@UCMAIL.UC[redacted] "Bingham,
> Eula (binghael)" <BINGHAEL@UCMAIL.UC[redacted] "BOL-Bermudez, Mei-Ling
> (bermudmn)" <bermudmn@mail.uc[redacted] "BOL-Frank, Evan (franken)"
> <franken@mail.uc[redacted] "BOL-Hsieh, Heidi (hsiehhi)"
> <hsiehhi@mail.uc[redacted] "BOL-Krishan, Mansi (krishami)"
> <krishami@mail.uc[redacted] "BOL-Meng, Qinghang (mengqg)"
> <mengqg@mail.uc[redacted] "BOL-Miller, David (mille3dl)"
> <mille3dl@mail.uc[redacted] "BOL-Vonhandorf, Andrew (vonhanap)"
> <vonhanap@mail.uc[redacted] "BOL-Wang, Qin (wangq4)" <wangq4@mail.uc[redacted]
> "Borchers, Michael (borchemt)" <BORCHEMT@UCMAIL.UC[redacted] "Buncher, C.
> Ralph (bunchecr)" <BUNCHECR@UCMAIL.UC[redacted] "Burns, Katherine
> (burns2ki)" <burns2ki@ucmail.uc[redacted] "Carreira, Vinicius (carreivs)"
> <carreivs@ucmail.uc[redacted] "CHM-Butsch.Kovacic, Melinda
> (Melinda.Butsch.Kovacic)" <Melinda.Butsch.Kovacic@cchmc[redacted]
> "CHM-Fukuda, Tsuyoshi (Tsuyoshi.Fukuda)" <Tsuyoshi.Fukuda@cchmc[redacted]
> "CHM-Hershey, Gurjit (gurjit.hershey)" <GURJIT.HERSHEY@CCHMC[redacted]
> "CHM-Mersha, Tesfaye (Tesfaye.Mersha)" <Tesfaye.Mersha@cchmc[redacted]
> "CHM-Prows, Daniel (daniel.prows)" <DANIEL.PROWS@CCHMC[redacted]
> "CHM-Ryan, Patrick (Patrick.Ryan)" <Patrick.Ryan@cchmc[redacted] "Choubey,
> Divaker (choubedr)" <choubedr@ucmail.uc[redacted] "Nebert, Daniel
> (nebertdw)" <NEBERTDW@UCMAIL.UC.EDU>, "Deka, Ranjan (dekar)"
> <DEKAR@UCMAIL.UC[redacted] "Desai, Pankaj (desaipb)"
> <DESAIPB@UCMAIL.UC[redacted] "dococcmed@[redacted] <dococcmed@[redacted]
> "Elam, Sarah (elamsb)" <elamsb@UCMAIL.UC[redacted] "Fan, Yunxia (fanyi)"
> <fanyi@UCMAIL.UC[redacted] "Geh_Esmond (gehen@[redacted] <gehen@[redacted]
> "Genter, Mary Beth (gentermb)" <GENTERMB@UCMAIL.UC[redacted]
> "glendon.zinser@gmail[redacted] <glendon.zinser@gmail[redacted] "Greis, Ken
> (greiskd)" <greiskd@ucmail.uc[redacted] "Haynes, Erin (haynesen)"
> <haynesen@UCMAIL.UC[redacted] "Ho, Shuk-mei (hosm)" <hosm@ucmail.uc[redacted]
> "Huang, Shouxiong (huangsx)" <huangsx@ucmail.uc[redacted] "Hugo, Eric
> (hugoe" <LNebert@[redacted]>, "Johnson_Abby (abbyleajo@[redacted])"
> <abbyleajo@[redacted]>, "Kadekaro, Ana Luisa (kadekaal)"
> <kadekaal@ucmail.uc[redacted]>, "Kasper, Susan (kaspersn)"
> <kaspersn@ucmail.uc[redacted] "Kim, KyoungHyun (kim2ku)"
> <kim2ku@ucmail.uc[redacted] "Ko, Chia-I (koci)" <koci@ucmail.uc[redacted]
> "Kopras, Elizabeth (koprasej)" <koprasej@ucmail.uc[redacted] "Langevin,
> Scott (langevst)" <langevst@ucmail.uc[redacted] "Leggett, Carmine
> (leggetce)" <leggetce@ucmail.uc[redacted] "Leung, Ricky Y. K. (leungyk)"
> <leungyk@ucmail.uc[redacted] "Maier, Michael (maierma)"
> <maierma@ucmail.uc[redacted] "Mccann, Kathy (mccannks)"
> <mccannks@ucmail.uc[redacted] "Mcgraw, Dennis (mcgrawdw)"
> <MCGRAWDW@UCMAIL.UC[redacted] "Medvedovic, Mario (medvedm)"
> <medvedm@UCMAIL.UC[redacted] "Meller, Jaroslaw (mellerj)"
> <mellerj@ucmail.uc[redacted] "Miller, Marian (millermn)"
> <millermn@ucmail.uc[redacted] "Ovesen, Jerald (oversejl)"
> <oversejl@UCMAIL.UC[redacted] "Papautsky, Ian (papauti)"

> <papauti@ucmail.uc[redacted] "Pinney, Susan (pinneysm)"
> <PINNEYSM@UCMAIL.UC[redacted] "Puga, Alvaro (pugaa)"
> <PUGAA@UCMAIL.UC[redacted] "Rao, Marepalli (raomb)" <raomb@UCMAIL.UC[redacted]
> "Reponen, Tiina (reponeta)" <REPONETA@UCMAIL.UC[redacted] "Rice, Carol
> (ricech)" <ricech@ucmail.uc[redacted] "Rubinstein, Jack (rubinsjk)"
> <rubinsjk@ucmail.uc[redacted] "Sanders, Holly (sanderhy)"
> <sanderhy@UCMAIL.UC[redacted] "Stambrook, Peter (stambrpj)"
> <STAMBRPJ@UCMAIL.UC[redacted] "Tarapore, Pheruza (tarapopp)"
> <tarapopp@ucmail.uc[redacted] "Varughese_Eunice
> (varughese.eunice@epamail.epa[redacted]
> <varughese.eunice@epamail.epa[redacted] "Wang, Hong-Sheng (wanghs)"
> <WANGHS@UCMAIL.UC[redacted] "Watson, Deena (watsondm)"
> <watsondm@ucmail.uc[redacted] "Wu, Tianying (wutg)" <wutg@ucmail.uc[redacted]
> "Xia, Ying (xiay)" <xiay@ucmail.uc[redacted] "Xie, Changchun (xiecn)"
> <xiecn@UCMAIL.UC[redacted] "Yadav, Jagjit (yadavjs)"
> <YADAVJS@UCMAIL.UC[redacted] "Zhang, Xiang (zhanx5)"
> <zhanx5@ucmail.uc[redacted]
> Date: Saturday, October 15, 2016, 5:56 PM
>
>
>
>
>
>
>
>
> Glyphosate [N-(phosphono-methyl)glycine] is a broad-spectrum
> organophosphorus
>
> systemic
> herbicide and crop
> desiccant. More specifically,
> it is
> a phosphonate—used
> to kill weeds,
> especially annual broadleaf weeds
> and grasses that compete with
> agricultural
> crops.
> An ongoing controversy (more intense in the EU than in the rest of
> the world) involves whether or not Glyophosate is cancer-causing
> (carcinogenic).
>
> For those interested, please note
> that there has just recently appeared:
> a Special Issue of Critical
> Reviews in Toxicology (CRT), Vol. 46, titled "An Independent Review of
> the Carcinogenic Potential of Glyphosate".
>
> This issue has been published online
> and can be accessed via the following
> link: http://tandfonline.com/toc/itxc20/46/sup1?nav=tocList .

>
> The issue begins with a brief
> foreword by Roger O McClellan,
> DVM,
> MMS, DSc[Honorary], Diplomate-ABT, followed by five papers prepared by
> the Glyophosphate Panel. It is especially worth noting the
> comprehensive "Declaration of Interests"
> statements for each of the papers. Such DOI statements routinely
> accompany each article published in CRT. These strong statements are
> probably among the most comprehensive published today in scientific
> journals.
>
>
> It is also worth noting that the
> papers were extensively reviewed by a total of 27 independent
> Reviewers; several individuals reviewed all five papers..!! The
> Reviewers' comments proved very useful to the authors and contributed
> to increasing the overall quality of the published papers and the
> entire Special Issue.
>
> It is my understanding that the US
> Environmental Protection AGency (EPA) will be holding a 3-day meeting
> later this month focusing on Glyphosate. The papers in this Special
> Issue are available (open access) which should encourage readership.
> I understand that the European Food Safety Authority (EFSA) has become
> quite interested in Glyophosate. Also, the broader issue of how the
> International Agency for Research on Cancer (IARC) approaches
> evaluating the "carcinogenic hazard" of various agents is becoming
> of increasing concern and interest.
>
> DwN
>
>
>
> http://tandfonline.com/toc/itxc20/46/sup1?nav=tocList
>
>
>
>

Total Quality. Assured.

(14) All communications with any of the authors of Williams, et al., *A Review of the Carcinogenic Potential of Glyphosate by Four Independent Expert Panels and Comparison to the IARC Assessment* 46 Crit. Rev. Toxicol. 3-20 (2016), including all communications with any of the authors of the four companion papers by the Intertek Expert Panel, related to GBs, AMPA, and/or surfactants for GBFs.

Response:

As noted above, the primary communications between authors and the Editor are initially conducted electronically using the Manuscript Central/Scholar One system provided by the publisher, Taylor and Francis. After critical review and acceptance by the Editor-in-Chief, the accepted manuscripts are electronically transferred to the Central Article Tracking System (CATS) operated by Taylor and Francis. The CATS system is used for processing of the accepted manuscripts, including production of galley proofs for review and approval by the authors before proceeding to on-line publication. CATS is maintained and used by Taylor and Francis to publish the approximate 2600 journals in its portfolio.

As Editor-in-Chief, I do not maintain files to duplicate the CATS system.

Aardema

MARILYN J. AARDEMA, PH.D.
[redacted]
Fairfield OH, [redacted] USA
[redacted]

mjaardema[redacted] www.linkedin.com/in/marilynaardema

PRESIDENT, MARILYN AARDEMA CONSULTING, LLC

Solving complex global safety and regulatory genetic toxicology issues

Internationally recognized expert and leader in the field of toxicology, specializing in genetic toxicology. High-achieving professional who leverages expertise to readily develop successful strategies that meet critical business needs. Extensive experience identifying emerging issues and solving complex problems across diverse product categories. Active involvement in influential multi-disciplinary teams and global scientific/policy expert groups leads to state-of-the art solutions to genetic toxicology issues.

Areas of Expertise Include:

- High-impact strategy development
- Complex problem solving
- Design of optimal testing strategies
- Management of contract research organization testing
- Design and manage new assay development and validation
- Building and leading multi-disciplinary global teams
- Communicating complex technical information
- External influence
- Regulatory guideline development
- Scientific writing

PROFESSIONAL EXPERIENCE

MARILYN AARDEMA CONSULTING, LLC. Fairfield OH **Jan 2010 to present**

President, Marilyn Aardema Consulting, LLC

- Providing expert solutions to pharmaceutical, consumer products, chemical Companies, to scientific expert groups, and to industry associations in support of human safety assessments

BIORELIANCE CORPORATION. Rockford MD **Nov 2010 to May 2012**

Chief Scientific Officer, Toxicology

- Oversight os BioReliance's Toxicology division
- Developing guidance and strategies for new services offerings
- Expert solutions to BioReliance clients
- Represented BioReliance as leader in external scientific communities

PROCTER & GAMBLE (P&G), Cincinnati, OH **1985-2010**

Principal Scientist, Central Product Safety 1994-2010

- Leader of P&G genetic toxicology group and Genotoxicity Expert Team for dealing with complex issues.
- Managed overall genetic toxicology battery design/risk assessment/external defense of key ingredients for diverse products worldwide.
- Leader in new assays/genetic toxicology approaches including development of novel 3D human skin micronucleus assay; lead of multi-cosmetic industry project on 3D skin genotoxicity assays for cosmetics; novel screening approaches, P&G nanogenotoxicity research, global evaluation of invitro micronucleus assay, reducing and eliminating animal use in genetic toxicology.
- Leader of a multi-disciplinary P&G Toxicogenomics team; co-led ILSI Toxicogenomics Genotoxicity Team
- Trained and mentored numerous young scientists
- Leader of internal and external scientific teams and workshops on harmonizing genetic toxicology testing approaches, guidelines, genetic toxicology assay protocols
- Interfaced with global regulatory scientists

Senior Scientist, Central Product Safety 1993-1994

- Leader of P&G genetic toxicology group. Managed global genetic toxicology battery design/risk assessment.
- Developed screening approaches for genetic toxicology safety assessments including a microwell micronucleus assay,
- Member of various external scientific leadership groups including OECD US experts, ECETOC, AIHC.

Staff Scientist, Group Leader, Human Safety Department 1985-1993

- Designed and managed cytogenetic assays for P&G global safety assessments
- Designed, conducted research on aneuploidy, germ cells, cell transformation, mechanisms of genotoxicity
- Conducted research on thresholds resulting in establishment of an indirect mechanism and threshold for sodium fluoride
- Member of various external groups providing guidance on thresholds, aneuploidy, pharmaceutical testing

Prior Experience Includes: The Upjohn Company, Kalamazoo, MI, Intern

EDUCATION

Ph.D. Genetics, University of Tennessee-Oak Ridge Graduate School of Biomedical Sciences Oak Ridge National Laboratory Oak Ridge, TN 1981-1985

B.S. Biology, Hope College Holland, MI 1977-1981

AWARDS AND HONORS

Environmental Mutagen Society Alexander Hollaender Award for outstanding contributions to environmental mutagen research and for global leadership in applied genetic toxicology, Sept. 2012

Genetic Toxicology Excellence in Science Award Oct. 2012

PROFESSIONAL ACTIVITIES

Member, Society of Toxicology, 2011-present

Member, Genetic Toxicology Association, 1991, Elected Board Member

Member, Environmental Mutagen and Genomics Society with numerous leadership roles 1983-present

Member, European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC) Task Force on Aneuploidy 1993-1997

Member European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC) Threshold-mediated Mechanisms Task Force 1997-1999

Member, American Industrial Health Council (AIHC), Co-Chair of the Mutagenicity Subcommittee, 1992-93

Member Mutagenicity subcommittee 1994-1999

Member Molecular Epidemiology Task Group, 1998-1999

Member, International Congress on Harmonization (ICH 2) US Pharmaceutical Manufacturer's Association Genetic Toxicology Task Force, 1992-1998

Member, US Pharmaceutical's Manufacturer's Association Genetic Toxicology committee 1992-2009

Member, Ethylene Oxide Industrial Council Toxicology Task Group, Chemical Manufacturer's Association, 1992

Member, OECD US Experts on Genetic Toxicity Test Methods, 1994-present

Member, Toxicology Excellence for Risk Assessment (TERA) Peer Reviewer 1999-present

Member, International Association of Environmental Mutagen Societies Scientific Steering Committee 2000/2002

International Life Science Institute (ILSI), Health and Environmental Sciences Institute (HESI) Subcommittee on Application of Genomics to Mechanism Based Risk Assessment, Rapportuer, Genotoxicity Working Group 1999-2004

Invited reviewer, various National Institute of Environmental Health Sciences (NIEHS) contracts/proposals (e.g. In vivo cytogenetics contracts 1992; In vivo contract plan 1996, In vivo small business genetic toxicology contracts, 1997, etc.)

Scientific Advisor to Collaborative International Study on the Invitro Micronucleus Test 1998-2005

Invited reviewer, International Life Sciences Institute's (ILSI) Risk Science Institute, Peer Consultation on Genotoxicity for Categorization of "Inherent Toxicity " to Humans under CEPA'99, for Health Canada, 2002

Invited reviewer, Project Proposal for Health Canada's Genomics Research Program: Evaluation of Environmental Toxicogenomics for Use in Regulatory Toxicology & Risk Assessment, 2002

Invited Member, European Center for Validation of Alternative Methods (ECVAM) Committee: Establishment of timetables for the phasing out of animal experiments for cosmetics, 2003

Invited Member, European Center for Validation of Alternative Methods (ECVAM) Cell Transformation Steering Committee, 2004-present

Member, European Cosmetics Association (COLIPA) Animal Alternatives Genotoxicity Subgroup, 2004-2009

Chair, European Cosmetics Association (COLIPA) 3D skin genotoxicity steering committee 2006-2009

Chair, European Cosmetics Association (COLIPA) 3D skin genotoxicity micronucleus subgroup 2006-2009

Invited Member Steering Committee International Life Sciences Institute's (ILSI) Risk Science Institute, Health and Environmental Sciences (HESI) Emerging issues Subcommittee on the Relevance and Follow-up of Positive Results in *In Vitro* Genetic Toxicity (IVGT) Testing, now Genetic Toxicology Technical Committee (GTTC) 2006-present

-Member, numerous workgroups including PigA, Data Interpretation, Germ cells, Nanomaterials, Framework for Adoption of New Test Methods, In Vivo Follow-up.

Invited, Editorial Board, Mutation Research, Genetic Toxicology Testing Section, 1994-2006

Invited, Editorial Board, Environmental and Molecular Mutagenesis, 1994-2008

Consultant to MatTek Small Business Initiative Research (SBIR) grant 2006-2007

Invited, Rapportuer, International Workshop on Genotoxicity Testing (IWGT) Invitro Cytogenetics Assay Working Group, Aug 2009

Invited, Member, International Workshop on Genotoxicity Testing (IWGT) Integration Working Group 2009-present

Institute for Invitro Sciences Scientific Advisory Panel 2007-2009

AltTox Editorial Board 2007-2009

RoundTable of Toxicology Consultants 2010; 2012-present

The American Society for Cellular and Computational Toxicology (ASCCT) 2010

-Board of Directors ASCCT 2012-2015

Invited Reviewer NC3R grant 2010, 2011 (Human cell-based carcinogenicity assays)

Invited Reviewer Health Canada 2013

Invited, Editor Mutation Research, Reviews in Mutation Research 2014-present

PUBLICATIONS AND BOOK CHAPTERS

1. Gentile J. M., S. Gaff-Brown, **M. J. Aardema,** D. Clark, H. Blankespoor. Modification of Carcinogen Metabolism in Parasite-Infected Organisms, Archives of Environmental Health 40, 5-12, 1985

2. **Aardema M. J.**, R. J. Preston, W. W. Au. Differential Sensitivity of a Mouse Myeloid Leukemia Cell Line and Normal Mouse Bone Marrow Cells to X-Ray Induced Chromosome Aberrations, Cancer Research 45, 5321-5327, 1985

3. **Aardema M. J.**, R. J. Preston. DNA Repair Kinetics and the Sensitivity of Cells to X Ray-Induced Chromosome Aberrations: A Mouse Myeloid Leukemia Cell Line and Normal Mouse Bone Marrow Cells, Mut. Res. 162, 225-232, 1986

4. **Aardema M. J.**, D. P. Gibson, R. A. LeBoeuf. Sodium fluoride-induced chromosome aberrations in different stages of the cell cycle: a proposed mechanism, Mut. Res. 223, 191-203, 1989

5. Thompson E. D., **M. J. Aardema**, R. A. LeBoeuf. Lack of genotoxicity with acrylate polymers in five short-term mutagenicity assays, Env. Mole. Mutagen., 14, 98-106, 1989

6. Petersen D. W., J. F. Powers, **M. J. Aardema**, R. A. LeBoeuf, L. A. Smith. Acute, distribution, and subchronic toxicological studies of succinate tartrates, Fund. Appl. Toxicol. 13, 137-145, 1989

7. LeBoeuf R. A., G. A. Kerckaert, **M. J. Aardema**, D. P. Gibson. Multi-stage neoplastic transformation of Syrian hamster embryo cells cultured at pH 6.70, Cancer Research 50, 3722-3729, 1990

8. LeBoeuf R. A., G. A. Kerckaert, **M.J. Aardema**, J. A. Poiley, R. Raineri. Enhanced Morphological and Neoplastic Transformation of Syrian Hamster Embryo Cells Cultured at pH 6.70, in: "Mutation and the Environment, Part D", 219-228, 1990

9. Mailhes J. B., Z. P. Yuan, **M.J. Aardema.** Cytogenetic analysis of mouse oocytes and one cell zygotes as a potential assay for heritable germ cell aneuploidy, Mut. Res. 242, 89-100, 1990

10. Thompson E. D., J. L. Seymour, **M. J. Aardema**, R. A. LeBoeuf, B. L. B. Evans, D. B. Cody. Lack of Genotoxicity of Cross-linked Acrylate Polymers in Four Short-Term Genotoxicity Assays, Env. Mole. Mutagen. 18, 184-199. 1991

11. LeBoeuf R. A., G. A. Kerckaert, **M. J. Aardema**, D. P. Gibson. Development of an In Vitro Cell Transformation Model In Syrian Hamster Embryo Cells For Carcinogen Detection and Mechanistic Studies , J. Jap Soc Alt Animal Exp., 1, 60-64, 1991

12. Mailhes J. B., **M. J. Aardema**. Benomyl-induced aneuploidy in mouse oocytes, Mutagenesis, 7, 303-309, 1992

13. McCarthy K. L., W. C. Thomas, **M. J. Aardema**, J. L. Seymour, D. L. Putman, L. L. Yang, R. D. Curren, R. Valencia. Genetic Toxicology of Acrylic Acid, Food & Chemical Toxicology, 30, 505-515, 1992

14. **Aardema M. J.** The Genotoxicity of Benzoyl Peroxide, Proceedings of the 1992 Annual Summer meeting of The Toxicology Forum, CASET publishers, Fairfax, VA.,pp.262-269, 1992

15. LeBoeuf R.A., G. A. Kerckaert, R. J. Isfort, **M. J. Aardema**, D. B. Cody, D. P. Gibson, R. Brauninger. Transformation of Syrian hamster embryo cells cultured at pH 6.70 for assessing the carcinogenic

potential of chemicals, Proceedings of the 1992 Annual Summer meeting of The Toxicology Forum, CASET publishers, Fairfax, VA, pp. 325-338, 1992

16. **Aardema M. J.** Updated Regulatory Guidelines For Genotoxicity Testing. Workshop Proceedings from the 1992 Environmental Mutagen Society Meeting, Environ. Mole. Mutagen. 21, 1, 1993

17. Mailhes J. B., **M. J. Aardema**, F. Marchetti. Investigation of Aneuploidy induction in mouse oocytes following exposure to vinblastine-sulfate, pyrimethamine, diethylstilbestrol diphosphate, or chloral hydrate. Environ. Mole. Mutagen. 22, 107-114, 1993

18. Mailhes J. B., F. Marchetti, **M. J. Aardema**. Griseofulvin-induced aneuploidy and meiotic delay in mouse oocytes: effect of dose and harvest time. Mut. Res., 300, 155-163, 1993

19. Galloway S.M., **M. J. Aardema**, M. Ishidate Jr, J. L. Ivett, D. J. Kirkland, T. Morita, P. Mosesso, T. Sofuni. Report from working group on in vitro tests for chromosomal aberrations, Mut. Res., 312, 241-261, 1994

20. Marchetti F., J. B. Mailhes, **M. J. Aardema.** Comparison of the aneugenic activity of diazepam in mouse oocytes and other mammalian cells, Mut. Res., 322, p. 69-75, 1994

21. Robison S. H., M. R. Odio, E. D. Thompson, **M. J. Aardema**, A. L. Kraus. Assessment of the in vivo genotoxicity of 2-hydroxy 4-methoxybenzophenone, Env. Mole. Mutagen., 23, 312-317, 1994

22. Gibson D. P. , **M. J. Aardema**, G. A. Kerckaert, R. M. Brauninger R. A. LeBoeuf. Detection of aneuploidy-inducing carcinogens in the Syrian hamster embryo cell transformation assay, Mut. Res., 343, 7-24,1995

23. **Aardema M. J.** Current Topics in In Vivo Cytogenetics: Proceedings of 1994 Environmental Mutagen Society Meeting Workshop. Env. Mole. Mutagen., 25, 300-301, 1995

24. Driscoll K.E., J. M. Carter, P.T. Iype, H. L. Kumari, L. L. Crosby, **M. J. Aardema**, R. J. Isfort, D. Cody, M.H. Chestnut, J. L. Burns, R. A. LeBoeuf. Establishment of immortalized alveolar type II epithelial cell lines from adult rats, In vitro Cellular and Development Biology 31, 516-527, 1995

25. Binder R.L., **M. J. Aardema**, E.D. Thompson. Benzoyl Peroxide: Review of experimental carcinogenesis and human safety data, Growth Factors and Tumor Promotion Implications for Risk Assessment, Wiley Liss, New York, 245-294, 1995

26. **Aardema M. J.,** T. Tsutsui. Sodium-fluoride-induced chromosome aberrations in different cell cycle stages, Mut. Res., 331, 171-172, 1995

27. **Aardema M. J.**, R. J. Isfort, E. D. Thompson, R. A. LeBoeuf. The low pH Syrian hamster embryo (SHE) cell transformation assay: A revitalized role in carcinogen prediction, Mut. Res., 356, 5-9, 1996

28. Wyrobek A. J., **M. Aardema**, U. Eichenlaub-Ritter, L. Ferguson, F. Marchetti. Mechanisms and targets involved in maternal and paternal age effects on numerical aneuploidy, Env. Mole. Mutagen., 28, 254-264, 1996

29. Kerckaert G. A., R. J. Isfort, G. J. Carr, **M. J. Aardema**, R. A. LeBoeuf. A Comprehensive protocol for conducting the Syrian hamster embryo cell transformation assay at pH 6.70 Mut. Res., 356, 65-84, 1996

30. LeBoeuf R. A., G.A. Kerckaert, **M. J. Aardema,** D. P. Gibson, R. Brauninger, R. J. Isfort. The pH 6.7 Syrian hamster embryo cell transformation assay for assessing the carcinogenic potential of chemicals Mut. Res., 356, 85-127, 1996

31. Williams G. M., **M. J. Aardema**, P. H. Long, E. D Thompson, G. S. Allgood. Genotoxicity and Subchronic Toxicity Studies with Heated Olestra, Food Chem. Tox., 34 941-950, 1996

32. Gorelick N. J., J.L. Andrews, D.P Gibson, G. J. Carr, **M. J. Aardema.** Evaluation of lacI mutation in germ cells and micronuclei in peripheral blood after treatment of male lacI transgenic mice with ethylnitrosourea, isopropylmethane sulfonate, or methylmethane sulfonate, Mut. Res., 388, 187-195, 1997

33. Gibson D. P. , R. M. Brauninger, H. Shaffi, G. Kerckaert, R. A. LeBoeuf, R. J. Isfort, **M. J. Aardema**. Induction of Micronuclei in Syrian Hamster Embryo Cells: Comparison to Results in The SHE Cell Transformation Assay For National Toxicology Program Test Chemicals, Mut. Res., 392, 61-70, 1997

34. Mailhes J.M., D. Young, **M. J. Aardema**, S. N. London. Thiabendazole-induced cytogenetic abnormalities in mouse oocytes, Env. Mol. Mutagen., 29, 367-371, 1997

35. **Aardema M. J.,** L.L. Crosby, D.P. Gibson, G.A. Kerckaert, R.A. LeBoeuf. Aneuploidy and consistent structural chromosome changes associated with transformation of Syrian hamster embryo cells, Cytogenetic and Cell Genetics, 96 (2), 140-150, 1997

36. **Aardema M. J.,** S. Albertini, P. Arni, L.M. Henderson, M. Kirsch-Volders, J. M. MacKay, A.M. Sarrif, D. A. Stringer. R.D.F. Taalman Aneuploidy: a report of an ECETOC task force, Mut. Res., 410, 3-79, 1998

37. Gibson D.P., X. Ma, G. Switzer, V. A. Murphy, **M. J. Aardema.** Comparative genotoxicity of quinolone and quinolonyl-lactam antibacterials in the in vitro micronucleus assay in chinese hamster ovary cells, Env. Mole. Mutagen., 31, 345-351, 1998

38. LeBoeuf R. A., K. A. Kerckaert, **M. J. Aardema**, R. J. Isfort. Use of Syrian hamster embryo and BALB/c 3T3 cell transformation for assessing the carcinogenic potential of chemicals, in The Use of Short-and Medium-term Tests for Carcinogens and Data on Genetic Effects in Carcinogenic Hazard Evaluation, ed. D. B. McGregor, J. M. Rice and S. Venitt, IARC Sci. Pub. 146, 409-425, 1999

39. Hu T., C.M. Miller, G. M. Ridder, **M. J. Aardema**. Characterization of p53 in Chinese hamster cell lines CHO-K1, CHO-WBL, and CHL: implications for genotoxicity testing, Mut. Res., 426, 51-62, 1999

40. Henderson L, S. Albertini , **M. J. Aardema.** Thresholds in Genotoxicity responses, Mut. Res., 464, 123-128, 2000

41. Kirsch-Volders M., **M. J Aardema**, A. Elhajouji. Concepts of Threshold in Mutagenesis and Carcinogenesis Mut. Res. 464, 3-11, 2000

42. Sarrif A.M, **M. J. Aardema**, S. Albertini, P. Arni, LM Henderson, M. Kirsch-Volders, H. Vrijhof. ECETOC-EEMS Symposium on Dose Response and Threshold-Mediated Mechanisms in Mutagenesis Mut. Res., 464, 1-2, 2000

43. Kirsch-Volders M., T. Sofuni , **M. J. Aardema**, S. Albertini, D.Eastmond, M.Fenech, M. Ishidate,E. Lorge, H. Norppa, J.Surrallés, W. Von der Hude, A. Wakata. Report from the In vitro Micronucleus Assay Working Group, Env. Mole Mutagen., 35, 167-172, 2000

44. Custer L., D.P. Gibson, **M. J. Aardema**, R. A. LeBoeuf. A refined protocol for conducting the low pH 6.7 Syrian hamster embryo (SHE) cell transformation assay. Mut. Res., 455, 129-139, 2000

45. **Aardema M. J.**, M. Kirsch-Volders. The In Vitro Micronucleus Assay, In: Genetic Toxicology and Cancer Risk Assessment, Ed: W. N. Choy, Marcel Dekker, Basel Switzerland, pp. 163-186, 2001

46. **Aardema M. J.**, J. T. MacGregor. Toxicology and Genetic Toxicology in the New Era of "Toxicogenomics": Impact of "-omics" Technologies, Mut. Res., 499, 13-25, 2002

47. Murli H, **Aardema M. J.**, T. Lawlor, C. Spicer. Photoclastogenicity-an improved protocol, its validation and investigation of the photogenotoxicity of DMBA, Env. Mole. Mutagen., 40, 41-49, 2002

48. **Aardema M. J.** , J. T. MacGregor. Toxicology and Genetic Toxicology in the New Era of "Toxicogenomics": Impact of "-omics" Technologies, in T. Inoue and W.D. Pennie (Eds) Toxicogenomics, Springer-Verlag, Tokyo, , pp 171-193, 2003

49. M. Kirsch-Volders, Toshio Sofuni , **M. J. Aardema**, S. Albertini, D. Eastmond, M. Fenech , M. Ishidate, Jr. , S. Kirchner , E. Lorge , T. Morita , H. Norppa , J. Surrallés , A. Vanhauwaert , A. Wakata. Report from the in vitro micronucleus assay working group Mut. Res., 540, 153-163, 2003

50. Hu T., D. Gibson, G. Carr, S. Torontali, J. Tiesman, J. Chaney, **M. J Aardema**. Identification of a gene expression profile that discriminates indirect-acting genotoxins from direct-acting genotoxins, Mut. Res., 549, 5-27, 2004

51. Newton, R, **M. J. Aardema**, J. Aubrecht. The Utility of DNA microarrays for characterizing genotoxicity, Env. Health Perspectives, 112, 4, 420-422, March 2004

52. Kirkland D., **M. J. Aardema**, L. Henderson, L. Müller. Evaluation of the ability of a battery of 3 *in vitro* genotoxicity tests to discriminate rodent carcinogens and non-carcinogens. I. Sensitivity, specificity and relative predictivity Mut. Res., 584, 1-256, 2005

53. Maurici D., **M. J. Aardema**, R. Corvi, M. Kleber, C. Krul, C. Laurent, N. Loprieno, M. Pasanen, S. Pfuhler, B. Phillips, E. Sabbioni, T. Sanner, P. Vanparys. Chapter 3.7 Carcinogenicity ATLA 33, Suppl. 1, 117–130, 2005

54. Maurici D., **M. J. Aardema**, R. Corvi, M. Kleber, C. Krul, C. Laurent, N. Loprieno, M. Pasanen, S. Pfuhler, B. Phillips, E. Sabbioni, T. Sanner, P. Vanparys. Chapter 3.7 Genotoxicity and Mutagenicity ATLA 33, Suppl. 1, 177-182, 2005

55. Müller A., E. Boitier, T. Hu, G. J. Carr, A-C Le Fèvre, J-P Marchandeau, M. Flor, F. Jefferson, **M. J. Aardema**, V. Thybaud. Laboratory variability does not preclude identification of biological functions impacted by hydroxyurea, Env. Mole. Mutagen., 46, 221-235, 2005

56. Lorge E., V. Thybaud , **M. J. Aardema** , J. Oliver , A. Wakata, G. Lorenzon, D. Marzin. SFTG International Collaborative Study on InVitro Micronucleus Test I. General Conditions and Overall Conclusions of The Study, Mut. Res., 607, 13-36, 2006

57. **Aardema M. J.**, R. D. Snyder, C. Spicer, K. Divi , T. Morita , R. J. Mauthe , D. P. Gibson , S. Soelter , P. T. Curry , V. Thybaud , G. Lorenzon , D. Marzin , E. Lorge. SFTG International Collaborative Study on InVitro Micronucleus Test III. Using CHO Cells, Mut. Res., 607, 61-87, 2006

58. Curren R. D., G. C. Mun, D. P. Gibson, **M. J. Aardema**. Development of a method for assessing micronucleus induction in a 3D human skin model (EpiDerm™), Mut. Res., 607, 192-204, 2006

59. Kirkland D. J., **M. J. Aardema**, L. Müller, M. Hayashi. Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens: II. Further analysis of mammalian cell results, relative predictivity and tumour profiles, Mut. Res., 608, 29-42, 2006

60. Kirkland D. J., **M. J. Aardema**, N. Banduhn, P. Carmichael, R. Fautz, J-R Meunier, S. Pfuhler. In vitro approaches to develop weight of evidence (WoE) and mode of action (MoA) discussions with positive in vitro genotoxicity results, Mutagenesis 22 161-175, 2007

61. Kirkland D.J., S. Pfuhler, D. Tweats, **M. J. Aardema**, R. Corvi, F. Darroudi, A. Elhajouji, H-R Glatt, P. Hastwell, M. Hayashi, P. Kasper, S. Kirchner, A. Lynch, D. Marzin, D. Maurici, J-R Meunier, L. Müller, G. Nohynek, J. Parry, E. Parry, V. Thybaud, R. Tice, J. Van Benthem, P. Vanparys and P. White. How to reduce false positive results when undertaking *in vitro* genotoxicity testing and thus avoid unnecessary follow-up animal tests: Report of an ECVAM Workshop, Mut. Res., 628, 31-55, 2007

62. Thybaud V., **M. J. Aardema**, J. Clements, K. Dearfield, S. Galloway, M. Hayashi, D. Jacobson-Kram, D. Kirkland, J. MacGregor, D. Marzin, W. Ohyama, M. Schuler, H. Suzuki, and E. Zeiger. Strategy for genotoxicity testing: follow-up testing and evaluation of results for positive or equivocal results. Report of IWGT workshop, Mut. Res., 627, 41-58, 2007

63. Thybaud V., **M. J. Aardema**, D. Casciano, V. Dellarco, M. R. Embrye, B. B. Gollapudi, M. Hayashi, M. P. Holsapple, D. Jacobson-Kram, P. Kasper, James T. MacGregor, R. Rees. Relevance and follow-up of positive results in *in vitro* genetic toxicity assays: An ILSI-HESI initiative Mut. Res., 633, 67–79, 2007

64. **Aardema M. J.,** S. H. Robison, D. Gatehouse, G. Johnston. An evaluation of the genotoxicity of the anti-tussive drug Dextromethorphan, Regulatory Toxicology and Pharmacology, 50, 285-293, 2008

65. Pant K., **M. J. Aardema.** The Syrian hamster Embryo (SHE) low pH Cell Transformation Assay, Current Protocols in Toxicology 35, 20.3.1-20.3.16 Feb. 2008

66. Pérez-Rivera, A.A, T. Hu, **M. J. Aardema**, J F. Nash. Evaluation of the genotoxicity of the imidazole antifungal climbazole: comparison to published results for other azole compounds, Mut. Res., 672, 27-39, 2009

67. Mun G.C., **M. J. Aardema**, T. Hu, B. Barnett, Y. Kaluzhny, M. Klausner , V. Karetsky, Rodger D. Curren. Further Development of the EpiDerm 3D Reconstructed Human Skin Micronucleus (RSMN) Assay Mut. Res., 673, 92-99, 2009

68. Hu T., Y. Kaluzhny, G. C. Mun, B. Barnett, V. Karetsky, N. Wilt, M. Klausner, R. D. Curren, **M. J. Aardema**. Intralaboratory and Interlaboratory Evaluation of the EpiDerm 3D Human Reconstructed Skin Micronucleus (RSMN) Assay Mut. Res., 673, 100-108, 2009

69. Hu T., R. E. Bailey, S. W. Morrall, J. A. Skare, L. A. Stanley, **M. J. Aardema.** Dermal uptake and metabolism of *p*-aminophenol and *p*-phenylenediamine: Application of the EpiDerm human reconstructed epidermis model, Toxicology Letters, 188, 119-129, 2009

70. Preston, RJP, J. A. Skare, **M.J. Aardema**. A review of biomonitoring studies measuring genotoxicity in humans exposed to hair dyes, Mutagenesis, 25, 17-23, 2010

71. Hu T., Z. S. Khambatta, P.J. Hayden, J.Bolmarcich, R. L. Binder, M.K. Robinson, G. J. Carr, J. P. Tiesman, B. B. Jarrold, R.Osborne, T.D. Reichling, S.M. Nemeth, **M. J. Aardema**. Xenobiotic Metabolism Gene Expression in an *in vitro* 3D Human Epidermal Model Compared to Human Skin, Toxicology In Vitro, 24, 1450-1463, 2010

72. Pfuhler, S., A. Kirst, **M. J. Aardema**, N. Banduhn, C. Goebel, D. Araki, M. Costabel-Farkas, E. Dufour, R. Fautz, J. Harvey, N. J. Hewitt, J. Hibatallah, P. Carmichael, M. Macfarlane, K. Reisinger, J. Rowland, F. Schellauf, A. Schepky, J. Scheel, A tiered approach to the use of alternatives to animal testing for the safety assessment of cosmetics: Genotoxicity. A COLIPA analysis. Reg. Tox. Pharm., 57, 315-324, 2010

73. **Aardema M. J.,** B. Barnett, Z. Khambatta, K. Reisinger, G. Ouedraogo, B. Faquet, A.C. Ginestet, G. Mun, E. Dahl, N.J. Hewitt, R. Corvi, R. Curren. International Validation of the EpiDerm™ 3D Human Reconstructed Skin Micronucleus (RSMN) Assay: Transferability and Reproducibility, Mut. Res., 701, 123-131, 2010

74. Lynch, A. J., Sasaki, R. Elespuru, D. Jacobson-Kram, V. Thybaud, M. De Boeck, **M. J. Aardema,** J. Aubrecht, R. D. Benz, S. Dertinger, G. Douglas, P. A. Escobar, A. Fornace, , M. Honma, R.T. Naven, J. F. Rusling, R.H. Schiestl, R.M. Walmsley, E. Yamamura, J.H. Kim. New and Emerging Technologies for Genetic Toxicity Testing, Env. Mole. Mutagen., 52, 205-223, 2011

75. Kirsch-Volders, M., A. Elhajouji, I. Decordier, G. Plas, **M.J. Aardema**, M. Fenech In Vitro Genotoxicity Testing Using The Micronucleus Assay in Cell Lines, Human Lymphocytes and 3D Human Skin Models, Mutagenesis, 26, 177–184, 2011

76. Dahl E, R. Curren, B. Barnett, Z. Khambatta, K. Reisinger, G. Quedraogo, B. Faquet, G. Mun, N. Hewitt, **M. J. Aardema.** The reconstructed skin micronucleus assay (RSMN) in EpiDerm™: detailed protocol and harmonized scoring atlas, Mut. Res., 720, 42-52, 2011

77. Rothfuss A., M. Honma, A. Czich, **M. J. Aardema**, B. Burlinson, S. Galloway, S. Hamada, D. Kirkland, R.H. Heflich, J. Howe, M. Nakajima, M. O'Donovan, U. Plappert-Helbig, C. Priestley, L. Recio, M. Schuler, Y. Uno, H-J.Martus. Improvement Of *In Vivo* Genotoxicity Assessment: Combination of Acute Tests and the Link to Standard Toxicity Testing, Mut. Res., 723, 108-120, 2011

78. **Aardema M.J**., S. Galloway, E. Zeiger, M.C.Cimino, M. Hayashi, Guidance for understanding solubility as a limiting factor for selecting the upper test concentration in the OECD *In Vitro* Micronucleus Assay Test Guideline No. 487, Mut. Res., 722, 89-90, 2011

79. Creton S., **M.J. Aardema**, P. L. Carmichael, J. S. Harvey, F. L. Martin, R. F. Newbold, M. R. O'Donovan, K. Pant, A. Poth, A. Sakai, K. Sasaki, A. D. Scott, L. M. Schechtman, R. R. Shen, N. Tanaka, H. Yasaei, Cell transformation assays for prediction of carcinogenic potential: state of the science and future research needs, Mutagenesis Advance Access published August 17, 2011

80. Galloway, S., E. Lorge, **M. J. Aardema**, D. Eastmond, M. Fellows, R. Heflich, D. Kirkland, D. D. Levy, A.M. Lynch, D. Marzin, T. Morita, M. Schuler, Workshop summary: Top concentration for in vitro mammalian cell genotoxicity assays; and report from working group on toxicity measures and top concentration for in vitro cytogenetics assays (chromosome aberrations and micronucleus), Mut. Res, 723, 77-83, 2011

81. R. Corvi, **M.J. Aardema**, L. Gribaldo, M. Hayashi, S. Hoffmann, L.M. Schechtman, P. Vanparys, ECVAM prevalidation study on in vitro cell transformation assays: general outline and conclusions of the study. Mut. Res., 744, 8-11, 2012

82. P. Vanparys, R. Corvi, **M.J. Aardema,** L. Gribaldo, M. Hayashi, S. Hoffmann, L.M. Schechtman, Application of in vitro cell transformation assays in regulatory toxicology for pharmaceuticals, chemicals, food products and cosmetics Mut. Res., 744 111-116, 2012.

83. C. Eskes, K. Sullivan, **M. Aardema**, H. Spielmann, E. Hill, G. Schoeters, R. Curren, M. Vinken, B. Blaauboer, Comparing the Challenges in Developing and Implementing 3Rs Alternative Methods in Europe and the United States: Industrial and Academic Perspectives, Altex Proceedings 1/12 205-209, 2012

84. J. Clarke, W. Madraymootoo, R. Young, V. Wagner, K. Pant, **M.J. Aardema**, Summary of invitro genotoxicity assay results: Expected and unexpected effects of recent study design modifications Env. Mole. Mutagen. 53, 631-635, 2012

85. **Aardema M.J.**, B. Barnett, G. Mun, E. Dahl, R. Curren, N. Hewitt. Evaluation of Chemicals Requiring Metabolic Activation in The EpiDerm™ 3D Human Reconstructed Skin Micronucleus (RSMN) Assay, Mut. Res., 750, 40-49, 2013

86. Pfuhler,S., R. Elespuru, **M. J. Aardema**, S. H. Doak, E. M. Donner, M. Honma, M. Kirsch-Volders, R. Landsiedel, M. Manjanatha, T. Singer, J. H. Kim, Genotoxicity of Nanomaterials: Refining Strategies and Tests for Hazard Identification Environ. Mole. Mutagen., 54, 229-239, 2013

87. **Aardema, M. J.** The Holy Grail in Genetic Toxicology: Follow-up Approaches for Positive Results in the Ames Assay, Environ. Mole. Mutagen., Environ. Mole. Mutagen. 54, 617-620, 2013

88. Fellows M.D., A. McDermott, K. R. Clare, A. Doherty, **M. J. Aardema**, The Spectral Karyotype of L5178Y $TK^{+/-}$ Mouse Lymphoma Cells Clone 3.7.2c and Factors Affecting Mutant Frequency at the Thymidine Kinase (*tk*) Locus in the Microtitre Mouse Lymphoma Assay, Environ. Mole. Mutagen. 55, 35-43, 2014

89. Young R. R., **Aardema, M.J.**; V.O. Wagner III, J. J. Clarke, R. Kulkarni, S. Roy, Y.Xu, K. Pant, L.F. Stankowski, Jr., T. Lawlor, , Genetic Toxicology, Chapter 13, in Handbook of Toxicology, 3rd Addition, CRC Press, ed. Michael J. Derelanko; Carol Auletta, pp 487-515, Feb. 2014

90. Young R.R., M. Powley, T. E. Lawlor, **M. J. Aardema,** Chapter 23 Genetic Toxicology Studies, in The Role of the Study Director in Nonclinical Studies Pharmaceuticals, Chemicals,Medical Devices, and Pesticides, Ed. William J. Brock, Associate Editors Barbara Mounho, Lijie Fu, Wiley, 2014

91. Poirier M.C., J. L. Schwartz, **M. J. Aardema**, Achieving Professional Success in US Government, Academia, and Industry: An EMGS Commentary, Environ. Mole. Mutagen. 55, 525–529, 2014

92. Zhang L., C. M. McHale, N. Greene, R. D. Snyder, I. N. Rich, **M J. Aardema**, S. Roy, S. Pfuhler, S. Venkatactahalam, Emerging Approaches in Predictive Toxicology, Environ. Mole. Mutagen. 55, 679–688, 2014

93. Pant K, S. Springer, S. Bruce, T. Lawlor, N. Hewitt, **M.J. Aardema,** Vehicle and Positive Control Values from the *In Vivo* Rodent Comet Assay and Biomonitoring Studies Using Human Lymphocytes: Historical Database and Influence of Technical Aspects, Environ. Mole. Mutagen. 55, 633-42, 2014

94. Zeiger E., B. Gollapudi, **M.J. Aardema,** S. Auerbach, D. Boverhof, L. Custer, P. Dedon, M. Honma, S. Ishida, A. Kasinski, J. H. Kim, M. Manjanatha, J. Marlowe, S. Pfuhler, I. Pogribny, W. Slikker, L. F. Stankowski, J. Y. Tanir, R. Tice, J. van Benthem, P. White, K. L. Witt, V. Thybaud, Genetic Toxicology: Opportunities to Integrate New Approaches, Environ. Mole. Mutagen. 56, 277-85, 2015

95. Stankowski, L., **M.J. Aardema**, T. Lawlor, S. Roy, Y. Xu, R. Elbekai, Integration of Pig-a, micronucleus, chromosome aberration, and Comet assay endpoints in a 28-day rodent toxicity study with urethane, Mutagenesis, 30, 335-42, 2015

96. Pant, K., L. Krsmanovic, S. W. Bruce, T. Kelley, M. Arevalo, S. Atta-Safoh, F. Debelie, M. L. La Force, S. Springer, J. Sly, M. Paranjpe, T. Lawlor, **M. Aardema,** Combination comet/micronucleus assay validation performed by BioReliance under the JaCVAM initiative. Mutat Res 2015 in press 2015

Acquavella

CURRICULUM VITAE

as of June 29, 2015

Personal Information

Name John F. Acquavella, PhD FACE

Present Position Professor, Department of Clinical Epidemiology
Aarhus University
Aarhus, Denmark
email: acquajohn@[redacted] (personal) joac@clin.au[redacted] (academic)
phone #: 928-515-2871; 928-227-7465 (mobile)

Education

B.A. Psychology, State University of New York at Buffalo, 1976
M.S. Epidemiology/Natural Science, State University of New York at Buffalo, 1977
Ph.D. Epidemiology, Roswell Park Memorial Institute, State University of New York at Buffalo 1989.

Previous Positions

Amgen, Inc. Thousand Oaks, CA, USA 11/2004 to 11/2014

Executive Director & Oncology Therapeutic Area Head
Center for Observational Research

Executive Director & Head, Global Epidemiology

Responsibilities: Developed Amgen's Global Epidemiology function through 2010. Then, until retirement, headed the largest therapeutic area (oncology) in Amgen's nascent Center for Observational Research. Was elected and served as President American College of Epidemiology. Was elected chair of the Industry Council for the International Society for Pharmacoepidemiology (term through 2017).

Monsanto Company (temp. Pharmacia), St. Louis, MO, USA 9/1989 to 11/2004

Sr. Fellow, Epidemiology

Responsibilities: Served as a member of Monsanto's executive scientist core. Led industry-wide programs with funding by relevant trade associations. Did original research in support of Monsanto's businesses.

Exxon Biomedical Sciences, East Millstone, NJ, USA 12/1983 to 9/1989

9/86-9/89 Epidemiology Group Head
12/83-9/86 Senior Epidemiologist
Exxon Biomedical Sciences Inc.

Responsibilities: Published extensively in occupational/environmental epidemiology and became the head of the epidemiology program for Exxon.

University of California @ Los Alamos National Laboratory 5/1981 to 12/1983
Los Alamos NM, USA

8/82-12/83 Epidemiology Group Leader
5/81-8/82 Epidemiologist
Los Alamos National Laboratory
Los Alamos, New Mexico 87545

Responsibilities: Started as a researcher on the plutonium workers cohort study, published extensively in radiation epidemiology, and became head of the Epidemiology Group. Had responsibilities for program direction, scientific content, personnel, and interface with the sponsor (Dept of Energy).

US Environmental Protection Agency, Res Tri Park, NC 10/1978 to 5/1981
10/78-5/81 Staff Epidemiologist, Population Studies Division, HERL

Responsibilities: Project officer and researcher – mostly in cancer epidemiology.

Honors

Lilienfeld Prize Paper, Society for Epidemiologic Research, 1989
Fellow, American College of Epidemiology 1996 -
Monsanto Global Health and Safety Award 2002
Monsanto Excellence Award 2003
CropLife America Special Recognition Award 2003
American College of Epidemiology Distinguished Service Award 2009

Professional Societies, Offices held
Secretary, American College of Epidemiology & Chair Admissions Committee 1996-2003
President, American College of Epidemiology 2006-7
Chair American College of Epidemiology Nominating Committee 2009
Chair, American College of Epidemiology Publication Committee 2011-2014
Chair, Society for Epidemiologic Research Awards Committee 2013 – present
Co-chair International Society for Pharmacoepidemiology Industry Council 2014 -

Editorships
Associate Editor, Environmental Health Perspectives (2008 to 2011)
Associate Editor, Annals of Epidemiology (2015 -)

Past Adjunct Professorships
Dept of Epidemiology & Biostatistics, School of Public Health, University of Massachusetts at Amherst
Dept of Epidemiology, Arnold School of Public Health, University of South Carolina

Publications

Journal Articles (in order of recency)

Ehrenstein V, Gammelager H, Schi0dt M, Norholt SE, Neumann-Jensen B, Folkmar TB, Pedersen L, SvCErke S, S0rensen HT, Acquavella J. Osteonecrosis of the Jaw: positive predictive value and sensitivity of an ICD-10-based algorithm to monitor osteonecrosis of the jaw (ONJ) and clinical characteristics of ONJ patients in Denmark. Pharmacoepidemiol Drug Safety *(online DOI: 10.1002/pds.3786)*.

Holland-Bill L, Xu H, Sørensen HT Acquavella J, Sværke C, Gammelager H, Ehrenstein V. Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish National Registry of Patients. Ann Epidemiol 2014;24:593-7.

Cronin-Fenton DP, Antonsen S, Cetin K, Daniels A, Borre M, Acquavella J, Lash T L. Mortality and incidence of new primary cancers in men with prostate cancer: a Danish population-based cohort study. Cancer Epidemiol 2013; 37;5:562-8.

Cronin-Fenton DP, Antonsen S, Cetin K, Acquavella J, Daniels A, Lash T L. Methods and rationale used in a matched cohort study of the incidence of new primary cancers following prostate cancer. Clin Epidemiology 2013;5:429-437.

Li S, Peng Y, Weinhandl ED, Blaes AH, Cetin K, Chia VM, Stryker S, Pinzone JJ, Acquavella JF, Arneson TJ. Estimated number of prevalent cases of metastatic bone disease in the US adult population. *Clin Epidemiol* 2012;4:87-93.

Arneson TJ, Li S, Gilbertson DT, Bridges KR, Acquavella JF, Collins AJ. Impact of Centers for Medicare & Medicaid Services National Coverage Determination on Erythropoiesis-Stimulating Agent and Transfusion Use in Chemotherapy-Treated Cancer Patients. Pharmacoepidemiology and Drug Safety 2012; 21:857-864.

Gammelager H, Erichsen R, Antonsen S, Nørholt SE, Neumann-Jensen B, Ehrenstein V, Acquavella J, Sørensen HT. Positive predictive value of the International Classification of Diseases, 10th revision, codes to identify osteonecrosis of the jaw in patients with cancer in a population-based hospital registry. *Cancer Epidemiol.* 2012; 4:381-3.

Nielsson MS, Erichsen R, Frøslev T, Taylor A, Acquavella A, Ehrenstein V. Positive Predictive values of the coding for bisphosphonate therapy among cancer patients in the Danish National Registry of Patients. *Clin Epidemiol* 2012;4:233-6.

Beebe-Dimmer JL, Cetin K, Shahinian V, Morgenstern H, Yee C, Schwartz KL, Acquavella JF. Recency of Androgen Deprivation Therapy Use and Fracture among Elderly Men with Prostate Cancer in the United States. Pharmacoepidemiology and Drug Safety 2012;21:70-78.

Beebe-Dimmer J, Morgenstern H, Cetin K, Yee C, Bartoces M, Shahinian V, Fryzek J, Acquavella J, Schwartz K. Androgen Deprivation Therapy and Cataract Incidence among Elderly Prostate Cancer Patients in the United States. Annals Epidemiol 2011;21(3):156-163.

Cronin-Fenton DP, Søndergaard F, Pedersen LA, Fryzek JP, Cetin K, Acquavella J, Baron JA, Sørensen HT. Hospitalisation for venous thromboembolism in cancer patients and the general population: a population-based cohort study in Denmark, 1997-2006. *Br J Cancer.* 2010; 103:947-53.

Wang O, Kilpatrick RD, Critchlow CW, Ling X, Bradbury BD, Gilbertson DT, Collins AJ, Rothman KJ, Acquavella JF. Relationship between ESA dosing and mortality: results from a marginal structural model. Clin J Am Soc Nephrol 2010;5:182-188.

Bradbury BD, Brookhart MA, Winkelmayer W, Critchlow CW, Kilpatrick RD, Feldman HI, Joffe MM, Acquavella JF, Wang O, Rothman KJ. Evolving Statistical Methods to Facilitate Evaluation of the Causal Association between ESA Dose and Mortality in non-experimental research: Strengths and Limitations. Am J Kidney Dis 2009;54:554-560.

Critchlow CW, Bradbury BD, Acquavella JF, Ruixo JJP, Krishnan M, Chow AT, Brenner RM. Letter to the Editor re: The effect of Epoetin dose on Hematocrit. Kidney Int 2008;74:827

Bradbury BD, Wang O, Critchlow CW, Rothman KJ, Heagerty P, Keen M, Acquavella JF. Exploring relative mortality and Epoetin alfa dose among hemodialysis patients. Am J Kidney Dis 2008:51:62-70

Scher DP, Alexander BH, Adgate JL, Eberly LE, Mandel JS, Acquavella JF, Bartels MJ, Brzak KA. Agreement of pesticide biomarkers between morning void and 24-h urine samples from farmers and their children. Journal of Exposure Science & Environmental Epidemiology 2007;17(4):350-7.

Alexander BH, Burns CJ, Bartels MJ, Acquavella JF, Mandel JS, Gustin C, Baker B. 2,4-D exposure in farm families: Results from the Farm Family Exposure Study. /Environmental Health Perspectives 2007;115:370-376.

Acquavella JF. Why Focus only on Financial Interests? Epidemiology 2006; 17:248-9.

Alexander BH, Burns CJ, Bartels MJ, Acquavella JF, Mandel JS, Gustin C, Baker B. Chlorpyrifos Exposure in Farm Families: Results from the Farm Family Exposure Study. Journal of Exposure Science and Environmental Epidemiology 2006;16; 447–456.

Baker BA, Alexander BH, Mandel JS, Acquavella JF, Honeycutt R, Chapman P. Farm Family Exposure Study: methods and recruitment practices for a biomonitoring study of pesticide exposure. Journal of Exposure Analysis and Environmental Epidemiology 2005; 15:491-499.

Barr D, Thomas K, Curwin B, Landsittel D, Raymer J, Lu C, Donnelly KC, Acquavella J. Biomonitoring of exposure in farmworker studies. Environ Hlth Perspect 2006;114:936-942..

Acquavella, JF, Alexander BH, Mandel J, Burns C, Gustin C. Exposure Misclassification in Epidemiologic Studies of Agricultural Pesticides: Insights from Biomonitoring Studies of Farmers. Epidemiology 2006; 17: 69-74.

Baker BA, Alexander BH, Mandel JS, Acquavella J, Honeycutt R, Chapman P. Farm Family Exposure Study: Methods and Recruitment Practices for a Biomonitoring Study of Pesticide Exposure. J Exp Assess Environ Epidemiol 2005;15(6):491-9.

Alexander BH, Burns C, Bartels M, Acquavella JF, Mandel JS, Gustin C. Chlorpyrifos exposure in farm families: Results from the Farm Family Exposure Study. Environ Health Perspect (submitted for publication). J Expo Sci Environ Epidemiol 2006:16(5):447-56.

Acquavella JF, Delzell E, Cheng, H, Lynch CF, Johnson G. Mortality and Cancer Incidence among Alachlor Manufacturing Workers 1968-1999. Occup Environ Med 2004;61:680-685.

Pastides H, Doll R, Acquavella JF, Alavanja M. Preface: International Symposium. Scand J Work Environ Health 2005;31 suppl 1:3-4.

Mandel JS, Alexander BH, Baker B, Honeycutt R, Chapman P, Acquavella JF. Farm Family Exposure Study. Scand J Work Environ Health 2005:31 suppl 1:98-104.

Acquavella JF, Gustin C, Alexander B, Mandel JS. Implications for Epidemiologic Research of Observed Variation by Pesticide in Biomonitoring Studies of Farmers and their Families. Scand J Work Environ Health 2005:31 suppl 1:105-109.

Acquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, Chapman P, Bleeke M. Glyphosate Biomonitoring for Farmer-Applicators and their Families: Results from the Farm Family Exposure Study. Environ Health Perspect 2004:112:321-326.

Acquavella JF, Delzell E, Cheng, H, Lynch CF, Johnson G. Mortality and Cancer Incidence among Alachlor Manufacturing Workers 1968-1999. Occup Environ Med 2004;61:680-685.

Acquavella JF, Doe J, Tomenson J, Chester G, Cowell J, Bloemen L. Epidemiologic Studies of Occupational Pesticide Exposure and Cancer: Regulatory Risk Assessments and Biologic Plausibility. Annals of Epidemiology 2003; 13: 1-7.

Goldstein DA, Acquavella JF, Farmer DR, Mannion RM. Telephone Reports as an Index of Herbicide Poisoning Frequency and Severity: An Analysis of Glyphosate Data from the California Environmental Protection Agency Pesticide Illness Surveillance Program. J Clinical Experimental Toxicology 2002; 40(7): 885-892.

Acquavella JF, Leonard R. A review of the epidemiology of 1,3-butadiene and chloroprene. Chemico-Biological Interactions 2001; 135-136:43-52.

Acquavella JF, Cowell JE, Cullen MR, Farmer DR, Pastides H. Implications of Glyphosate Toxicology and Human Biomonitoring Data for Epidemiologic Research. J Agromedicine 2001; 7:7-27.

Acquavella JF, Tomenson J, Doe J, Bloemen L, Chester G, Cowell J. Cancer Epidemiology and Pesticides: Thoughts on Biologic Plausibility using a Risk Assessment Paradigm. [abstract] Amer J Epidemiol 2001;11:S39.

Acquavella J, Burns C. Pesticides and fetal death due to congenital abnormalities. (letter to the editor) Epidemiology 2001; 12:593-594.

Acquavella J, Olsen G, Cole P, Ireland B, Kaneene J, Schuman S, Holman L. Farming and cancer: The authors respond. (letter to the editor) Annals Epidemiol 1999;9:72.

Acquavella JF, Weber J, Cullen MR, Cruz OA, Martens M, Holden L, Riordan S, Thompson M. Ocular Effects from Reported Exposures to Formulated Glyphosate Herbicides. Human & Experimental Toxicology 1999;18:479-486.

Acquavella J. Farming and prostate cancer. Epidemiology 1999;10: 349-351.

Acquavella JF, Cullen MR, Farmer D. re: re: A Case-control Study of non-Hodgkin Lymphoma and Exposure to Pesticides. (letter to the editor) Cancer 1999;86:729-730.

Acquavella JF, Cullen MR. re: Glutathione transferase null genotype, broccoli, and lower prevalence of colorectal adenomas. (letter to the editor) Cancer Epidemiology, Biomarkers, & Prevention 1999; 8:947.

Acquavella J, Olsen G, Cole P, Ireland B, Kaneene J, Schuman S, Holman L. A meta-analysis of cancer among farmers. Annals Epidemiol 1998;8:64-74.

Acquavella JF, Burns C, Flaherty D, Holsapple M, Kimber I, Ladics G, Loveless S, Tobia A. A Critique of the World Resources Institute's Report "Pesticides and the Immune System: The Public Health Risks." Environ Health Pers 1998;106:51-54.

Acquavella JF, Burns C, Flaherty D, Holsapple M, Kimber I, Ladics G, Loveless S, Tobia A. Response re: A Critique of the World Resources Institute's Report "Pesticides and the Immune System: The Public Health Risks." (letter to the editor) Environ Health Pers 1998;106:A53-A54.

Collins JJ, Acquavella JF. Review and meta-analysis of studies of acrylonitrile workers. Scand J Work Environ Health 1998;24:71-80.

Himmelstein MW, Acquavella JF, Recio L, Medinski MA, Bond JA. Review of the toxicology and epidemiology of butadiene. Crit Rev Toxicol 1997;27:1-108.

Acquavella J, Ramlow J. Epidemiology faces its limits. (letter to the editor). Am J Epidemiol 1997;145:476.

Collins JJ, Acquavella JF, Esmen NA. Formaldehyde Exposure and Upper Respiratory Cancers: An Updated Review and Meta-analysis and a Critique of Past Meta-analyses. J Occup Env Med 1997;39:639-651.

Acquavella J. The politics of identity in epidemiology. Annals Epidemiol 1997;7:431-433.

Acquavella JF. Butadiene Epidemiology: A summary of results and outstanding issues. Toxicology 1996;113:148-156.

Acquavella JF, Riordan SG, Anne M, Lynch CF, Collins JJ, Ireland BK, Heydens WF. An Evaluation of Mortality and Cancer Incidence among Alachlor Manufacturing Workers. Environ Health Pers 1996; 104:728-733.

Leet TL, Acquavella JF, Lynch C, Anne M, Weiss NS, Vaughan T, Checkoway H. Cancer Incidence among Alachlor Manufacturing Workers. Am J Ind Med 1996;30:300-306.

Acquavella JF, Collins JJ, Raabe G, Teta MJ. Disclosure of Interest: A Time for Clarity? Am J Indust Medicine 1995; 28:609-610.

Acquavella JF, Friedlander B, Ireland B. Interpretation of moderate relative risks in environmental epidemiologic studies. Annual Reviews of Public Health 1994; 15:179-201.
Acquavella JF, Delzell E, Cole P. Butadiene and lymphopoietic cancers: The authors reply. Epidemiology 1994;5:262-3.

Ireland BK, Acquavella JF, Olsen G. Herbicides and prostate cancer? (letter to the editor) Am J Epidemiol 1994;11:1057-1058.

Ireland BK, Acquavella JF, Anne M, Farrell T, Fuhremann T. Evaluation of Ocular Health among alachlor manufacturing workers. J Occup Med 1994;36:738-742.

Acquavella JF, Collins JJ. Perspective on the content of worker notifications. Am J Ind Med 1993;23:77-83.

Cole P, Delzell E, Acquavella J. Exposure to Butadiene and Lymphatic and Hematopoietic Cancer. Epidemiology 1993; 4:86-93.

Ireland BK, Acquavella JF, Kier LD. Ras oncogene activation and occupational exposures in acute myeloid leukemia. J Nat'l Cancer Inst (letter to the editor) 1993;85:920-1.

Acquavella JF, Leet T, Johnson G. Occupational experience and mortality among a cohort of metal components manufacturing workers. Epidemiology 1993:4;428-434.

Acquavella JF, Cowles SR. Butadiene exposure and leukemia. Amer J Epidemiology (letter to the editor) 1993;138:765-766.

Cole P, Delzell E, Acquavella J. The authors reply: Exposure to Butadiene and Lymphatic and Hematopoietic Cancer. Epidemiology 1993; 4:560-561.

Gelbke HP, Acquavella JF, Fedtke N, Poole A. Risk Assessment and Industrial Health - Evaluating the Carcinogenic Risk: Styrene and Butadiene as Examples. IARC Sci Publ No. 127: 389-399, 1993.

Acquavella JF, Ramlow JM, Ireland BK. Organochlorines and breast cancer? (letter to the editor) J Natl Cancer Inst 1993;85:1872-3.

Collins JJ, Acquavella JF, Friedlander BR. Reconciling Old and New Findings on Dioxin. Epidemiology 1992;3:65-69.

Shallenberger LG, Acquavella JF, Donaleski D. An Updated Mortality Study of Workers in Three Major U.S. Refineries and Chemical Plants. Brit J Ind Med 1992; 49:345-354.

Owen C, Acquavella JF, Lynch J, Bird MG. An Exposure Estimating Methodology in Support of a Retrospective Morbidity Case-Control Study. Am Ind Hyg Assn Journal 1992; 53:540-547.

Acquavella JF, Owen CV, Bird MG, Yarborough CM, Lynch J. An Adenomatous Polyp Case Control Study to Assess Occupational Risk Factors for a Workplace Colorectal Cancer Cluster. Amer J Epidemiol 1991; 133:357-368.

Acquavella JF, Leet TL. A Cohort Study among Workers at a Metal Components Manufacturing Facility. J Occup Med 1991;33:896-900.

Acquavella JF. Are Non-whites at Greater Risk for Occupational Cancer? (Letter to the editor) Am J Ind Med 1991;20:811.

Acquavella JF. Improving the Conduct of Epidemiologic Studies: An Introduction to Quality Principles. J Occup Med 1991;33:1244-1246.

Acquavella JF, Wilson JD, Conner P, Bannister R. An alternative hypothesis for bladder cancer among workers exposed to o-toluidine and aniline. J Nat'l Cancer Inst (letter to the editor) 1991; 22:1686.

Acquavella JF. Future Directions in Epidemiologic Studies of Butadiene Exposed Workers. Environ Health Pers 1990;86:129-134.

Melnick RL, Huff JE, Bird MG, Acquavella JF. Symposium Overview: Toxicology, Carcinogenesis, and Human Health Aspects of 1,3-Butadiene. Environ Health Pers 1990;86:3-6.

Schnatter AR, Acquavella JF, Thompson FS, Donaleski D. An Analysis of Death Ascertainment and Follow-up Through Statistics Canada's Mortality Data Base System. Canadian J Public Health 1990;81:60-5.

Vernon S, Acquavella JF, Yarborough CM, Hughes JI, Thar WE. Reasons for Participation and Nonparticipation in a Colorectal Cancer Screening Program for a Cohort of High Risk Polypropylene Workers. J Occup Med 1990;32:46-51.

Acquavella JF, Owen CV. Assessment of Colorectal Cancer Incidence Among Polypropylene Pilot Plant Employees. J Occup Med 1990;32: 127-30.

Acquavella JF, Douglass TS, Vernon SW, Hughes JI, Thar WE. re An Assessment of Colorectal Cancer Screening Outcomes among Workers Involved in the Manufacture of Polypropylene by a Heavy Diluent Process. (letter to the editor) J Occup Med 1990; 32:1143-44.

Vernon S, Acquavella JF. Factors Associated with Participation in an Occupational Colorectal Cancer Screening Program. J Occup Med 1989;31:458-63.

Acquavella JF, Douglass TS, Vernon SW, Hughes JI, Thar WE. An Assessment of Colorectal Cancer Screening Outcomes among Workers Involved in the Manufacture of Polypropylene by a Heavy Diluent Process. J Occup Med 1989;31:785-91.

Acquavella JF. The Paradox of Butadiene Epidemiology. Experimental Path 1989;37:114-8.

Acquavella JF, Douglas TS, Phillips SC. An Evaluation of Excess Colorectal Cancer Incidence among Workers Involved in the Manufacture of Polypropylene. J. Occup Med. 1988;30:438-42.

Wilkinson GS, Voelz G, Tietjen GL, Wiggs LD, Galke WA, Acquavella JF. re: Mortality Among Plutonium and Other Radiation Workers at a Plutonium Weapons Facility. (letter to the editor) Amer J Epidemiol 1988;127:1323-5.

Wilkinson GS, Tietjen GL, Wiggs LD, Galke WA, Acquavella JF, Reyes-Waxweiler M, Voelz GL, Waxweiler RJ. Mortality Among Plutonium and Other Radiation Workers at a Plutonium Weapons Facility. Amer J Epidemiol 1987;125:231-50.

Acquavella JF, Donaleski D, Hanis NM. An Assessment of Mortality Followup through the National Death Index for a Cohort of Petrochemical Workers. Amer J Indust Med 1986;9:181-7.

Acquavella JF, Hanis NM, Nicolich M, Phillips SC. An Assessment of Clinical, Metabolic, Dietary, and Occupational Correlations with PCB Blood Levels among Employees at an Electrical Capacitor Manufacturing Plant. J Occup Med 1986;28:1177-80.

Acquavella JF, Wiggs LW, Waxweiler RJ, MacDonell DG, Tietjen GL, Wilkinson GS. Mortality Among Workers at the Pantex Nuclear Facility. Health Physics 1985;48:735-46.

Reyes M, Wilkinson GS, Tietjen GL, Voelz GL, Acquavella JF, Bistline R. Brain Tumors at a Nuclear Facility. J Occup Med 1984;26:721-4.

Voelz GL, Wilkinson GS, Acquavella JF, et al. An update of Epidemiologic Studies of Plutonium Workers. Hlth Phys 1983;(Suppl. No 1):493-503.

Acquavella JF, Tietjen GL, Wilkinson GS, et al. A Melanoma Case-Control Study at the Los Alamos National Laboratory. Health Physics 1983;45:587-92.

Acquavella JF, Tietjen GL, Wilkinson GS et al. A Study of Malignant Melanoma Incidence at the Los Alamos National Laboratory. Lancet 1982;i:883-4.

Conference Proceedings, Books, etc.

Acquavella JF, Bradbury B, Critchlow C, Litten JB, Sprafka JM, Sullivan J. Pharmacoepidemiology as part of pharmacovigilance for biologic therapies. Mann's Pharmacovigilance 3rd edition, eds. EB Andrews, N Moore, John Wiley & Sons, Ltd., Oxford, UK, 2014, pp 685-702.

Voelz GL, Wilkinson GS, Acquavella JF, et al. A Review of Epidemiologic Studies at the Los Alamos National Laboratory. In Proceedings of the DOE Radiation Epidemiology Contractors Workshop, April 13-14,1982.

Acquavella JF, Tietjen GL, Wilkinson GS, et al. An Analysis of Malignant Melanoma Incidence from 1969-1978 among Employees at the Los Alamos National Laboratory. Los Alamos Technical Report LA-9465, August 1982.

Acquavella JF, Wiggs LD, Waxweiler RJ, et al. Supplementary Documentation for an Environmental Impact Statement Regarding the Pantex Plant: Occupational Mortality Study, Los Alamos Technical Report LA-9445-PNTX-Q, December, 1982.

Acquavella JF, Tietjen GL, Wilkinson GS. A Quantitative Consideration of Lost-to-Follow-up Bias in an Occupational Mortality Analysis. Los Alamos Technical Report LA-9530, December 1982.

Wiggs LD, Wilkinson GS, Tietjen GL, Acquavella JF, et al. Supplementary Documentation for an Environmental Impact Statement Regarding the Pantex Plant: A Comparison of County and State Cancer Mortality Rates. Los Alamos Technical Report LA-9445-PNTX-P, December 1982.
Acquavella JF, Wilkinson GS. The National Plutonium Workers Study: Considerations and Some Preliminary Results. Los Alamos Technical Report LA-9545-SR, March 1983.

Acquavella JF, Wilkinson GS, Key C, et al. An Evaluation of Cancer Incidence at the Los Alamos National Laboratory. In: National Technical Information Service. Epidemiology Applied to Health Physics: Proceedings of the 16th Midyear Topical Symposium of the Health Physics Society. Springfield, VA 1983 (CONF-830101).

Wilkinson GS, Voelz GS, Acquavella, JF, et al. Mortality among Plutonium and Other Workers at a Nuclear Facility. In: National Technical Information Service. Epidemiology Applied to Health Physics: Proceedings of the 16th Midyear Topical Symposium of the Health Physics Society. Springfield, VA 1983 (CONF-830101).

Riggan WF, Van Bruggen J, Acquavella JF, Baubier J. U.S. Cancer Mortality Rates and Trends 1950-1978: Vols 1-3, U.S. Government Printing Office, 1983.

Acquavella JF. Assessing an Occupational Colorectal Cancer Cluster - A Unique Multi-Phased Approach. PhD Dissertation, State University of New York at Buffalo, 1988.

Acquavella JF. Direct written testimony submitted to the Occupational Safety and Health Administration on 1,3 butadiene epidemiology. November 1990.

Acquavella JF, Ireland BK, Leet T, Anne M, Farrell TF, Martens M. Epidemiologic studies of morbidity and mortality among alachlor manufacturing workers. Proceedings of the XII Joint CIGR, IAAMRH, IUFRO International Symposium: Health, Safety and Ergonomic Aspects in Use of Chemicals in

Agriculture and Forestry. June 8-11, 1993, Kiev, Ukraine, Institute for Occupational Health, 1994 pp 184-194.

Acquavella JF, Ireland BK, Heydens WF. Epidemiologic Studies of Alachlor Manufacturing Workers. Monsanto report number MSL 13819, November 1994.

Acquavella JF. A Researcher's Perspective on Ethics. TCM Newsletter, August 1996.

Acquavella JF. The Politics of Identity in Epidemiology. State University of New York at Buffalo School of Social and Preventive Medicine Sesquicentennial Colloquium, September 1996.

Whitford F, Acquavella J, Burns C. Pesticides and Epidemiology; Unraveling Disease Patterns. Purdue Pesticide Programs, Purdue University Cooperative Extension Service, West Lafayette, Indiana, 1998.

Berry

CURRICULUM VITAE

PROFESSOR SIR COLIN BERRY

Date of Birth	28th September, 1937
Nationality	British
Status	Married, 2 children

QUALIFICATIONS

MB BS	(London)	May 1961
MD	(London)	Sept 1968
PhD	(London)	May 1970
DSc	(London)	Nov 1992
Hon MD Ionnina (Greece)		Sept 2003
MRCPath		Nov 1967
FRCPath		April 1979
FFPM		August 1989
FRCP		July 1993
FFOM		May 1995
FRCP (Ed)		June 1998
F Acad Med Sci		

PREVIOUS APPOINTMENTS

House Physician	Charing Cross Hospital	July '61-Jan. '62
House Surgeon	Charing Cross Hospital	Jan. '62-July '62
Senior House Officer in Pathology	Charing Cross Hospital	July '62-July '63
Registrar in Pathology	Charing Cross Hospital	July '63-July '64
Senior Registrar in Pathology	Fulham Hospital	July '64-Oct. '64
Lecturer & Senior Lecturer in Morbid Anatomy	Hospital for Sick Children & Institute of Child Health, London	Nov. '64-Dec. '68
British Heart Foundation Senior Res. Fellow & Hon Lecturer in Pathology	Institute of Child Health, London	Jan. '68-Oct. '70
University Reader in Pathology & Hon Consultant Pathologist	Department of Histopathology, Guy's Hospital Medical School	Oct. '70-Sept '76
Deputy Director	IRC Biomedical Materials, Queen Mary & Westfield College, London	
Visiting Professor	University of Singapore	Oct. '88-Jan. '89

MAJOR APPOINTMENTS

Professor of Morbid Anatomy, Director of the Pathological Institute, Consultant Histopathologist	The Royal London Hospital	Oct. '76
Dean-Elect and Dean	The London Hospital Medical College	Dec. '92-July '94
Warden	St Bartholomew's & The Royal London School of Medicine & Dentistry	July '94 -Sept '96

DISTINCTIONS

Civil

Knight Bachelor, Birthday Honours List	June 1993

Undergraduate

Governors Clinical Gold Medal
Llewllyn Scholarship
Gordon M Holmes Prize in Medicine
Norman C Lake Prize in Surgery
Pierera Prize in Clinical Subjects
Steadman Prize in Pathology
Year Prizes in Orthopaedics
- Otorhinolaryngology
- Ophthalmology
- Psychological Medicine
- Dermatology

Huxley Prize in Physiology

Postgraduate

Gillson Scholarship in Pathology - Worshipful Society of Apothecaries of London	1967 - 1968
Re-awarded	1970 - 1972
Founder Member by Distinction of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians of London	1989
Corresponding Member, Rheinish-Westfalische Akademie der Wissenschaften	May 1993
Member, Deutsch Akademie der Naturforscher „Leopoldina“	Oct. 1993
Honorary Fellow Faculty of Occupational Medicine of the Royal College of Physicians	May 1995
Honorary Fellow of the University of Central Lancashire	Oct 1999
Corresponding Member, The German Pathological Society	May 2002
Honorary Fellow, The German Pathological Society	May 2005
Honorary Fellow, The British Toxicology Society	March 2006
Honorary Curator, The Deutsches Museum, Munich	June 2006

ADMINISTRATIVE POSTS AND APPOINTMENTS HELD

The London Hospital Medical College

Professor of Morbid Anatomy and Director of the Institute of Pathology	1976 - 2002
Chairman of Academic Board, Academic Session	1989 - 1990
Member of the Clinical Curriculum Group	
Member of the City and East London Confederation Joint Academic Committee	1988 -
Dean-Elect The London Hospital Medical College	1992 - 1994
Dean, The London Hospital Medical College	1994 - 1994
Warden and Vice Principal of Medicine and Dentistry, Queen Mary and Westfield College	1994 - 1996

President

European Society of Pathology	1989 - 1991
(President-Elect)	1987 - 1989
Developmental Pathology Society	1976 - 1980
British Academy of Forensic Sciences	2003 - 2005
(President Elect)	2001 - 2003

Chairman

Advisory Committee on Pesticides, Ministry of Agriculture, Fisheries and Food	1988 - 1999
(Member)	1981 - 1988
Scientific Sub-Committee on Pesticides of the Ministry of Agriculture, Fisheries and Food and Department of Education and Science	1985 - 1988
(Member)	1977 - 1985
Committee of Dental and Surgical Materials	1982 - 1992
(Member)	1978 - 1981
Physiological Systems and Disorders Board of the Medical Research Council	1990 - 1992
(Member)	1988 - 1990
National Health & Medical Research Council Independent Panel of Assessors, Commonwealth of Australia	1982 - 2000
Association of Professor of Pathology	1987 - 1989
Union Europeenne des Medecins Specialistes, Board of Anatomic Pathology	1990 - 2001
Council, Research Defence Society	1993 - 1996

Master

The Worshipful Society of Apothecaries of the City of London (Senior Warden 2001 -2002, Junior Warden, 2000-2001) Treasurer 2004-	2003 – 2004

Secretary

Foundation Secretary, Developmental Pathology Society	1971 - 1975
Meetings Secretary, Association of Clinical Pathologists	1980 - 1982
Hon Secretary, Association of Clinical Pathologists	1982 - 1985
Secretary, Federation of Associations of Clinical Professors	1987 - 1990

Member

Medical Research Council	1990 - 1994
Toxicology Group, Expanded Programme on Human Reproduction, World Health Organization	1979 - 1985, 1987 - 1989, 1992 -
Committee of Toxicity of Chemicals in Food, Consumer Products and the Environment	1984 - 1989
Committee on Safety of Medicines	1990 - 1992
Committee on Safety of Medicines Advisory Panel	1994- 2002
Scientific Committee for Pesticides of the Commission of the European Communities	1985 - 1989
General Dental Council's Panel of Visitors of Examinations	1985 - 1987
Research Defence Society Council	1992 - 1998
N.E. Thames Regional Research and Development Committee	1992 - 1994
Ministry of Agriculture, Fisheries and Food Pesticide Safety Directorate Ownership Board	1993 - 1999
General Medical Council	1993 - 1996
Council of the British Toxicology Society	1994 - 1996
General Dental Council	1994 - 1996
Steering Committee on Environment and Health European Science Foundation	1996 - 2000
Member of the Gulf War Investigation Illness Research Programme Steering Committee.	1996 - 2000
Member of the Evaluation Board, National Institute for Clinical Excellence	1999 - 2002
Member of the Board of Science and Policy Advisors, The American Council on Science and Health	2002 -
Programme Committee, European Science Open Forum 2004	2000 - 2004
Steering Committee, European Science Open Forum 2006.	2004 - 2008
Advisory Board, The Scientific Alliance	2003 -
Advisory Council, Sense About Science	2003 -

Royal College of Pathologists

Assistant Registrar	1981 - 1984
Treasurer	1988 - 1993

Scientific Advisor

Ministry of Agriculture Scientific Advisor to the British Industrial Biological Research Association	1986 - 1989

Chief Medical Officer's Committees

Standing Medical Advisory Committee	1988 - 1992
Academic Forum	1988 - 1991

Charitable

Advisor, The Infantile Hypercalcaemia Foundation Medical Advisory Panel	1980 -
Chairman of Trustees of Advance in Medicine (AIM), a medical charity of The Royal London Hospital	1984 - 2002

Appeals Committee, Royal College of Pathologists	1989 – 1993
Appeals Committee, Royal College of Pathologists	2005 -

And several other medical charities

EXAMINATION APPOINTMENTS

External Examiner for BSc examinations in London Colleges (Anatomy and Pathology) and in Manchester University, The University of Glasgow and of Wales
Final BDS (Pathology) for the Schools of Dentistry of the Universities of London, Cardiff, Edinburgh and Leeds
Senior Examiner for the Final MB BS (Pathology) University of London
External Examiner for the Final MB BS (Pathology), Universities of Cambridge, Wales Belfast and Oxford
Visiting Examiner in Pathology of the University of Benin, Nigeria, the National University of Singapore, and Chinese University, Hong Kong
External Examiner in Applied Toxicology, University of Surrey

I have also acted as Examiner for more than 40 PhD or MD theses in the Universities of London, Manchester, Cambridge, Guilford, Dublin, Leicester and Liverpool and for the University of Christchurch, New Zealand

Member of the Panel of Examiners for the Final MRCPath (Histopathology and Toxicology).

External Examiner DSc, Liverpool
Local Examiner for (i) Part I BDS and
(ii) MB BS Pathology
Member of the MD Panel, University of London

OTHER PROFESSIONAL ACTIVITIES

I was Joint Managing Editor of the Journal "Virchows Archiv" for 25 years.

I am a member of the Editorial Boards of:

- Archives of Toxicology
- British Journal of Experimental Pathology
- Human Toxicology
- Journal of Pathology
- Patologica

I am a referee for:

- Annals of Contemporary Diagnostic Pathology
- Archives of Diseases in Childhood
- British Heart Journal
- British Journal of Surgery
- British Medical Journal
- Carcinogenesis
- Journal of Cardiovascular Research
- Journal of Clinical Pathology
- Journal of Hypertension
- Journal of Medical Genetics
- Journal of Pathology
- Lancet
- Medicine, Science and the Law
- Nature
- Paediatric Research

and have reviewed books for these and other journals

INTERNATIONAL BODIES

I continue to serve on a Commission of the Portuguese Government on the development of new medical schools 2000-

MAJOR INVITED LECTURES

Arris and Gale Lecturer, Royal College of Surgeons of England		1973
Sir Frederick Bawden Lecturer, British Crop Protection Council		1990
John Hull Grundy Lecturer, Royal Army Medical College		1992
Distinguished Visitor Lecture, College of Pathologists of Australia, Cairns	Sept	1993
Lucas Industries Lecturer, Royal College of Physicians	May	1994
Gesselschaft Deutscher Chemiker Lecturer, Bayer AG Leverkusen, Germany	Nov	1994
The Royal Institution of Great Britain; Friday Evening Discourse	Feb	1995
Plenary Lecture 6th International Congress of Toxicology, Seattle	July	1995
First Anniversary Lecture, University of Central Lancashire	July	1996
5th Robert Lane Lecturer, University of Manchester	Nov	1996
Apothecaries' Lecture, Society of Occupational Medicine	Feb	1997
'ASCEPT' Toxicology Lecture, Brisbane	Sept	1997
Sentry Farming Conference 'Farming '98', Cambridge	Feb	1998
Plenary Lecturer 9th International Congress of Pesticide Chemistry, London	Aug	1998
National Farmers Union Annual Address	Feb	1999
University of Ontario (Guelph) 125th Anniversary Lecture	March	1999
The Institute of Biology Northern Branch Charter Lecture, University of Newcastle upon Tyne	Oct	2000
The Royal Institution of Great Britain; Friday Evening Discourse	March	2001
International Life Science Institute; Plenary lecture. Miami	Jan	2002
Scientific Alliance; Risk and GM Crops meeting.	March	2002
Public Debate with the Secretary of State for Agriculture Bloomberg Auditorium. London	Jan	2004
Society of the Chemical Industry; Plenary lecture. Edinburgh	March	2004
The Precautionary Principle, ESOF 2004. Stockholm	August	2004
The Sir Michael Davies Lecture, The Expert Witness Institute	April	2005

Presidential Address, BAFS	June	2005
DANA Institute for the Brain, London	Nov	2006
Agrochemical Forum, Berlin	Sept	2007
British Potato Council, Harrogate	Nov	2007
EPPA – Animals and toxicity testing, Brussels (High Level EC workshop)	April	2008
University of Surrey, Foundation Lecture	July	2008
Syngenta Foundation; World Food Day Lecture	Oct	2008
The Royal Institution of Great Britain; Wellcome Series Lecture	Oct	2008
CEFIC Long range initiative Address	Nov	2008
American Society of Toxicology, Washington, DC (Plenary lecture).	Dec	2008
The Sir Roy Cameron Lecture of the Royal College of Pathologists	May	2009
The Minty Lecture, The Medico-Legal Society	October	2009
Inaugural Lecture. SCAHT. Geneva	November	2009
Plenary Lecture, IUPAC, Melbourne, Australia	July	2010
3rd Environmental Lecture, The South London Botanical Institute	October	2010
Principal Lecturer, Swiss Society of Toxicology, Basle	November	2010
Toxicology Forum, Lisbon	March	2011
SCI, Science for Policy. London	October	2011
ANVISA, Brazil	December	2011
University of Surrey, Anniversary Lecture	June	2012
Eponymous Lecture, The Medical Society of London	May	2013
Plenary Lecture, Eurotox, Interlaken 2013	September	2013
Plenary Lecture, Toxicology Forum 34th Annual meeting. Brussels.	October	2013
Sir William Paton Lecture of the British Toxicology Society	April	2014
NC3Rs, London. Publication Bias	Feb	2015
Olavian Lecture, St Olaves, Orpington	Nov	2015

Brusick

DAVID J. BRUSICK, Ph.D., A.T.S.

Consultant

[redacted]
Bumpass VA [redacted]

Telephone ([redacted]
E-mail Brusick41[redacted]

EDUCATION

University of Virginia, Darden School of Business, The Executive Program, 1991
NAS/NRC Postdoctoral Fellow 1970 -1971.
Ph.D., Microbial Genetics, Illinois State University, Normal, Illinois, 1970.
M.S., Genetics, Illinois State University, Normal, Illinois, 1965.
B.S., Biology, University of Illinois, Urbana, Illinois, 1963.

BACKGROUND

2005-2015	Independent Consultant in Genetic Toxicology and General Toxicology
2003 – 2005	Vice President, Global Resource Management, Covance Labs Inc. (Retired 7/1/05)
2000 – 2003	Vice President, Global Toxicology, Covance Labs Inc.
1996 - 1999	Global Vice President Toxicology, Covance Laboratories Inc.
1995 - 1996	Director Covance Labs NA Toxicology
1988 - 1995	Director, Corning Hazleton North America Toxicology, Corning Hazleton Inc., Vienna, Virginia.
1986 - 1987	Director, Molecular Toxicology Division, Hazleton Laboratories America, Inc., Kensington, Maryland.
1985 - 1986	Vice President, Biological Laboratories Division, Hazleton Biotechnologies, Kensington, Maryland.
1984 - 1985	Vice President, Biological Safety Evaluation Directorate, Litton Bionetics, Inc., Kensington, Maryland.

1981 - 1984	Vice President, Molecular Sciences Directorate, Litton Bionetics, Inc., Kensington, Maryland.
1974 - 1981	Director, Department of Molecular Toxicology, Litton Bionetics, Inc., Kensington, Maryland.
1971 - 1974	Assistant Professor of Microbiology, College of Medicine, Howard University, Washington, D.C.
1970 - 1971	National Academy of Sciences, National Research Council Postdoctoral Research Associate, Genetic Toxicology Branch. U.S. Food and Drug Administration, Washington, D.C
1968 - 1970	Graduate Research and Teaching Assistant, Department of Biology, Illinois State University, Normal, Illinois.
1963 - 1967	Graduate Research and Teaching Assistant, Department of Biology, Illinois State University, Normal, Illinois.

ACADEMIC APPOINTMENTS

1981 - 2003	Adjunct Associate Professor in the Department of Biological Sciences, George Washington University, Washington, D.C.
1985 - 2000	Adjunct Associate Professor in the Department of Genetics and Human Genetics, Howard University, College of Medicine, Washington, D.C.
1967 - 1968	Assistant Professor of Biology, Bridgewater College, Bridgewater, Virginia.

BUSINESS EXPERIENCE

- Graduate of the University of VA Darden Business School's Executive Program in 1991
- Established the first commercial Genetic Toxicology testing laboratory in the United States in1974.
- Established a Genetic Toxicology testing laboratory in Europe (The Netherlands) for Litton Bionetics (1978).
- Managed the global toxicology business for Covance Labs (over 1,000 staff with annual revenues of more than $200 million).
- Increased the productivity and operating profits of Covance toxicology businesses by 200% during a 5 year period from 1995-2000.
- Developed and implemented a Resource Management infrastructure across the entire global Covance organization.
- Created the first automated system for client's to have direct access to their study data in toxicology (now known as StudyTracker™).
- Developed and implemented an activity (metric)-based cost estimation system for Covance testing services.
- Provided consulting services for the development and expansion of contract toxicology research laboratories in China (2005-2007).
- Consultant to major international pharmaceutical, chemical and agrochemical companies.

SCIENTIFIC EXPERIENCE

Scientific Director, Corning Hazleton Inc., Vienna, VA. Manager of mammalian toxicology and pathology sciences.
Principal Investigator on mutagenicity testing contracts from agencies of the Federal government (e.g. EPA, FDA, NIEHS, NIOSH, DOD) and private sponsors.
Research experience in mutagenicity of chemical carcinogens and other environmental agents, carcinogen mechanisms. Research included in vitro and in vivo investigations.
Scientific Director of mutagenicity testing and molecular toxicology for Hazleton Laboratories worldwide.
Member of the editorial board of three scientific journals in genetics and toxicology. (Mutation Res., Environ. Molec. Mutagenesis, Toxicological Sciences).
Associate Editor for Toxicological Sciences 1998 – 2003.
Editor of In Vitro Toxicology, an international journal published by Mary Ann Liebert, Inc. (1988-1993).
Member of U.S. National Academy of Sciences Committees with Mutagenesis and Toxicology -
(1) Diesel Impact Committee and (2)Toxicology Data Elements Committee .
Chairman of a National Research Council subcommittee on the toxicological significance of DNA adducts.
Member of the International Commission for Protection Against Environmental Mutagens and Carcinogens (1986 - present). Chairman 1989 - 1995.
Past President of the U.S. Environmental Mutagen Society (1978).
Panel Member of the U.S.-Japan Environmental Mutagen Cooperative Program (1977-1979).
Councilor to the EMS Society.
Member of the Steering Committee for the EPA on the Gene-Tox Program for Genetic Testing Evaluation.
Member of NIH Study Section on Toxicology, 1992-1996.
Consultant to government agencies and private industrial firms regarding mutagenesis testing.
Member of the Center for Alternatives to Animal Testing (CAAT), Technology Transfer Committee.
Board Member, Academy of Toxicological Sciences (1990-1993).
Board Member, Industrial In Vitro Toxicology Group (1989-1995).
Secretary/Treasurer, Academy of Toxicological Sciences (1995-1996).
Lecturer for Mid-America Toxicology Course (1983-Present).
Member of several EPA advisory panels (e.g. Acrylamide; Arsenic)
Consultant to major pharmaceutical and chemicals companies, trade associations (ACC, ILSI) and regulatory agencies (US FDA, US EPA).
Special Issue Editor for Food Chemical Toxicology journal: Safety of Steviol Glycosides. 2008
Associate Editor, Food and Chemical Toxicology, 2009-2014
Senior consultant to Covance Nonclinical operations 2005-2012
Advisory Board Member for Hua Zheng Primate Breeding Center Guangzhou, China 2007-2012
Advisory on EPA's Assessments of Carcinogenic Effects of Organic
and Inorganic Arsenic: An Advisory Report of the US EPA Science
Advisory Board, 2006

MEMBERSHIPS

- Environmental Mutagen Society
- Society of Toxicology
- Academy of Toxicological Sciences

HONORS/AWARDS/CERTIFICATIONS

Chairman, International Commission for the Protection against Environmental Mutagens and Carcinogens (1989-1995).
President, Environmental Mutagen Society (1978-79)
EMS, Environmental Mutagenesis Recognition Award, 1984.
Toxicology Fellow, The Academy of Toxicological Sciences.
Alumni Achievement Award, Illinois State University, 1994.

Selected for Illinois State University Hall of Fame, 2004.
Illinois State University Distinguished Alumni Award, 2008

PUBLICATIONS

Brusick, D.J.: Reversion of acridine mustard-induced ad-3 mutants of Neurosporacrassa. Mutat. Res., 8:247-254, 1969.

Brusick, D.J.: The mutagenic activity of ICR-170 in Saccharomyces cerevisiae. Mutat. Res., 10:11-19, 1970.

Pittman, D. and Brusick, D.J.: Detection of presumptive basepair substitution and frameshift mutations in Saccharomyces cerevisiae. Molec. Gen., 111:352-356, 1971.

Brusick, D.J. and Legator, M.S.: Utilization of S. cerevisiae in the host-mediated assay. Environ. Mutagen Soc. Newsletter, 4:30, 1971.

Zeiger, E. and Brusick, D.J.: The host-mediated assay: A protocol for Salmonella and Saccharomyces. Environ. Mutagen Soc. Newsletter, 5-32, 1971.

Brockman, H.E., Brusick, D.J. and Ong, T.: Mutagenic activity of acridine mustards in Neurospora crassa. Florida State University Alumni Studies Conference, Vol. II, Session 4, 1971.

Brusick, D.J. and Zeiger, E.: A comparison of chemically induced reversion patterns of S. typhimurium and S. cerevisiae mutants, using in vitro plate tests. Mutat. Res., 14:271-275, 1972.

Brusick, D.J.: Induction of cyclohexamide-resistant mutants in Saccharomyces cerevisiae with N-methyl-N'-nitro-N-nitrosoguanidine and ICR-170. J. Bacteriol., 109:1134-1138, 1972.

Brusick, D.J.: The mutagenic activity of -propiolactone in Saccharomyces cerevisiae. Mutat. Res., 15:425-434, 1972.

Brusick, D.J., Gletten, F. and Weekes, U.: In vitro liver microsome activation of chemical mutagens. Mutat. Res., 21:214, 1973 (Abstract).

Brusick, D.J. and Mayer, V.W.: New developments in mutagenicity screening techniques using yeast. Environ. Health Perspect., 6:83-96, 1973.

Brusick, D. and Andrews, H.: Comparison of the genetic activity of dimethylnitrosamine, ethyl methanesulfonate, 2-acetylaminofluorene, and ICR-170 in Saccharomyces cerevisiae strains D3, D4, and D5 using in vitro assays with and without metabolic activation. Mutat. Res., 26:491-500, 1974.

Gletten, F., Weekes, U. and Brusick, D.: In vitro metabolic activation of chemical mutagens. I. Development of an in vitro mutagenicity assay using liver microsomal enzymes for the activation of dimethylnitrosamine to a mutagen. Mutat. Res., 28:113-122, 1975.

Weekes, U. and Brusick, D.: In vitro metabolic activation of chemical mutagens II. The relationships among mutagen formation, metabolism, and carcinogenicity for dimethylnitrosamine and diethylnitrosamine in the livers, kidneys, and lungs of BALB/cJ, C57B1/6J, and RF/J mice. Mutat. Res., 31:175-183, 1975.

Mayer, V.W., Hybner, C.J. and Brusick, D.J.: Genetic effects induced in Saccharomyces cerevisiae by cyclophosphamide in vitro without liver enzyme preparations. Mutat. Res., 37:201-212, 1976.

Brusick, D., Jagannath, D. and Weekes, U.: The utilization of in vitro mutagenesis techniques to explain strain, age, and sex-related differences in dimethylnitrosamine tumor susceptibilities in mice. Mutat. Res., 41:51-60, 1976.

Brusick, D.: The genetic properties of betapropiolactone. Mutat. Res., 39:241-255, 1977.

Brusick, D. and Matheson, D.: Mutagenic evaluation of 1,1-dimethylhydrazine, methylhydrazine, and n-phenyl- -naphthylamine. In, Proceedings of the 7th Annual Conference on Environmental Toxicology, 13, 14, and 15 October 1976. Aerospace Medical Research Laboratory. Wright-Patterson Air Force Base, OH, pp. 108-129, April 1977.

Brusick, D.J.: The role of short-term testing in carcinogen detection. Chemosphere, 5:403-417, 1978.

Matheson, D., Brusick, D. and Carrano, R.: Comparison of the relative mutagenic activity for eight antineoplastic drugs in the Ames Salmonella/Microsome and TK-/-mouse lymphoma assays. Drug and Chemical Toxicology, 1:277-304, 1978.

Brusick, D.J.: Alterations of germ cells leading to mutagenesis and their detection. Environ. Health Perspect., 24:105-112, 1978.

Brusick, D., Matheson, D., Jagannath, D., Braude, M. and Brockman, H.: Genetic screening of compounds used in drug abuse treatment I. Naltrexone hydrochloride Drug and Chemical Toxicology, 1:103-135, 1978.

PUBLICATIONS (Continued)

Brusick, D.: Genetic toxicology: Testing approaches. In, Proceedings of the 3rd Toxic Substances Control Conference, 4, 5, December 1978. Government Institutes Inc., Washington, D.C., pp. 63-70, December 1978.

Dutta, S.K., Nelson, W.H., Blackman, C.F. and Brusick. D.J.: Lack of microbial and genetic response to 2.45-GHz. CW and 8.5- to 9.6-GHz pulsed Microwaves Power., 14:275-280, 1979.

Brusick, D., Matheson, D., Jagannath, D., Goode, S., Lehowitz, H., Reed, M., Roy, G. and Benson, S.: A comparison of the genotoxic properties of tris (2,3-dibromopropyl) phosphate and tris (1,3-dichloro-2-propyl) phosphate in a battery of short-term bioassays. J. of Environmental Pathology and Toxicology, 3:207-226, 1980.

Brusick, D.: Cellular effects in microbial tester strains caused by exposure to microwaves or elevated temperatures. J. of Environmental Pathology and Toxicology, 3:195-206, 1980.

Jagannath, D.R., D'Addario, A.P. and Brusick, D.: Mutagenic activity of 1-fluoro-2,4-dinitrobenzene in the Ames Test. Mutat. Res., 78:91-95, 1980.

Bakshi, K., Brusick, D.J., Bullock, L.P. and Bardin, C.W.: Regulation of dimethylnitrosamine metabolism by androgenic hormones. Environ. Mutagen., 2:51-57, 1980.

Bakshi, K. and Brusick, D.: Bioactivation of dimethylnitrosamine in intrasanguinous, host-mediated assay and its association with in vitro mutagenesis assays. Mutat. Res., 72:79-89, 1980.

Brusick, D.J., Simmon, V.F., Rosenkranz, H.S., Ray, V.A. and Stafford, R.S.: An evaluation of the Escherichia coli WP_2 and WP_2uvrA reverse mutation assay. Mutat. Res., 76:169-190, 1980

Kirwin, C.J., LeBlanc, J.V., Thomas, W.C., Haworth, S.R., Kirby, P.E., Thilager, A., Bowman, J.T. and Brusick, D.J.: Evaluation of the genetic activity of industrially produced carbon black. J. Toxicol. Environ. Health, 7:973-89, 1981.

Brusick, D., Matheson, D., Jagannath, D., Braude, M., Brockman, H. and Hung, C.: Genetic screening of compounds used in drug abuse treatment II. Methodone Drug and Chemical Toxicology, *4*:1-18, 1981.

Brusick, D., Matheson, D., Jagannath, D., Braude, M., Brockman, H. and Hung, C.: Genetic screening of compounds used in drug abuse treatment III. LAAM Drug and Chemical Toxicology, *4*:19-35, 1981.

Sweeny, J.G., Iacobucci, G.A., Brusick, D. and Jagannath, D.R.: Structure-activity relationships in the mutagenicity of quinone methides of 7-hydroxy-flavylium slats for Salmonella typhimurium. Mutat. Res., 82:275-83, 1981.

Brusick, D.J.: The future of short-term testing for mutagens and carcinogens. In, Trends in Pharmacological Sciences. Elsevier Biomedical Press, New York, 4(3):111-115, March 1983.

Brusick, D.J., et al.: Screening strategy for chemicals that are potential germ-cell mutagens in mammals. Mutat. Res., 114:117-177, 1983.

Hinderer, R.K., Myhr, B., Jagannath, D.R., Galloway, S.M., Mann, S.W., Riddle, J.C., and Brusick, D.J.: Mutagenic evaluations of four rubber accelerators in a battery of in vitro mutagenic assays. Environ. Mutagen., 5:193-215, 1983.

Brusick, D.J.: Mutagenicity and carcinogenicity correlations between bacteria and rodents. Annals NYAS, 164-176, 1983.

Sorenson, W.G., Whong, W., Simpson, J.P., Brusick, D.J., and Ong, T.: Genotoxic properties of 2,4,7-trinitro-9-fluorenone (MR 0793). Mutat. Res., 118:167-176, August 1983.

de la Iglesia, F.A., Lake, R.S., Fitzgerald, J.E., Bueding, E., Brusick, D.: Bacterial mutagenesis and cell transformation assays of pyrvinium pamoate (Povan), an antiparasitic agent. J. Amer. Coll. Toxicol., 3: No. 4:285-294, 1984.

Brusick, D.J.: Current trends in the development of short-term predictive toxicology assays. Concepts Toxicol., 1:190-199, 1984.

Dunkel, V.C., Zeiger, E., Brusick, D., McCoy, E., McGregor, D., Mortelmans, K., Rosenkranz, H.S., and Simmon, V.F.: Reproducibility of microbial mutagenicity assays: I. Tests with Salmonella typhimurium and Escherichia coli using a standardized protocol. Environ. Mutagen., 6: Supplement 2:1-254, 1984.

PUBLICATIONS (Continued)

Brusick, D., and Auletta, A.: Development status of bioassays in genetic toxicology: A report of Phase II of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat. Res., 153:1-10, 1985.

Dunkel, V.C., Zeiger, E., Brusick, D., McCoy, E., McGregor, D., Mortelmans, K., Rosenkranz, H.S., and Simmon, V.F.: Reproducibility of microbial mutagenicity assays: II. Testing of carcinogens and noncarcinogens in Salmonella typhimurium and Escherichia coli. Environ. Mutagen., 7: Supplement 5: 1-248, 1985.

Nemchin, R.G., and Brusick, D.J.: Basic principles of laboratory safety. Environ. Mutagen., 7: Supplement 6: 947-971, 1985.

Brusick, D., Myhr, B., Galloway, S., Rundell, J., Jagannath, D.R., and Tarka, S.: Genotoxicity of cocoa in a series of short-term assays. Mutat. Res., 169:115-121, 1986.

Brusick, D., Myhr, B., Galloway, S., Rundell, J., Jagannath, D.R., and Tarka, S.: Genotoxicity of theobromine in a series of short-term assays. Mutat. Res., 169:105-114, 1986.

Lin, G.H.Y., and Brusick, D.: Mutagenicity studies on FD&C Red No. 3. Mutagenesis, Vol. 1, No. 4: 253-259, July, 1986.

Kier, L.E., Brusick, D.J., Auletta, A.E., Von Halle, E.S., Brown, M.M., Simmon, V.F., Dunkel, V., McCann, J., Mortelmans, K., Prival, M., Rao, T.K., and Ray, V.: The Salmonella typhimurium/mammalian microsomal assay. A Report of the U.S. Environmental Protection Agency Gene-Tox Program. Mutat. Res., 168:69-240, Sept. 1986.

Brusick, D.: Genotoxic effects in cultured mammalian cells produced by low pH treatment conditions and increased ion concentrations. Environ. Mutagen., Vol. 8: No. 6: 879-886, 1986.

Brusick, D.J.: Current Approaches to Toxicity Testing - Status and Prospects. Comments on Toxicology (Comments on Modern Biology Part B) Vol. I, No. 5, 257-264 (1987).

D.M. DeMarini, D.J. Brusick, J. Lewtas: Use of limited protocols to evaluate the genotoxicity of hazardous wastes in mammalian cell assays: Comparison to salmonella. J. Toxicol. and Environ. Health, 22:225-239, 1987.

Brusick, D.J.: Evolution of testing strategies for genetic toxicity. Mutat. Res., 205:69-78, 1988.

Brusick, D.J.: Implications of treatment-condition-induced Genotoxicity Produced in Cultured Mammalian Cell Assays by Treatment Conditions. Mutat. Res., 189:1-6, 1987.

Brusick, D.J., Jagannath, D.R., Myhr, B., Sernau, R., Orr, J.C. and Chappel, C.I.: Genetic toxicology evaluation of commercial beers. I. Development of procedures for the preparation of extracts from commercial beer products. Mutat. Res., 206:33-39, 1988.

Brusick, D.J., Jagannath, B., Myhr, R., Sernau, R., Chappel, C.I.: Genetic toxicology evaluation of commercial beers. II. Mutagenic activity of commercial beer products in Salmonella typhimurium strains TA98, TA100 and TA102. Mutat. Res., 206:41-46, 1988.

Brusick, D.: Role of Metabolism in Short-Term Test Development. Environ. and Mol. Mutagen., Vol. 14, Supplement 16:60-65 (1989).

Brusick, D., Cifone, M., Young, R, Benson, S.: Assessment of the Genotoxicity of Calcium Cyclamate and Cyclohexylamine. Environmental and Molecular Mutagenesis. Vol. 14:188-199 (1989).

Brusick, David: A computer-assisted procedure for the assembly and analysis of short-term genotoxicity test data. In, Toxicology Letters, 49:123-138 (1989).

Myhr, B. and Brusick, D.: A transgenic mouse model for genetic toxicology studies. Lab Animal, *20*: 31-35, 1991.

D. Scott, S.M. Galloway, R.R. Marshall, M. Ishidate, Jr., D. Brusick, J. Ashby and B.C. Myhr: International Commission for Protection Against Environmental Mutagens and Carcinogens. A report from ICPEMC Task Group 9. Mutat. Res., 257:147-204, 1991.

Brusick, D.: A Proposed Method for Assembly and Interpretation of Short-Term Test Data. Environ. Health Perspect., 96: 101-111, 1991.

Brusick, D.J., Ashby, J., de Serres, F.J., Lohman, P.H.M., Matsushima, T., Matter, B.E., Mendelsohn, M.L., Moore, D.H., Nesnow, S. and Waters, M.D.: A method of combining and comparing short-term genotoxicity test data: Preface. A Report from ICPEMC Committee 1. Mutat. Res., 266: 1-6, 1992.

PUBLICATIONS (Continued)

Lohman, P.H.M., Mendelsohn, M.L., Moore D.H., Waters, M.D., Brusick, D.J., Ashby, J. and Lohman, W.J.A.: A method for comparing and combining short-term genotoxicity test data: The basic system. A Report from ICPEMC Committee 1. Mutat. Res., 266:7-25, 1992.
Lin, G.H.Y. and Brusick, D.J.: Mutagenicity Studies on Two Triphenylmethane Dyes, Bromophenol Blue and Tetrabromophenol Blue. J. of Applied Tox., 12: 267-274, 1992.
Ivett, J.L, Brusick, D.J., Young, R.R., Chappel, C.I. and Nestmann E.R.: Genetic toxicology evaluaiton of commercial beers, III. SCE, chromosome aberrations, and forward mutation (HGPRT) of commercial beer products in CHO cells. Mutat. Res., 298:43-51, 1992.
Brusick, D.J., Jagannath, D.R., Galloway, and Nestmann, E.R.: Genotoxicity Hazard Assessment of Caramel Colours III and IV. Food and Chemical Toxic., 30, No. 5, pp. 403-410, 1992.
Murli, H. and Brusick, D.: Induction of Chromosomal Aberrations by High Concentrations of Butylated Hydroxyanisole (BHA) in Chinese Hamster Ovary (CHO) Cells in the Presence of Washed Microsomes. J. of In Vitro Toxicology, 5, No. 2, 1992.
Hoorn, A.J.W., Custer, L.L., Myhr, B.C., Brusick, D., Gossen, J. and Vijg, J.: Detection of chemical mutagens using Muta®Mouse: a transgenic mouse model. Mutagenesis, 8, No. 1, pp. 77-10, 1993.
Brusick, D.J.: Series: Current Issues in Mutagenesis and Carcinogenesis, No. 39. Letter to the Editor from ICPEMC chairman. Mutat. Res., *319*:243-244, 1993.
Brusick, D.J.: Structure - activity relationships in mutation and cancer: A preface from ICPEMC chairman. Mutat. Res., *305*:1, 1994.
Brusick, D.J.: An assessment of the genetic toxicity of atrazine: Relevance to human health and environmental effects. Mutat. Res., 317:133-144, 1994.
Brusick, David: Personal Thoughts on the Future of the Environmental Mutagen Society. Environ. and Mol. Mutagen., 23, Supplement 24:15-17, 1994.
Favor, J., Layton, D., Sega, G., Wassom, J., Burkhart, J., Douglas, G., Dearfield , K. and Brusick, D.: Genetic risk extrapolation from animal data to human disease. Mutat. Res., *330*:23-35, 1995.
Brusick, D.J.: An assessment of the genetic toxicity of atrazine: Relevance to human health and environmental effects, Mutation Research 317 (1994) 133-144.
Dearfield, Kerry L., Douglas, George R., Ehling, Udo H., Moore, Martha M., Sega, Gary A., and Brusick, David J.: Acrylamide: a review of its genotoxicity and an assessment of heritable genetic risk. Mutation Research 330 (1995) 71-99.
Brusick, D., and Mengs, Ulrich: Assessment of the Genotoxic Risk From Laxative Senna Products. Environmental and Molecular Mutagenesis 29:1-9 (1997).
Brusick, D., Albertini, Richard, McRee, Donald, Peterson, Williams, Gary, Hanawalt, Phillip, and Preston, Julian: Genotoxicity of Radiofrequency Radiation. Environmental and Molecular Mutagenesis 32:1-16 (1998).
Goodman, J.Brusick,D.,Busey, W.,Cohen,S., Lamb,J., Starr, T. 2000. Re-evaluation of the Cancer Potency Factor of Toxaphene: Recommendations from a peer review panel. Toxicological Sciences, 55: 3-16.
Anderson. M.E., Meek, M.E., Boorman, G.A., Brusick, D.J., Cohen, S. M., Dragan, Y.P., Frederick, C.B., Goodman, J.I., Hard, G.C., O'Flaherty, E.J., and Robinson, D.E., Lessons learned in applying the US EPA proposed cancer guidelines to specific compounds. Toxicol. Sci., 53: 159-172, 2000.
Brusick, D. Analysis of genotoxicity and the carcinogenic mode of action for ortho-phenyl-phenol. Environ. Molec. Mutagenesis, 45:460-48, 2005.
Henderson, L, Brusick, D., Ratpan, F., Veenstra, G. A review of the genetic toxicology of ethybenzene.. Mutation Research, 635: 81-90, 2007.
Brusick, D. A critical review of the genetic toxicology of steviol and steviol glycosides. Food and Chemical Toxicology, 46 (Supplement 7s): 2008.

Brusick, D. A critical review of the genetic toxicity of Naphthalene.. Regulatory Toxicology and Pharmacology, 51 (Supplement 1): 37-42. 2008.
Brusick, D., M. Small, E. Cavalieri, J. Nakamura, E. Rogan, and J. Swenberg. Possible genotoxic modes of action for naphthalene. Regulatory Toxicology and Pharmacology, 51 (Supplement 1): 43-50, 2008.
Brusick, D., J Borzelleca, M. Gallo, G. Williams, J. Kille, A. Wallace Hayes, F. Xavier Pi-Sunyer, C. Williams and W. Burks, Expert panel report on a study of splenda in male rats. Regulatory Toxicology and Pharmacology, 55: 6-12, 2009.
Brusick, D.J., A Perspective on Testing of Existing Pharmaceutical Excipients for Genotoxic Impurities, Regulatory Toxicology and Pharmacology, 55: 200-204, 2009.
Brusick, D., Grotz, V.L., Slesinski, R., Kruger, C., Hayes, A.W., The absence of genotoxicity of sucralose, Food Chemical Toxicology 48: 3067-3072, 2010.
Simpkins et al Atrazine and Breast Cancer: A Framework Assessment of the
Toxicological and Epidemiological Evidence. TOXICOLOGICAL SCIENCES 123(2), 441–459 (2011)
Urban, JD, Carakostas MC, Brusick DJ. 2013. Steviol glycoside safety: is the genotoxicity database sufficient? Food Chem. Toxicol. ;51:386-390.

BOOK CHAPTERS

Brusick, D., Bakshi, K. and Jagannath, D.R.: The application of in vitro mutagenesis techniques to investigations of comparative metabolism in mice. In, *In Vitro Metabolic Activation in Mutagenesis Testing*, F.J. de Serres, et al., (Ed.), Elsevier North Holland Biomedical Press, Amsterdam, pp. 125-141, 1976.
Brusick, D.: In vitro mutagenesis assays as predictors of chemical carcinogenesis in mammals. In, *Toxicology Annual,* C.L. Winek (Ed.), Volume 2, Marcel Dekker, Inc., New York, pp. 79-109, 1977. Clin. Tox., 10:79-109, 1977.
Brusick, D.J.: The value and significance of carcinogenic, mutagenic, and teratogenic tests. In, *Cutaneous Toxicity*, V.A. Drill and P. Lazar (Eds.), Academic Press, NY, pp. 189-201, 1977.
Bakshi, K., Brusick, D., Bullock, L. and Bardin, C.W.: Hormonal regulation of carcinogen metabolism in mouse kidney. In, *Origins of Human Cancer.* Cold Spring Harbor Laboratory, NY, 6:683-695, 1977.
Brusick, D.J.: Observations and recommendations regarding routine use of bacterial mutagenesis assay as indicators of potential chemical carcinogens. In, *Strategies for Short-Term Testing for Mutagens/Carcinogens,* B.E. Butterworth, (Ed.), CRC Press, Inc., pp. 3-12, 1979.
Brusick, D.: Bacterial Mutagenesis and its role in the identification of potential animal carcinogens. In, *Carcinogens: Identification and Mechanisms of Action,* A.C. Griffin and C.R. Shaw (Eds.), Raven Press, New York, pp. 93-105, 1979.
Brusick, D.J., Matheson, D.W. and Jagannath, D.R.: Commercial screening of environmental chemicals. In, *Chemical Mutagens: Principles and Methods for their Detection*, F.J. de Serres and A. Hollaender (Eds.), Plenum Press, NY, Volume 6, pp. 81-107, 1980.
Brusick, D.: Unified scoring system and activity definitions for results from in vitro and submammalian mutagenesis test batteries. In, *Health Risk Analysis*, C.R. Richmond, P.J. Walsh and E.D. Copenhaver (Eds.), Franklin Institute Press, Philadelphia, pp. 273-286, 1981.
Brusick, D.J., de Serres, F., Everson, R., Mendelsohn, M., Neel, J., Shelby, M., and Waters, M.: Monitoring the human population for mutagenic effects: Detection of gene mutations and DNA damage. In, *Guidelines for Studies of Human Populations Exposed to Mutagenic and Reproductive Hazards*, Arthur D. Bloom (Ed.), March of Dimes Birth Defects Foundation, pp. 111-140, 1981.
Jagannath, D.R., Vultaggio, D.M. and Brusick, D.J.: Genetic activity of 42 coded compounds in the mitotic gene conversion assay using Saccharomyces cerevisiae strain D_4. In, *Progress in Mutation Research, Vol. I, Evaluation of Short-Term Tests for Carcinogens,* F.J. de Serres and J. Ashby (Eds.), Elsevier North Holland, Inc., New York, pp. 456-467, 1981.
Brusick, D.J.: Value of short-term mutagenicity tests in human population monitoring. In, *Progress in Mutation Research, Vol. III, Chemical Mutagenesis, Human Population Monitoring and Genetic Risk*

Assessment, K.C. Bora, G.R. Douglas and R.R. Nestmann (Eds.), Elsevier Biomedical Press, New York, pp. 125-135, 1982.

Williams, G.M., Weisburger, J.H. and Brusick, D.: The role of genetic toxicology in a scheme of systematic carcinogen testing. In, *The Pesticide Chemist and Modern Toxicology*, S.K. Bandal, G.J. Marco, L. Goldberg and M.L. Leng (Eds.). ACS Symposium Series, American Chemical Society, Washington, D.C., pp. 57-88, 1981.

Brusick, D.: Genetic toxicology. In, *Principles and Methods of Toxicology*, A.W. Hayes (Ed.), Raven Press, New York, pp. 223-272, 1982.

Brusick, D.: Evaluation of chronic rodent bioassays and Ames assay test as accurate models for predicting human carcinogens. In, *Application of Biological Markers to Carcinogen Testing*, H.A. Milman and S. Sell (Eds.), Plenum Publishing Corporation, pp. 153-163, 1983.

Brusick, D.J.: Mutagenesis and carcinogenesis in mammalian cells. In, A *Guide to General Toxicology*, F. Homburger, J.A. Hayes and E.W. Petikan (Eds.), Karger Continuing Education Series, Basel, pp. 326-343, 1983.

Jagannath, D.R. and Brusick, D.J.: Mutagens and carcinogens in bacteria. In, *A Guide to General Toxicology*, F. Homburger, J.A. Hayes and E.W. Pelitsan (Eds.), Harger Continuing Education Series, Basel, pp. 344-363, 1983.

Brusick, D.J.: Genetic and transforming activity of formaldehyde. In, *Formaldehyde Toxicity,* J.E. Gibson (Ed.), Hemisphere Publishing Corp., New York, pp. 72-84, 1983.

Brusick, D.J.: The use of short term in vitro and submammalian tests as alternatives to large scale animal bioassays. In, *Annals of the New York Academy of Sciences*, pp. 68-73, 1983.

Brusick, D.J.: Genetic toxicology: Applications and testing strategies. In, *Carcinogenesis and Mutagenesis Testing,* J.F. Douglas (Ed.), Human Press, Clifton, New Jersey, pp. 7-16, 1984.

BOOK CHAPTERS (Continued)

Brusick, D.J.: Consequences of genotoxic effects. In, *Carcinogenesis and Mutagenesis Testing*, J.F. Douglas (Ed.), Humana Press, Clifton, New Jersey, pp. 17-38, 1984.

Brusick, D.J.: Yeast assays in mutagen and carcinogen screening. In, *Carcinogenesis and Mutagenesis Testing,* J.F. Douglas (Ed.), Humana Press, Clifton, New Jersey, pp. 199-205, 1984.

Brusick, D.J.: Chinese hamster ovary mutation assays. In, *Carcinogenesis and Mutagenesis Testing*, J.F. Douglas (Ed.), Humana Press, Clifton, New Jersey, pp. 227-233, 1984.

Brusick, D.J.: *Drosophila* assay systems. In, *Carcinogenesis and Mutagenesis Testing*, J.F. Douglas (Ed.), Humana Press, Clifton, New Jersey, pp. 235-242, 1984.

Brusick, D.J.: Detection of DNA damage and repair in bacteria. In, *Carcinogenesis and Mutagenesis Testing*, J.F. Douglas (Ed.), Humana Press, Clifton, New Jersey, pp. 245-250, 1984.

Brusick, D.J.: Mammalian DNA repair assays. In, *Carcinogenesis and Mutagenesis Testing*, J.F. Douglas (Ed.), Humana Press, Clifton, New Jersey, pp. 251-262, 1984.

Brusick, D.J.: Cytogenetic assays: aberrations and SCE techniques. *In, Carcinogenesis and Mutagenesis Testing,* J.F. Douglas (Ed.), Humana Press, Clifton, New Jersey, pp. 265-276, 1984.

Brusick, D.J.: New developments in short-term tests for carcinogenicity: Genetic toxicology testing. In, *Chemical Induction of Cancer: Structural Basis and Biological Mechanisms.* Volume 3B, *Aliphatic and Polyhalogenated Carcinogens.* by Wu, Y., Lai, D.Y., Arcos, J.C., and Arcos, M.F., Academic Press, Orlando, Fla., pp. 481-521, 1985.

Brusick, D.J.: Genotoxicity of hexachlorobenzene and other chlorinated benzenes. In, *Hexachlorobenzene: Proceedings of An International Symposium held at IARC*, Lyon France 24-28 June 1985, C.R. Morris and J.R.P. Cabral (Eds.), IARC Scientific Publications No. 77 (distributed by Oxford University Press, Oxford, UK), pp. 393-397, 1986.

Brusick, D.J., Ashby, J., de Serres, F., Lohman, P., Matshushima, T., Matter, B., Mendelsohn, M., Waters, M.: Weight-of-Evidence Scheme for Evaluation and Interpretation of Short-Term Results. In, *Genetic Toxicology of Environmental Chemicals, Part B: Genetic Effects and Applied Mutagenesis,* C. Ramel, B. Lambert, J. Magnusson (Eds.), Alan R. Liss, Inc., N.Y., Volume 209B, pp. 121-129, 1986.

Hart, R.W., Brusick, D.: Assessment of the Hazard of Genetic Toxicity. In, *Toxic Substances and Human Risk -Principles of Data Interpretation,* R.G. Tardiff and J.V. Rodricks (Eds.), Plenum Press, New York, pp. 339-355, 1987.

Brusick, D.: Genetic Toxicology. In, *Principles and Methods of Toxicology*, Second Edition, A. Wallace Hayes (Eds.), Raven Press, Ltd., N.Y., pp. 407-434, 1989.
Brusick, D.: Methods of Genetic Toxicology Testing Strategies. In, *New Trends in Genetic Risk Assessment*. Academic Press, London, 1989.
Brusick, D.J.: Environmental Mutagenesis: An Assessment of the Past Twenty Years. In, *Mutation and the Environment,* Wiley-Liss, Inc., Part A, pp. 1-16, 1990.
Brusick, D.J.: Carcinogenicity: The Use of Animal Models and Short-Term Predictive Tests. In, *In Vitro Toxicity Testing,* Marcel Dekker, Inc., New York, pp. 221-244, 1992.
Brusick, D.: Genotoxicity of Phenolic Antioxidants. In, *Antioxidants: Chemical, Physiological, Nutritional and Toxicological Aspects.* Princeton Scientific Publishing Co., Inc., Princeton, NJ, pp. 223-230, 1993.
Brusick, D.: Genetic Toxicology. In, *Principles and Methods of Toxicology,* Third Edition, A. Wallace Hayes (Eds.), Raven Press, Ltd., N.Y., pp. 545-577, 1994.
Brusick, D.: Genetic Toxicology. In, *Principles and Methods of Toxicology*, Fourth Edition, A. Wallace Hayes (Eds.), Raven Press, Ltd., N.Y., pp. 545-577, 2001.
Brusick, D.: Genetic Toxicology, In, *Toxicology,* Marquardt, H., Schafer, S, McClellan, R., Welsh, F. (Eds). Academic Press, N.Y., pp 127-149, 1999.
Brusick, D.J.: Applications for transgenic animals in toxicology. In, *Toxicology in Transition*: Proceedings of the 1994 EUROTOX Congress Meeting held in Basel, Switzerland, August 21-24, 1994, G.H. Degen, J.P. Seiler and P. Bentley (Eds.), Archives of Toxicology, Supplement 17, Springer-Verlag, Berlin Heidelberg, pp. 23-34, 1995.
Brusick, D. Genetic Toxicology and Regulatory Policy. In, *Toxicology and Regulatory Process*, S. Green, ed. Taylor & Francis Group, NY, pp 261-281, 2006.
Brusick, D., Fields, W., Myhr, B. and Doolittle, D.: Genetic Toxicology. In, *Principles and Methods of Toxicology,* Fifth Edition, A. Wallace Hayes (Eds.), Raven Press, Ltd., N.Y., pp. 545-577, 2001.
Brusick, D., Fields, W.: Genetic Toxicology Chapter. In, *Principles and Methods of Toxicology,Sixth* Edition, A. Wallace Hayes (Ed.), Raven Press, Ltd., N.Y., 2014.

BOOKS

- Principles of Genetic Toxicology, Brusick, D.J., Plenum Press, New York, 1980: (Second Edition 1987).
- Assessing The Risk of Genetic Damage, Brusick, D.J., Gopalan, H.N.B., Heseltine, E., Huismans, J.W., and Lohman, P.H.M., Hodder & Stoughton, Gaborone London Sydney Auckland, 1993.
- Methods for Genetic Risk Assessment, Brusick, David J., Lewis Publishers, 1994.

Burns

Harvard Medical School Curriculum Vitae

Date Prepared: **September 21, 2015**

Name: **Michele M. Burns, MD, MPH, FAAP, FACMT, FACCT**

Office Address: Boston Children's Hospital
Division of Emergency Medicine/Medical Toxicology
300 Longwood Avenue
Boston, MA 02115

Home Address: [redacted]
Belmont, MA [redacted]

Work Phone: [redacted]

Work Email: michele.burns@childrens.harvard[redacted]

Work FAX: [redacted]

Education

1983-1987	B.S.	Biology	Emory University, Atlanta GA
1988-1992	M.D.	Medicine	Emory University School of Medicine, Atlanta GA
2010-2013	M.P.H.	Clinical Effectiveness	Harvard School of Public Health, Boston MA

Postdoctoral Training

1992-1993	Intern	Pediatrics	Children's Medical Center, Dallas TX
1993-1995	Resident	Pediatrics	Children's Medical Center, Dallas TX
1995-1997	Clinical Fellow	Pediatrics	Harvard Medical School
1995-1997	Clinical Fellow	Medicine	Boston Children's Hospital
1995-1999	Fellow	Pediatric Emergency Medicine	Boston Children's Hospital
1997-1999	Fellow	Clinical Pharmacology/Toxicology	Children's Hospital, Massachusetts Poison Control Center, Boston MA

Faculty Academic Appointments

1997-2006	Instructor	Pediatrics	Harvard Medical School
2002-	Adjunct Assistant Professor	Pharmacy Practice	School of Pharmacy-Boston, Massachusetts College of Pharmacy and Allied Health Sciences
2007-	Assistant Professor	Pediatrics	Harvard Medical School
2015-	Assistant Professor	Emergency Medicine	Harvard Medical School

Appointments at Hospitals/Affiliated Institutions

1997-	Assistant	Medicine	Boston Children's Hospital
1999-	Staff Physician	Emergency Medicine	Boston Children's Hospital

Major Administrative Leadership Positions

Local

2001-	Medical Director	MA & RI Poison Control Center
2001-	Chief: Program in Medical Toxicology	Boston Children's Hospital
2002-	Fellowship Director: Harvard Medical Toxicology Fellowship	Harvard Medical School

Committee Service

Local

2004-	Pharmacy & Therapeutics	Boston Children's Hospital
	2004-	Formulary Subcommittee
2010-	"The Academy"	Harvard Medical School
	2010-	Member

Professional Societies

1992-	American Academy of Pediatrics	
	1992-	Member
1997-	Ambulatory Pediatric Association	
	1997-	Member
1997-	American Academy of Clinical Toxicology	
	1997-	Member
	1999-	Pediatric Special Interest Group
	2010-	Fellow
1999-	American Academy of Pediatrics: Section on Emergency Medicine	
	1999-	Member
1999-	American Academy of Pediatrics: Section on Injury, Violence and Poison Prevention	
	1999-	Member
	2010-	Executive Council
2001-	American Academy of Pediatrics	
	2001-	Fellow
2002-	American College of Medical Toxicology	
	2002-	Education Subcommittee
	2007-	Fellow
	2010-	Board of Directors

2008-	Association of Pediatric Program Directors	
	2008-	Member

Editorial Activities

Ad hoc Reviewer

2000- *Pediatrics*
2001- *Pediatrics in Review*
2002- *Journal of Toxicology: Clinical Toxicology*
2004- *The Journal of Medical Toxicology*
2007- *Pediatric Emergency Care*
2008- *Annals of Emergency Medicine*
2010- *Clinical Pharmacology & Therapeutics*
2010- *New England Journal of Medicine*

Other Editorial Roles

2001	Contributing Editor	*Poisindex*
2007-2008	Editorial Board	*ToxED*
2009-	Pediatric Toxicology Section Editor	*UptoDate*
2012-	ABEM Medical Toxicology Subboard	

Honors and Prizes

1995	Pediatric Resident Best Research Award	Children's Medical Center of Dallas	Analytical Research Skills & Methodology
2009	Gary R. Fleisher Best Teaching Award	Boston Children's Hospital Emergency Department	Clinical Teaching Excellence
2013	Professionalism Award	Boston Children's Hospital Emergency Department	Compassionate Care Boston Marathon Patients
2014	Affiliate Attending Teaching Award	Beth Israel Deaconess Medical Center Emergency Department	Clinical Teaching Excellence
2015	Janeway Teaching Award	Boston Children's Hospital	Clinical Teaching Excellence

Report of Funded and Unfunded Projects

Funding Information

Past

1997 Clinical Research in Activated Charcoal $1,500
Industry Award (Requa, Inc.) / Individual Research Project
PI ($1,500)
Study acceptance rates of activated charcoal in children ≤ 5 years of age

1997 American Academy of Clinical Toxicology Postdoctoral Fellowship Award for Toxicological Research
Postdoctoral Fellowship Award
PI ($7,500)
Examine surface areas of various commercially available activated charcoal preparations

9/2001-8/2004	Poison Control Stabilization and Enhancement Program HRSA (H4BMC00050-01) PI ($1,187,729) Provide clinical expertise in the medical diagnosis, management and prevention of poisonings by maintaining a standard of excellence in research, professional development and public education
9/2001-8/2003	A Proposal to Develop Region Wide Improvements in Poison Control: A New England Consortium HRSA (H4BMC00055-01) PI ($250,000) Develop essential public healthcare infrastructure to facilitate timely communication between the 3 Poison Centers based in New England
4/2003	General Clinical Research Center grant NIH/Children's Hospital Boston PI ($5,000) Investigate the interference from carbamazepine (Tegretol) and oxcarbazepine (Trileptal) with screening urine and serum assay for tricyclic antidepressants
9/2003-8/2007	An Expanded New England Consortium of Poison Control Centers: Addressing Concerns Regarding Low-Intensity Environmental Exposures HRSA (H4BMC00934-01) PI ($300,000) Update and enhance staff's existing knowledge bases regarding pertinent environmental toxicology issues for local New England communities
9/2004-8/2007	Poison Control Stabilization and Enhancement Program HRSA (2H4BMC00050-04-00) PI ($1,399,155) Provide clinical expertise in the medical diagnosis, management and prevention of poisonings by maintaining a standard of excellence in research, professional development and public education.
9/2007-8/2010	Poison Control Stabilization and Enhancement Program HRSA (H4BH500050-08-00) PI ($1,730,048) Provide clinical expertise in the medical diagnosis, management and prevention of poisonings by maintaining a standard of excellence in research, professional development and public education.
9/2007-8/2010	Substance Abuse Surveillance/Reporting System HRSA (1U4BH508564-01-00) Co-PI ($353,390) Participate in substance abuse real-time case surveillance efforts utilizing our National Poison Data System as well as local Department of Public Health partner agencies to look for trends and anomalies in Center call volume.

9/2010 – 8/2013	Poison Control Stabilization and Enhancement Program HRSA (6 H4BHS15490-03-01) PI ($1,533,321) Provide clinical expertise in the medical diagnosis, management and prevention of poisonings by maintaining a standard of excellence in research, professional development and public education.
9/2013-8/2016	HRSA (H4BHS15490-07-00) PI ($1,278,513) Provide clinical expertise in the medical diagnosis, management and prevention of poisonings by maintaining a standard of excellence in research, professional development and public education.

Report of Local Teaching and Training

Teaching of Students in Courses

2002-	Principles of Toxicology - EH 504 25 graduate students	Harvard School of Public Health 1 hour lecture Prep time 4 hours per year
2012-	Clinical Pharmacology and Therapeutics PHM 350 100 medical students	Harvard Medical School 2 hour lecture Prep time 10 hours per year

Formal Teaching of Residents, Clinical Fellows and Research Fellows (post-docs)

1995-	Fellow/Staff Mock Code Lecture Series: Pediatric Emergencies + Toxicology 5-15 pediatric residents and Harvard Medical students	Division of Emergency Medicine, Boston Children's Hospital 1 hour lecture Prep time 2 hours per year
1997-	Fellow/Staff Core Lecture Series: Toxicology Emergencies 15-30 pediatric emergency medicine physicians	Division of Emergency Medicine, Boston Children's Hospital 1 hour lecture Prep time 3 hours per year

Clinical Supervisory and Training Responsibilities

2001-	Poison Center/Medical Toxicology Rotation	1 Harvard Medical student 4 hours per week 50 Harvard Medical School students per year

2001-	Poison Center/Medical Toxicology Rotation	4 residents and/or fellows per month 50 Emergency Medicine Residents and Pediatric EM Fellows per year

Formally Supervised Trainees

2001-2003	**Steven Salhanick, MD** / Assistance Professor of Medicine, Harvard Medical School; Emergency Medicine/Toxicology Attending, Beth Israel Deaconess Medical Center Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that allowed both board certification in Medical Toxicology and also development of research interest in acetaminophen poisoning
2002-2004	**Heikki Nikkanen, MD** / Instructor of Medicine, Harvard Medical School; Emergency Medicine/Toxicology Attending, Mt. Auburn Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that allowed both board certification in Medical Toxicology and also development of research interest in cardiovascular poisons
2003-2005	**Melisa Lai Becker, MD** / Instructor of Medicine, Harvard Medical School; Emergency Medicine/Toxicology Attending, Cambridge Hospital; Chief-The Whidden Hospital Emergency Department; Toxicology Program Director, Cambridge Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that allowed both board certification in Medical Toxicology and also development of interest in program clinical growth and administration
2004-2006	**Ann-Jeannette Geib, MD** /Clinical Assistant Professor of Emergency Medicine, UMDNJ Emergency Medicine/Toxicology Attending, UMDNJ-Newark, NJ Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that allowed both board certification in Medical Toxicology and also development of research interest in intralipid therapy
2006-2008	**Mathew George, MD** / Private Practice Pediatrics Middleton, New York Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that allowed both board certification in Medical Toxicology and also development of application of poisoning prevention to private practice
2007-2009	**Nadeem Al-Duaij, MD, MPH** / Instructor of Medicine, Harvard Medical School; Emergency Medicine/Toxicology Attending, Milton Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that will allow for both board certification in Medical Toxicology and also development of research interest in international antidotes
2007-2009	**Katie O'Donnell, MD** / Instructor of Pediatrics, Harvard Medical School; Toxicology & Hospitalist Medicine Attending, Boston Children's Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that allowed for both board certification in Medical Toxicology and also development of research interest in pediatric poisonings
2008-2010	**Nilam Patil, DO** / Clinical Fellow in Toxicology, Children's Hospital Boston Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that will allow for both board certification in Medical Toxicology and also development of research interest in toxicology screen interpretation
2009-2011	**Kishan Kapadia, DO** / Clinical Fellow in Toxicology, Children's Hospital Boston Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that will allow for both board certification in Medical Toxicology and also development of research interest in EKG/tricyclic antidepressant poisonings

2010-2012	**Russ Berger, MD**/ Instructor of Medicine, Harvard Medical School Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that allowed for both board certification in Medical Toxicology and also development of research interest in dabigatran anticoagulant adverse effects.
2011-2013	**May Yen, MD**/Clinical Fellow in Toxicology, Boston Children's Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that will allow for both board certification in Medical Toxicology and also development of research interest in pediatric sulfonylurea ingestions.
2012-2014	**Diana Felton, MD**/Clinical Fellow in Toxicology, Boston Children's Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that will allow for both board certification in Medical Toxicology and also development of research interest in overdoses that mimic brain death.
2013-2015	**Rebeccal Bruccoleri, MD**/Clinical Fellow in Toxicology, Boston Children's Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that will allow for both board certification in Medical Toxicology and also development of research interest in xenobiotics with clinically significant EKG changes.
2014-2016	**Bradley Demeter, MD**/Clinical Fellow in Toxicology, Boston Children's Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that will allow for both board certification in Medical Toxicology and also development of research interest in predictors of toxicity in pediatric clonidine ingestions.
2015-2017	**Michael Toce, MD**/Clinical Fellow in Toxicology, Boston Children's Hospital Harvard Medical Toxicology Fellowship Director; provide clinically robust curriculum and mentorship that will allow for both board certification in Medical Toxicology and also development of research interest in predictors of toxicity in pediatric buprenorphine ingestions.

Formal Teaching of Peers (e.g., CME and other continuing education courses)

1998	Emergency Medicine into the 21st Century. "Pediatric Overdoses: Management and Strategies" Massachusetts General Hospital and Brigham & Women's Hospital CME Course	Single One Hour Lecture Boston, MA
2004	Review of Pediatric Toxicology American College of Emergency Physicians: Life-Long Learning CME	Single One Hour Lecture Boston, MA
2009	Pediatric Toxicology Updates Massachusetts General Hospital: Emergencies & Procedures in Pediatrics	Single One Hour Lecture Boston, MA
2012	Updates in Pediatric Toxicology BCH Division of Emergency Medicine CME Course	Single 45 Minute Lecture Boston, MA
	Pediatric Toxicology-One Pill can Kill BCH Division of Emergency Medicine CME Course	Single 45 Minute Lecture Boston, MA

Local Invited Presentations

1998-	Certified Specialists in Poison Information Annual Board Review Course / Lecture MA & RI Poison Control Center
1999	Pediatric Firm Rounds Seminar: Herbal Preparations & Theophylline resulting in Ventricular Tachycardia / Lecture Children's Hospital Boston
2000-	Harvard Affiliated Emergency Medicine Residency Lecture Series: Pediatric Toxicology / Lecture Brigham & Women's Hospital, Massachusetts General Hospital
2001-	Beth Israel Emergency Medicine Residency Lecture Series: Pediatric Toxicology / Lecture BIDMC
2002	Toxicology & Pediatric Advanced Life Support / Anesthesia Grand Rounds Children's Hospital Boston
2007	Updates in Pediatric Toxicology / Pediatric Grand Rounds Children's Hospital Boston
2009	Bites & Stings / Pediatric Grand Rounds Children's Hospital Boston
2012	Pediatric Toxicology Updates/Emergency & Critical Care Communication Didactic Series Boston Children's Hospital
2012	Poison Prevention Week: Impact of Adult Prescription Use on Pediatric Ingestions Massachusetts State House/Department of Public Health
2013	Poison Prevention Week: The Opioid Epidemic Massachusetts State House/Department of Public Health
2014	Poison Prevention Week: Poisoning Prevention Strategies Massachusetts State House/Department of Public Health
2015	Poison Prevention Week: Medication Safety

Report of Regional, National and International Invited Teaching and Presentations

Invited Presentations and Courses

Regional

Those presentations below sponsored by outside entities are so noted and the sponsor is identified

1996 American Academy of Pediatrics Annual Meeting, Section on Emergency Medicine. Platform case presentation for the Emergi-Quiz Fellows' Competition: "Weakness in a 15 year old trauma patient" / Case Presentation / Lecturer
Boston, MA

1997- Toxicology Lecture to Pharmacy Students / Lecture / Lecturer
Boston, MA (Massachusetts College of Pharmacy and Allied Health)

2002-2003 New England Regional Toxicology Conference: Poisoning Case Studies / Lecture Lecturer and Course Director
Boston, MA (New England Poison Control Center Consortium)

2005 "Pediatric Toxicology: Antidotes and the Evidence Behind Them" / Grand Rounds
Hasbro Children's Hospital, Rhode Island

2005 "Pediatric Toxicology Emergencies" / Grand Rounds
Framingham Metrowest Hospital, MA

2005 "Pitfalls in Pediatric Poisoning" / Grand Rounds
Connecticut Children's Hospital

2006 "Agents of Opportunity" Bioterrorism Course / Invited Lecturer
Hasbro Children's Hospital, Rhode Island (American College of Medical Toxicology)

2007 "Agents of Opportunity" Bioterrorism Course / Invited Lecturer
Berkshire Medical Center, MA (American College of Medical Toxicology)

2007 "Updates in Pediatric Toxicology" / Grand Rounds
South Shore Hospital, MA

2008 "Poison Centers and NBC Antidotes" / Invited Lecturer
Boston, MA (Massachusetts Department of Public Health)

2010 "Agents of Opportunity" Bioterrorism Course / Invited Lecturer
Hanscomb Air Force Base, Lexington, MA (American College of Medical Toxicology)

2011 "Pediatric Toxicology Updates"/Pediatric Grand Rounds
South Shore Hospital S. Weymouth, MA

2012 "Updates in Pediatric Poisonings"/Grand Rounds
Holy Family Hospital Methuen, MA

2013 "Updates in Pediatric Substance Abuse"/Pediatric Grand Rounds
South Shore Hospital S. Weymouth, MA

National

1999 Herbal Toxicities Workshop / Invited Lecturer
San Francisco, CA (Pediatric Academic Societies' Annual Meeting)

2004 Workshop on Nuclear, Biological, and Chemical Terrorism Exposures: Diagnosis, Treatment Recommendations, and State-of-the-Art Resources / Invited Lecturer
San Francisco, CA (Pediatric Ambulatory Societies' Annual Meeting)

2004 Plenary Session: Digoxin Poisoning - Who Needs Treatment? / Invited Lecturer
Seattle, WA (American College of Medical Toxicology Annual Symposium)

2004 Plenary Session: Pediatric Arsenic Poisoning/Invited Lecturer
Seattle, WA (American Academy of Clinical Toxicology Acute Care Symposium)

2004 Plenary Session "CNS and Pyschotropic Drugs" American College of Medical Toxicology Board Review Course / Invited Lecturer
Dallas, TX (American College of Medical Toxicology)

2005 Industrial Toxicology North American Congress of Clinical Toxicology Annual Meeting / Case Presentation
Orlando, FL (American College of Medical Toxicology)

2006 Plenary Session "Analgesics & Antimicrobials" American College of Medical Toxicology Board Review Course / Invited Lecturer
Dallas, TX (American College of Medical Toxicology)

2010 "Pediatric Toxicology Updates"/ Grand Rounds
Mt. Sinai Medical Center, New York, NY

2010 "Neonatal Abstinence Syndrome" American College of Medical Toxicology Symposium
North American Congress Clinical Toxicology Annual Meeting, Denver CO

2011 Plenary Session: "Weight Loss Drug Abuse in Teenagers: The Skinny"
American College of Medical Toxicology Annual Meeting, Clearwater FL

2011 Panel Discussion: "Drugs of Abuse: Pediatric Clinical Cases"
American College of Medical Toxicology Annual Meeting, Clearwater FL

2011 Plenary Session: "Recreational Drug Toxicity: A Pediatric Perspective"
European Association of Poison Centers and Clinical Toxicologists Annual Congress, Dubrovnik, Croatia

2011 Plenary Session: "Updates in Pediatric Toxicology"
Managing Medical Emergencies Medical Conference: Elliot Hospital, Manchester NH

2012 Plenary Session: "Pediatric Opioid Toxicity"

American College of Medical Toxicology Annual Meeting, San Diego, CA

2014 Plenary Session: "The Field of Medical Toxicology"
American College of Medical Toxicology Annual Meeting, Phoenix, AZ

Report of Clinical Activities and Innovations

Current Licensure and Certification

Licensure

1995 Commonwealth of Massachusetts
1997 State of Georgia (Inactive)

Board Certification

1993 National Board of Medical Examiners
1995 American Board of Pediatrics
2002 American Board of Pediatrics Re-certification
2002 Pediatric Emergency Medicine SubBoard certification
2002 Medical Toxicology SubBoard certification
2012 Medical Toxicology SubBoard Re-certification
2012 Pediatric Emergency Medicine SubBoard Re-certification
2012 American Board of Pediatrics Re-certification

Other Certification

1993 Neonatal Resuscitation Certification
1995 Massachusetts Controlled Substances Registration
1995 Advanced Cardiac Life Support Certification
1996 Basic Life Support Re-certification
1997 Drug Enforcement Administration Registration
1998 Pediatric Advanced Life Support Provider Re-certification
1999 Advanced Trauma Life Support Certification
2004 Pediatric Advanced Life Support Instructor Certification
2006 National Provider Identifier (NPI)
2010 Pediatric Advanced Life Support/ Advanced Cardiac Life Support Re-Certification
2012 Pediatric Advanced Life Support/ Advanced Cardiac Life Support Re-Certification
2014 Pediatric Advanced Life Support/ Advanced Cardiac Life Support Re-Certification

Practice Activities

1999-	Staff Physician, Emergency Medicine	Children's Hospital Boston Emergency Department	Full-time (1-2 shifts per week including nights, holidays and weekends)
2000-	Program Chief, Toxicology	Children's Hospital Boston	Full-time (admitting attending physician 80% of month)
2000-	Medical Director	Massachusetts & Rhode Island Poison Center	Full-time (daily case review, medical back-up to staff 24/7)

Report of Education of Patients and Service to the Community

Activities

2001- American Association of Poison Control Centers
Annual Poison Prevention Week Outreach to Underserved Populations

Report of Scholarship

Publications

Peer reviewed publications in print or other media

1. Chumpa A, Kaplan R, **Burns M**, Shannon M. Nalmafene for elective reversal of pediatric sedation in children. Am J Emerg Med 2001;19: 545-48.

2. Saidinejad M, Law T, **Burns Ewald M**. Interference by carbamazepine and oxcarbazepine with serum and urine screening assays for tricyclic antidepressants. Pediatrics 2007; 120 (3): e504-9.

3. Pories S, Bard T, Bell S, Borus J, Brodsky D, **Burns M**, Catic A, Fazio S, Fisher J, Frontado L, Garfield J, Huang G, Peters A, Pian-Smith M, Quan S, Schwaitzberg S. A Writer's Toolkit. MedEdPORTAL, Association of American Medical Colleges; 2012. Available September 2012 from: www.mededportal.org/publication/9238.

4. Levine M, Froberg B, Ruha AM, **Burns Ewald M**, Yen M, Claudius IA, Arthur AO, Tormoehlen L, Thomas SH. Assessing the toxicity and associated costs among pediatric patients admitted with unintentional poisonings of attention-deficity/hyperactivity disorder drugs in the United States. Clin Toxicol 2013; 51(3):147-50.

5. Burghardt L, Brownstein J, **Burns Ewald M**, Bronstein A, Bourgeois FT. Impact of adult prescription drug use on pediatric exposures and ingestions. Pediatrics 2013; 132 (1) 18-27.

6. Tay KY, **Burns Ewald M**, Bourgeois FT. Use of QT prolonging medications in US Emergency Departments, 1995-2009. Pharmacoepidemiology & Drug Safety. 2014; 23 (1); 9-17.

7. Lebowitz M, Olson K, **Burns M**, Harper M, Bourgeios F. Drug-Drug interactions among hospitalized children receiving chronic antiepileptic drug therapy. Pediatric Hospitalist (Accepted with revisions-August 2015.

Non-peer reviewed scientific or medical publications/materials in print or other media

1. **Burns M**. Activated charcoal as the sole intervention for treatment after childhood poisoning. Current Opinion In Pediatrics: Therapeutics and Toxicology section. 2000;12: 166-71.

2. **Burns M**. Advances and Controversies in Pediatric Toxicology: Herbal Preparations. Clin Pediatr Emerg Med 2000;1:186-190.

3. **Burns M**. Toxicology. In: Sharma S, Wang V, editors. Review for Textbook of Pediatric Emergency Medicine. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 254-63.

4. **Burns M**. Unusual Odors. In: Sharma S, Wang V, editors. Review for Textbook of Pediatric Emergency Medicine. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 129-31.

5. **Burns M**. Dermatology. In: Sharma S, Wang V, editors. Review for Textbook of Pediatric Emergency Medicine. Philadelphia: Lippincott Williams & Wilkins; 2000. p. 312-17.

6. Mannix R, **Burns Ewald M**. Airway Management in the Poisoned Child. In: Erickson T, Ahrens W, Aks S, Baum CR and Ling L, editors. Pediatric Toxicology: Diagnosis and Management of the Poisoned Child. New York: McGraw-Hill; 2004. p. 84-88.

7. Saidinejad M, **Burns M**. Ocular Irrigation Alternatives in Pediatric Emergency Medicine. Pediatr Emerg Care 2005; 21: 23-6.

8. Osterhoudt K, **Burns Ewald M**, et al. Toxicologic Emergencies. In: Fleisher GR, Ludwig S, Henretig FM, editors. Textbook of Pediatric Emergency Medicine 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 951-1007.

9. **Burns Ewald M**, Baum C. Environmental Emergencies. In: Fleisher GR, Ludwig S, Henretig FM, editors. Textbook of Pediatric Emergency Medicine 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p.1009-31.

10. Lai M, **Burns Ewald M**. Silver. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, editors. Goldfrank's Toxicologic Emergencies 8th ed. New York: McGraw-Hill; 2006. p. 1358-1363.

11. Nikkanen H, **Burns Ewald M**. Phosphorous. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, editors. Goldfrank's Toxicologic Emergencies 8th ed. New York: McGraw-Hill; 2006. p. 1486-1491.

12. **Burns Ewald M**. Zinc. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, editors. Goldfrank's Toxicologic Emergencies 8th ed. New York: McGraw-Hill, 2006. p. 1378-1383.

13. Geib AJ, **Burns Ewald M**. Food & Waterborne Agents. In: Antosia R, editor. Handbook of Bioterrorism and Disaster Medicine. New York: Springer Science, 2006: p. 151-156.

14. Geib AJ, **Burns Ewald M**. Pulmonary Agents. In: Antosia R, Cahill J,editors. Handbook of Bioterrorism and Disaster Medicine. New York: Springer Science, 2006: p. 171-176.

15. Lai M, **Burns Ewald M**. Anticoagulants. In: Shannon MW, Borron SW, Burns MJ, editors. Haddad & Winchester's Clinical Management of Poisoning and Drug Overdose 4th ed. Philadelphia; W.B. Saunders Company; 2007. p. 1051-64.

16. Mannix R, **Burns Ewald M**. Over-the Counter and Diabetic Agents. In: Zaoutis LB, Chiang VW, editors. Comprehensive Pediatric Hospital Medicine. Philadelphia: Elsevier; 2007. p. 1110-20.

17. Nigrovic L, **Burns Ewald M**. Heat Disorders. In: Zaoutis LB, Chiang VW, editors. Comprehensive

Pediatric Hospital Medicine. Philadelphia: Elsevier; 2007. p. 1148-52.

18. Scalzo A, **Burns Ewald M**. Toxicology. In: Wang V, Sharma S, Flood R. Pediatric Emergency Medicine Question Review Book 2009. Lulu, 2009: p. 166-176.

19. Osterhoudt K, **Burns Ewald M**, Henretig F. Toxicology Emergencies. Fleisher GR, Ludwig S, Henretig FM, editors. Textbook of Pediatric Emergency Medicine 6th ed. Philadelphia: Lippincott Williams & Wilkins 2010; p. 1171-1223.

20. **Burns Ewald M**, Baum C. Environmental Emergencies. In: Fleisher GR, Ludwig S, Henretig FM, editors. Textbook of Pediatric Emergency Medicine 6th ed. Philadelphia: Lippincott Williams & Wilkins 2010; p. 783-804.

21. Lai Becker M, **Burns Ewald M**. Silver. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, editors. Goldfrank's Toxicologic Emergencies 9th ed. New York: McGraw-Hill; 2011: p.1321-1324.

22. O'Donnell K, **Burns Ewald M.** Toxicology. In: Kliegman RM, Behrman RE, Jenson HB, Stanton BM, editors. Nelson's Pediatrics 19th ed. Philadelphia: Elsevier; 2011: p. 250-270.

23. Lai Becker M, **Burns MM**. Silver. In: Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS, editors. Goldfrank's Toxicologic Emergencies 10th ed. New York: McGraw-Hill; 2015: p. 1271-1275.

24. O'Donnell KA**, Burns MM**, Calello DP, Henretig FH, Osterhoudt KC. In: Fleisher and Ludwig's Toxicologic Emergencies 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2015: In press.

Letters

1. Lai MW, Moen M, **Burns Ewald M**. Pesticide-like poisoning from a prescription drug. N Engl J Med 2005; 353: 317-18.

2. George M, Al-Duaij N, Lai Becker M, **Burns Ewald M**. Ethylene glycol ingestion treated only with fomepizole. J Med Toxicol 2008; 4: 67.

3. George M, Al-Duaij N, Nikkanen H, **Burns Ewald M**. Mouthwash: A time for policy change. Pediatr Emerg Care 2009; 25: 58-59.

4. **Burns Ewald M**, Mandl K. Pediatric disaster readiness: A tribute to Michael Shannon. Clin Pediatr Emerg Med 2009;10 (3): 240 – 244.

5. Easter J, Waltzman M, **Burns Ewald M**. Inside out: Ectopia Cordis. Lancet 2010; 376 (9751): 1497.

Clinical Guidelines and Reports

1. Matos M, **Burns M**, Shannon M. False-positive tricyclic antidepressant drug screens leading to the diagnosis of carbamazepine intoxication. Pediatrics 2000; 105: e67.

2. Nikkanen HE and **Burns MM**. Severe hydrogen sulfide exposure in a working adolescent. Pediatrics

2004; 113: 927-29.

3. Saidinejad M, **Burns MM**, Harper MB. Disseminated histoplasmosis in a nonendemic area. Pediatr Infect Dis J. 2004; 23: 781-82.

4. Evans J, **Burns M**. Pyomyositis: A fatal case in a healthy teenager. Pediatr Emerg Care 2005; 21: 375-77.

5. Saidinejad M, **Burns Ewald M**, Shannon M. Transient psychosis in an immune competent patient after oral trimethoprim-sulfamethoxazole administration. Pediatrics 2005; 115: e739-41.

6. Lai MW, Boyer EW, Kleinman ME, Rodig NM, **Burns Ewald M**. Acute arsenic poisoning in two siblings. Pediatrics 2005;116: 249-57.

7. Hickey L, Cross C, **Burns Ewald M**. Nutritional rickets: beyond the chief complaint. Pediatr Emerg Care 2006; 22: 121-23.

8. Geib A, Babu K, **Burns Ewald M**, Boyer E. Adverse effects in children after unintentional buprenorphine exposures. Pediatrics 2006; 118: 1746-1751.

9. George M, Sheroff A, **Burns Ewald M**, Shannon M. Index of suspicion in the nursery: Ergot poisoning. NeoReviews 2009; 10 (6): e303-306.

10. O'Donnell K, **Burns Ewald, M**. Pick your poison: Huffing and puffing to lose weight: salicylate toxicity. Pediatr Emerg Care 2009; 25 (9): 605-607.

11. Skolnik AB, **Burns Ewald, M**. Case Files of the Harvard Medical Toxicology Fellowship at Children's Hospital Boston: An Insulin Overdose. J Med Toxicol 2010; 6:413-419.

12. Yen M, **Burns Ewald M**. Toxicity of weight loss agents. J Med Toxicol 2012; 8 (2): 145-152.

13. Macias Konstantopoulos W, **Burns Ewald M**, Pratt DS. Case Records of the Massachusetts General Hospital 22-2012: A 34-year-old man with intractable vomiting after ingestion of an unknown medication (Antimony). N Eng J Med 2012; 367(3):259-68.

14. George M, Kitzmiller JP, **Burns Ewald M**, O'Donnell KA, Becker ML, Salhanick S. Methadone toxicity and possible induction and enhanced elimination in a premature neonate. J Med Toxicol 2012; 8(4): 432-5.

15. Skolnik AB, **Burns Ewald M**. Pediatric scorpion envenomation in the United States: morbidity, mortality, and therapeutic interventions. Pediatr Emerg Care. 2013; 29(1):98-103.

16. Bruccoleri RE, **Burns MM**. A literature review of the use of sodium bicarbonate for the treatment of QRS widening. J Med Toxicol July 2015 (Epub ahead of print).

Narrative Report

My research, teaching, and clinical contributions to Boston Children's Hospital stem from my training in the fields of Pediatric Emergency Medicine and Medical Toxicology. As such, I am committed to

promoting optimal health care for acutely injured and poisoned children, advocating for state-of-the-art treatment while contributing to national consensus guidelines and prevention efforts on a more global level.

My clinical time is spent as a staff physician within the Division of Emergency Medicine and Program in Medical Toxicology, where I provide both direct patient care and supervise trainees. I participate in treating critically ill and injured children where numerous procedures, often invasive, must be performed in an adept fashion. I am also responsible for recommendations given to the annual 52,000 callers to the Poison Control Center where I serve as the Medical Director. Our Center is certified within the American Association of Poison Control Centers, and I actively participate within this national milieu to ensure that optimal care is provided to our poisoned patients. I maintain my board certification in 3 areas: pediatrics, pediatric emergency medicine, and medical toxicology.

I have been the Medical Director of the Regional Center for Poison Control & Prevention serving Massachusetts and Rhode Island for the last 14 years. During my tenure, I have made contributions to the Center from an administrative, patient care, research and teaching perspective. Organizationally, the two states have worked in unison to provide expertise in the medical diagnosis and management of poisonings. The total budget has consistently increased over the last 6 fiscal years with the procurement of federal funds as well as through innovative fundraising efforts. Diligent endeavors came to fruition when the toxicology fellowship became ACGME re-certified in 2008. The incredibly detailed application to maintain Poison Center certification resulted in continued certification of the Poison Center as of November 2011. In terms of patient care, the number of toxicology consults and children admitted to our in-patient service has grown. Such a wealth and diversity of patients has led to an amplified interest in the specialty of toxicology, with our fellowship having routinely attracted top-notch applicants such as one of our institution's current chief residents in pediatrics.

I am deeply involved in teaching at every level of the institution. As an attending physician in the Emergency Department, I supervise Harvard Medical students, residents in Pediatrics and Emergency Medicine, fellows within our Division, and serve as a resource for our Urgent Care staff. Teaching is done both at the bedside and as an integral part of the didactics of our pediatric emergency medicine fellowship curriculum; the importance of the physical exam in generating a differential diagnosis is highlighted. At the Poison Center I lead daily rounds for Harvard Medical and rotating pharmacy students, emergency medicine residents, and the toxicology fellows. I also participate in formal training to the poison specialists on an annual basis, and I lecture on a bi-annual basis during a toxicology course at the Massachusetts College of Pharmacy. As Chief of the Program in Medical Toxicology, I teach while caring for poisoned patients on our own in-patient and consultant service; I concurrently developed a reading curriculum for the poison center rotators which emphasizes using the literature and national guidelines to formulate treatment plans. Within New England I have given Grand Rounds at Hasbro, Metrowest, Southshore, Holy Family, Boston Children's Hospital and Connecticut Children's Hospital. I have also made toxicology presentations both nationally as well as internationally, including an invitation to give a keynote lecture at the European Association of Poison Control Center's annual meeting in Croatia in May, 2011.

My academic productivity to date has been in two categories: 1) clinical research investigating the epidemiological trends of pediatric poisoning exposures by using large national databases, and 2) clinical communications that describe novel and innovative case presentations and/or treatment modalities in the pediatric toxicology patient. My clinical contributions to the pediatric literature include original research examining the efficacy/safety of using the opioid antagonist nalmafene for elective reversal of pediatric sedation patients. Other pertinent publications include detailed descriptions of a novel antidote for arsenic in two pediatric patients, an adolescent exposed to hydrogen

sulfide in the workplace with important public health sequelae, a toddler presenting with nicotinic symptoms after ingesting a prescription acetylcholinesterase inhibitor, and a neonate with iatrogenic methadone toxicity. Furthermore, the number of children presenting with potential drug-drug interactions while receiving antiepileptic drug therapy is rising; an epidemiological analysis of this patient subset has been submitted in order to identify risk factors. Lastly, a review of sodium bicarbonate therapy for those xenobiotics resulting in QRS widening is complete. Because there is a dearth of research and clinical information geared towards the pediatric toxicology patient, it is imperative that I make future contributions to the field.

https://www.researchgate.net/profile/Joao_Lauro_De_Camargo
https://www.linkedin.com/profile/view?id=118817378&trk=spm_pic

A CARRIER DEVELOPMENT

1998	Full Professor	Departament of Pathology, Botucatu Medical School (FMBo), UNESP, Brazil
1991	Associate Professor	FMBo, UNESP
1989	Pos-Doc	Nagoya City Univ. Medical School, Japan
1983	Pos-Doc	Massachusetts Institute of Technology, MIT, USA
1981	Ph.D.	FMBo, UNESP
1978	M. Sc.	FMBo, UNESP
1973	Pathologist	Brazilian Society of Pathology Board Qualified
1971	M.D.	Catholic University at São Paulo Sorocaba (PUC/SP)

B CURRENT POSITIONS

B.1 Permanent Faculty and Supervisor, Post-graduate Program in Pathology (CAPES, rank 5,0), FMBo, since 1992.
B.2 Research Fellow, National Council for Research (CNPq), Ministry of Science and Technology, Brazil, since 1998.
B.3 Coordinator, Centre for Evaluation of the Environmental Impacto n Human Health (TOXICAM), FMBo, since 1996.
B.4 Faculty member, Latin America Risk Assessment Workshop (LARAW), held annualy by the International Union of Toxicology (IUTOX) and by the Brazilian Society of Toxicology (SBTox), Águas de São Pedro, SP, since 2008.
B.5 Fellow - International Academy of Toxicologic Pathology (IATP), 2014.
B.6 Roster member (2011-2016), JMPR (Joint Meeting for Pesticides Residues, FAO/World Health Organization).
B.7 Member, Committee for Environmental Health Reference, São Paulo State Secretary of Health, SP, Brazil.
B.7 Member, Scientific Consulting Committee (C3) - International Life Science Institute, Brazil (ILSI/Brazil).
B.8 Editorial Board, *European Journal of Toxicological Sciences, ISRN, Applied Research in Toxicology.*
B.9 Consulting or *ad hoc* referee – Brazilian governmental agencies: ANVISA, CTNBio, IBAMA, CNPq, FAPESP, Scientific journals: *Toxicol Pathol, Crit Rev Toxicol, Food Chem Toxicol, Histol Histopathol, Inter J Biotech, Braz J Med Biol Res.* Private companies: BASF, Bayer, DuPont, Monsanto, Ihara, Adama, etc.

C OTHER POSITIONS DURING THE LAST 10 YEARS

1998-2011	Full Professor (retired in 2011)	Department of Pathology, FMBo, UNESP
1974-2011	Pathologist	UNESP General Hospital

2011-2013	Dean for Academic Affairs	UNESP General Hospital – São Paulo State Secretary of Health
2006-2013	Editorial Board	*Toxicol. Pathol., J. Bras. Patol. Med. Lab., Rev. Bras. Toxicol.*
2005-2010	Two-term President	Latin American Society of Toxicologic and Experimental Pathology (LASTEP)
2004-2008	Board member	São Paulo State Oncology Center Foundation (FOSP)
1993-1997	Vice-Dean	FMBo, UNESP
1986-1990	Supervisor	Division for Medical Support, UNESP General Hospital
1984-1986	Head of Department	Department of Pathology, FMBo, UNESP
1974-1991	Assistant Professor	Department of Pathology, FMBo, UNESP

D POS-DOC TRAINING

1988-1989, Japan - Nagoya University Medical School, Department of Pathology. Fellow of the Japanese Foundation for Cancer Research, Tokyo. Development of medium-term alternative bioassays for chemical carcinogens identification. Necropsies of rodents submitted to conventional long-term bioassays at the Dai-Yukai Institute of Medical Sciences (DIMS). Supervisor: Dr. Nobuyuki Ito.

1981-1984, USA – Visiting scientist, Massachusetts Institute of Technology (MIT), Department of Nutrition and Food Science, Laboratory of Animal Pathology. Lipotropes deficiency; focus on B6C3F1 mice liver toxicity. *In vivo* evaluation of the tricotecenic mycotoxin anguidine in the CD-1 mice. Supervisor: Dr. Paul M. Newberne.

E PUBLICATIONS (Last 05 years)

E.1 Fava RM, Cardoso APF, da Rocha MS, Nascimento e Pontes MG, **de Camargo JLV**, de Oliveira MMCS. Evaluation of early changes induced by diuron in the rat urinary bladder usinf different processing methods for scanning electron microscopy. Toxicology, 333:100-106, 2015. doi: 10.1016/j.tox.2015.04.006

E.2 Pascotto \VM, Guerra MT, Franci JAA, **de Camargo JLV**, Kempinas WG, Franchi CAS. Effects of a mixture of pesticides on the adult female reproductive system of Sprague-Dawley, Wistar, and Lewis rats. J. Toxicol. Environ. Health, Part A, 78 (9):602-606. doi: 10.1080/15287394.2015.1010467

E.3 Solano MLM, Montagner CC, Vaccari C, Jardim WF,, Anselmo-Franci JA, Carolino ROG, Luvizutto JFL, Umbuzeiro GA, **de Camargo JLV**. Potential endocrine disruptor activity of drinking water samples. Endocrine Disruptors. http://dx.doi.org/10.4161/23273747.2014.983384

E.4 Luvizutto JFL, Solano MLM, Martinez MF, Fernadez CDB, Umbuzeiro GA, de Camargo JLV. Potential androgenic effects of urban sewage sludge in male rats. Endocrine Disruptors. http://dx.doi.org/10.1080/23273747.2015.1066656

E.5 Ihlaseh-Catalano SM, Bailey K, Cardoso APF, Ren H, Fry R, **de Camargo JLV**, Wolf DC. Dose and temporal effects on gene expression profiles of urothelial cells from rats exposed to diuron. Toxicology, 325: 21-230, 2014. doi: 10.1016/j.tox.2014.08.005

E.6 da Rocha MS, Arnold LL, de Oliveira MLCS, Catalano SMI, Cardoso APF, Pontes MGN, Ferrucio B, Dodmane PR, Cohen SM, **de Camargo JLV.** Diuron-induced rat urinary bladder carcinogenesis: Mode of action and human relevance evaluations using the International Programme on Chemical Safety framework. Crit. Rev.Toxicol., 44(5):393-406, 2014. doi: 10.3109/10408444.2013.877870

E.7 Marcondes JPC, de Oliveira MLCS, Gontijo AM, **de Camargo JLV**, Salvadori DMF. Genetic instability persists in non-neoplastic urothelial cells from patients with a history ofurothelial cell carcinoma. PLOS One, 9:e86162-e86162, 2014. doi: 101371/ journal.pone.0086162

E.8 de Camargo JLV. Chemical carcinogenesis – mode of action to inform quantitative human risk. BMC Proceedings, 2013, 7 (Suppl 2):K10. doi:10.1186/1753-6561-7-S2-K10

E.9 da Rocha MS, Arnold, LL, Dodmane PR, Pennington KL, Qiu F, **de Camargo JLV**, Cohen SM. Diuron metabolites and urothelial cytotoxicity: *In vivo, in vitro* and molecular approaches. Toxicology, 314: 238-246, 2013. doi:10.1093/toxsci/kfs256

E.10 da Rocha MS, Arnold LL, Pennnington KL, Muirhead D, Dodmane PR, Anwar MM, Battalora M, **de Camargo** JLV, Cohen SM. Diuron-induced rat bladder epithelial cytotoxicity. Toxicol. Sci.,130 (2): 281-288, 2012. doi:10.1093/toxsci/kfs256

E.11 Cardoso APF, Catalano SMI, da Rocha MS, Pontes MGN, **de Camargo JLV,** Oliveira MLCS. Dose-response of diuron [3-(3,4-dichlorophenyl)-1,1-dimethylurea] in the urothelial mucosa of Wistar rats. Toxicology, 312:1-5, 2013. doi.org/10.1016/j.tox.2013.07.007

E.12 de Camargo MR, Barbisan LF, Martinez MF, Da Franchi, CAS, **de Camargo JLV**, Spinardi-Barbisan ALT. Macrophage activity and histopathology of the lymphohematopoietic organs in male Wistar rats orally exposed to single or mixed pesticides. J. Environ. Sci. Health. Part B. Pest. Food Contam. Agr. Wastes. 48: 607-613, 2013. doi: 10.1080/03601234.2013. 775020

E.13 Ihlaseh SM, Drigo S, Jesus CMN, Domingues MA, Trindade Filho JCS, Soares FA, **de Camargo JLV**, Rogatto SR. STEAP1 protein overexpression is an independet marker for biochemical recurrence in prostate carcinomas. Histopathology, 63(5):678-85, 2013. doi: 10.1111/his.12226.

E.14 Toledo Netto P, Teixeira Jr. OJ, **de Camargo JLV**, Ribeiro ML, de Marchi MRR. A rapid, environmentally friendly, and reliable method for pesticide analysis in high-fat samples. Talanta (Oxford), 101: 322-329, 2012. doi: 10.1016/j.talanta.2012.09.034

E.15 Nascimento e Pontes MG, Silveira SM, Trindade Filho JC, Rogatto SR, **de Camargo JLV**. Chromosomal imbalances in successive moments of human bladder urothelial carcinoma. Urologic Oncol.: Seminars and Original Investigations. doi:10.1016/j.urolonc.2011.05.015.

E.16 **de Camargo JLV**, Barros SBM. Informação científica e avaliação do risco toxicológico. Rev. Bras. Toxicol., 24:1- 9, 2011.

E.17 Ihlaseh SM, Bailey KA, Hester SD, Jones C, Ren H, Cardoso APF, Oliveira MLCS, Wolf DC, **de Camargo JLV**. Transcriptional profile of diuron-induced toxicity on the urinary bladder of male Wistar rats to inform mode of action. Toxicol. Sci., 122: 330-338, 2011. doi: 10.1093/ toxsci/kfr108.

E.18 Grassi TF, Rodrigues MAM, **de Camargo JLV**, Barbisan LF. Evaluation of carcinogenic potential of diuron in a rat mammary two-stage carcinogenesis model. Toxicol. Pathol., 39: 486-495, 2011. doi: 10.1177/0192623310396904

E19 Ferrucio B, Franchi CAS, Boldrin N, de Oliveira MLCS, **de Camargo JLV**. Evaluation of diuron (3-[34-dichlororophenyl]-1-1-dimethylurea) in a two-stage mouse skin carcinogenesis assay. Toxicol. Pathol., 38(5):756-764, 2010. doi: 10.1177/0192623310375452

E20 da Rocha MS, Nascimento MG, Cardoso APF, de Lima LA; Zelandi E, **de Camargo JLV,** de Oliveira MLCS. Cytotoxicity and regenerative proliferation as the mode of action for diuron-induced urothelial carcinogenesis in the rat. Toxicol. Sci., 113:37-44, 2010. doi:10.11.093/toxsci/kfp241

E.21 Luvizutto JFL, Solano MLM, Passareli D, Franchi CAS, Umbuzeiro GA, **de Camargo JLV**. Subchronic toxicity evaluation of treated urban sewage sludge. J. Toxicol. Environ. Health Part A, 73: 916-925, 2010. doi: 10.1080/152873910037 45036

E.22 Perobelli JE, Martinez MF, Franchi CAS, Fernandez CAD, **de Camargo JLV**, Kempinas WG. Decreased sperm motility in rats orally exposed to single or mixed pesticides. J. Toxicol. Environ. Health, Part A, 73:991-1002, 2010. doi: 10.1080/1528739100375180

E.23 **de Camargo JLV**. Brazilian experience with the medium-term multi-organ bioassay: scientific and regulatory developments. Asian Pacific J. Cancer Prev., 11:7-8, 2010.
E.24 Said RA, Grassi TF, Scolastici C, de Lima ROA, Darros B, Barbisan LF, **de Camargo JLV**. Absence of chemopreventive influence of propolis on the rat liver altered foci development. Exper. Toxicol. Pathol., 62: 405-412, 2010. doi:10.1016/ j.etp.2009.05.012

F BOOKS AND BOOK CHAPTERS (Last 5 years)

F.1 Rodrigues MAM, **de Camargo JLV**. Carcinogênese. IN: Mario R. Montenegro, Marcello Franco. (Org.) Patologia - Processos Gerais. 5ª. Edição. Ed. Atheneu, 2010. p. 255-272.[*Portuguese*]
F.2 Rodrigues MAM, **de Camargo JLV**. Doenças Nutricionais IN: Mario R. Montenegro, Marcello Franco (Org.) Patologia - Processos Gerais. 5ª Edição. Ed. Atheneu, 2010. p. 287-305.[*Portuguese*]
F.3 **de Camargo JLV**. Identificação do Potencial Cancerígeno. IN: Cristiana L. Corrêa; Ione P. Lemonica; Flávio A.D. Zambrone; **J.L.V. de Camargo** (Org.). Bases Científicas para a Avaliação da Toxicidade de Agrotóxicos. 1ª. Ed. São Paulo: ILSI Brasil International Life Science Institute do Brasil. 2009. p. 131-169.[*Portuguese*]
F.4 **de Camargo JLV** e Oliveira DE (Org.). Patologia Geral: Abordagem Multidisciplinar. 1ª. Ed. Rio de Janeiro: Guanabara-Koogan. 2007. 5ª. reimpressão (2012). 204 p. .[*Portuguese*]

G BIOASSAY PROTOCOL - OFFICIAL ACCEPTANCE

G.1 IBAMA (Brazilian Institute for the Environment) Technical Norm # 84/1996 – Protocol of an alternative *in vivo* assay for the detection of the carcinogenic potential of pesticides.

H ORGANIZATION AND COORDENATION OF SCIENTIFIC MEETINGS (Last five years)

H.1. III Brazilian Symposium on "Toxicologic Pathology and the Safety of Industrial Chemicals", ALAPT/ILSI/IFSTP, São Paulo, March 2010.
H.2. Symposium on "Environmental Pathology", during the International Academy of Pathology (IAP) Congress, São Paulo, SP, October 2010.

I INVITED TALKS (Last five years)

I.1 "Evaluation of the safety of genetically modified food/feed (GMF)". National Technical Committee of Biotechnology (CTNBio). Brasília, DF, November 06th, 2014.
1.2 "Pathogenseis of cancer and MoA of putative human carcinogens". Workshop "Mode of Action (MoA): desenvolvimentos recentes e aplicação regulatória". Intl. Life Science Institute/Brasil, Brasília, DF, April, 14-15th, 2014.
I.2 "Chemical carcinogenesis – mode of action to inform quantitative human risk". Keynote Lecture Presentation. São Paulo Advanced School of Comparative Oncology/FAPESP. Águas de São Pedro, SP. September, 30th, 2012.
I.3 "In vivo toxicity testing in Brazil – today and tomorrow", Symposium "Alternative and in vitro methods for the safety of chemicals and their impact to the health and the environment: updating and perspectives". UNESP/São Paulo State University Symposium. São Paulo/SP, Outubro, 2010.
I.4 "Chemical carcinogenesis: from the bench to regulation". III International Meeting of Investigative Pathology. Hospital A.C. Camargo, São Paulo/SP, August, 2010.

J RESEARCH GRANTS (Last five years)

J.1 FAPESP 2011/09870-2. "In vivo evaluation of endocrine disrupting potential of treated sewage sludge, drinking water and of a pesticide mixture".
J.2 FAPESP 2009/02754-7. "Gene expression in the urothelium of male Wistar rats exposed to the herbicide Diuron (3-(3,4-dichlorophenyl)-1,1-dimethylurea".

K POS-DOC SUPERVISION

K.1 Merielen G. Nascimento e Pontes, Ph.D., 2012-2015. "Establishment of a testicular germ cell tumor model in Sprague-Dawley rats". FAPESP Proc. No. 2012/09873-4.

L SUPERVISION OF GRADUATION PROJECTS

L.1 Ph.D., Viviane M. Pascotto. "Evaluation of the individual or mixed influences of the fungicides prochloraz, propiconazole and miclobutanil on the reproductive system of female Sprague-Dawley rats".
L.2 Ph.D., Ana Paula F. Cardoso. "Cryptorchidism establishment in Sprague-Dawley rats".
L.3 M.Sc., Nathalia P. de Souza, CNPq 132667/2013-4. "Cryptorchidism and in utero exposure to di(n-butyl)phtalate or to acrylamide – evaluation of SD rats Leydig cells".
L.4 M.Sc., Ligia M. M. Rodrigues, CNPq 830850/1999-6. "Evaluation of Sertoli cells development and ultrastructure in an experimental modelo of cryptorchidism and orchidopexia".

M SCIENTIFIC SOCIETIES

International Academy of Toxicologic Pathology (IATP, 2014)
Society of Toxicology (SoT, 2011)
Latin-american Society of Toxicologic and Experimental Pathology (LASTEP, 2005)
Brazilian Society of Toxicology (SBTox, 1992)
The Society of Toxicology Pathology (STP) (1996)
American Association for Cancer Research (AACR) (1989)
Brazilian Society of Pathology (SBP, 1972)
++

Garabrant

David H. Garabrant, MD, MPH, MS, FACOEM, FACPM
Emeritus Professor of Occupational Medicine and Epidemiology
The University of Michigan School of Public Health
2100 Commonwealth Boulevard, Suite 203
Ann Arbor, Michigan 48105
[redacted]
dhg@umich[redacted]

Education and Training

High School:	Westfield High School Westfield, New Jersey 1965-1968
Undergraduate:	Tufts University Medford, Massachusetts. Sept 1968-June 1972 B.S., Chemical Engineering, June 1972
Graduate:	Tufts University School of Medicine Boston, Massachusetts. Sept 1972-June 1976. M.D. received June 1976
Internship:	Medicine Intern Georgetown University Hospital Washington, D.C. July 1976 - June 1977
Fellowship	Internal Medicine, Ambulatory Care Georgetown University Hospital Washington, D.C. September 1977 - June 1978
Residency:	Occupational Medicine Harvard School of Public Health Boston, Massachusetts September 1978 - June 1980 M.P.H. degree received June 1979 M.S. in Physiology (Occupational Medicine) received June 1980
	Internal Medicine Boston University Medical Center Boston, Massachusetts July 1980 - June 1981

Certification and Licensure

Licensure	District of Columbia, 1978, (Certificate - 10775) (inactive) Maryland, 1977, (Certificate - D-20626) (inactive) Massachusetts, 1978, (Certificate - 42987) (inactive) California, 1982, (Certificate - G-47344) (inactive) Michigan, 1989, (Certificate - 054132) (active)
Board Certification	Internal Medicine, 1981 Preventive Medicine, 1982 Subspecialty certification, Occupational Medicine, 1982

Academic, Adminstrative, and Clinical Appointments

Teaching Assistant in Medicine, Boston University School of Medicine, July 1980 - June 1981

Assistant Professor, University of Southern California School of Medicine, August 1981 – June 1988

Associate Professor, University of Southern California School of Medicine, June 1988 – November 1988

Associate Professor , University of Michigan School of Public Health, December 1988 – June 1996

Associate Professor of Medicine, Department of Medicine, University of Michigan School of Medicine, December 1989 – September 2002

Visiting Faculty, University of Indonesia School of Medicine, August 1995- June 1996 (Sabbatical)

Professor of Occupational Medicine, University of Michigan School of Public Health, June 1996 – September 2007

Associate Professor, Department of Emergency Medicine, University of Michigan School of Medicine, September 2002- September 2007.

Professor of Epidemiology, University of Michigan School of Public Health, June 2003 – September 2007

Founding Director, University of Michigan, Center for Risk Science and Communication, 2004 – present.

Emeritus Professor of Occupational Medicine and Epidemiology, University of Michigan School of Public Health, September 2007 – present

Emeritus Associate Professor of Emergency Medicine, University of Michigan School of Medicine, September 2007 – present

Honors And Awards

Graduated Magna Cum Laude, Tufts University, 1972.

Tufts University, Tau Beta Pi Engineering Honor Society, 1971

Awarded Training Grant for Study and Research in Occupational Medicine from the National Institute for Occupational Safety and Health, 1978, renewed 1979

Recipient of Preventive Oncology Academic Award, National Cancer Institute, 1987-1992

Chair, Safety and Occupational Health Study Section, National Institutes of Health, 1995-96.

Excellence in Research Award, University of Michigan School of Public Health, April 28, 2006

Top Docs 2006. Hour Detroit Magazine

Emeritus Professor, University of Michigan, September 2007

Research Excellence Award. University of Michigan Risk Center, October 16, 2007.

Franzblau, A., L. Zwica, K. Knutson, Q. Chen, S.-Y. Lee, B. Hong, P. Adriaens, A. Demond, **D. Garabrant**, B. Gillespie, J. Lepkowski, W. Luksemburg, M. Maier, and T. Towey, 2009, "An Investigation of Homes with High Concentrations of PCDDs, PCDFs and/or Dioxin-Like PCBs in House Dust," *J. Occupational and Environ. Hygiene*, 6:188-199. Best Indoor Environmental Quality Paper Award for 2009 awarded by American Industrial Hygiene Association.

Memberships in Professional Societies

American Occupational Medical Association 1982-88. Elected to fellowship, 1986
Western Occupational Medical Association, 1982-88
    Board of Directors, 1984-88
    Chairman, Educational Affairs Committee, 1986-88
American College of Preventive Medicine, 1985-present. Elected to fellowship, 1986
American Academy of Occupational Medicine, 1985-88
American College of Occupational and Environmental Medicine, 1988-present.
    Elected to fellowship, 1988
    Council of Scientific Advisors, 2009-present
Michigan Occupational Medical Association Board of Directors, 1989-91
Society for Epidemiologic Research, 1988-present
Michigan Public Health Association, 2001-present
Society for Risk Analysis, 2002-present
International Epidemiological Association, 2002-present
American Chemical Society, 2008-present

Editorial Positions, Boards, and Peer-Review Service

State of Washington Department of Labor and Industries. Chemically Related Illness Scientific Advisory Board. 1994-95.

Charter member, Safety and Occupational Health (SOH) Study Section for the National Institutes of Health, 1992-1996. Chairman, 1995-96.

Chair, Clinical Sciences Special Emphasis Panel. Alcohol and Toxicology (ZRG4) Study Section for the National Institutes of Health, November 1996.

Chair, NCI Review Panel on Breast Cancer and the Environment on Long Island. National Institutes of Health, January 31, 1997.

Member, NCI Review Panel on Regional Variation in Breast Cancer Rates in the United States. National Institutes of Health, Rockville, MD, November 9, 1998.

Member, NIOSH Special Emphasis Panel on Disease, Disability, and Injury Prevention Control Grants, National Institute for Occupational Safety and Health, Florence KY. February 21-23, 1999.

Member, NIEHS Special Emphasis Panel on Superfund Basic Research Projects, National Institute of Environmental Health Sciences, Research Triangle Park, NC. October 25-27, 1999.

Chair, NIOSH Site Visit to University of Washington Educational Resource Center. Seattle, Washington, November 7-9, 2001.

Chair, NIOSH Special Emphasis Panel on Training Programs in Occupational Health and Safety. St. Petersburg, Florida. February 17-20, 2002.

Mickey Leland National Urban Air Toxics Research Center, Houston, Texas. Appointed to Scientific Advisory Board, 2002-2009.

Member, NIH Special Emphasis Panel/Scientific Review Group 2006/10 ZLM1 ZH-P (O1), July 14, 2006

Member NIEHS Special Emphasis Panel/Scientific Review Group 2007/10. National Institute of Environmental Health Sciences, Research Triangle Park, NC. July 11-14, 2007.

Member, American Cancer Society Peer Review Committee on Physician Training Award in Preventive Medicine. American Cancer Society, Atlanta, Georgia. 2008-2012

Institute of Medicine of the National Academies of Sciences. Participant – GAO Workshop on Cancers Added to the World Trade Center Health Program (WTCHP) List of Covered Conditions. Washington, D.C. October 21, 2013.

Scientific Journal Board of Editors:

Journal of Occupational Medicine, Editorial Board. 1987-1992

Medical Journal of Indonesia, Editorial Board. 2000-present

Journal of Environmental and Public Health. 2009-2011

Reviewer, Scientific Manuscripts:

American Journal of Epidemiology
American Journal of Industrial Medicine
Chemosphere
Critical Reviews in Toxicology
Environmental Health Perspectives
Environmental Science and Technology
Epidemiology
Journal of Exposure Science and Environmental Epidemiology
Journal of Occupational and Environmental Medicine
Journal of the National Cancer Institute
Risk Analysis

Teaching

Attending Physician, Occupational Medicine Outpatient Clinic, University of Michigan Medical Center, Ann Arbor, Michigan, 1989-2011

Director, Occupational and Environmental Epidemiology Program, University of Michigan School of Public Health 2001-2007

Past and current courses:
EHS 501 Occupational & Environmental Disease (Lecturer)

EHS 504 Genes & the Environment (Lecturer)
EHS 508 Principles of Risk Assessment (Course Director)
EHS 656 Research Methods in Occupational Health (Lecturer)
EHS 666 Occupational & Environmental Medicine Seminar (Lecturer)
EHS 697 Readings (Course Director)
EHS 698 Research (Course Director)
EHS 762 Clinical Occupational Medicine (Lecturer)
EPID 657 Field Internship in Epidemiology (Course Director)
EPID 655 Field Studies in Epidemiology (Lecturer)

Graduate Student Advisor, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1989-Present

Ph.D. Thesis Committee Member

N. Seixas, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1990

A. Rocskay, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1991

N. Nelson, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1992

Carol Burns. The epidemiology of systemic sclerosis: a population based case control study. Ph.D. in Epidemiologic Science, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1994

Jane Krebs. Mortality at an automotive stamping and assembly facility. Ph.D. in Epidemiologic Science, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1995. Doctoral Committee Co-Chair.

Jacqueline Kurtz. An evaluation of peer and professional trainers in an occupational health and safety training program. Ph.D. in Environmental and Industrial Health, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1995

Jon Fryzek. A case-control study of DDT and related compounds and pancreas cancer. Ph.D. in Epidemiologic Science, University of Michigan, School of Public Health, Ann Arbor, Michigan, 1996. Doctoral Committee Co-Chair.

Stephen Martin. 1,1 dichloro-2,2-bis(p-chlorophenyl)ethylene, testosterone levels and lipid profile in African American farmers and farm workers. University of Michigan, School of Public Health, Ann Arbor, Michigan, 2001.

Jeanette Jane Rainey. Epidemiological and environmental co-factors linked to endemic Burkitt's lymphoma in Kenya. Ph.D. in Epidemiologic Science, University of Michigan, School of Public Health, Ann Arbor, Michigan 2005

Gena Pauline Kucera. Hormone replacement therapy and nonsteroidal anti-inflammatory drugs on the risk of colorectal cancer in women. Ph.D. in Environmental and Industrial Health, University of Michigan, School of Public Health, Ann Arbor, Michigan, 2006. Doctoral Committee Chair.

Aaron Sussell. Incidence And Prevalence Of Occupational Contact Dermatitis In Automobile Manufacturing. PhD in Environmental Health Sciences, University of Michigan School of Public Health, 2007.

Andrea Steege. Access to health care among migrant farm workers. University of Michigan, School of Public Health, Ann Arbor, Michigan, 2009. Doctoral Committee Co-Chair.

Qixuan Chen. Bayesian Model Based Approach to Complex Survey Data Analysis. Department of Biostatistics, University of Michigan, School of Public Health, Ann Arbor, Michigan, 2009.

Committee, Organizational, and Volunteer Service

Director, Occupational Medicine, University of Michigan School of Public Health, Ann Arbor, Michigan, December 1988-94

Member, School of Public Health Executive Committee, University of Michigan, Ann Arbor, Michigan, 1989-1991.

Director, Center for Occupational Health, Safety, and Engineering, University of Michigan, Ann Arbor, Michigan, 1990-1995

Associate Director, Center for Occupational Health, Safety, and Engineering, University of Michigan, Ann Arbor, Michigan, 1995-2000

Director, Division of Occupational Health, University of Michigan School of Public Health. 1992 -1995

Member, Executive Committee, Department of Environmental and Industrial Health, University of Michigan School of Public Health, Ann Arbor, MI. January 1992-1995.

Chair, Curriculum Committee, Department of Environmental and Industrial Health, University of Michigan School of Public Health, 1996-97.

Chair, Advisory Committee on Academic Rank, University of Michigan School of Public Health, 1997-99. Member 1996-97, 1999-00.

Member, Executive Committee, University of Michigan School of Public Health. 2000-2003.

Member, Student Recruitment Committee, Department of Environmental Health Sciences, University of Michigan School of Public Health, 2001-03

Founding Director, Center for Risk Science and Communication, University of Michigan School of Public Health, 2003-present

Member, Search Committee for Dean of University of Michigan School of Public Health, 2004-05

Member, Executive Committee, University of Michigan School of Public Health, 2006-07

Member, Office of the Vice President for Research Conflict of Interest Committee, University of Michigan, Ann Arbor, Michigan, 2009-2012

Member, Dean's Advisory Council, University of Michigan School of Public Health, 2012-present

Visiting Professorships, Seminars, and Extramural Invited Presentations

1. "Colon Cancer and Job Activity." Invited Paper at Occupational Epidemiology Forum, sponsored by USC, UCLA, and UC Irvine Schools of Medicine. Irvine, CA, 1983.
2. Annual Meeting of the Western Occupational Medical Association, "Pulmonary disease in borax workers", San Francisco, California, 1982.
3. 4th Annual Rocky Mountain Conference on Occupational and Environmental Health, "Respiratory symptoms from borax and boric acid aerosols", Park City, Utah, 1982.
4. American Occupational Medical Association Annual Meeting, "Occupational cancer", Los Angeles, California, 1984.
5. "Respiratory Effects of Borax Dust." Invited Paper at Occupational Epidemiology Forum, sponsored by USC, UCLA, and UC Irvine Schools of Medicine, Irvine, CA, 1984.
6. Panel Chairman. "Health Issues for Women in the Workplace." Annual Scientific Meeting, American Occupational Medical Association, Los Angeles, CA, 1984.
7. "Occupational Cancer." Postgraduate Education Conference at the American Occupational Medical Association Basic Curriculum Course, Salt Lake City, UT, 1984.
8. "Epidemiology for the Occupational Physician." Postgraduate Education Conference at the Annual Scientific Meeting, American Occupational Medical Association, Los Angeles, CA, 1984.
9. "Contact Dermatitis from Aziridine Hardener in Printing Ink." Invited Paper at Occupational Epidemiology Forum, sponsored by USC, UCLA, and UC Irvine Schools of Medicine, Irvine, CA, 1985.
10. Western Occupational Medical Association Conference, "Epidemiology of occupational cancer", Stanford University, Palo Alto, California, 1985.
11. "Toxicology." Workshop on evaluation of workers compensation patients exposed to hazardous chemicals. Postgraduate Education Conference. Presented by the State of California Division of Industrial Accidents and USC School of Medicine, Los Angeles, CA, 1985.
12. Special Studies Unit, Division of Occupational Safety and Health, Department of Industrial Relations, State of California, Sacramento, California, 1985.
13. V International Symposium, Epidemiology in Occupational Health, "Cancer mortality in the aircraft manufacturing industry", Los Angeles, California, 1986.
14. Epidemiology and cancer registries in the Pacific Basin V, "Cancer risks in the aircraft manufacturing industry", Kauai, Hawaii, 1986.
15. "Cancer Mortality in the Aircraft Manufacturing Industry." Invited Paper at Occupational Epidemiology Forum, sponsored by USC, UCLA, and UC Irvine Schools of Medicine, Irvine, CA, 1986.
16. "Occupational exposure to electromagnetic fields and adult leukemia." Invited Paper at Occupational Epidemiology Forum, sponsored by USC, UCLA, and UC Irvine Schools of Medicine, Irvine, CA 1987.
17. "Studies of electromagnetic fields and cancer risk." Seminar at Joint Symposium sponsored by Fred Hutchinson Cancer Research Center, University of Washington School of Medicine and Department of Preventive Medicine, USC. Seattle, WA, 1987.
18. "Electromagnetic fields and cancer risk," and "Exposure assessment in occupational and residential studies of ELF and leukemia." Invited lecturer, International Agency for Research on Cancer, Lyon, France, May 1988.

19. California Cancer Registries Conference 1988: Innovations in Research, "Coding and use of cancer registry data to look for occupational cancers", Newport Beach, California, October 1988.
20. 32nd Annual Western Occupational Health Conference, "When is cancer work related?", Irvine, California, October 1988.
21. "Toxicology of chrome." Invited guest, Aerospace Hazardous Waste Minimization Symposium, Los Angeles, CA, May 1988.
22. "Medical/Ethical Pitfalls of Occupational Medicine From a Clinicians Standpoint." Invited speaker, Southern California Edison Company, Oxnard, CA, July 1988.
23. "Prospective Study of Respiratory Effects of Formaldehyde in Medical Students". Invited speaker, UC Irvine, Department of Community and Environmental Medicine. October 20, 1988.
24. Invited lecturer, California Cancer Registries Conference 1988: Innovations in Research. Lecture topic: Coding and Use of Cancer Registry Data to Look for Occupational Cancers", Newport Beach, California, October 1988.
25. Lecturer, "Physical Activity and Colon Cancer Risk", seminar sponsored by the University of Michigan, Ann Arbor, Michigan, September 1989
26. Chairperson, 41st Annual Selby Discussional, School of Public Health, University of Michigan, Ann Arbor, Michigan, September 1989
27. Lecturer, "Lung Disease in Borax Miners: Was Borax the Culprit?". School of Public Health, University of Michigan, Ann Arbor, Michigan, October 1989
28. Session Reporter, "Human Health Impacts of Halogenated Biphenyls and Related Compounds". University of Michigan, Ann Arbor, Michigan, November 8-9, 1989
29. Keynote Speaker, Joint Annual Meeting of The Michigan Occupational Medical Association, The Detroit Michigan Association of Occupational Health Nurses, and The Michigan Industrial Hygiene Society, "Electromagnetic Fields and Leukemia". Dearborn, Michigan, November 1989.
30. Lecturer, "Physical Activity and Colon Cancer". Ford World Headquarters, Dearborn, Michigan, January 1990.
31. Lecturer, "Multiple Chemical Sensitivities", press briefing at Dow-Elanco. Midland, Michigan, March 1990.
32. Speaker, "Man made mineral fibers and lung cancer". Presented at Pulmonary Division Grand Rounds, University of Michigan Medical Center, Ann Arbor, Michigan, December 7, 1990.
33. Speaker, "Epidemiologic study of end users of man-made mineral fiber". Report to Annual Scientific Session of the Thermal Insulation Manufacturers Association. Del Mar, California, October 30, 1990.
34. Conference Chairman, 42nd Annual Selby Discussional held at the University of Michigan, Ann Arbor, Michigan, November 8-9, 1990.
35. Invited speaker, "DDT and pancreas cancer". National Institute for Occupational Safety and Health, Cincinnati, Ohio, January 29, 1991.
36. Invited speaker, "Case control study of pancreas cancer among chemical manufacturing workers". University of Cincinnati School of Medicine, Department of Environmental Health Seminar Series. January 30, 1991.
37. Invited speaker, Epidemiologic studies of morbidity of man-made mineral fiber workers". In: Man-made mineral fibers: status of health risk assessment. Course given by the

Department of Environmental Health Sciences, Johns Hopkins University School of Hygiene and Public Health. Baltimore, Maryland, March 4, 1991.

38. Invited speaker, "Electromagnetic fields and cancer". Annual meeting of the Semiconductor Industry Safety Association. Phoenix, Arizona, April 15, 1991.
39. Invited presentation, "DDT and pancreas cancer in a case control study of chemical workers." Society for Epidemiological Research Annual Meeting. Buffalo, New York, June 1991.
40. Conference Chairman, 43rd Annual Selby Discussional held at the University of Michigan, Ann Arbor, Michigan, November 1991.
41. Invited Faculty, National Cancer Institute, Division of Cancer Prevention and Control. 1992. Cancer Prevention and Control Academic Course. "Surveillance and special populations: occupations exposed to asbestos". August 7, 1992.
42. Conference Chairman, 44th Annual Selby Discussional held at the University of Michigan, Ann Arbor, Michigan, November 1992.
43. Invited speaker, Occupational Health Symposium Co-Sponsored by Bay Medical Education and the University of Michigan Center for Occupational Health and Safety. Saginaw, Michigan, March 12, 1993. "Occupational Cancers".
44. Invited speaker, Department of Epidemiology, University of Michigan Department of Epidemiology, March 18, 1993. "Recent Studies on EMF and Cancer".
45. Invited speaker, First Annual Cancer Conference. Recent Advances in Colorectal Carcinoma. Sponsored by the American Cancer Society, Detroit, Michigan, April 14, 1993. Epidemiology of Colorectal Cancer.
46. Conference Chairman, 45th Annual Selby Discussional held at the University of Michigan, Ann Arbor, Michigan, September 1993.
47. Invited speaker. Michigan State Medical Society Annual Meeting. "Electromagnetic Fields and Health". Detroit, Michigan, November 11, 1993.
48. Invited presentation. "Occupational exposures and urogenital cancers among leather workers". National Cancer Institute Workshop on Occupational Exposures and Urogenital Cancers. May 23-24, 1994, Rockville, Maryland.
49. Conference Chairman, 46th Annual Selby Discussional held at the University of Michigan, Ann Arbor, Michigan, October 13-14, 1994.
50. University of Michigan Comprehensive Cancer Center Grand Rounds. "DDT and Related Compounds and Pancreas Cancer. October 21, 1994.
51. Western Ohio Occupational Medical Association Annual Scientific Meeting. "Integration of Residents into Occupational Medicine Training". Toledo, Ohio, March 11-12, 1995.
52. Invited Speaker. BASF Corporation Isocyanates Review. Respiratory Disease from TDI and MDI. Wyandotte, Michigan, April 6, 1995.
53. Invited Speaker. Department of Public Health, Wellington School of Medicine. "DDT and pancreas cancer". July 28, 1995, Wellington, New Zealand.
54. Invited Speaker. First Annual Jakarta International Epidemiology Course. "Occupational Disease Epidemiology". December 4-15, Jakarta, Indonesia.
55. Invited Speaker. Faculty of Public Health, University of Indonesia. "Current Issues in Occupational Health". December 19, 1995, Depok, West Java, Indonesia.
56. Invited Speaker. Department of Cardiology, Faculty of Medicine, University of Indonesia. "Preparing an International Manuscript" April 9, 1996. National Cardiac Center, Harapan Kita Hospital, Jakarta, Indonesia.

57. Invited Speaker. Editorial Board of the Medical Journal of Indonesia. "Publishing in the International Medical Literature" April 9, 1996. University of Indonesia School of Medicine, Jakarta, Indonesia.
58. Invited Speaker. "Guidelines for Publishing in the International Medical Literature". May 21, 1996. Department of Internal Medicine Grand Rounds, University of Indonesia School of Medicine, Jakarta, Indonesia.
59. Invited Speaker. Symposium of Occupational Safety and Health to Anticipate the Era of Free Trade in the Year 2020. "Occupational Safety and Health in Developed Industrial Countries". May 23, 1996, University of Indonesia School of Medicine, Jakarta, Indonesia.
60. Invited Faculty, National Cancer Institute, Division of Cancer Prevention and Control. 1996 Cancer Prevention and Control Academic Course. "Special Populations and the Environment. High Risk Populations: Asbestos". August 9, 1996.
61. Invited Speaker. "Epidemiology of Pancreatic Neoplasia". Symposium: Current Concepts in Pancreas Cancer. Barbara Ann Karmanos Cancer Institute. Detroit, MI. September 12, 1997
62. Invited Speaker. "DDT and Related Materials and Pancreatic Cancer". NIEHS Center for Molecular and Cellular Toxicology, Wayne State University Institute of Chemical Toxicology. October 16, 1997.
63. Invited speaker. "Occupational Asthma". Symposium: Global Management of Airway Disease. University of Michigan Medical School, Division of Pulmonary and Critical Care Medicine. May 9, 1998 Livonia, Michigan.
64. Invited Speaker. "Occupational and Environmental Cancer". Annual Scientific Meeting of the Michigan Occupational and Environmental Medicine Association. September 11, 1998. Traverse City, Michigan
65. Invited Speaker. Epidemiology of Natural Rubber Latex Allergies in Health Care Workers. International Conference on Natural Rubber Latex Sensitivity. San Francisco, CA. Feb 9-10, 2001
66. Invited Speaker. Measurement of physical activity in the occupational setting. American Society for Preventive Oncology 25th Annual Meeting. New York City, NY. March 12, 2001.
67. Invited Speaker. XVI World Congress of Epidemiology. Montreal, Quebec. Risk of Solvent Exposure among Women with Scleroderma. August 20, 2002.
68. Invited Speaker. "Research studies of pesticide exposed populations." National Institute of Environmental Health Sciences, Division of Extramural Research and Training (DERT) Science Retreat. Wilmington, NC. November 21-22, 2002.
69. Invited presentation. Williams JM, Garabrant DH. Assessment of sight and hearing protection use in high school vocational, technical, and industrial education programs. Best Practices in Occupational Safety and Health, Education, Training and Communication. 6th International Conference, Scientific Committee on Education and Training in Occupational Health, ICOH. Baltimore, MD. October 28-30, 2002.
70. Invited presentation. Garabrant DH. Environmental and familial risks to pancreas cancer. University of Texas M.D. Anderson Cancer Center, Division of Cancer Prevention and Program in Cancer Prevention & Control. Houston, Texas. April 25, 2003.
71. Invited discussant. Garabrant DH. Manufacturing Science in Regulated Environments. Presented at the International Symposium on Development and Manufacturing Needs in Health Care Industries in the 21st Century. University of Michigan College of Engineering. Ann Arbor, Michigan September 19, 2003

72. Invited Speaker. Garabrant DH. 2003 Carey Pratt McCord Lecture. "Latex allergy in health care workers". Presented at the annual meeting of the Michigan Occupational and Environmental Medicine Association. Royal Oak, Michigan. November 6, 2003.
73. Invited Speaker. Garabrant DH. "The Michigan Dioxin Exposure Study". MidMichigan Medical Center-Midland Family Practice Department and Continuing Medical Education Department. Ann Arbor, Michigan. May 20, 2004.
74. Invited Speaker. Garabrant DH. "Biomarkers and Risk Assessment". Presented at the Association of Schools of Public Health Conference on Environmental Health Risk: Assessment, Management, and Communications. Minneapolis, Minnesota. July 11-13, 2004.
75. Keynote Speaker. Garabrant DH. "The University of Michigan Dioxin Exposure Study". Michigan Epidemiology Conference 2005. Ann Arbor, Michigan. March 11, 2005.
76. Invited Speaker. Garabrant DH. "Meta Analysis as a Tool for Understanding Asbestos-Related Disease". Presented at the AIHce 2005 Annual Conference of the American Industrial Hygiene Association and American Conference of Governmental Industrial Hygienists. Anaheim, CA May 25, 2005
77. Invited Speaker. Garabrant DH. Mesothelioma risks among auto mechanics. Annual Scientific Meeting of the Michigan Occupational and Environmental Medicine Association. Lansing, MI. September 22, 2005.
78. Invited Speaker. Garabrant DH. "The University of Michigan Dioxin Exposure Study". Michigan's Premier Public Health Conference. Partnerships: Working Together to Improve the health of Michigan's Citizens. Michigan Association for Local Public Health. Grand Rapids, MI October 12, 2005
79. Moderator. Garabrant DH. Session IV Exposure Assessment. First Annual Air Toxics Research Workshop. Mickey Leland National Air Toxics Research Center. Houston, Texas. October 17, 2005.
80. Invited Speaker. Garabrant DH. Biomonitoring in Epidemiology Studies. Michigan Society of Toxicology Fall 2005 Meeting. Lansing, MI. November 4, 2005.
81. Invited speaker. DH Garabrant. Cohort mortality study of transmission and chassis workers. American Osteopathic College of Occupational and Preventive Medicine Mid-Year Conference. Pittsburgh, Pennsylvania. March 18, 2006.
82. Invited Speaker, Grand Rounds. Garabrant DH. Environmental and genetic factors in pancreas cancer. Department of Medicine, University of California, Irvine Medical Center, March 28, 2006.
83. Invited Presentation. Franzblau A, Garabrant D. The University of Michigan Dioxin Exposure Study: Project Overview. Dioxin 2006 Conference, Oslo, Norway. August 21, 2006.
84. Invited Presentation. Olson K, Garabrant D. Prevalence of Exposure Routes in The University of Michigan Dioxin Exposure Study: Food Consumption, Recreational and Household Activities, Occupations and Demographics. Dioxin 2006 Conference, Oslo, Norway. August 21, 2006.
85. Invited Presentation. Adriaens P, Garabrant D. Measurements of Soil Concentrations of PCDDs, PCDFs, and PCBs From a Community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway. August 21, 2006.
86. Invited Presentation. Zwica L, Garabrant D. Measurements of Household Dust Concentrations of PCDDs, PCDFs, and PCBs From a Community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway. August 21, 2006.

87. Invited Presentation. Hedgeman E, Garabrant D. Measurements of Serum Concentrations of PCDDs, PCDFs, and PCBs From a Community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway. August 21, 2006.
88. Invited Presentation. Garabrant D. Environmental Factors That Explain Variation in Serum Dioxin Concentrations in a Community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway. August 21, 2006.
89. Invited Presentation. Chang S-C, Garabrant D. Analysis of Patterns in PCDD, PCDF, and PCB Soil Concentrations From a Community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway. August 21, 2006.
90. Invited Presentation. Lepkowski J, Garabrant D. Survey methodology in an environmental exposure study: methods to assure sound inference. Dioxin 2006 Conference, Oslo, Norway. August 21, 2006.
91. Invited Presentation. Garabrant D. Factors that predict serum dioxin concentrations in Michigan, USA. Dioxin 2007. Tokyo, Japan. September 3, 2007.
92. Invited Presentation. Chen Q, Garabrant D. Serum 2,3,7,8-TCDD concentration in a Michigan, USA population with no unusual sources of exposure. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
93. Invited Presentation. Knutson K, Garabrant D. Linear regression modeling to predict household dust TEQ and TCDD concentration. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
94. Invited Presentation. Hong B, Garabrant D. Impact of the changes in WHO TEF values from 1998 to 2005 on the total TEQ values in serum, household dust and soil. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
95. Invited Presentation. Franzblau A, Garabrant DH. Human exposure to dioxins from clay: a case report. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
96. Invited Presentation. Jolliet O, Garabrant D. Effect of age and historical intake on blood dioxin concentrations: pharmakokinetic modeling to support statistical analyses. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
97. Invited Presentation. Towey T, Garabrant, D. Multivariate statistical analysis of dioxin profiles to explain source contributions to serum dioxins. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
98. Invited Presentation. Trinh H, Garabrant D. spatial distribution of dioxins from an incinerator; a validation study. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
99. Invited Presentation. Garabrant DH. Biomonitoring Results from the University of Michigan Dioxin Exposure Study. The NAS and WHO on Dioxin and Dioxin-like Compounds: International Policy Implications and Potential Impact, Michigan State University, September 19, 2007.
100. Invited Presentation. Garabrant, DH. Factors that predict serum dioxin concentrations in Michigan, USA. 17th Annual Conference of the International Society for Exposure Assessment, Durham, NC. October 16, 2007.
101. Garabrant D. Effective messages in concerned communities: the dioxin exposure study. 2007 Bernstein Symposium. Nanotechnology and Health: Evidence and Impact. University of Michigan Risk Science Center. October 26, 2007.
102. Invited Presentation. Garabrant, DH. Factors that predict serum dioxin concentrations in Michigan, USA. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007..

103. Invited Presentation. Garabrant D. The University of Michigan Dioxin Exposure Study project overview. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
104. Invited Presentation. Garabrant D. Chlorpyrifos exposure, inhibition of butyrylcholinesterase, and paraoxonase (PON1) activity in pesticide manufacturing workers. EPICOH-NEUREOH 2008 Conference, San Jose, Costa Rica, June 11, 2008.
105. Invited Presentation. Jolliet O, Wenger Y, Adriaens P, Chang C-W, Chen Q, Franzblau A, Gillespie BW, Hedgeman E, Hong B, Jiang X, Knutson K, Lepkowski J, Milbrath MO, Reichrt H, Towey T, Garabrant, D. Explaining age dependency using pharmakokinetic modeling in the analysis of blood TCDD concentrations. Dioxin 2008 Conference, Birmingham, England, August, 2008.
106. Invited Presentation. Garabrant DH. Project overview and results of linear regression models of serum dioxin levels. Dioxin 2008 Conference, Birmingham, England, August, 2008.
107. Invited presentation. Garabrant DH. Cancer Mortality among U.S. Automotive Transmission Manufacturing Workers Exposed to Metal Working Fluids," 2008 MRF SYMPOSIUM. October 5-8, Dearborn, Michigan.
108. Invited Presentation. Jiang X, Chen Q, Garabrant D, Hong B, Gillespie B,Lepkowski J, Franzblau A, Adriaens P, Demond A. Logistic Regression Models of High Serum Dioxin Level. Dioxin 2009 Conference, Beijing, China, August 27, 2009.
109. Invited Presentation. Hong B, Garabrant D, Jiang X, Chen Q, Franzblau A, Gillespie B, Lepkowski J, Adriaens P, Demond A. Factors that Predict Serum Concentration of 2,3,7,8-TCDD in People from Michigan, USA. Dioxin 2009 Conference, Beijing, China, August 27, 2009.
110. Invited Presentation. Gillespie B, Reichert H, Chen Q, Franzblau A, Lepkowski J, Adriaens P, Demond A, Luksemburg W, Garabrant D. Estimating Population Percentiles Using the Turnbull Estiamtor When Some Data Are Below the Limit of Detection. Dioxin 2009 Conference, Beijing, China, August 27, 2009.
111. Invited Presentation. Garabrant D, Hong B, Jolliet O, Chen Q, Jiang X, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Towey T, Gillespie B. Public Health Impact of Dioxin Exposure Pathways in the UMDES, Based on Linear Regression Models. Dioxin 2009 Conference, Beijing, China, August 27, 2009..
112. Invited Presentation. Franzblau A, Hedgeman E, Jiang X, Chen Q, Hong B, Knutson K, Towey T, Adriaens P, Demond A, Gillespie B, Jolliet O, Lepkowski J, Garabrant D. The University of Michigan Dioxin Exposure Study: An Investigation of Serum Outliers for TEQ, 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, and PCB-126. Dioxin 2009 Conference, Beijing, China, August 27, 2009.
113. Invited Presentation. Franzblau A, Garabrant D, Gillespie B, Jiang X, Adriaens P, Demond A, Jolliet O, Lepkowski J. Implications of the EPA's new preliminary remediation goals for residential soil based on the University of Michigan Dioxin Exposure Study. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010.
114. Invited Presentation. Garabrant D, Jiang X, Franzblau A, Adriaens P, Demond A, Gillespie B, Jolliet O, Lepkowski J, Hao W. The University of Michigan Dioxin Exposure Study: Relationship between residential soil, household dust, and serum dioxin levels. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010.
115. Invited Presentation. Hao W, Jolliet O, Jiang X, Garabrant D, Franzblau A, Adriaens P, Demond A, Gillespie B, Lepkowski J. The University of Michigan Dioxin Exposure Study:

Dioxin intake due to fish and game consumption in a dioxin-contaminated area. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010.

116. Invited Presentation. Hao W, Jolliet O, Jiang X , Chang C-W, Towey T, Wenger Y, Garabrant D, Franzblau A, Adriaens P, Demond A, Gillespie B, Lepkowski J. The University of Michigan Dioxin Exposure Study: A pharmacokinetic modeling approach to investigate the predictors of serum TCDD concentration. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010.
117. Invited Presentation. Evidence of dioxin exposure in Michigan residents exposed to contaminated soils. The 37th Annual Summer Meeting of the Toxicology Forum. The Aspen Institute, Aspen, Colorado. July 12, 2011.
118. Invited Presentation. Garabant DH. Improving measures in epidemiology: prospective cohort study of chlorpyrifos manufacturing workers. Symposium ILSI Argentina – ILSI HESI – SETAC Capitulo Argentino. Advances in Epidemiology: the impact of pesticides. September 28, 2011. Argentine Scientific Society, Buenos Aires, Argentina.
119. Invited Presentation. Garabrant DH. The University of Michigan Dioxin Exposure Study: Predictors of human serum dioxin concentrations in Midland and Saginaw Michigan. Society of Toxicology of Canada 43rd Annual Symposium. Montreal, Canada. December 4-6, 2011.
120. Invited Presentation. Franzblau A, Broadwater K, Luksemburg W, Maier M, Jiang X, Garabrant DH, Demond A. Serum Concentrations of Polychlorinated Dibenzo-p-dioxins Among Users of Ball Clay. Joint ISEE, ISES and ISIAQ Environmental Health Conference. 19-23 August 2013, Basel, Switzerland.
121. Invited presentation: Garabrant DH. Biomonitoring of chlorpyrifos excretion, butyryl cholinesterase activity, and acetyl cholinesterase activity among chlorpyrifos manufacturing workers. In: Use of spot biomonitoring samples for environmental epidemiology. International Society of Exposure Sciences 25th Annual Meeting. Henderson, NV October 22, 2015.

Bibliography

Peer Reviewed Journals and Publications:

1. Peters JM, Wright WE, Garabrant DH. Occupational epidemiology: detection of cancer in the workplace. West J Med 1982; 137:555-559.
2. Bernstein RS, Sorenson WG, Garabrant DH, Reaux I, Keough B, Hunninghake G, Treitman M. Exposures to respirable airborne penicillium from a contaminated ventilation system: clinical, environmental, and epidemiological aspects. Am Indus Hygiene Assoc J 1983; 44:161-169.
3. Garabrant DH, Peters JM, Mack TM, Bernstein L. Job activity and colon cancer risk. Am J Epidemiol 1984; 119:1005-1014.
4. Garabrant DH, Peters JM, Bernstein L, Smith T. Respiratory and eye irritation from boron oxide and boric acid dusts. J Occup Med 1984; 26:584-586.
5. Garabrant DH, Wegman DH. Cancer mortality among shoe and leather workers in Massachusetts. Am J Indust Med 1984; 5:303-314.
6. Garabrant DH, Peters JM, Bernstein L, Smith T, Wright WE. Respiratory effects of borax dust. Brit J Indust Med 1985; 42:831-837.
7. Garabrant DH. Dermatitis to an aziridine hardening agent used in water based printing ink. Contact Dermatitis 1985; 12:209-212.

8. Peters JM, Garabrant DH, Wright WE, Bernstein L, Mack TM. Uses of a cancer registry to assess occupational cancer risks. National Cancer Institute Monograph 1985; 69:157-161.
9. Osorio AM, Bernstein L, Garabrant DH, Peters JM. Investigation of lung cancer among female cosmetologists. J Occup Med 1986; 28:291-295.
10. Froines JR, Garabrant DH. Quantitative evaluation of manicurists exposure to methyl, ethyl, and isobutyl methacrylate during production of synthetic fingernails. App Indust Hyg 1986; 1:70-74.
11. Garabrant DH, Fine LJ, Oliver C, Bernstein L, Peters JM. Abnormalities of pulmonary function and pleural disease among titanium metal production workers. Scand J Work Health Environ 1987; 13:47-51.
12. Kawamoto MM, Garabrant DH, Balmes JR, Fynboh R, Dimick DV, Simonowitz JA, Held J, Bernstein L. Respiratory effects of cotton dust exposure in the cotton garneting industry. Am J Ind Med 1987; 11:505-515.
13. Garabrant DH, Held J. Mortality study of aircraft manufacturing employees. Scand J Work Health Environ 1987; 13:170-171.
14. Peters JM, Garabrant DH, Preston-Martin S, Yu MC. Is trichloroethylene a human carcinogen? Scand J Work Health Environ 1987; 13:180.
15. Goldberg R, Garabrant DH, Peters JM, Simonowitz J. Excessive lead absorption resulting from exposure to lead naphthenate. J Occup Med 1987; 29:750-751.
16. Barone JA, Peters JM, Garabrant DH, Bernstein L, Krebsbach R. Smoking as a risk factor for noise-induced hearing loss. J Occup Med 1987; 29:741-745.
17. Preston-Martin S, Garabrant DH. Occupational risks for meningiomas of the CNS in Los Angeles County. J Occup Med 1988; 30:14-18.
18. Wright W, Bernstein L, Peters JM, Garabrant DH, Mack TM. Adenocarcinoma of the stomach and exposure to occupational dust. Am J Epidemiol 1988; 128:64-73.
19. Garabrant DH, Held JL, Langholz B, Bernstein L. Mortality of aircraft manufacturing workers in Southern California. Am J Indust Med 1988; 13:683-693.
20. Bowman JD, Garabrant DH, Sobel E, Peters JM. Exposures to extremely low frequency (ELF) electromagnetic fields in occupations with elevated leukemia rates. App Indus Hyg 1988; 3:189-194.
21. Goldberg R, Garabrant DH. Excessive lead absorption. J Occup Med 1988; 30:482.
22. Yu M, Mack TM, Garabrant DH, Peters JM. Tobacco, alcohol, diet, occupation, and carcinoma of the esophagus. Cancer Research 1988; 48:3843-3848.
23. Preston-Martin S, Peters JM, Yu MC, Garabrant DH, Bowman JD. Myelogenous leukemia and electric blanket use. Bioelectromagnetics 1988;9:207-213.
24. Ross RK, Bernstein L, Garabrant DH, Henderson BE. Avoidable non-dietary lifestyle risk factors for cancer. Family Physician 1988;38:153-160.
25. Uba G, Pachorek D, Bernstein J, Garabrant DH, Balmes JR, Wright WE. Prospective study of pulmonary function and symptoms among medical students exposed to formaldehyde. Am J Indust Med 1989;15:91-101.
26. Goldberg R, Bernstein L, Peters JM, Garabrant DH. Occupational fatalities in California, 1972-83. Am J Indust Med 1989;15:177-185.
27. Buckley JD, Robison LL, Swotinsky R, Garabrant DH, LeBeau M, Manchester P, Nesbit ME, Odom L, Peters JM, Woods WG, Hammond GD. Occupational exposures of parents of children with acute nonlymphocytic leukemia. A report from the Children's Cancer Study Group. Cancer Research 1989;49:4030-4037.

28. Hull C, Doyle E, Peters JM, Garabrant DH, Bernstein L, Preston-Martin S. Case-control study of lung cancer in Los Angeles County welders. Am J Indust Med 1989;16:103-112.
29. Peters RK, Garabrant DH, Yu M, Mack TM. A case-control study of occupational and dietary factors in colorectal cancer in young men by subsite. Cancer Research 1989;49:5459-5468.
30. Yu M, Garabrant DH, Huang TB, Henderson BE. Combustion products and other non-dietary risk factors for nasopharyngeal carcinoma in Guangzhou, China. Int J Cancer 1990; 45:1033-1039.
31. Coleman M, Cardis E, Ahlbom A, Aldrich T, Boyle P, Bracken D, Breysse P, Cabanes J, Cartwright R, Cox R, Feychting M, Floderus B, Garabrant D, Goldberg M, Heroux P, Knave B, Maddock B, Pearce N, Salzberg M, Saracci R, Savitz D, Silva M, Theriault G, Vineis P. Extremely low-frequency electric and magnetic fields and risk of human cancer. Bioelectromagnetics 1991; 11:91-99.
32. Ciccioni C, London SJ, Garabrant DH, Bernstein L, Phillips K, Peters JM. Occupational asbestos exposure and mesothelioma risk in Los Angeles County: Application of an occupational hazard survey job-exposure matrix. Amer J Indust Med 1991: 20:371-379.
33. Garabrant DH, Held J, Langholz B, Peters JM, Mack TM. DDT and related compounds and risk of pancreas cancer. J Nat Cancer Inst 1992;84:764-771.
34. Garabrant DH, Peters RK, Homa DM. Asbestos and colon cancer: lack of association in a large case control study. Am J Epidemiology 1992;135:843-853.
35. Peters RK, Pike MC, Garabrant DH, and Mack TM. Diet and colon cancer in Los Angeles County, California. Cancer Causes and Control 3:1992;457-473.
36. Garabrant DH, Held J, Homa D. DDT and pancreatic cancer. J. National Cancer Institute 1993;85:328-329.
37. Homa DM, Garabrant DH, Gillespie B. A meta-analysis of colorectal cancer and asbestos exposure. Amer J Epidemiol 1994;139: 1210-1222.
38. London SJ, Bowman JD, Sobel E. Thomas DC, Garabrant DH, Pearce N, Bernstein L, Peters JM. Exposure to magnetic fields among electrical workers in relation to leukemia risk in Los Angeles County. Amer J Indust Med 1994;26:47-60.
39. Patellos MC, Garabrant DH. Occupational cancer. Primary Care Clinics. 1994; 21 vol 2: 329-348.
40. Wegman DH, Eisen EA, Xu X, Woskie SR, Smith RG, Garabrant DH. Acute and chronic respiratory effects of sodium borate particulate exposures. Environ Health Perspectives 1994; 102 (Suppl 7): 119-128.
41. Bunn WB, Brandt-Rauf PW, Christian JH, Engelberg AL, Garabrant DH, Greaves WW, Guidotti TL, Harris JS, Herzstein J, Hoffman BH, Holthouser MG, McCunney RJ, McLellan RK, Richman J, Stave J, Wald P. Recommended library for occupational and environmental physicians. J Occup Med 1994; 7; 779-783.
42. Garabrant DH, Sulistomo A. The functions of occupational medicine clinics. Indonesian Journal of Occupational Medicine. 1996; 1: 4-8.
43. Mankani S, Homa D, Garabrant DH. Effectiveness of nicotine patches in a workplace smoking cessation program: an eleven month follow-up study. J Occup Med 1996; 38: 184-189.
44. Simpson C, Garabrant DH, Torrey S, Robins TG, Franzblau A. Hypersensitivity pneumonitis-like reaction and occupational asthma associated with 1,3,-bis(isocyanatomethyl) cyclohexane pre-polymer. Amer J Indust Med 1996; 30: 48-55.

45. Burns CJ, Liang TJ, Gillespie BW, Heeringa S, Alcser K, Mayes MD, Wasko MCM, Cooper BC, Garabrant DH, Schottenfeld D. The epidemiology of scleroderma among women: assessment of risk from exposure to silicone and silica. J Rheumatology. 1996; 23: 1904-11.
46. Fryzek JP, Garabrant DH, Greenson JK, Schottenfeld D. A review of the epidemiology and pathology of pancreas cancer. GI Cancer. 1997; 2: 99-110.
47. Akbar N, Basuki B, Garabrant DH, Waspadji S, Noer S. Risk of anti-hepatitis A virus in an urban population in Jakarta. Medical Journal of Indonesia. Oct-Dec 1996.
48. Akbar N, Basuki B, Mulyanto, Garabrant DH, Sulaeman A, Noer HMS. Ethnicity, socioeconomic status, transfusion and risk of hepatitis B and C infection. J Gastroenterol Hepatol 12; 752-757:1997.
49. Fryzek JP, Garabrant DH, Harlow SD, Severson RK, Gillespie BW, Schenk M, Schottenfeld D. A case-control study of self-reported exposures to pesticides and pancreas cancer in southeastern Michigan. Int J Cancer 1997; 72: 62-67.
50. Wald PH, Herzstein J, Brandt-Rauf PW, Bunn WB, Chester TJ, Engleberg AL, Garabrant DH, Greenberg GN, Guidotti TL, et al. Recommended library and electronic resources for occupational and environmental physicians. Journal of Occupational and Environmental Medicine, vol 39; 469-480: 1997.
51. Simpson CL, Garabrant DH, Fryzek J, Homa DM, Peters RK. Wood dust exposure and colon cancer. Int J Occup Environ Health. 1998 Jul;4(3):179-183.
52. Lacey JV Jr, Garabrant DH, Laing TJ, Gillespie BW, Mayes MD, Cooper BC, Schottenfeld D. Risk of solvent exposure among women with undifferentiated connective tissue disease. Amer J Epidemiology 1999; 149:761-770.
53. Garabrant DH, Dumas C. Epidemiology of organic solvents and connective tissue disease. Arthritis Research 2000; 2:5-15.
54. Albers JW, Wald JJ, Garabrant DH, Trask CL, Berent S. Neurologic evaluation of workers previously diagnosed with solvent-induced toxic encephalopathy. Journal of Occupational and Environmental Medicine 2000; 42:410-423.
55. Fryzek JP, Lipworth LL, Garabrant DH, Mandel JS, McLaughlin JK. Comparison of surrogate with self-respondents for occupational factors. Journal of Occupational and Environmental Medicine 2000; 42: 424-429.
56. Garabrant DH. Epidemiologic principles in the evaluation of suspected neurotoxic disorders. Neurology Clinics 2000; 18, number 3: 631-648.
57. Garabrant DH, Roth HD, Parsad R, Ying GS, Weiss J. Latex sensitization in health care workers and in the U.S. general population. American Journal of Epidemiology 2001; 153: 515-522.
58. Garabrant DH, Roth HD, Parsad R, Ying GS, Weiss J. Garabrant et al. respond to Wartenberg and Buckler. (RE: Latex sensitization in health care workers and in the U.S. general population.) American Journal of Epidemiology 2001; 153: 527-528.
59. Schenk MJ, Schwartz AG, O'Neal E, Kinnard M, Greenson J, Fryzek JP. Ying GS, Garabrant DH. Familial risk of pancreas cancer. Journal National Cancer Institute 2001; 93: 640-644.
60. Albers JW, Wald JJ, Trask CL, Garabrant DH, Berent S. Evaluation of blink reflex results obtained from workers previously diagnosed with solvent induced toxic encephalopathy. J Occup Environ Med 2001; 43:713-722.
61. Korczak JF, Barnholtz-Sloan JS, Schenk MJ, Bunner SH, Kinnard M, Schwartz AG, Garabrant DH. A putative codominant gene and smoking account for cancer susceptibility

in families of pancreatic cancer patients. American Journal Human Genetics 2001; 69(4):405.
62. Laing TJ, Schottenfeld D, Lacey JV, Gillespie BW, Garabrant DH, Cooper BC, Heeringa SG, Alcser K, Mayes MD. Potential risk factors for undifferentiated connective tissue disease among women: implanted medical devices. Amer J Epidemiology 2001; 154:610-617.
63. Michalek JE, Akhtar FZ, Arezzo JC, Garabrant DH, Albers JW. Serum dioxin and peripheral neuropathy in veterans of Operation Ranch Hand. NeuroToxicology 2001; 22:479-490.
64. Garabrant DH, Philbert MA. Review of 2,4-dichlorophenoxyacetic acid (2,4-D) epidemiology and toxicology. Critical Reviews in Toxicology. 2002; 32(4):233-257.
65. Garabrant DH, Schweitzer S. Epidemiology of latex sensitization and allergies in health care workers. Journal of Allergy and Clinical Immunology. 2002; 110: S82-S95.
66. Martin SA, Harlow SD, Sowers MF, , Longnecker MP, Garabrant DH, , Shore DL, Sandler DP. DDT metabolite and androgens in African-American farmers. Epidemiology 2002; 13:454-458.
67. Garabrant DH, Lacey JV Jr, Laing TJ, Gillespie BW, Mayes MD, Cooper BC, Schottenfeld D. Scleroderma and solvent exposure among women. American Journal of Epidemiology 2003; 157: 493-500.
68. Akhtar, FZ, Garabrant, DH, Michalek, JE. Cancer in US Air Force Veterans of the Vietnam War. Organohalogen Compounds 64, 243-246 (2003)
69. Goodman M, Teta MJ, Hessel PA, Garabrant DH, Craven, VA, Strafford CG, Kelsh MA. Mesothelioma and lung cancer among motor vehicle mechanics: a meta analysis. Annals of Occupational Hygiene 2004; 48: 309-326.
70. Albers JW, Garabrant DH, Schweitzer SJ, Garrison RP, Richardson RJ, Berent S. The effects of occupational exposure to chlorpyrifos on the peripheral nervous system: a prospective cohort study. Occupational & Environmental Medicine, 2004; 61:201-211.
71. Albers JW, Garabrant DH, Schweitzer SJ, Garrison RP, Richardson RJ, Berent S. Absence of sensory neuropathy among workers with occupational chlorpyrifos exposure. Muscle & Nerve, 2004; 29: 677-686.
72. Akhtar FZ, Garabrant DH, Ketchum NS, Michalek JE. Cancer in US air force veterans of the Vietnam war. Journal of Occupational & Environmental Medicine, 2004; 46:123-136.
73. Albers JW, Berent S, Garabrant DH, Giordani BG, Schweitzer SJ, Garrison RP, Richardson RJ. The effects of occupational exposure to chlorpyrifos on the neurological examination of central nervous system function: A prospective cohort study. Journal of Occupational & Environmental Medicine, 2004 ; 46:367-378.
74. Kingman A, Albers JW, Arezzo JC, Garabrant, DH, Michalek, JE. Amalgam Exposure and Neurological Function. NeuroToxicology, 2005 26: 241-255.
75. Fryzek JP, Schenk M, Kinnard M, Greenson JK, Garabrant DH. The association of body mass index and pancreatic cancer in residents of southeastern Michigan – 1996-1999. American Journal of Epidemiology, 2005; 162 (3): 222-228.
76. Burns CJ, Garabrant DH, Schweitzer S, Albers JW, Berent S, Giordani B, Garrison R. Chlorpyrifos exposure and biological monitoring among manufacturing workers. Occupational & Environmental Medicine 2006; 63 (3): 218-220.
77. Adriaens P, Demond A, Towey T, Chang S-C, Chen Q, Franzblau A, Garabrant D, Gillespie B, Gwinn D, Hedgeman E, Hong B, Knutson K, Ladronka K, Lee CY, Lepkowski J, Olson K, Sima C, Sinibaldi J, Ward B, and Zwica L. Measurements of soil

concentrations of PCDD/PCDF/PCBs from a community in Michigan, USA. Organohalogen Compounds, vol 68: 217-219: 2006.

78. Chang S-C, Adriaens P, Towey T, Wright D, Demond A, Gillespie B, Franzblau A, and Garabrant D. Analysis of patterns in PCDD, PCDF, and PCB soil concentrations from a community in Michigan USA. Organohalogen Compounds, vol 68: 229-231: 2006.
79. Franzblau A, Garabrant D, Adriaens P, Gillespie BW, Demond A, Olson K, Ward B, Hedgeman E, Knutson K, Zwica L. Towey T, Chen Q, Ladronka K, Sinibaldi J, Chang S-C, Lee S-Y, Gwinn D, Sima C, Swan S, and Lepkowski J The University of Michigan Dioxin Exposure Study: project overview. Organohalogen Compounds, vol 68: 205-208: 2006.
80. Garabrant D, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Zwica L, Chen Q, Olson K, Ward B, Towey T, Ladronka K, Sinibaldi J, Chang S-C, Lee S-Y, Gwinn D, Sima C, Swan S, and Gillespie, BW. Environmental factors that explain variation in serum dioxin concentrations in a community in Michigan, USA. Organohalogen Compounds, vol 68: 225-228: 2006.
81. Hedgeman E, Chen Q, Gillespie BW, Franzblau A, Knutson K, Zwica L, Sima C, Lee S-Y, Lepkowski J, Ward B, Ladronka K., Olson K, Sinibaldi J, Towey T, Adriaens P, Demond A, Chang S-C, Gwinn D, Swan S, and Garabrant D. Measurements of serum concentrations of PCDDs, PCDFs, and PCBs from a community in Michigan, USA. Organohalogen Compounds, vol 68: 223-224: 2006.
82. Olson K, Lepkowski J, Lohr-Ward B, Ladronka K, Sinibaldi J, Garabrant D, Franzblau A, Adriaens P, Gillespie B, Bandyk J, Chang S-C, Chen Q, Demond A, Gwinn D, Hedgeman E, Hong B, Knutson K, See S-Y, Sima C, Towey T, Wright D, and Zwica L. Prevalence of exposure routes in the University of Michigan Dioxin Exposure Study: food consumption, recreational and household activities, occupations and demographics. Organohalogen Compounds, vol 68: 213-216: 2006.
83. Zwica L, Knutson K, Towey T, Hedgeman E, Franzblau A, Chen Q, Lee S-Y, Sima C, Gillespie BW, Adriaens P, Demond A, Lepkowski J, Ward B, Ladronka K, Olson K, Sinibaldi J, Chang S-C, Gwinn D, Swan S, and Garabrant D. Measurements of household dust concentrations of PCDDs, PCDFs, and PCBs from a community in Michigan, USA. Organohalogen Compounds, vol 68: 220-222: 2006.
84. Lepkowski, J. Survey methodology in an environmental exposure study: methods to assure sound inference. Organohalogen Compounds, vol 68: 209-212: 2006.
85. Chen Q, Lee –SY, Hedgeman E, Ghosh D, Gillespie BW, Lepkowski J, and Garabrant D. Comparison of machine learning methods and linear regression models in identifying important predictor variables for serum dioxin TEQ for a community in Michigan, USA. Organohalogen Compounds, vol 68: 1305-1307: 2006.
86. Chen Q, Lee S-Y, Hedgeman E, Olson K, Little RJA, Elliott MR, Gillespie BW, Lepkowski J, Garabrant D, and Franzblau A. Environmental factors that explain variation in the upper percentiles of serum dioxin concentrations in a community in Michigan, USA. Organohalogen Compounds, vol 68: 1302-1304: 2006.
87. Franzblau A, Hedgeman E, Chen Q, Lee SY, Adriaens P, Demond A, Garabrant D, Gillespie B, and Lepkowski J. A follow-up investigation of high serum outliers from the University of Michigan Dioxin Exposure Study. Organohalogen Compounds, vol 68: 1313-1314: 2006.
88. Franzblau A, Nosowsky R, Garabrant D, Lepkowski J, Olson K, Gillespie BW, Adriaens P, Demond A, and Churchill SJ. Human subject considerations in the environmental

research: the University of Michigan Dioxin Exposure Study. Organohalogen Compounds, vol 68: 1315-1318: 2006.
89. Garabrant D, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Zwica L, Chen Q, Olson K, Ward B, Towey T, Ladronka K, Sinibaldi J, Chang S-C, Lee S-Y, Gwinn D, Sima C, Swan S, and Gillespie BW. Background levels of PCDDs, PCDFs, and PCBs in blood, soil and household dust in the general population of Michigan, USA. Organohalogen Compounds, vol 68: 1319-1322: 2006.
90. Gillespie BW, Chen Q, Lee S-Y, Hong B, Garabrant D, Hedgeman E, Sima C, Lepkowski J, Olsen K, and Luksemburg W. A comparison of data analysis options when some values are below the limit of detection (LOD). Organohalogen Compounds, vol 68: 1323-1326: 2006.
91. Hedgeman E, Chang S-C, Towey T, Demond A, Adriaens P, Chen Q, Franzblau A, Gillespie BW, Sima C, and Garabrant D. Principal components analysis of serum PCDDs, PCDFs, and PCBs from a community in Michigan, USA. Organohalogen Compounds, vol 68: 1331-1332: 2006.
92. Hedgeman E, Chen Q, Gillespie BW, Franzblau A, and Garabrant D. A comparison of serum PCDD, PCDF, and PCB levels from a community in Michigan, USA with the United States population. Organohalogen Compounds, vol 68: 1329-1330: 2006.
93. Hedgeman E, Maier M, Luksemburg W, Patterson D, Lee S-Y, Knutson K, Franzblau A, and Garabrant D. Quality assurance methods during the serum analyses of PCDD, PCDF, and PCB levels for the University of Michigan Dioxin Exposure Study. Organohalogen Compounds, vol 68: 1327-1328: 2006.
94. Knutson K, Chen Q, Gillespie BW, Hong B, Hedgeman E, Ward B, Olson K, Franzblau A, and Garabrant D. Pregnancy and breast feeding and their relationship to serum PCDD, PCDF, and PCB levels for a community in Michigan, USA. Organohalogen Compounds, vol 68: 1333-1335: 2006.
95. Ladronka K, Ward B, Olson K, Freeland S, Sinibaldi J, Hedgeman E, Zwica L, Towey T, Demond A, Franzblau A, Garabrant D, Adriaens P, and Lepkowski J. Cross-organizational training on the University of Michigan Dioxin Exposure Study: ensuring consistency, confidentiality and cooperation in data collection. Organohalogen Compounds, vol 68: 1336-1339: 2006.
96. Ward B, Ladronka K, Skoman M, Olson K, Sinibaldi J, Lepkowski J, Blackburn Z, Freeland S, Franzblau A, Hedgeman E, Zwica L, Towey T, Demond A, and Garabrant D. Considerations for managing a large multi-faceted study involving multiple organizations. Organohalogen Compounds, vol 68: 1363-1366: 2006.
97. Zwica L, Chang S-C, Towey T, Knutson K, Adriaens P, Demond A, Chen Q, Gillespie BW, Franzblau A, and Garabrant D. Principal components analysis of household dust concentrations of PCDDs, PCDFs, and PCBs from a community in Michigan, USA. Organohalogen Compounds, vol 68: 1367-1369: 2006.
98. Zwica L, Franzblau A, Knutson K, Gillespie BW, Chen Q, Lee S-Y, Hong B, and Garabrant D. Predictors of household dust concentrations of PCDDs, PCDFs, and PCBs in a community in Michigan, USA. Organohalogen Compounds, vol 68: 1373-1375: 2006.
99. Adriaens P, Towey T, Chang S-C, Demond A, Chen Q, Hong B, Lee CY, Gillespie BW, Luksemburg W, Maier M. Analysis of vegetation concentrations of PCDD/F/PCBS from a community in Michigan, USA. Organohalogen Compounds, vol 68: 1360-1362: 2006.
100. Fryzek JP, Garabrant DH, Schenk M, Kinnard M, Greenson JK, Sarkar FH. The association between selected risk factors for pancreatic cancer and the expression of p53

and K-ras codon 12 mutations. International J of Gastrointestinal Cancer 2006; 37: 139-145.
101. Franzblau A, Zwica L, Knutson K, Chen Q, Lee S-Y, Hong B, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski J, Luksemburg W , Maier M, Towey T. A follow-up investigation of homes with 'high' concentrations of PCDDs, PCDFs and dioxin-like PCBs in house dust. Organohalogen Compounds, vol 69: 2192-2195: 2007.
102. Towey T, Adriaens P, Demond A, Gillespie B, Franzblau A, Garabrant D. Sensitivity analysis of soil dioxin cluster profiles to regional specification for a community in Michigan, USA. Organohalogen Compounds, vol 69: 2256-2259: 2007.
103. Goovaerts P, Trinh H, Adriaens P. Construction and validation of a geostatistical model of PCDD and PCDF deposition from incineration. Organohalogen Compounds, vol 69: 234-238: 2007.
104. Trinh H, Adriaens P. Congener-specific differentiation of soil samples in the city of Midland, Michigan using multidimensional scaling. Organohalogen Compounds, vol 69: 2207-2211: 2007.
105. Towey, T, Barabas, N, Chang, S-C, Hedgeman, E, Zwicka, L, Garabrant, D, Adriaens, P. Multivariate statistical analysis of dioxin profiles to explain source contributions to serum dioxins. Organohalogen Compounds, vol 69: 230-233: 2007.
106. Jolliet O, Wenger Y, Milbrath MO, Chang C-W, Chen Q, Franzblau, A, Garabrant D, Towey T, Adriaens P and Gillespie, BW. Effect of age and historical intake on blood dioxin concentrations: pharmakokinetic modeling to support statistical analyses. Organohalogen Compounds, vol 69: 226-229: 2007.
107. Chen Q, Elliott MR, Little RJA, Hedgeman E, Gillespie BW, Garabrant D. Methods in estimating quantiles of serum dioxin concentration by age, with values below limit of detection. Organohalogen Compounds, vol 69: 2232-2235: 2007.
108. Milbrath MO, Chang C-W, Emond C, Franzblau A, Garabrant D, Gillespie BW, Wenger Y,Adriaens P and Jolliet O. Half-lives of dioxins, furans, and PCBs as a function of age, body fat, breastfeeding, and smoking status. Organohalogen Compounds, vol 69: 2252-2255: 2007.
109. Milbrath MO, Wenger Y, Gillespie BW, Jolliet O. Apparent half-lives of dioxins, furans, and PCBs in adults and children. Organohalogen Compounds, vol 69: 2248-2251: 2007.
110. Wenger Y, Adriaens P, Franzblau A, Garabrant D, Gillespie BW, Milbrath MO, Towey T, Jolliet O. Historical trends of dioxins and furans in sediments and fish from the Great Lakes. Organohalogen Compounds, vol 69: 2228-2231: 2007.
111. Lee S-Y, Zwica L, Knutson K, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust PCDD congener concentrations. Organohalogen Compounds, vol 69: 2244-2246: 2007.
112. Lee S-Y, Zwica L, Knutson K, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust PCB congener concentrations. Organohalogen Compounds, vol 69: 2240-2242: 2007.
113. Garabrant D, Hong B, Chen Q, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Zwica L, Chang C-W, Lee S-Y, Olson K, Towey T, Trin H, Wenger Y, Luksemburg W, Maier M, Gillespie BW. Factors that predict serum dioxin concentrations in Michigan, USA. Organohalogen Compounds, vol 69: 206-209: 2007.

114. Knutson K, Zwica L, Lee S-Y, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust PCDF congener concentrations. Organohalogen Compounds, vol 69: 2236-2239: 2007.
115. Knutson K, Zwica L, Lee S-Y, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust TEQ and TCDD concentration. Organohalogen Compounds, vol 69: 214-217: 2007.
116. Chang C-W, Garabrant D, Franzblau A, Hedgeman E, Knutson K, Gillespie B, Hong B,Chen Q, Lee S-Y, Adriaens P, Demond A, Trin H, Towey T, Sima C, Lepkowski J. Association of soil dioxin concentration with serum dioxin concentrations in Midland, Michigan, USA. Organohalogen Compounds, vol 69: 2216-2219: 2007.
117. Franzblau A, Towey T, Demond A, Adriaens P, Chang SC, Garabrant D, Gillespie B, Gwinn D, Hong B, Lepkowski J, Luksemburg W, Maier M, Olson K, Trin H. Case study of residences with anomalous soil concentrations of PCDDs, PCDFs, and PCBs in a community in Michigan, USA. Organohalogen Compounds, vol 69: 2224-2226: 2007.
118. Hong B, Olson K, Lepkowski J, Hedgeman E, Chen Q, Lee S-Y, Chang C-W, Ward B, Ladronka K, Gillespie BW, Franzblau A, Adriaens P, Demond A , Garabrant D. The effects of sample design on statistical inferences from the University of Michigan Dioxin Exposure Study. Organohalogen Compounds, vol 69: 2212-2215: 2007.
119. Hedgeman E, Chen Q, Hong B, Knutson K, Lee S-Y, Olson K, Lohr-Ward B, LaDronka K, Maier M, Luksemburg W, Lepkowski J, Gillespie B, Franzblau A, Garabrant D. Current estimates of background serum TCDD levels in the United States. Organohalogen Compounds, vol 69: 2196-2199: 2007.
120. Franzblau A, Hedgeman E, Chen Q, Lee S-Y, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski J, Luksemburg W , Maier M. Human exposure to dioxins from clay: a case report. Organohalogen Compounds, vol 69: 222-225: 2007.
121. Gillespie BW, Chang C-W, Hedgeman E, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olsen K, Adriaens P, Demond A, Towey T, Zwica L, LaDronka K, Ward B, Luksemburg W, Maier M, Franzblau A, and Garabrant D. Predictors of serum 2378-TCDD concentration in a background population in Michigan, USA. Organohalogen Compounds, vol 69: 2264-2267: 2007.
122. Chen Q, Hedgeman E, Little RJA, Elliott MR, Gillespie BW, Lee S-Y, Hong B, Chang C-W, Olson K, Knutson K, Zwica L, Adriaens P, Demond A, Lepkowski J, Franzblau A, Patterson D, Garabrant D. Serum 2,3,7,8-TCDD concentration in a Michigan, USA population with no unusual sources of exposure. Organohalogen Compounds, vol 69: 210-213: 2007.
123. Chang C-W, Gillespie BW, Hedgeman E, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olsen K, Adriaens P, Demond A, Towey T, Zwica L, LaDronka K, Ward B, Luksemburg W, Maier M, Franzblau A, and Garabrant D. Predictors of serum 2378-pentacdf concentration in a background population in Michigan, USA and in a representative USA sample. Organohalogen Compounds, vol 69: 2188-2191: 2007.
124. Demond A, Adriaens P, Towey T, Chang SC, Franzblau A, Garabrant D, Gillespie B, Hong B, Lepkowski J, Luksemburg W, Maier M, Trin H. Impact of changes in who TEF values from 1998 to 2005 on measurements of soil concentrations of PCDDs, PCDFs and PCBs in a community in Michigan, USA. Organohalogen Compounds, vol 69: 2220-2223: 2007.

125. Garabrant D, Chen Q, Hong B, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Zwica L, Chang C-W, Lee S-Y, Olson K, Towey T, Jolliet O, Wenger Y, Gillespie BW. Logistic regression models for high serum 2,3,7,8-TCDD concentrations in residents of Midland, Michigan, USA. Organohalogen Compounds, vol 69: 2203-2206: 2007.
126. Hong B, Hedgeman E, Gillespie BW, Chen Q, Lee S-Y, Chang C-W, Zwical L, Knutson K, Towey T, Olson K, Sima C, Luksemburg W, Maier M, Adriaens P, Demond A, Lepkowski J, Franzblau A, Garabrant D. Impact of the changes in who TEF values from 1998 to 2005 on the total TEQ values in serum, household dust and soil. Organohalogen Compounds, vol 69: 218-221: 2007.
127. Hedgeman E, Hong B, Chen Q, Knutson K, Lee S-Y, Olson K, Lohr-Ward B, LaDronka K, Maier M, Luksemburg W , Lepkowski J, Gillespie B, Franzblau A, Garabrant D. Change in background serum levels with the new 2005 TEFs. Organohalogen Compounds, vol 69: 2200-2202: 2007.
128. Albers JW, Garabrant DH, Mattsson JL, Burns CG, Cohen SS, Sima C, Garrison RP, Richardson RJ, Giordani B, Berent S. Dose effect analyses of occupational chlorpyrifos exposure and peripheral nerve electrophysiology. Toxicological Sciences 2007; 97(1):196-204.
129. Garabrant DH. Case-control study design: spurious associations between exposure and outcome. J Occup Environ Med 2007; 49(9): 941-942.
130. Cote ML, Schenk MJ, Schwartz AG, Vigneau FD, Greenson JK, Fryzek JP, Ying GS, Garabrant DH. Risk of other cancers in individuals with a family history of pancreas cancer. J Gastrointestinal Cancer 2007;38(2-4):119-26.
131. Franzblau A, Hedgeman E, Chen Q, Lee S-Y, Adriaens P, Demond A, Garabrant D, Gillespie B, Hong B, Jolliet O, Lepkowski J, Luksemburg W, Maier M, Wenger Y. Human Case Report: Exposure to Dioxins from Clay. Environmental Health Perspectives 2008; 116(2):238-42.
132. Goovaerts P, Trinh HT, Demond A, Franzblau Garabrant D, Gillespie B, Lepkowski J, Adriaens P. Geostatistical Modeling of the Spatial Distribution of Soil Dioxins in the Vicinity of an Incinerator. 1. Theory and Application to Midland, Michigan. Environmental Science and Technology 2008; 42 (10): 3648-3654.
133. Demond A, Adriaens P, Towey T, Chang SC, Hong B, Chen Q, Chang C-W, Franzblau A, Garabrant D, Gillespie B, Hedgeman E, Knutson K, Lee CY, Lepkowski J, Olson K, Ward B, Zwica L, Luksemburg W, Maier M. Statistical Comparison of Residential Soil Concentrations of PCDDs, PCDFs and PCBs from Two Communities in Michigan, USA. Environmental Science and Technology 2008; 42: 5441-5448.
134. Goovaerts P, Trinh HT, Demond AH, Towey T, Chang S-C, Gwinn D, Hong B, Franzblau A, Garabrant D, Gillespie BW, Lepkowski J, Adriaens P. Geostatistical Modeling of the Spatial Distribution of Soil Dioxin in the Vicinity of an Incinerator. 2. Verification and Calibration Study. Environmental Science and Technology, 2008; 42: 3655-3661.
135. Gillespie BW, Reichert H, Chang C-W, Hedgeman E, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olsen K, Adriaens P, Demond A, Towey T, Ward B, Luksemburg W, Maier M, Franzblau A. Predictors of 8 furan congeners in background U.S. populations: data from two Michigan counties in the U.S. National Health and Nutrition Examination Survey (NHANES). Organohalogen Compounds, vol 70: 1112-1115: 2008.

136. Franzblau A, Demond A, Towey T, Adriaens P, Chang SC, Garabrant D, Gillespie B, Hong B, Lepkowski J, Luksemburg W, Maier M. Mechanisms of contamination of soils with dioxin-like compounds in background areas in Michigan USA. Organohalogen Compounds, vol 70: 90-93: 2008.
137. Demond A, Towey T, Knutson K, Hong B, Adriaens P, Chang S-C, Chen Q, Franzblau A, Garabrant D, Gillespie B, Lepkowski J, Luksemburg W, Maier M. Relationship between concentrations of PCDDs, PCDFs and dioxin-like PCBs in vegetation and soil on residential properties. Organohalogen Compounds, vol 70: 1032-1035: 2008.
138. Gillespie BW, Reichert H, Chang C-W, Hedgeman E, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olsen K, Adriaens P, Demond A, Towey T, Ward B, Luksemburg W, Maier M, Franzblau A, Garabrant D. Predictors of 7 dioxin congeners in background U.S. populations: data from two Michigan counties and the U.S. National Health and Nutrition Examination Survey (NHANES). Organohalogen Compounds, vol 70: 1108-1111: 2008.
139. Knutson K, Hong B, Chen Q, Chang C-W, Jiang X, Hedgeman E, Towey T, Gillespie BW, Franzblau A, Lepkowski J, Adriaens P, Demond A, Garabrant DH. The relationship between dioxin concentrations (TEQ) in blood and breast feeding. Organohalogen Compounds, vol 70: 1387-1390: 2008.
140. Trinh H, Goovaerts P, Garabrant D, Hong B, Gwinn D, and Adriaens P. Congener-specific deposition of dioxins from an incinerator in Midland, Michigan. Organohalogen Compounds, vol 70: 1434-1437: 2008.
141. Jolliet O, Wenger Y, Adriaens P, Chang C-W, Chen Q, Franzblau A, Gillespie BW, Hedgeman E, Hong B, Jiang X, Knutson K, Lepkowski J, Milbrath MO, Reichert H, Garabrant D. Influence of age on serum dioxin concentrations as a function of congener half-life and historical peak environmental contamination. Organohalogen Compounds, vol 70: 1936-1938: 2008.
142. Jolliet O, Jiang X, Wenger Y, Milbrath MO, Chang C-W, Chen Q, Hong B, Hedgeman E, Garabrant D, Franzblau A, Lepkowski J, Towey T, Adriaens P, Gillespie BW. Model formats and use of pharmakokinetic modeling for the statistical analysis of blood dioxin concentrations. Organohalogen Compounds, vol 70: 102-105: 2008.
143. Garabrant D, Hong B, Chen Q, Chang C-W, Jiang X, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Towey T, Gillespie BW. Predictors of serum PCDF concentrations in people from Michigan, USA. Organohalogen Compounds, vol 70: 2047-2050: 2008.
144. Garabrant D, Hong B, Chen Q, Chang C-W, Jiang X, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Towey T, Gillespie BW. Predictors of serum TEQ and PCDD concentrations in people from Michigan, USA. Organohalogen Compounds, vol 70: 94-97: 2008.
145. Garabrant D, Hong B, Chen Q, Chang C-W, Jiang X, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Towey T, Gillespie BW. Predictors of serum PCB concentrations in people from Michigan, USA. Organohalogen Compounds, vol 70: 1236-1239: 2008.
146. Franzblau A, Hedgeman E, Knutson K, Chen Q, Hong B, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski, J. The University of Michigan Exposure Study: a follow-up investigation of cases with high serum concentrations of 2,3,4,7,8-pentaCDF. Organohalogen Compounds, vol 70: 943-945: 2008.

147. Franzblau A, Hedgeman E, Knutson K, Towey T, Chen Q, Hong B, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski, J. The University of Michigan Exposure Study: a follow-up investigation of a case with high serum concentrations of 2,3,4,7,8-pentachlorodibenzofuran. Organohalogen Compounds, vol 70: 86-89: 2008.
148. Hedgeman E, Hong B, Chen Q, Chang C-W, Knutson K, Demond A, Adriaens P, Gillespie B, Lepkowski J, Franzblau A, Garabrant D. Sport fish consumption by the general population from a waterway contaminated with PCDDs and PCDFs. Organohalogen Compounds, vol 70: 1391-1394: 2008.
149. Towey T, Noemi B, Demond A, Zwica L, Knutson K, Franzblau A, Garabrant D, Adriaens P. Statistical fingerprinting of PCBs using the subset with dioxin-like activity. Organohalogen Compounds, vol 70: 2348-2351: 2008.
150. Towey T, Barabas N, Demond A, Hedgeman E, Garabrant D, Adriaens, P. Age adjustment approaches for multivariate analysis of serum dioxins and furans. Organohalogen Compounds, vol 70: 110-113: 2008.
151. Chen Q, Garabrant D, Hedgeman E, Gillespie B, Hong B, Knutson K, Lepkowski J, Franzblau A, Patterson DG,Jr. Serum dioxin concentrations among the U.S. non-Hispanic white general population. Organohalogen Compounds, vol 70: 106-109: 2008.
152. Trinh H, Goovaerts P, Garabrant D, Hong B, Gwinn D, Adriaens P. Comparison of ISCST3 and AERMOD air dispersion model to predict dioxin deposition from an incinerator in Midland, Michigan. Organohalogen Compounds, vol 70: 1431-1433: 2008.
153. Milbrath MO, Wenger Y, Chang C-W, Emond C, Garabrant D, Gillespie BW, Jolliet O. Apparent Half-Lives of Dioxins, Furans, and PCBs as a function of Age, Body Fat, Smoking Status, and Breastfeeding. Environmental Health Perspectives. 2009; 117 (3): 417-425.
154. Jolliet O, Yvan W, Milbrath MO, Garabrant DH, Jang X, and Gillespie B. Pharmacokinetic modeling to support the statistical analysis of blood dioxin concentration. Epidemiology, November 2008; 19(6):S372.
155. Hong B, Garabrant DH, Chen Q, Chang C-W, Jang X, Hedgeman E, Gillespie BW, Lepkowski J, and Franzblau A. Variable selection methods influence the identification of factors that predict serum dioxin concentrations in Michigan, USA. Epidemiology, November 2008; 19(6):S282.
156. Garabrant DH, Hong B, Chen Q, Chang C-W, Jiang X, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Towey T, and Gillespie BW. Factors that predict serum PCB, PCDD, and PCDF concentrations in Michigan, USA. Epidemiology, November 2008; 19(6):S265.
157. Hedgeman E, Chen Q, Hong B, Knutson K, Lee S-Y, Olson K, Lohr-Ward B, LaDronka K, Lepkowski J, Gillespie BW, Franzblau A, and Garabrant DH. Current estimates of population serum PCDD, PCDF, and dioxin-like PCB levels in the United States. Epidemiology, November 2008; 19(6):S235.
158. Chen Q, Garabrant DH, Hedgeman E, Gillespie BW, Hong B, Knutson K, Lepkowski J, Franzblau A, and Jolliet O. Serum dioxin, furan, and PCB concentrations and half-life study among the U.S. general population. Epidemiology, November 2008; 19(6):S233-234.
159. Knutson K, Hong B, Chen Q, Chang C-W, Hedgeman E, Towey T, Jolliet O, Gillespie BW, Franzblau A, Lepkowski J, Adriaens P, Demond A, and Garabrant DH. The relationship between blood serum dioxin levels and breast feeding. Epidemiology, November 2008; 19(6):S179.

160. Franzblau A, Hedgeman E, Knutson K, Towey T, Chen Q, Hong B, Adriaens P, Demond A, Garabrant, DH, Gillespie BW, and Lepkiowski J. The University of Michigan Dioxin Exposure Study: A follow-up investigation of cases with high serum concentrations of 2,3,4,7,8-PentaCDF. Epidemiology, November 2008; 19(6):S236.
161. Franzblau A, Zwica L, Knutson K, Chen Q, Lee S-Y, Hong B, Adriaens P, Demond A, Garabrant D, Gillespie B, Lepkowski J, Luksemburg W, Maier M, Towey T. An investigation of homes with high conentrations of PCDDs, PCDFs, and/or dioxin-like PCBs in house dust. Journal of Occupational and Environmental Hygiene 2009;6:188-199.
162. Garabrant DH, Franzblau A, Lepkowski J, Gillespie BW, Adriaens P, Demond A, Ward B, LaDronka K, Hedgeman E, Knutson K, Zwica L, Olson K, Towey T, Chen Q, and Hong B. The University of Michigan Dioxin Exposure Study: methods for an environmental exposure study of polychlorinated dioxins, furans and biphenyls. Environmental Health Perspectives 2009; 117(5):803-810.
163. Hedgeman B, Chen Q, Hong B, Chang C-W, Olson K, LaDronka K, Ward B, Adriaens P, Demond A, Gillespie BW, Lepkowski J, Franzblau A, and Garabrant DH. The University of Michigan Dioxin Exposure Study: population survey results and serum concentrations for polychlorinated dioxins, furans and biphenyls. Environmental Health Perspectives 2009; 117(5):811-817.
164. Garabrant DH, Franzblau A, Lepkowski J, Gillespie BW, Adriaens P, Demond A, Hedgeman E, Knutson K, Zwica L, Olson K, Towey T, Chen Q, Hong B, Chang C-W, Lee S-Y, Ward B, LaDronka K, Luksemburg W, and Maier M. The University of Michigan Dioxin Exposure Study: predictors of human serum dioxin concentrations in Midland and Saginaw, Michigan. Environmental Health Perspectives 2009; 117(5):818-824.
165. Franzblau A, Demond A, Towey T, Adriaens P, Chang SC, Luksemburg W, Maier M, Garabrant D, Gillespie B, Lepkowski J, Chang CW, Chen Q, Hong B. Residences with anomalous soil concentrations of dioxin-like compounds in two communities in Michigan, USA: a case study. Chemosphere 2009; 74:395-403.
166. Salay E, Garabrant DH. Polychlorinated biphenyls and thyroid hormones in adults: a critical appraisal of epidemiological studies. Chemosphere, 2009; 74(11):1413-9.
167. Stolzenberg-Solomon RZ, Sheffler-Collins S, Weinstein S, Garabrant DH, Mannisota S, Taylor P, Virtamo J, Albanes D. Vitamin E intake, α-tocopherol status, and pancreatic cancer in a cohort of male smokers. American Journal of Clinical Nutrition, 2009; 89 (2): 584-91.
168. Garabrant DH, Aylward LL, Berent S, Chen Q, Timchalk C, Burns CJ, Hays SM, Albers JW. Cholinesterase inhibition in chlorpyrifos workers: Characterization of biomarkers of exposure and response in relation to urinary TCPy. Journal of Exposure Science and Environmental Epidemiology, 2009; 19: 634-642.
169. Albers JW, Garabrant DH, Berent S, Richardson RR. Paraoxonase (PON1) status and plasma butyrylcholinesterase activity in chlorpyrifos manufacturing workers. Journal of Exposure Science and Environmental Epidemiology, 2010; 20: 79-89.
170. Towey T, Adriaens P, Chang S-C, Demond A, Wright D, Barabás N, Franzblau A, Garabrant DH, Gillespie BW, Lepkowski J, Luksemburg W. Hierarchical cluster analysis of dioxins and furans in Michigan soils: evaluation of industrial and background congener profiles. Environmental Toxicology and Chemistry 2010; 29: 64-72.
171. Chen Q, Garabrant DH, Hedgeman E, Little RJA, Elliott MR, Gillespie B, Hong B, Lee SY, Lepkowski JM, Franzblau A, Adriaens P, Demond AH, Patterson DG, Jr.. Estimation

of background serum 2,3,7,8-TCDD concentrations using quantile regression in the Michigan (UMDES) and NHANES populations. Epidemiology 2010; 21:S51-S57.
172. Gillespie BW, Chen Q, Reichert H, Franzblau A, Hedgeman E, Lepkowski J, Adriaens P, Demond A, Luksemburg W, Garabrant DH.. Estimating population distributions when some data are below a limit of detection by using a reverse Kaplan-Meier estimator. Epidemiology 2010; 21:S64-S70.
173. Franzblau A, Hedgeman E, Jolliet O, Knutson K, Towey T, Chen Q, Hong B, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski J. 2010. Case report: the University of Michigan dioxin exposure study: a follow-up investigation of a case with high serum concentration of 2,3,4,7,8-pentachlorodibenzofuran. Environmental Health Perspectives 2010; 118: 1313-1317.
174. Hong B, Garabrant D, Hedgeman E, Demond A, Gillespie B, Chen Q, Chang C-W, Towey T, Knutson K, Franzblau A, Lepkowski J, Adriaens P. Impact of WHO 2005 revised toxic equivalency factors for dioxins on the TEQs in serum, household dust and soil. Chemosphere 2009; 76: 727-733.
175. Demond A, Towey T, Adriaens P, Zhong X, Knutson K, Chen Q, Hong B, Gillespie B, Chang S-C, Franzblau A, Garabrant D, Lepkowski J, Luksemburg W, Maier M. 2010. Relationship between PCDD, PCDF, and dioxin-like PCB concentrations in vegetation and soil on residential properties. Environmental Toxicology and Chemistry 2010;29(12):2660-2668.
176. Demond A,Franzblau A, Garabrant DH, Jiang X,Adriaens P, Chen Q,Gillespie B, Hao W, Hong B, Jolliet O, Lepkowski J. Dioxins in soil and human exposure. Environmental Science and Technology 2012; 46: 1296-1302.
177. Towey T, Barabas N, Demond D, Franzblau A, Garabrant D, Gillespie B, Lepkowski J, Adriaens P. Polytopic vector analysis of soil, dust, and serum samples to evaluate exposure sources of PCDDs/Fs. Environmental Toxicology and Chemistry 2012; 31 (10):2191-2200.
178. Chen Q, Jiang X, Hedgeman E, Knutson K, Gillespie B, Hong B, Lepkowski J, Franzblau A, Jolliett O, Adraiens P, Demond A, Garabrant D. Estimation of Age- and Sex- Specific Background Human Serum Concentrations of PCDDs, PCDFs, and PCBs in the UMDES and NHANES Populations. Chemosphere 2013; 91:817-823.
179. Dourson ML, Gadagbui B, Griffin S, Garabrant DH, Haws L, Kirman C, Tohyama C. The importance of problem formulations in risk assessment: a case study involving dioxin-contaminated soil. Regulatory Pharmacology and Toxicology 2013; 66: 208-216.
180. Fryzek JP, Pastula S, Jiang X, Garabrant DH. Childhood cancer incidence in Pennsylvania counties in relation to living in counties with hydraulic fracturing sites. Journal of Occupational and Environmental Medicine 2013; 55 (7): 796-801.
181. Broadwater K; Meeker JD, Luksemburg W, Maier M, Garabrant D, Demond A, Franzblau A. Evaluation of the release of dioxins and PCBs during kiln-firing of ball clay. Chemosphere 2014; 94: 70-75.
182. Berent S, Giordani B, Albers JW, Garabrant DH, Cohen SS, Garrison RP, Richardson RR. Effects of occupational exposure to chlorpyrifos on neuropsychological function: a prospective cohort study. Neurotoxicology 2014; 41: 44-53.
183. Cohen SC, Sadoff MM, Jiang X, Fryzek JP, Garabrant DH. A review and meta-analysis of cancer risks in relation to Portland cement exposure. Occup Environ Med 2014; 71(11):796-802.

184. Alexander DD, Jiang X, Bylsma LC, Garabrant DH, Irvin SR, Fryzek JP. Historical cancer incidence and mortality assessment in an Illinois community proximal to a former manufactured gas plant. BMJ Open 2014; 4: e006713/bmjopen-2014-006713.
185. Garabrant DH, Alexander DD, Miller PE, Fryzek JP, Boffetta P, Teta MJ, Hessel PA, Craven VA, Kelsh MA, Goodman M. 2015. Mesothelioma among Motor Vehicle Mechanics: An Updated Review and Meta-analysis. Ann Occup Hyg1-19.

Non Peer Reviewed Publications

186. Mosely C, Garabrant DH, Fine L. Health Evaluation Report 79-17-751, RMI Metals Reduction Plant. U.S. Department of Health and Human Services, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio, 1979.
187. Garabrant DH, Peters JM, Bernstein L, Smith T, Wright WE. US Borax and Chemical Corporation, Boron, California: Health Hazard Evaluation. Final Report. National Institute of Occupational Safety and Health, Cincinnati, Ohio, 1983.
188. Kawamoto MM, Garabrant DH, Balmes JR, Dimick DV, Simonowitz JA, Held J, Bernstein L. Respiratory effects of cotton dust exposure in the cotton garneting industry. I. Epidemiological study. Health Hazard Evaluation. Special Studies Unit, Division of Occupational Safety and Health, Department of Industrial Relations, State of California, Sacramento, California, 1985.
189. Garabrant DH. Mortality study of Rohr employees. Final report. November 4, 1986.
190. Koehler G, Papanek PJ, Karbus J, Antebi S, Arterberry JD, Bayer M, Davies D, Garabrant DH, McCarthy E, Medina A, Notani-Sharma P, Ridgeway M. Hazardous materials medical management protocols, first edition. Hazardous Materials Advisory Committee, California Emergency Medical Services Authority. Sacramento, California. March 1989
191. Garabrant DH, Held J. Final report: Case control study of pancreas cancer at the Philadelphia plant of the Rohm & Haas Corporation. January 1991.
192. Kern DG, Christiani DC, Kelsey KT, Hu H, Frumkin H, Kreiss K, Rose C Newman LS, Jarvis J, Garabrant DH, et al. Asbestos-related diseases [letter]. New England J Med 1991;324:195-197.
193. Bowman JD, Sobel E, London SJ, Thomas DC, Garabrant DH, Pearce N, Peters JM. Electric and magnetic field exposures, chemical exposures and leukemia risk in "electrical" occupations. Palo Alto, CA. Electric Power Research Institute. October 1992.
194. Garabrant DH, Held J. Standardized mortality analysis of Uniroyal Goodrich Tire Company employees at the Woodburn, Indiana Plant. March 25, 1993.
195. Robins TG, Garabrant DH, Franzblau A, Perlman D. Board certified occupational physicians: a non-residential training program in occupational medicine [letter]. Journal of Occupational Medicine 1993; 35:350-352.
196. Garabrant DH, Held J. Study of pulmonary function among Kimberly-Clark employees exposed to polyacrylate polymer absorbent. November 1994.
197. Garabrant DH, Levine SP. A critical review of the methods of exposure assessment and the pulmonary effects of TDI and MDI in epidemiologic studies. Chemical Manufacturers' Association. November 1994.
198. Garabrant DH, Harlow S. Investigation of pregnancy outcomes at Nissan Research & Development, Farmington Hills, Michigan. November 1994.

199. Franzblau A, Minoshima S, Robins TG, Garabrant DH. Re: Comparison of single photon emission computed tomography in cases of healthy adults and solvent exposed adults. [letter] Amer J Indust Med 1997;32:695-697.
200. Garabrant DH, Kinnard M, Fryzek J. The Epidemiology of Pancreatic Cancer. Michigan Oncology Journal. Pages 4-5. Summer 1997.
201. Garabrant DH. Assessment of Health Risks Related to Airborne Emissions from the Environmental Quality Site in Van Buren Township, Michigan. February, 1998.
202. Garabrant DH, Philbert MA. Review of 2,4-dichlorophenoxyacetic acid (2,4-D) epidemiology and toxicology. Industry Task Force II on 2,4-D Research Data. April 2000.
203. Garabrant DH, Franzblau A. Incidence of latex sensitization [Letter]. American Journal of Respiratory and Critical Care Medicine 2001; 63: 1501.
204. Garabrant DH, Roth HD, Parsad R, Ying GS, Weiss J. Reply to Budnick LD. Re: Latex sensitization in health care workers and in the U.S. general population. [Letter]. American Journal of Epidemiology 2001; 154:190-191.
205. Albers JW, Wald JJ, Garabrant DH, Trask CL, Berent S. Reply to letter RE: Neurologic evaluation of workers previously diagnosed with solvent-induced toxic encephalopathy. Journal of Occupational and Environmental Medicine 2002; 44 (5):394-395.
206. Garabrant DH, Schweitzer S. Reply to Baur X. Re: Epidemiology of latex sensitization and allergies in health care workers. J Allergy Clin Immunol 2003; 113:652-653.
207. Albers JW, Berent S, Garabrant DH, Garrison R, Giordani B, Richardson RJ, Casenas L, Freymuth AK, Wolfe J, Levine SP, Baughman J, Humpert E, Kauszler M, Meima E, Schultz AM, Schweitzer S, Martinez S, Li Z, Gillespie B, Raz J, Bradsahw N. The effects of chlorpyrifos on human behavior and the nervous system. Submitted to Dow AgroSciences, October 20, 2003.
208. Franzblau A, Garabrant DH. Re: Respiratory impairment due to asbestos exposure in brake-lining workers [Letter] Environmental Research 2004; 96: 102-108.
209. Garabrant DH, Simpson C, Ying GS. Case-Control Study of Leukemia and Lymphoma at the Ford Sharonville Plant. Submitted to the UAW-Ford National Joint Committee for Health and Safety. Jan 3, 2004.
210. Garabrant DH, Pastula S, Fryzek J, Ying GS. Final Report. A mortality study of transmission and chassis and stamping plant workers. Submitted to the UAW-Ford National Joint Committee for Health and Safety. Jan 5, 2004.
211. Garabrant DH. Blood Study Ongoing: Too Soon for Conclusions. The Saginaw News (Michigan), Sunday, February 13, 2004.
212. Adriaens P, Garabrant DH, Franzblau A, Gillespie B, Lepkowski J. Michigan dioxin exposure study: planning phase and protocol development. Organohalogen Compounds 2004; 66: 2497-2503.
213. Garabrant, DH, Dow Won't Influence Study, The Saginaw News (Michigan), Sunday, Sept. 19, 2004.
214. Garabrant DH, Privacy Key Word In Dioxin Study, Midland Daily News (Michigan), Sunday, Nov. 7, 2004
215. Garabrant DH, James RC. Trichloroethylene and cancer in humans: recognizing the need for an evidence based analysis. [Letter] Toxicology 2005; 212: 80-84.

Book Chapters

216. Garabrant DH, Olin R. Carcinogens and cancer risks in the microelectronics industry. In: LaDou J, editor, State of the Art Reviews: Occupational Medicine. Vol 1, No 1, January-March, 1986. Hanley and Belfus, Inc, Philadelphia, pp 119-134.
217. Peters RK, Mack TM, Garabrant DH, Homa DM, Pike MC. Calcium and colon cancer in Los Angeles County. In: Lipkin M, Newmark HL, Kelloff G, editors. Calcium, Vitamin D, and Prevention of Colon Cancer. CRC Press, Boca Raton, 1991, 113-118.
218. Roth V, Garabrant DH. Required worker training and communication in occupational medicine. In: McCunney R., editor. Handbook of Occupational Medicine. 2nd Edition. Little, Brown and Company, Boston, 1994.
219. Garabrant DH, Kinnard M, Schenk MJ, Fryzek J, Braselton E. The epidemiology of pancreatic cancer: environmental and medical risk factors. In: Sarkar F and Dugan M, editors. Pancreatic Cancer: Molecular and Clinical Management Prospects. Natick, Massachusetts. Eaton Publishing, 1998.
220. Albers JW, Garabrant DH. Arsenic poisoning. In: Lynn DJ, Kissle JT, Newton H, and Rae-Grant A, Editors. The 5 minute neurology consult. Philadelphia, Pennsylvania, Lippincott Williams & Wilkins. 2002.
221. Roth V, Garabrant DH, Turet C. Health risk communication. In McCunney, RJ., editor. A practical approach to occupational and environmental medicine. 3rd Edition. Lippincott Williams & Wilkins, Philadelphia, 2003, pages 690-698.
222. Franzblau A, Garabrant DH. Chromium. In Rosenstock L and Cullen MR, editors. Textbook of Clinical Occupational and Environmental Medicine, 2nd Edition. W.B. Saunders Company, Philadelphia. 2005, pages 958-960.
223. Franzblau A, Garabrant DH. Nickel. In Rosenstock L and Cullen MR, editors. Textbook of Clinical Occupational and Environmental Medicine, 2nd Edition. W.B. Saunders Company, Philadelphia. 2005, pages 961-963.
224. Albers JW, Garabrant DH. Arsenic poisoning. In: Lynn DJ, Kissle JT, Newton H, and Rae-Grant A, Editors. The 5 minute neurology consult, 2nd Edition. Philadelphia, Pennsylvania, Lippincott Williams & Wilkins. 2011.

Abstracts

225. Program Chairman. 29th Annual Western Occupational Health Conference. Western Occupational Medical Association. Irvine, California, 1985
226. Program Committee Member. American Occupational Medical Association Annual Meeting. Los Angeles, California, 1984
227. Seminar Faculty Member. Epidemiology for the Occupational Medicine Physician. American Occupational Medical Association. Los Angeles, California, 1984
228. Seminar Faculty Member. Toxicology. Quality Care in the Workers' Compensation system. Post graduate course sponsored by the State of California, Division of Industrial Accidents Workers' Compensation Appeals Board and USC School of Medicine. Los Angeles, California, 1985
229. Seminar Faculty Member. American Occupational Medical Association Basic Curriculum in Occupational Medicine. Denver, Colorado, 1984
230. Occupational Epidemiology Forum, held 3 times a year jointly by Occupational Medicine Departments at USC, UCLA, and Irvine. 1981-1987
231. Program Chairman. American College of Occupational Medicine. State of the Art Conference. Pittsburgh, Pennsylvania, October 1990.

232. London SJ, Bowman JD, Sobel E, Pearce NE, Garabrant DH, Peters JM. Assessment of electric and magnetic field exposures by job. Presented at the 23rd International Conference on Occupational Health, Montreal, Quebec, September 22-28, 1990
233. Garabrant DH, Held J, Langholz B. DDT and pancreas cancer in a case-control study of chemical workers. Presented at the Society for Epidemiological Research Annual Meeting, Buffalo, NY, June 1991
234. Bowman JD, Sobel E, Peters JM, London SJ, Garabrant DH. Assessment of occupational exposures to magnetic fields (abstract). Department of Energy/EPRI Contractor's Review Meeting, November, 1989, Portland, OR.
235. Homa DM, Garabrant DH, Gillespie, B. A meta-analysis of colorectal cancer and asbestos exposure assessing direct estimators and proxies of exposure. Poster presented at the Department of Epidemiology Research Meeting, University of Michigan School of Public Health, October 19, 1992.
236. Abstract. Schenk M, Garabrant DH. Gender specific patterns of malignant mesothelioma in metropolitan Detroit. Proceedings of the American Public Health Association, November 1993
237. Scientific Planning Committee. American Occupational Health Conference. Annual Meeting of the American College of Occupational and Environmental Medicine. June 3-4, 1994, Chicago, Illinois. April 15-22, 1994
238. Scientific Planning Committee. Annual Scientific Meeting of the Michigan Occupational and Environmental Medicine Association, June 3-4, 1994
239. Poster. Fryzek JP, Garabrant DH, Hanash S, Braselton EW, Schenk MJ. DDT and Related Compounds and Pancreas Cancer. Histopathobiology of Neoplasia Workshop. Keystone, Colorado. June 1995.
240. Abstract. Liang TJ, Gillespie BW, Burns C, Garabrant DH, Heeringa SG, Alcser, Schottenfeld D. American College of Rheumatology National Scientific Meeting. Risk factors for scleroderma among Michigan women. San Francisco, CA. October 22-26, 1995.
241. Poster. Akbar N, Basuki B, Garabrant DH, Waspadji S, Noer S. Risk of anti-hepatitis A virus in an urban population in Jakarta. IX Triennial International Symposium on Viral Hepatitis and Liver Disease. Rome, Italy. April 21-25, 1996.
242. Abstract. London SJ, Bowman JD, Sobel E. Thomas DC, Garabrant DH, Pearce N, Bernstein L, Peters JM. Exposure to magnetic fields among electrical workers in relation to leukemia risk in Los Angeles County. Journal of Safety Research, Volume 27, Issue 1, Spring 1996, Page 57
243. Abstract. Liang TJ, Gillespie BW, Lacey JV, Garabrant DH, Cooper BC, Heeringa SG, Alcser KH, Cho S, Mayes M, Schottenfeld D. American College of Rheumatology 60th National Scientific Meeting. Orlando, FL. The association between silicone exposure and undifferentiated connective tissue disease among women in Michigan and Ohio. October 18-22, 1996.
244. Abstract. Schenk M, Fryzek JP, Garabrant DH, Braselton EW, VaitkeviciusVK. A case control study of serum DDE levels and pancreas cancer. Joint Conference of the American Association for Cancer Research and the International Agency for Research on Cancer. Carcinogenesis from Environmental Pollution: Assessment of Human Risk and Strategies for Prevention. Budapest, Hungary. October 6-9, 1996.

245. Abstract. Schenk M, Fryzek JP, Garabrant DH, Braselton EW. A case control study of serum DDE levels and pancreas cancer. American Public Health Association 124th Annual Meeting. New York, NY. November 17-21, 1996.
246. Abstract. Kinnard MF, Garabrant DH, Fryzek J. The association of peptic ulcer disease and pancreatic cancer. Digestive Disease Week. Meeting of the American Gastroenterological Association. Washington, DC. May 12, 1997.
247. Abstract. Lacey JV, Garabrant DH, Gillespie BW, Cooper BC, Laing TJ, Mayes MD, Schottenfeld D. Self-reported exposure to solvents in women with undifferentiated connective tissue disease (UCTD). American College of Rheumatology 61st National Scientific Meeting. Washington, DC. November 8-12, 1997.
248. Abstract. Lacey JV, Garabrant DH, Gillespie BW, Cooper BC, Laing TJ, Mayes MD, Schottenfeld D. Self-reported exposure to solvents in women with systemic sclerosis (SSc). American College of Rheumatology 61st National Scientific Meeting. Washington, DC. November 8-12, 1997.
249. Panel Discussion. Garabrant DH, discussant. Measurement of physical activity. Workshop on physical activity and breast cancer. Sponsored by the National Action Plan on Breast Cancer, American Cancer Society, Susan G. Komen Breast Cancer Foundation, and US Public Health Service's Office on Women's Health. Albuquerque, NM. November 13-14, 1997.
250. Scientific Session. Garabrant, DH, moderator. Health Effects of Pesticides. Society for Epidemiologic Research 31st Annual Meeting. Chicago, IL June 25, 1998
251. Abstract. Lacey JV, Garabrant DH, Mayes MD, Laing TJ, Gillespie BW, Schottenfeld D. Self-reported exposure to pesticides and herbicides as risk factors for undifferentiated connective tissue disease. American College of Rheumatology 62nd National Scientific Meeting. San Diego, CA. November 1998.
252. Abstract. Lacey JV, Mayes MD, Laing TJ, Gillespie BW, Garabrant DH, Schottenfeld D. Self-reported medical history and medication use among women with undifferentiated connective tissue disease. American College of Rheumatology 62nd National Scientific Meeting. San Diego, CA. November 1998.
253. Abstract. Williams JM, Garabrant DH. Assessment of sight and hearing protection use in high school vocational, industrial and technical education programs. American Public Health Association 128th Annual Meeting, Boston, MA. November 12-16, 2000.
254. Abstract. Garabrant DH. Epidemiology of Natural Rubber Latex Allergies in Health Care Workers. International Conference on Natural Rubber Latex Sensitivity. San Francisco, CA. Feb 9-10, 2001
255. Abstract. Korczak JF, Barnholtz-Sloan JS, Schenk MJ, Bunner SH, Kinnard M, Schwartz AG, Garabrant DH. A putative codominant gene and smoking account for cancer susceptibility in families of pancreatic cancer patients. American Society of Human Genetics Annual Meeting. San Diego, CA. Oct 16, 2001.
256. Invited Presentation and Session Moderator. Garabrant DH. Risk Assessment in the Context of Trade Disputes: How Well Are the Scientific Principles Incorporated Into the Resolution of Science-Based Trade Disputes? University of Michigan International Institute, Ann Arbor, Michigan November 1-2, 2001.
257. Abstract. Korczak JF, Johnson OE, Schenk M, Kinnard M, Schwartz AG, Garabrant DH. The Contribution of Genes and Smoking to the Transmission of Pancreatic Cancer Susceptibility. International Genetic Epidemiology Society Annual Meeting, New Orleans, November 2002.

258. Abstract: Akhtar, FZ, Garabrant, DH, Michalek, JE (2003), Cancer in US Air Force Veterans of the Vietnam War. Dioxin 2003 Conference. Boston, Massachusetts, August 24-29, 2003. http://www.dioxin20xx.org/pdfs/2003/03-578.pdf
259. Abstract. Goodman M, Teta MJ, Hessel PA, Garabrant DH, Craven, VA, Strafford CG, Kelsh MA. Mesothelioma and lung cancer among motor vehicle mechanics: a meta analysis. Society for Risk Analysis 2003 Annual Meeting. Baltimore, MD, December 7-10, 2003
260. Abstract. Berent S, Giordani B, Garabrant DH, Schweitzer S, Garrison RP, Richardson RJ, Albers JW. Neuropsychological function in workers with occupational exposure to chlorpyrifos (CPF). 56th Annual Meeting of the American Academy of Neurology. San Francisco, CA. April 24, 2004
261. Abstract. Adriaens P, Garabrant DH, Franzblau A, Gillespie B, Lepkowski J. Michigan dioxin exposure study: planning phase and protocol development. Presented at Dioxin 2004. Berlin, Germany. Sept 8, 2004.
262. Abstract. Wadström, T., Fryzek, J.P., Demirjian, S., Choi, J.W., Garabrant D.H., Nyrén, O., Ye, W., Nilsson, I., Ljungh, Å.H. Antibodies to Helicobacter bilis in patients with pancreatic carcinoma. European Helicobacter Study Group XVII International Workshop, September 22 - 24, 2004, Vienna, Austria.
263. Medical Monitoring Expert Panel. Hexavalent Chromium Exposure in Willits, California. California Department of Health Services. San Francisco, California. March 29, 2006
264. Poster. Adriaens P, Towey T, Chang S-C, Demond A, Chen Q, Hong B, Lee S-Y, Gillespie B, Maier M, and Luksemburg W. Analysis of vegetation concentrations of PCDD/F/PCBS from a community in Michigan USA. Dioxin 2006, Oslo, Norway, August 21-25, 2006.
265. Poster. Adriaens P, Goovaerts P, and Swan S. Geostatistical analysis of PCDD and PCDF deposition from incineration using stack emissions and soil data. Dioxin 2006, Oslo, Norway, August 21-25, 2006.
266. Poster. Olson K, Sinibaldi J, Lepkowski J, Lohr-Ward B, and LaDronka K. Examination of nonresponse bias in the University of Michigan Dioxin Exposure Study. Dioxin 2006, Oslo, Norway, August 21-25, 2006.
267. Poster. Chen Q, Lee S-Y, Gillespie BW, Ghosh D, Hong B, Hedgeman E, Lepkowski J, and Garabrant D. Comparison of machine learning method and linear regression models in identifying important predictor variables for serum PCDD, PCDF, and PCB levels for a community in Michigan USA. Dioxin 2006, Oslo, Norway, August 21-25, 2006.
268. Poster. Olson K, Lohr-Ward B, Hedgeman E, Bandyk J, LaDronka K, Alcser K, Collings T, Franzblau A, and Lepkowski J. M. Communicating complex research results regarding environmental risk to a lay audience: experiences from the University of Michigan Dioxin Exposure Study. Dioxin 2006, Oslo, Norway, August 21-25, 2006.
269. Poster. Towey T, Wenger Y, Adriaens P, Chang S-C, Hedgeman E, Demond A, and Jolliet O. Combined intake and pharmacokinetic model to predict serum TCDD concentrations. Dioxin 2006, Oslo, Norway, August 21-25, 2006.
270. Poster. Towey T, Adriaens P, Demond A, Wright D, Gwinn D, and Gillespie B. Spatial analysis of PCDD, PCDF and PCB soil concentrations from a community in Michigan USA. Dioxin 2006, Oslo, Norway, August 21-25, 2006.
271. Poster. Olson K, Sinibaldi J, Lepkowski J. M, Lohr-Ward B, LaDronka K, Towey T, Wright D, and Gillespie BW. Missing data in an environmental exposure study: imputation to improve survey estimation. Dioxin 2006, Oslo, Norway, August 21-25, 2006.

272. Poster. Chen Q, Lee S-Y, Hedgeman E, Olson K, Little, RJA, Elliott, MR, Gillespie BW, Lepkowski J, Garabrant D, Franzblau, A. Environmental factors that explain variation in the upper percentiles of serum dioxin concentrations in a community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
273. Poster. Chen Q, Lee S-Y, Hedgeman E, Ghosh D, Gillespie BW, Lepkowski J, Garabrant D. Comparison of machine learning methods and linear regression models in identifying important predictor variables for Serum Dioxin TEQ For a community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
274. Poster. Demond A, Towey T, Chang, SC, Adriaens P, Luksemburg, W, Maier, M, Favaro K, Wenning R, Kennington BP. Methods for sampling and analyzing soil for the University of Michigan Dioxin Exposure Study. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
275. Poster. Franzblau A, Hedgeman E, Chen Q, Lee, SY, Adriaens P, Demond A, Garabrant D, Gillespie B, Lepkowski J. A follow-up investigation of high serum outliers from the University of Michigan Dioxin Exposure Study. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
276. Poster. Franzblau A, Nosowsky R, Garabrant D, Lepkowski J, Olson K, Gillespie BW, Adriaens P, Demond A, Churchill SJ. Human subject considerations in environmental research: The University of Michigan Dioxin Exposure Study. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
277. Poster. . Garabrant DH, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Zwica L, Chen Q, Olson K, Ward B, Towey T, Ladronka K, Sinibaldi J, Chang, S-C, Lee C, Gwinn D, Sima C, Swan S, Gillespie, B. Background levels of PCDDs, PCDFs, and PCBs in blood, soil, and household dust in the general population of Michigan, USA Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
278. Poster. Gillespie B, Chen Q, Lee, SY, Hong B, Garabrant D, Hedgeman E, Sima C, Lepkowski J, Olson K, Luksemburg, W. A comparison of data analysis options when some values are below the Limit of Detection (LOD). Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
279. Poster. Hedgeman E, Maier M, Luksemburg W, Patterson D, Knutson K, Franzblau A, Garabrant D, Lee, SY. Quality assurance methods during the serum analyses of PCDD, PCDF, and PCB levels for the University of Michigan Dioxin Exposure Study. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
280. Poster. Hedgeman E, Chen Q, Gillespie BW, Franzblau A, Garabrant D. A comparison of serum PCDD, PCDF, and PCB levels from a community in Michigan, USA with the United States population. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
281. Poster. Hedgeman E, Chang , S-C, Towey , T, Demond , A, Adriaens , P, Chen Q, Franzblau , A, Gillespie BW, Sima , C, Garabrant , D. Principal components analysis of serum PCDDs, PCDFs, and PCBs from a community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
282. Poster. Knutson K, Chen Q, Gillespie BW, Hong B, Hedgeman E, Ward B, Olson K, Franzblau A, Garabrant D. Pregnancy and breast feeding and their relationship to serum PCDD, PCDF, and PCB levels for a community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
283. Poster. Ladronka K, Ward B, Olson K, Freeland S, Sinibaldi J, Hedgeman E, Zwica L, Towey T, Demond A, Franzblau A, Garabrant D, Adriaens P, Lepkowski J. Cross-organizational training on the University of Michigan Dioxin Exposure Study: ensuring

consistency, confidentiality and cooperation in data collection. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.

284. Poster. Ward B, Ladronka K, Skoman M, Olson K, Sinibaldi J, Lepkowski J, Blackburn, Z, Freeland, S, Franzblau A, Hedgeman E, Zwica L, Towey T, Demond A, Garabrant D. Considerations for managing a large, multi-faceted study involving multiple organizations. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
285. Poster. Zwica L, Chang, S-C, Towey T, Knutson K, Adriaens P, Demond A, Chen Q, Gillespie B, Franzblau A, Garabrant D. Principal components analysis of household dust concentrations of PCDDs, PCDFs, and PCBs from a community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
286. Poster. Zwica L, Franzblau A, Knutson K, Gillespie BW, Chen Q, Lee S-Y, Hong B, Garabrant D. Predictors of household dust concentrations of PCDDs, PCDFs, and PCBs in a community in Michigan, USA. Dioxin 2006 Conference, Oslo, Norway, August 21-25, 2006.
287. Abstract. Variable Selection for Multiply-Imputed Large Data Set in Dioxin Exposure Study. Qixuan Chen, James Lepkowski, Brenda Gillespie, David Garabrant. ENAR Biostatistics Conference, New York City, March 17, 2007.
288. Poster. Franzblau A, Zwica L, Knutson K, Chen Q, Lee S-Y, Hong B, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski J, Luksemburg W , Maier M, Towey T. A follow-up investigation of homes with 'high' concentrations of PCDDs, PCDFs and dioxin-like PCBs in house dust. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
289. Poster. Towey T, Adriaens P, Demond A, Gillespie B, Franzblau A, Garabrant D. Sensitivity analysis of soil dioxin cluster profiles to regional specification for a community in Michigan, USA. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
290. Poster. Goovaerts P, Trinh H, Adriaens P. Construction and validation of a geostatistical model of PCDD and PCDF deposition from incineration. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
291. Poster. Trinh H, Adriaens P. Congener-specific differentiation of soil samples in the city of Midland, Michigan using multidimensional scaling. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
292. Poster. Towey, T, Barabas, N, Chang, S-C, Hedgeman, E, Zwicka, L, Garabrant, D, Adriaens, P. Multivariate statistical analysis of dioxin profiles to explain source contributions to serum dioxins. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
293. Poster. Jolliet O, Wenger Y, Milbrath MO, Chang C-W, Chen Q, Franzblau, A, Garabrant D, Towey T, Adriaens P and Gillespie, BW. Effect of age and historical intake on blood dioxin concentrations: pharmakokinetic modeling to support statistical analyses. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
294. Poster. Gillespie BW, Jolliet O, Chang C-W, Milbrath M, Wenger Y, Chen Q, Towey T, Lee S-Y, Hong B, Garabrant D, Franzblau A, Hedgeman E, Knutson K, Adriaens P, Demond A, Trin H, Lepkowski J, Olsen K, Luksemburg W. Comparing ways to model historical dioxin exposure in food as a predictor of current serum dioxin concentration. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
295. Poster. Chen Q, Elliott MR, Little RJA, Hedgeman E, Gillespie BW, Garabrant D. Methods in estimating quantiles of serum dioxin concentration by age, with values below limit of detection. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
296. Poster. Milbrath MO, Chang C-W, Emond C, Franzblau A, Garabrant D, Gillespie BW, Wenger Y,Adriaens P and Jolliet O. Half-lives of dioxins, furans, and PCBs as a function

of age, body fat, breastfeeding, and smoking status. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.

297. Poster. Wenger Y, Adriaens P, Franzblau A, Garabrant D, Gillespie BW, Milbrath MO, Towey T, Jolliet O. Historical trends of dioxins and furans in sediments and fish from the Great Lakes. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
298. Poster. Lee S-Y, Zwica L, Knutson K, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust PCDD congener concentrations. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
299. Poster. Lee S-Y, Zwica L, Knutson K, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust PCB congener concentrations. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
300. Poster. Garabrant D, Hong B, Chen Q, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Zwica L, Chang C-W, Lee S-Y, Olson K, Towey T, Trin H, Wenger Y, Luksemburg W, Maier M, Gillespie BW. Factors that predict serum dioxin concentrations in Michigan, USA. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
301. Poster. Knutson K, Zwica L, Lee S-Y, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust PCDF congener concentrations. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
302. Poster. Knutson K, Zwica L, Lee S-Y, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust TEQ and TCDD concentration. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
303. Poster. Chang C-W, Garabrant D, Franzblau A, Hedgeman E, Knutson K, Gillespie B, Hong B,Chen Q, Lee S-Y, Adriaens P, Demond A, Trin H, Towey T, Sima C, Lepkowski J. Association of soil dioxin concentration with serum dioxin concentrations in Midland, Michigan, USA. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
304. Poster. Franzblau A, Towey T, Demond A, Adriaens P, Chang SC, Garabrant D, Gillespie B, Gwinn D, Hong B, Lepkowski J, Luksemburg W, Maier M, Olson K, Trin H. Case study of residences with anomalous soil concentrations of PCDDs, PCDFs, and PCBs in a community in Michigan, USA. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
305. Poster. Hong B, Olson K, Lepkowski J, Hedgeman E, Chen Q, Lee S-Y, Chang C-W, Ward B, Ladronka K, Gillespie BW, Franzblau A, Adriaens P, Demond A , Garabrant D. The effects of sample design on statistical inferences from the University of Michigan Dioxin Exposure Study. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
306. Poster. Hedgeman E, Chen Q, Hong B, Knutson K, Lee S-Y, Olson K, Lohr-Ward B, LaDronka K, Maier M, Luksemburg W, Lepkowski J, Gillespie B, Franzblau A, Garabrant D. Current estimates of background serum TCDD levels in the United States. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
307. Poster. Franzblau A, Hedgeman E, Chen Q, Lee S-Y, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski J, Luksemburg W , Maier M. Human exposure to dioxins from clay: a case report. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
308. Poster. Gillespie BW, Chang C-W, Hedgeman E, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olsen K, Adriaens P, Demond A, Towey T, Zwica L, LaDronka K,

Ward B, Luksemburg W, Maier M, Franzblau A, and Garabrant D. Predictors of serum 2378-TCDD concentration in a background population in Michigan, USA. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.

309. Poster. Chen Q, Hedgeman E, Little RJA, Elliott MR, Gillespie BW, Lee S-Y, Hong B, Chang C-W, Olson K, Knutson K, Zwica L, Adriaens P, Demond A, Lepkowski J, Franzblau A, Patterson D, Garabrant D. Serum 2,3,7,8-TCDD concentration in a Michigan, USA population with no unusual sources of exposure. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
310. Poster. Chang C-W, Gillespie BW, Hedgeman E, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olsen K, Adriaens P, Demond A, Towey T, Zwica L, LaDronka K, Ward B, Luksemburg W, Maier M, Franzblau A, and Garabrant D. Predictors of serum 2378-pentacdf concentration in a background population in Michigan, USA and in a representative USA sample. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
311. Poster. Demond A, Adriaens P, Towey T, Chang SC, Franzblau A, Garabrant D, Gillespie B, Hong B, Lepkowski J, Luksemburg W, Maier M, Trin H. Impact of changes in who TEF values from 1998 to 2005 on measurements of soil concentrations of PCDDs, PCDFs and PCBs in a community in Michigan, USA. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
312. Poster. Garabrant D, Chen Q, Hong B, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Zwica L, Chang C-W, Lee S-Y, Olson K, Towey T, Jolliet O, Wenger Y, Gillespie BW. Logistic regression models for high serum 2,3,7,8-TCDD concentrations in residents of Midland, Michigan, USA. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
313. Poster. Hong B, Hedgeman E, Gillespie BW, Chen Q, Lee S-Y, Chang C-W, Zwical L, Knutson K, Towey T, Olson K, Sima C, Luksemburg W, Maier M, Adriaens P, Demond A, Lepkowski J, Franzblau A, Garabrant D. Impact of the changes in who TEF values from 1998 to 2005 on the total TEQ values in serum, household dust and soil. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
314. Poster. Hedgeman E, Hong B, Chen Q, Knutson K, Lee S-Y, Olson K, Lohr-Ward B, LaDronka K, Maier M, Luksemburg W , Lepkowski J, Gillespie B, Franzblau A, Garabrant D. Change in background serum levels with the new 2005 TEFs. Dioxin 2007 Conference, Tokyo, Japan. September, 2007.
315. Poster. Knutson K, Zwica L, Lee S-Y, Hong B, Chen Q, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, and Garabrant D. Linear regression modeling to predict household dust TEQ and TCDD concentration. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.
316. Poster. Milbrath, M. L, Adriaens P, Chang C-W, Franzblau A, Garabrant D, Gillespie B, Wenger Y, and Jolliet, O. Apparent half-lives of dioxins, furans, and PCBs as a function of age, body fat, breastfeeding, and smoking status. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.
317. Poster. Hong B, Hedgeman E, Gillespie BW, Chen Q, Lee S-Y, Chang C-W, Zwica L, Knutson K, Towey T, Olson K, Sima C, Luksemburg W, Maier M, Adriaens P, Demond A, Lepkowski J, Franzblau A, and Garabrant D. Impact of the changes in WHO TEF values from 1998 to 2005 on the total TEQ values in serum, household dust and soil. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.

318. Poster. Jolliet O, Wenger Y, Milbrath MO, Chang C-W, Chen Q, Franzblau A, Garabrant D. Towey T, Gillespie BW, and Adriaens, P. Effect of age and historical intake on blood dioxin concentrations: pharmakokinetic modeling to support statistical analyses. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.
319. Poster. Franzblau A, Zwica L, Knutson K, Chen Q, Lee S-Y, Hong B, Adriaens P, Demond A, Garabrant D. Lepkowski J, Luksemburg W, Maier M, and Towey, T. A follow-up investigation of homes with 'high' concentrations of PCDDs, PCDFs and dioxin-like PCBs in house dust. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.
320. Poster. Franzblau A, Hedgeman E, Chen Q, Lee S-Y, Adriaens P, Demond A, Garabrant D. Gillespie BW, Hong B, Jolliet O, Lepkowski J, Luksemburg W, Maier M, and Wenger, Y. Human exposure to dioxins from clay: a case report. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.
321. Poster. Chen Q, Elliott MR, Little RJA, Hedgeman E, Gillespie BW, and Garabrant D. Statistical methods in estimating quantiles of serum dioxin concentration by age, with values below limit of detection. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.
322. Poster. Chen Q, Hedgeman E, Little RJA, Elliott MR, Gillespie B, Lee S-Y, Hong B, Chang C-W, Olson K, Knutson K, Zwica L, Adriaens P, Demond A, Lepkowski J, Franzblau A, Patterson, D. G, and Garabrant D. Age- and sex-specific background human serum 2,3,7,8-tetrachlorodibenzo-p-dioxin levels in Michigan, USA. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.
323. Poster. Towey T, Barabas N, Adriaens P, Demond D, Hedgeman E, Knutson K, Zwica L, Chen Q, Olson K, Gillespie B, Garabrant D, Franzblau A, Lepkowski J. Polytopic vector analysis of UMDES soil, dust, and serum samples. 17th Annual Conference of the International Society of Exposure Analysis, Durham, NC, October 13-19, 2007.
324. Poster. Milbrath M, Adriaens P, Chang W-C, Franzblau A, Garabrant D, Gillespie B, Wenger Y, Jolliet O. Apparent half-lives of dioxins, furans, and PCBs as a function of age, body fat, breastfeeding, and smoking status. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
325. Poster. Jolliet O, Wenger Y, Milbrath M, Chang C-W, Chen Q, Franzblau A, Garabrant D, Towey T, Gillespie B, Adriaens P. Effect of age and historical intake on blood dioxin concentrations: Pharmacokinetic modeling to support statistical analyses. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
326. Poster. Towey T, Chang S-C, Adriaens P, Demond A, Franzblau A, Garabrant D, Gillespie B, Lepkowski J. Cluster analysis for the evaluation of soil dioxin congener profiles for a community in Michigan. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
327. Poster. Franzblau A, Zwica L, Knutson K, Chen Q, Lee S-Y, Hong B, Adriaens P, Demond A, Garabrant D, Lepkowski J, Luksenburg W, Maier M, Towey T. A follow-up investigation of homes with 'high' concentrations of PCDDs, PCDFs and dioxin-like PCBs in house dust. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
328. Poster. Hedgeman E, Hong B, Chen Q, Knutson K, Lee S-Y, Olson K, Ward B-L, Ladronka K, Maier M, Luksenburg W, Lepkowski J, Gillespie B, Franzblau A , Garabrant

D. Serum dioxin concentrations from the University of Michigan Dioxin Exposure Study. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.

329. Poster. Knutson K, Zwica L, Lee S-Y, Hong B, Chen Q, Towey T, Gillespie B, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. Linear regression modeling to predict household dust TEQ and TCDD concentration. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
330. Poster. Garabrant D, Franzblau A, Adriaens P, Gillespie B, Demond A, Lepkowski J, Olsen K, Hedgeman E, Knutson K, Zwica L. The University of Michigan Dioxin Exposure Study project overview. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
331. Poster. Gillespie B, Chang C-W, Hedgeman E, Reichert H, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olson K, Adriaens P, Demond A, Towey T, Zwica L, LaDronka K, Ward B, Luksenburg W, Maier M, Franzblau A, Garabrant D. Predictors of serum 2378-TCDD and 23478-PentaCDF concentration in a background population in Michigan, USA and in a representative USA sample. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
332. Abstract. Garabrant, DH. Factors that predict serum dioxin concentrations in Michigan, USA. Society for Risk Analysis 2007 Annual Meeting. San Antonio, TX, December 9-12, 2007.
333. Poster. Chen Q, Lepkowski J, Gillespie B, and Garabrant D. Variable selection for multiply-imputed large data set in dioxin exposure. Eastern North American Region, International Biometric Society, Arlington, VA, March 2008.
334. Abstract. David H. Garabrant, James W. Albers, Stanley Berent, and Rudy J. Richardson. Chlorpyrifos exposure, inhibition of butyrylcholinesterase, and paraoxonase (PON1) activity in pesticide manufacturing workers. EPICOH-NEUREOH 2008 Conference, San Jose, Costa Rica, June 9-13, 2008
335. Abstract. James W. Albers, David H. Garabrant, Stanley Berent, PhD, and Rudy J. Richardson. Paraoxonase (PON1) Status of Chlorpyrifos Manufacturing Workers Fails to Predict Serum Butyrylcholinesterase (BuChE) Activity. EPICOH-NEUREOH 2008 Conference, San Jose, Costa Rica, June 9-13, 2008
336. Abstract. James W. Albers, David H. Garabrant, Stanley Berent, PhD, and Rudy J. Richardson. Chlorpyrifos Exposure during the Manufacturing Process and Peripheral Neurotoxicity. EPICOH-NEUREOH 2008 Conference, San Jose, Costa Rica, June 9-13, 2008
337. Abstract. Garabrant DH, Hong B, Chen Q, Chang C-W, Jiang X, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Towey T, Gillespie BW. Factors that predict serum PCB concentrations in Michigan, USA. Dioxin 2008 Conference, Birmingham, England. August 2008.
338. Abstract. Knutson K, Hong B, Jiang X, Hedgeman E, Chen Q, Chang C-W, Towey T, Gillespie BW, Franzblau A, Lepkowski J, Adriaens P, Demond A, Garabrant DH. The relationship between dioxin concentrations in blood and breast feeding. Dioxin 2008 Conference, Birmingham, England. August 2008.
339. Abstract. Garabrant D, Hong B, Chen Q, Chang C-W, Jiang X, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Towey T, Gillespie B,W. Predictors of serum PCDF concentrations in people from, Michigan, USA. Dioxin 2008 Conference, Birmingham, England. August 2008.

340. Abstract. Franzblau A, Hedgeman E, Knutson K, Chen Q, Hong B, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski J. The University of Michigan Dioxin Exposure Study: A follow-up investigation of cases with high serum concentrations of 23478-pentaCD. Dioxin 2008 Conference, Birmingham, England. August 2008.
341. Abstract. Demond A, Towey T, Knutson K, Hong B, Zhong X, Adriaens P, Chang S-C, Chen Q, Franzblau A, Garabrant D, Gillespie B, Lepkowski J. Relationship between concentrations of PCDDs, PCDFs and dioxin-like PCBs in vegetation and soil on residential properties. Dioxin 2008 Conference, Birmingham, England. August 2008.
342. Abstract. Gillespie BW, Reichert H, Chang C-W, Hedgeman E, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olsen K, Demond A, Towey T, Ward B, Luksemburg W, Maier M, Franzblau A, Garabrant D. Predictors of 7 dioxin congeners in background US populations: Data from two Michigan counties and the US National Health and Nutrition Examination Survey. Dioxin 2008 Conference, Birmingham, England. August 2008.
343. Abstract. Gillespie BW, Reichert H, Chang C-W, Hedgeman E, Hong B, Chen Q, Jolliet O, Knutson K, Lee S-Y, Lepkowski J, Olsen K, Adriaens P, Demond A, Towey T, Ward B, Luksemburg W, Maier M, Franzblau A, Garabrant D. Predictors of 8 furan congeners in background US populations: Data from two Michigan counties and the US National Health and Nutrition Examination Survey. Dioxin 2008 Conference, Birmingham, England. August 2008.
344. Abstract. Hedgeman E, Hong B, Chen Q, Chang C-W, Knutson K, Demond A, Adriaens P, Gillespie B, Lepkowski J, Franzblau A, Garabrant D. Sport fish consumption by the general population from a waterway contaminated with PCDDs and PCDFs. Dioxin 2008 Conference, Birmingham, England. August 2008.
345. Abstract. Jolliet O, Wenger Y, Adriaens P, Chang Q, Franzblau A, Gillespie BW, Hedgeman E, Hong B, Jiang X, Knutson K, Lepkowski J, Milbrath MO, Reichert H, Towey T, Garabrant D. Influence of age on dioxin serum concentrations as a function of congener half-life and historical peak food consumption. Dioxin 2008 Conference, Birmingham, England. August 2008.
346. Abstract. Towey T, Barabás N, Demond A, Zwica L, Knutson K, Franzblau A, Garabrant D, Adriaens P. Statistical fingerprinting of PCBs using the subset with dioxin-like activity. Dioxin 2008 Conference, Birmingham, England. August 2008.
347. Abstract. Sussell A, Robins T, Garabrant D, Reeve G, Stout A, Lushniak B. A Case-Control Study of Occupational Contact Dermatitis Among Automobile Assembly Workers. Contact Dermatitis 2008: Blending Science with Best Practice (A Combined Meeting of the American Contact Dermatitis Society and the Experimental Contact Dermatitis Research Group). August 28 - 30, 2008.
348. Abstract. Trinh H, Gwinn D, Demond A, Towey T, Goovaerts P, Garabrant D, Adriaens P. Validation of the AERMOD Air Dispersion Model: Application to Congener-Specific Dioxin Deposition from an Incinerator in Midland, Michigan. Dioxin 2009 Conference, Beijing, China, August 27, 2009.
349. Abstract. Franzblau A, Hedgeman E, Jiang X, Chen Q, Hong B, Knutson K, Towey T, Adriaens P, Demond A, Garabrant D, Gillespie B, Jolliet O, Lepkowski J. The University of Michigan Dioxin Exposure Study: Follow-Up Investigation of Subjects With High Serum Concentrations of TEQ, 2,3,7,8-TCDD, 2,3,4,7,8-PeCDF, and PCB-126. Dioxin 2009 Conference, Beijing, China, August 27, 2009.

350. Abstract. Garabrant D, Hong B, Jolliet O, Chen Q, Jiang X, Franzblau A, Lepkowski J, Adriaens P, Demond A, Hedgeman E, Knutson K, Towey T, Gillespie B. Public Health Impact of PCDDs, PCDFs, and PCBs in Midland, Michigan, USA Dioxin 2009 Conference, Beijing, China, August 27, 2009.
351. Abstract. Gillespie B, Reichert H, Chen Q, Franzblau A, Lepkowski J, Adriaens P, Demond A, Luksemburg W, Garabrant D. Using the Reverse Kaplan-Meier to Estimate Population Distributions with Data Below a Limit of Detection. Dioxin 2009 Conference, Beijing, China, August 27, 2009. http://www.dioxin20xx.org/pdfs/2009/09-167.pdf
352. Abstract. Hong B, Garabrant D, Jiang X, Chen Q, Franzblau A, Gillespie B, Lepkowski J, Adriaens P, Demond A. Factors that Predict Serum Concentration of 2,3,7,8-TCDD in People from Michigan, USA. Dioxin 2009 Conference, Beijing, China, August 27, 2009.
353. Abstract. Jiang X, Chen Q, Garabrant D, Hong B, Gillespie B,Lepkowski J, Franzblau A, Adriaens P, Demond A. Logistic Regression Models of High Serum Dioxin Level in People from Michigan, USA. Dioxin 2009 Conference, Beijing, China, August 27, 2009.
354. Abstract. Towey T, Adriaens P, Barabás N, Demond A, Hedgeman E, Garabrant D. Factors Predictive of Congener Profiles Extracted by Polytopic Vector Analysis in Human Serum. Dioxin 2009 Conference, Beijing, China, August 27, 2009.
355. Abstract. James RC, Kerger BD, Garabrant DH. Lung cancer risks from asbestos exposure, asbestosis, and other fibrotic lung diseases: case examples and distinguishing factors in exposure and clinical features. 49th Annual Meeting, Society of Toxicology, Salt Lake City, UT. March 7-11, 2010.
356. Abstract. Garabrant D, Jiang X, Franzblau A, Adriaens P, Demond A, Gillespie B, Jolliet O, Lepkowski J, Hao W, Chen Q. The University of Michigan Dioxin Exposure Study: residential soil and household dust unrelated to serum dioxin levels. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010.
357. Abstract. Franzblau A, Jiang X, Adriaens P, Demond A, Gillespie B, Jolliet O, Lepkowski J, Garabrant D. The University of Michigan Dioxin Exposure Study: outlier investigations: main results and lessons learned. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010. http://www.dioxin20xx.org/pdfs/2010/10-1468.pdf
358. Abstract. Hao W, Garabrant DH, Franzblau A, Gillespie BW, Lepkowski J, Adriaens P, Demond A, Jiang X, Jolliet O. Dioxin intake due to fish and game consumption in a dioxin-contaminated area. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010. http://www.dioxin20xx.org/pdfs/2010/10-1572.pdf
359. Abstract. Hao W, Jiang X, Wenger Y, Chang C-W, Gillespie BW, Towey T, Chen Q, Hong B, Franzblau A, Lepkowski J, Adriaens P, Demond A, Garabrant DH, Jolliet O. A toxicokinetic modeling approach to investigate the predictors of serum TCDD concentration. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010. http://www.dioxin20xx.org/pdfs/2010/10-1552.pdf
360. Abstract. Gillespie BW, Reichert H, Jiang X, Jolliet O, Lepkowski J, Adriaens P, Demond A, Towey T, Luksemburg W, Maier M, Franzblau A, and Garabrant D. Food predictors of serum dioxin concentration in background populations. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010.
361. Abstract. Jiang X, Hao W, Garabrant DH, Franzblau A, Gillespie BW, Lepkowski J, Adriaens P, Demond A, Jolliet O. Associations of fish and game intake with human serum dioxin concentrations. Dioxin 2010 Conference, San Antonio, Texas. September 12-16, 2010. http://www.dioxin20xx.org/pdfs/2010/10-1550.pdf

362. Abstract: Jiang X, Knutson K, Zwica L, Lee S-Y, Chen Q, Hong B, Zhong X, Hao W, Towey T, Gillespie BW, Demond A, Adriaens P, Lepkowski J, Franzblau A, Garabrant D. The University of Michigan Dioxin Exposure Study: predictors of household dust PCDD, PCDF, and PCB concentrations. Dioxin 2011 Conference, Brussels, Belgium August 21-25, 2011. http://www.dioxin20xx.org/pdfs/2011/3713.pdf
363. Abstract: Franzblau A, Adriaens P, Demond A, Garabrant DH, Gillespie BW, Lepkowski J. The University of Michigan Dioxin Exposure Study - Communication and Community Involvement. Dioxin 2011 Conference, Brussels, Belgium August 21-25, 2011. http://www.dioxin20xx.org/pdfs/2011/3405.pdf
364. Abstract: Jiang X, Zwica L, Knutson K, Towey T, Hedgeman E, Franzblau A, Chen Q, Lee S-Y, Sima C, Gillespie BW, Adriaens P, Demond A, Lepkowski J, Ward B, Ladronka K, Olson K, Sinibaldi J, Chang S-C, Gwinn D, Swan S, Garabrant D. Measurements of Household Dust Concentrations of PCDDs, PCDFs and PCBs from a Community in Michigan, USA. Dioxin 2011 Conference, Brussels, Belgium August 21-25, 2011. http://www.dioxin20xx.org/pdfs/2011/3714.pdf
365. Abstract: Reichert H, Gillespie BW, Franzblau A, Jiang X, Hao W, Lepkowski J, Adriaens P, Demond A, Garabrant DH. Dealing With Data Below the Limit of Detection in Dioxin Research. Dioxin 2011 Conference, Brussels, Belgium August 21-25, 2011. http://www.dioxin20xx.org/pdfs/2011/0701.pdf
366. Abstract: Broadwater K, Franzblau A, Luksemburg W, Maier M, Jiang X, Garabrant DH, Demond A. Serum Concentrations of Polychlorinated Dibenzo-p-dioxins Among Users of Ball Clay. Joint ISEE, ISES and ISIAQ Environmental Health Conference. 19-23 August 2013, Basel, Switzerland.

Greim

Helmut A. Greim, MD
Professor emeritus of
Toxicology and Environmental Hygiene
Technical University Munich

June 2015

Curriculum Vitae

	Born in Berlin, Germany May 9, 1935
1955 - 1963	Medical Schools and Clinics in Freiburg und Berlin
1963 - 1964	Research Assistant, Inst. of Pharmacology, Freie Universität Berlin
1964 - 1970	Assistant Professor, Inst. of Toxicology, University of Tübingen
1970	Lecturer in Pharmacology and Toxicology, Univiversity of Tübingen
1970 - 1973	Visiting Associate Research Professor of Pathology, The Mount Sinai School of Medicine, New York City Visiting Fellow in Pharmacology, Yale University, New Haven, Connecticut
1973 - 1975	Associate Professor Pharmacology and Toxicology, Dept. of Toxicology, University of Tübingen
1975 - 2000	Director, Institute of Toxicology, Federal GSF-Reserch Center for Environment and Health, Neuherberg/München
1987-2003	Director and Chairman, Institute of Toxicology and Environmental Hygiene, Technical University München
1982 - 1985	Chairman of the Section Toxicology of the German Society of Pharmacology and Toxicology
1982 - 1990	Board of Experts on the Environment: The Federal Minister of Environment, Germany
1983 - 2007	Vice Chairman, 1998 Chairman of the German Advisory Committee on Existing Chemicals of Environmental Relevance (BUA) of Gesellschaft Deutscher Chemiker (GDCh)
1991 - 1993	President of The German Society of Pharmacology and Toxicology
1992 - 2007	Chairman of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Areas (MAK) of the Deutsche Forschungsgemeinschaft. Member since 1982
1992 – 1994	Member of the Enquète-Commission of the German Parliament "Protection of Mankind and Environment"

1996-2011	Research Expert Panel, Research Institute for Fragrance Materials (RIFM), Hackensack, New Jersey, (Chairman 2000-2008)
since 1993	Scientific Advisory Committee on Occupational Exposure Limits (SCOEL) of the General Directorate for Employment and Social Affairs, European Commission
1997-2004	Scientific Committee on Toxicology, Ecotoxicology and the Environment (CSTEE, Vice Chair), General Directorate for Health and Consumer Protection, European Commission
1998-2008	Health and Environmental Safety Institute (HESI) of the International Life Science Institute (ILSI). Washington, Chair of Board of Trustees 2001-2002
2000 - 2008	Research Committee, Health Effect Institute (HEI), Boston
since 2001	Scientific Committee of the European Center for Ecotoxicology and Toxicology of Chemicals (ECETOC)
1996 – 2011	Research Expert Panel Research Institute for Fragrance Materials, Hackensack, New Jersey, USA (Chair 2000 – 2008)
2004 - 2012	Chairman of Scientific Committee on Health and Environmental Risks (SCHER): General Directorate for Health and Consumer Protection, European Commission
2008-2013	Risk Assessment Committee, European Chemical Agency, (ECHA) Helsinki

Membership Scientific Societies

Academy of Toxicological Sciences
American Association for the Advancement of Sciences
Deutsche Gesellschaft für Pharmakologie undToxikologie
European Association for Cancer Research
European Environmental Mutagen Society
European Society of Toxicology
Gesellschaft für Umwelt-Mutationsforschung
Gesellschaft Deutscher Chemiker
Society of Toxicology (USA)

Some Awards

1998	Society of Toxicology (USA): Arnold J. Lehmann Award
2001	American Conference of Governmental Industrial Hygienists: Herbert E. Stockinger Award
2007	Honorary member of the German Society of Toxicology

His research experience is drug metabolism, toxicokinetics, mechanisms of carcinogenic agents, in vitro test systems. Dr. Greim has published over 500 papers in toxicology and risk assessment and has lectured on these subjects in Europe and abroad. Besides many contributions to text-books he has edited and published two text-books in Toxicology, one in German, the other by Wiley, London (H. Greim and R. Snyder: Toxicology and Risk Assessment. A comprehensive Introduction). Both tetbook are presently re-edited. In June 2012 the book "The cellular response to the genotoxic insult: the question of threshold for genotoxic carcinogens (H. Greim and R. Albertini) has been published by the Royal Society of Chemistry, London.

Kirkland

CURRICULUM VITAE
DAVID J KIRKLAND

PERSONAL DETAILS

Name KIRKLAND David John

Date of Birth 18 June 1949

Education

1967-1970 University of London
BSc Honours in Microbiology
Upper Second Class

1970-1973 Imperial Cancer Research Fund, London
Post-graduate research into the *in vitro* interactions of viral and chemical carcinogens. PhD awarded by Brunel University

PRESENT EOMPLOYMENT

2009-present **Kirkland Consulting**

Independent genetic toxicology consultant.

PREVIOUS EMPLOYMENT

1997 - 2009 **Covance Laboratories Europe (CLE)**

Vice President of Scientific and Regulatory Consulting: responsible for the pharmaceutical regulatory affairs group and expert reviews (consultancy). This includes developing and promoting the regulatory and scientific expertise within CLE to "add value" to client projects.

1992- 1997 **Hazleton Europe (Corning Hazleton, Covance)**

Director (subsequently Vice President) of Toxicology: responsible for the mammalian, molecular and cellular toxicology groups (study directors and operations staff) including planning, costing, GLP compliance, scientific interpretation, health and safety.

1990-1992 **Hazleton Microtest**

Head of Molecular Toxicology: overall responsibility for all the programmes of molecular toxicology for all clients. This included client liaison, planning, costing, GLP compliance and scientific interpretation, including regulatory requirements.

1984-1990	**Microtest Research Limited** Director of Molecular Toxicology: overall responsibility for all the programmes of molecular toxicology for all clients. This included client liaison, planning, costing, GLP compliance and scientific interpretation, including regulatory requirements.
1979-1984	**Toxicol Laboratories Limited** Research Director: responsible for managing sections providing chemistry, biochemistry, microbiology and genetic toxicology services, including being Head of Genetic Toxicology for the company.
1976-1979	**Chester Beatty Research Institute** Post-doctoral Fellow: two projects were undertaken, namely the cytogenetic monitoring of the circulating lymphocytes and bone marrow of Polycythaemia Rubra Vera patients on different forms of treatment, and investigations of cytogenetic abnormalities in humans exposed occupationally or as consumers to hair dyes.
1973-1976	Post-doctoral Fellow: projects to develop an *in vitro* mammalian cell malignant transformation system in Chinese hamster cells maintained in a diploid state by special culture techniques, and to investigate cytotoxicity and chromosomal damage induced by hair dyes.

PROFESSIONAL SOCIETIES

1977-Present	UK Environmental Mutagen Society
1977-Present	European Environmental Mutagen Society
1982-Present	Environmental Mutagen Society USA
1970-1994	British Association for Cancer Research
1988-Present	Genetic Toxicology Association USA
1989-2010	British Toxicology Society
1986-2010	Institute of Biology

RECOGNITION AND AWARDS

Fellow of the UK Environmental Mutagen Society (2002)

Honorary Professor of the University of Wales, Swansea (2006-present)

First recipient of the Industrial Genotoxicity Group (UKEMS) Distinguished Toxicologist Award (2010)

Recipient of the US Environmental Mutagen Society Alexander Hollaender Award for scientific contributions to the field of genetic toxicology and for global leadership in the regulation of toxicology testing (2010).

PROFESSIONAL ACTIVITIES

Member, UK Government Advisory Committee on Mutagenicity (2009-present)

Chairman, Industry and Regulatory Special Interest Group, European Environmental Mutagen Society, (2000-present)

President of UK Environmental Mutagen Society (1992 - 1994)

President of European Environmental Mutagen Society (2009-2011)

Mutagenesis Editorial Board Member (1992 - 2004)

Special Issues Editor, Mutation Research,(Genetic Toxicology and Environmental Mutagenesis section (2005-present)

Mutation Research Editorial Board Member (Genetic Toxicology Testing Section) (1990 - 2004)

Editor UK Environmental Mutagen Society Guidelines Reports (1986 - 1990)

Toxicology Advisory Panel Member for the Cosmetics, Toiletries and Perfumeries Association (1980 - 1984)

Local Organiser of 12th Annual UK Environmental Mutagen Society meeting, York 1988

Local Organiser of 20th European Environmental Mutagen Society meeting, York 1990

Organiser of "International Workshops on Standardisation of Genotoxicity Test Procedures", Melbourne, Australia 1993 and Washington D.C., 1999.

Chair of Peer Consultation Workshop on Genotoxicity for Categorization of "Inherent Toxicity" to Humans under the Canadian Environmental Protection Act (CEPA '99), co-sponsored by International Life Sciences Institute and Health Canada, Ottawa, Canada, 2002.

Organiser of the 3rd, 4th and 5th International Workshops on Genotoxicity Tests (Plymouth, Devon, England, 2002; San Francisco, California, USA, 2005; Basel, Switzerland, 2009) and co-organiser of the 6th IWGT (Foz do Iguacu, Brazil, 2013)..

SCIENTIFIC PUBLICATIONS

Kirkland D J and Pick C R (1973). The histological appearance of tumours derived from rat embryo cells transformed *in vitro* spontaneously and after treatment with nitrosomethylurea. Brit J Cancer 28:440-452.

Kirkland D J, Armstrong C & Harris R J C (1975). Spontaneous and chemically induced transformation of rat embryo cell cultures. Brit J Cancer 31:329-337.

Kirkland D J & Venitt S (1976). Cytotoxicity of hair colourant constituents: chromosome damage induced by two nitrophenylenediamines in cultured Chinese hamster cells. Mutat Res 40:47-56.

Kirkland D J (1976). Chemical transformation of Chinese hamster cells. I A comparison of some properties of transformed cells. Brit J Cancer 34:134-144.

Kirkland D J & Venitt S (1976). Chemical transformation of Chinese hamster cells. II Appearance of marker chromosomes in transformed cells. Brit J Cancer 34:145-152.

Roberts J J, Friedlos F, Van Den Berg H W & **Kirkland D J** (1977). Inhibition by caffeine of post-replication repair in Chinese hamster cells treated with 7-bromomethylbenz-(a)-anthracene. Enhancement of toxicity, chromosome damage and inhibition of ligation of newly-synthesised DNA. Chem Biol Interactions 17:265-290.

Kirkland D J, Lawler S D & Venitt S (1978). Chromosomal damage and hair dyes. Lancet ii:124-128.

Kirkland D J (1979). Hair dye genotoxicity. American Heart Journal 98:814.

Kirkland D J, Welch S J, Povey S, Najfeld V, Price D J & Lawler S D (1980). Glutamic pyruvate transaminase phenotypes in Polycythaemia Rubra Vera. Ann Hum Genetics 44:407-413.

Kirkland D J, Smith K L & Van Abbe N J (1981). Failure of chloroform to induce chromosome damage or sister chromatid exchanges in cultured lymphocytes and failure to induce reversion in *E coli*. Fd Cosmet Toxicol 19:651-656.

Kirkland D J, Honeycombe J R, Lawler S D, Venitt S & Crofton-Sleigh C (1981). Sister chromatid exchanges before and after hair dyeing. Mutat Res 90:279-286.

Kirkland D J, Smith K L & Parmar V (1982). Bacterial mutagenicity tests on 4-chloromethyl biphenyl and two structural analogues. Mutat Res 100:21-25.

Kirkland D J, Smith K L & Jenkinson P C (1982). Metaphase analysis of human lymphocytes treated with 4-chloromethyl biphenyl and benzyl chloride. Mutat Res 100:297-299.

Kirkland D J, Jenkinson P C & Smith K L (1982). Sister chromatid exchanges in human lymphocytes treated with 4-chloromethyl biphenyl and benzyl chloride. Mutat Res 100:301-304.

Kirkland D J (1982). Cytogenetic monitoring of human populations. In M Balls, R J Riddell & A N Warden, ed. Animals and Alternatives in Toxicity Testing. Academic Press, London, pp 409-414.

Kirkland D J (1983). The mutagenicity and carcinogenicity of hair dyes. A review. Int J Cosmet Sci 5:51-71.

Kirkland D J, Creed K L & Mannisto P (1983). Comparative bacterial mutagenicity studies with 8-methoxypsoralen and 4,5',8-trimethylpsoralen in the presence of near ultra violet light and in the dark. Mutat Res 116:73-82.

Scott D, Danford N, Dean B, **Kirkland D** & Richardson C (1983). *In vitro* chromosome aberration assays. In B Dean, ed. UKEMS Subcommittee on Guidelines for Mutagenicity Testing, Report, Part I, Basic Test Battery. United Kingdom Environmental Mutagen Society, Swansea, pp 41-64.

Perry P, Henderson L & **Kirkland D** (1984). Sister chromatid exchange in cultured cells. In B Dean, ed. UKEMS Sub-committee on Guidelines for Mutagenicity Testing, Report, Part II, Supplementary Tests. United Kingdom Environmental Mutagen Society, Swansea, pp 89-121.

Kirkland D, Gatehouse D, Sullman S, Venitt S, Watkins P, Reed P & Walters C (1984). Bacterial mutation assays with nitrosation products. In B Dean, ed. UKEMS Sub-committee on Guidelines for Mutagenicity Testing, Report, Part II, Supplementary Tests. United Kingdom Environmental Mutagen Society, Swansea, pp 245-260.

Varley R B, Rae J D & **Kirkland D J** (1985). A comparison of the effects of uninduced mouse, uninduced rat and Aroclor-induced rat liver S-9 on reversion in *Salmonella* by DAB and CDA. In J M Parry & C F Arlett, ed. Comparative Genetic Toxicology. Macmillan Press Limited, Basingstoke & London, pp 89-92.

Asquith J C, Hogan L K, Fullwood J N, Rae J D & **Kirkland D J** (1985). A comparison of the chromosome damaging effects, in cultured human lymphocytes, of benzidine (BZD) and 4,4'-diaminoterphenyl (DAT) in the presence of Aroclor-induced and uninduced rat liver S-9. In J M Parry & C F Arlett, ed. Comparative Genetic Toxicology. Macmillan Press Limited, Basingstoke & London, pp 355-362.

Mannisto P T, **Kirkland D J**, Viluksela M & Tikkanen L (1986). Toxicological studies with dithranol and its 10-acyl analogues. Arch Toxicol 59:180-185.

Garner R C & **Kirkland D J** (1986). Letter to the editor. Mutagenesis 1:233-235.

Kirkland D J (1986). Alternatives to animal tests for detecting carcinogens and mutagens. Biologist 33:79-82.

Kirkland D J 1987). Implications of germ cell cytogenetic tests in the regulatory process. Mutagenesis 2:61-67.

Garner R C, Campbell J, **Kirkland D J** & Kennelly J C (1987). Use of 6TG-resistance in wild type mouse lymphoma L5178Y cells for gene-mutagen screening. Environ Mutagenesis 9 Suppl 8:38 (abstract).

Kirkland D J & Garner R C (1987). Current issues in Mutagenesis and Carcinogenesis. No 8. Testing for genotoxicity - chromosomal aberrations *in vitro* - CHO cells or human lymphocytes? Mutat Res 189:186-187.

Kirkland D J (1989). Mammalian cells in culture. Report of a participant workshop. Mutat Res 213:41-42.

Kirkland D J, Marshall R R, McEnaney S, Bidgood J, Rutter A & Mullineux S (1989). Aroclor-1254 induced rat liver S-9 causes chromosomal aberrations in CHO cells, but not human lymphocytes: A role for active oxygen? Mutat Res 214:115-122.

D J Kirkland, ed. Statistical evaluation of mutagenicity test data. Cambridge University Press, Cambridge - New York - Port Chester - Melbourne - Sydney (1989).

Scott D, Danford N, Dean B & **Kirkland D** (1990). Metaphase chromosome aberration assays *in vitro*. In **D J Kirkland**, ed. Basic mutagenicity tests: UKEMS recommended procedures. Cambridge University Press, Cambridge - New York - Port Chester - Melbourne - Sydney, pp 62-86.

D J Kirkland (1990). Selection of Mutagenicity and Cell Transformation Tests - Interpretation of Results. In A Sundwall *et al*, eds. Preclinical Evaluation of Peptides and Recombinant Proteins. (Excerpts from a workshop). Skogs Grafiska AB, Malmo, pp 49-56.

Dean S W, Lane M, Dunmore R H, Ruddock S P, Martin C N, **Kirkland D J** and Loprieno N (1991). Development of assays for the detection of photomutagenicity of chemicals during exposure to UV light - I. Assay development. Mutagenesis 6:335-342.

Clare C B, Ballantyne M, **Kirkland D J**, Pickering S and Robinson D G (1991). Effects of alterations in the composition of the S-9 mix on the spontaneous mutation frequencies of some bacterial test strains. Mutagenesis 6:427 (abstract).

McEnaney S, Marshall R R, Campbell J, Riley S, Hudson L and **Kirkland D J** (1991). The clastogenic effects of non-physiological pH on human lymphocytes in whole blood and Chinese hamster ovary cells, *in vitro*, following pulse and continuous exposure. Mutagenesis 6:444 (abstract).

Clements J, Fellows M D, Oxley P A, Doran A, Clare C B and **Kirkland D J** (1991). A validation exercise for the TK assay in mouse lymphoma L5178Y cells using a Microtitre® fluctuation protocol. Mutagenesis 6:444 (abstract).

Kirkland D J (1992). Chromosomal aberration tests *in vitro*: problems with protocol design and interpretation of results. Mutagenesis 7:95-106.

Kirkland D J, Dresp J H, Marshall R R, Baumeister M, Gerloff C and Gocke E (1992). Normal chromosomal aberration frequencies in peripheral lymphocytes of healthy human volunteers exposed to a maximum daily dose of paracetamol in a double blind trial. Mutat Res 279:181-194.

Dean S W, Dunmore R H, Ruddock S P, Dean J C, Martin C N and **Kirkland D J** (1992). Development of assays for the detection of photo-mutagenicity of chemicals during exposure to UV-light. II. Results of testing 3 sunscreen ingredients.
Mutagenesis 7:179-182.

Fielder R J, Allen J A, Boobis A R, Botham P A, Doe J, Esdaile D J, Gatehouse D G, Hodson-Walker G, Morton D B, **Kirkland D J** and Richold M (1992). Dose setting *in vivo* mutagenicity assays. Report of a BTS/UKEMS Working Party.
Mutagenesis 7:313-319.

Kirkland D J (1993). Genetic toxicology testing requirements: Official and unofficial views from Europe. Envir Mol Mutag 21, 8-14.

Shibahara T, Kaneko E, Itoh T, Awogi T, Tsushimoto G, Takahashi N, Marshall R R and **Kirkland D J** (1993). Mutagenic and clastogenic properties of BOF-A2, a new 5-fluorouracil derivative with anti-tumour activity. J Tox Sci 18 (Suppl III), 11-19.

Kirkland D J (1993). The need for international standardisation of genotoxicity test procedures. In "International Workshop on Standardisation of Procedures in Genetic Toxicology", Ed T Sofuni, Scientist Inc, Tokyo, pp 3-8.

Kirkland D J (1993). Are chromosomal aberration tests *in vitro* particularly prone to artificial findings? In "Current Issues in Genetic Toxicology", Eds S Madle & L Müller, MMV Medizin Verlag, München, pp 43-51.

Kirkland D J (1994). Statistical evaluation of mutagenicity test data: recommendations of the UK Environmental Mutagen Society (UKEMS).
Environmental Health Perspectives Supplements 102:Suppl 1, 43-47.

Kirkland D J, Galloway S M & Sofuni T (1994). Report of the International Workshop on Standardisation of Genotoxicity Test Procedures. Summary of major conclusions. Mutat Res 312:205-209.

Kirkland D J (1994). Report of the International Workshop on Standardisation of Genotoxicity Test Procedures. Report of the *In vitro* Sub-group. Mutat Res 312: 211-215.

Galloway S M, Aardema M J, Ishidate M Jr, Ivett J L, **Kirkland D J**, Morita T, Mosesso P & Sofuni T (1994). Report from Working group on *in vitro* tests for chromosomal aberrations. Mutat Res 312:241-261.

Kirkland D J (1994). New approaches to design and interpretation of *in vitro* chromosomal aberration tests. In "Chromosomal alterations: Origin and Significance". Eds G Obe & A T Natarajan, Springer-Verlag, Berlin, pp 333-342.

Kirkland D J & Dean S W (1994). On the need for confirmation of negative genotoxicity results *in vitro* and on the usefulness of mammalian cell mutation tests in a core battery: experiences of a contract research laboratory. Mutagenesis 9:491-501.

Kirkland D J & Kim N N (1995). Special considerations for conducting genotoxicity tests with protein materials. Mutagenesis 10:393-398.

Aaron C S, Yu R L, Harbach P R, Mazurek J M, Swenson D H, **Kirkland D J**, Marshall R & McEnaney S (1995). Comparative mutagenicity for ceftiofur sodium: I. Positive results in *in vitro* cytogenetics. Mutat Res 345:27-35.

Aaron C S, Yu R L, Bacon J A, **Kirkland D J**, McEnaney S & Marshall R (1995). Comparative mutagenicity testing of ceftiofur sodium: II. Cytogenetic damage induced *in vitro* by ceftiofur is reversible and is due to cell cycle delay. Mutat Res 345:37-47.

Marshall R R, Murphy M, **Kirkland D J** & Bentley K S (1996). Fluorescence *in situ* hybridisation with chromosome-specific centromeric probes: a sensitive method to detect aneuploidy. Mutat Res **372**, 233-245.

Kirkland D J (1998). Use of transgenic animals in toxicology. Pharm. Sci. Technol. Today. **1,** 62-68.

Kirkland D J & Clements J (1998). Recommendations for spacing of test chemical concentrations in the mouse lymphoma *tk* mutation assay (MLA). Mutat Res **415,** 159-163.

Kirkland D J (1998). Chromosome aberration testing in genetic toxicology - past, present and future. Mutat Res **404,** 173-185.

Combes R, Balls M, Curren R, Fischbach M, Fusenig N, **Kirkland D J**, Lasne C, Landolph J, LeBoeuf R, Marquardt H, McCormick J, Müller L, Rivedal E, Sabbioni E, Tanaka N, Vaseur P & Yamasaki H (1999). Cell transformation assays as predictors of human carcinogenicity. ATLA **27**, 745-767.

Bentley K S, **Kirkland D J**, Murphy M & Marshall R (2000). Evaluation of thresholds for benomyl- and carbendazim-induced aneuploidy in cultured human lymphocytes using fluorescence in situ hybridization. Mutat Res **464**, 41-51.

Kirkland D J & Müller L (2000). Interpretation of the biological relevance of genotoxicity test results: the importance of thresholds. Mutat Res **464**, 137-147.

Kirkland D J (2000). Preface to conclusions from International Workshop on Genotoxicity Test Procedures. Env Mol Muta **35**, 159-161.

Kirkland D J, Hayashi M, MacGregor J T, Müller L, Schechtman L & Sofuni T (2000). Summary of major conclusions from the International Workshop on Genotoxicity Test Procedures. Env Mol Muta **35**, 162-166.

Kirkland D J (2002). The role of the UKEMS in the development of testing guidelines. Mutagenesis **17**(6), 451-455.

Marshall R, Tricta F, Galanello R, Leoni G, **Kirkland D J**, Minto S & Spino M (2003). Chromosomal aberration frequencies in patients with thalassemia major undergoing therapy with Deferiprone and Deferoxamine in a comparative crossover study. Mutagenesis **18**(5), 1-7.

Kirkland D J & Marzin D (2003). An assessment of the genotoxicity of 2-hydroxy-1,4-naphthoquinone, the natural dye ingredient of Henna. Mutat Res 537, 183-199.

Nohynek G J, **Kirkland D**, Marzin D, Toutain H, Leclerc-Ribaud C & Jinnai H (2003). An assessment of the genotoxicity and human health risk of topical use of kojic acid [5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one]. Fd Chem Toxicol. **42**, 93-105.

Kirkland D J (2003). 3rd International Workshop on Genotoxicity Tests. Preface. Mutat Res, **540,** 119-121.

Kirkland D J, Hayashi M, MacGregor J T, Müller L, Schechtman L M & Sofuni T (2003). 3rd International Workshop on Genotoxicity Tests. Summary of major conclusions. Mutat Res, **540,** 123-125.

Müller L, Blakey D, Dearfield K L, Galloway S, Guzzie P, Hayashi M, Kasper P, **Kirkland D**, MacGregor J T, Parry J M, Schechtman L, Smith A, Tanaka N, Tweats D & Yamasaki H (2003). Strategy for genotoxicity testing and stratification of genotoxicity test results – report on initial activities of the IWGT expert group. Mutat Res, **540**, 177-181.

Nohynek G J, **Kirkland D**, Marzin D, Toutain H, Leclerc-Ribaud C and Jinnai H (2004). An assessment of the genotoxicity and human health risk of topical use of kojic acid [5-hydroxy-2-(hydroxymethyl)-4H-pyran-4-one]. Fd. Chem. Toxicol. **42**, 93-105

Marzin D and **Kirkland D** (2004). 2-Hydroxy-1,4-naphthoquinone, the natural dye of Henna, is non-genotoxic in the mouse bone marrow micronucleus test and does not produce oxidative DNA damage in Chinese hamster ovary cells. Mutat. Res. **560**, 41-47.

Kirkland D and Snodin D (2004). Setting limits for genotoxic impurities in drug substances: Threshold-based and pragmatic approaches. Int. J. Pharm. Med. **18,** 197-207

Kasper P, **Kirkland D**, Leblanc B, Sjöberg P and Spindler P (2004). Acceptability of low levels of genotoxic impurities in new drug substances: Conclusions of the Drug

Information Association (DIA)/European Medicines Agency (EMEA) Workshop, October 27-28, 2003 in London, UK. Int. J. Pharm. Med **18,** 221-223

Spindler P, Silva Lima B, Vidal J-M, Kasper P, Sjöberg P, Olejniczak K, Liminga U, van der Laan J-W, **Kirkland D**, Newall D R, Bode G and Lodola A (2004). Preclinical Safety Assessment Update. Drug Information Journal

Kirkland D, Aardema M, Henderson L and Müller L (2005). Evaluation of the ability of a battery of three *in vitro* genotoxicity tests to discriminate rodent carcinogens and non-carcinogens. I. Sensitivity, specificity and relative predictivity. Mutat. Res. **584**, 1-256.

Thompson C, Ferdinandi E, Morley P, **Kirkland D** and Proudlock R (2005). Modified bacterial mutation test procedures for evaluation of peptides and amino-acid containing material. Mutagenesis **20**, 345-350.

Kirkland D J, Henderson L, Marzin D, Müller L, Parry J M, Speit G, Tweats D J and Williams G M (2005). Testing strategies in mutagenicity and genetic toxicology: an appraisal of the guidelines of the European Scientific Committee for Cosmetics and Non-Food Products for the evaluation of hair dyes. Mutat. Res. **588**, 88-105.

Dufour E K, Kumaravel T, Nohynek G J, **Kirkland D** and Toutain H (2006). Clastogenicity, photo-clastogenicity or pseudo-photo-clastogenicity: genotoxic effects of zinc oxide in the dark, in pre-irradiated or simultaneously-irradiated Chinese hamster ovary cells. Mutat. Res., **607**, 215-224

Garrigue J-L, Ballantyne M, Kumaravel T, Lloyd M, Nohynek G J, **Kirkland D** and Toutain H (2006). *In vitro* genotoxicity of para-phenylenediamine and its N-monoacetyl or N,N'-diacetyl metabolites. Mutat. Res. **608**, 58-71.

Kirkland D, Aardema M, Müller L and Hayashi M (2006). Evaluation of the ability of a battery of 3 *in vitro* genotoxicity tests to discriminate rodent carcinogens and non-carcinogens. II. Further analysis of mammalian cell results, relative predictivity and tumour profiles. Mutat. Res. **608**, 29-42.

Kirkland D and Beevers C (2006). Induction of *LacZ* mutations in Muta™Mouse can distinguish carcinogenic from non-carcinogenic analogues of diaminotoluenes and nitronaphthalenes. Mutat. Res. **608**, 88-96.

Kirkland D J, Hayashi M, Jacobson-Kram D, Kasper P, MacGregor J T, Müller L and Uno Y (2007). The International workshops on Genotoxicity Testing (IWGT): History and achievements. Mutat. Res., **627**, 1-4.

Kirkland D J, Hayashi M, Jacobson-Kram D, Kasper P, MacGregor J T, Müller L and Uno Y (2007). Summary of major conclusions from the 4th IWGT. Mutat. Res., **627**, 5-9.

Thybaud V, Aardema M, Clements J, Dearfield K, Galloway S, Hayashi M, Jacobson-Kram D, **Kirkland D,** MacGregor J T, Marzin D, Ohyama W, Schuler M, Suzuki H and Zeiger E

(2007). Strategy for genotoxicity testing: Hazard identification and risk assessment in relation to *in vitro* testing. Mutat. Res., **627**, 41-58.

Kirkland D, Whitwell J, Deyo J and Serex T (2007). Failure of antimony trioxide to induce micronuclei or chromosomal aberrations in rat bone marrow after sub-chronic dosing. Mutat. Res., **627**, 119-128.

Kirkland D, Pfuhler S, Tweats D, Aardema M, Corvi R, Darroudi F, Elhajouji A, Glatt H Hastwell P, Hayashi M, Kasper P, Kirchner S, Lynch A, Marzin D, Maurici D, Meunier J-R, Müller L, Nohynek G, Parry J, Parry E, Thybaud V, Tice R, van Benthem J, Vanparys P and White P (2007). How to reduce false positive results when undertaking *in vitro* genotoxicity testing and thus avoid unnecessary follow-up animal tests: Report of an ECVAM workshop. Mutat. Res., **628**, 31-55.

Tice R R, Gatehouse D, **Kirkland D** and Speit G (2007). The pathogen reduction treatment of platelets with S-59 HCl (Amotosalen) plus ultraviolet A light: Genotoxicity profile and hazard assessment. Mutat. Res. **630**, 50-68.

Kirkland D J, Aardema M, Banduhn N, Carmichael P, Fautz R, Meunier J-R and Pfuhler S (2007). *In vitro* approaches to develop weight of evidence (WoE) and mode of action (MoA) discussions with positive *in vitro* genotoxicity results. Mutagenesis **22**, 161-175.

Long L H, **Kirkland D** and Halliwell B (2007) Different cytotoxicities of epigallocatechin gallate or ascorbate in various cell culture media due to variable rates of oxidation in the culture medium. Mutat. Res. **634**, 177-183.

Theogaraj E, Riley S, Hughes L, Maier M and **Kirkland D** (2007). An investigation of the photo-clastogenic potential of ultrafine titanium dioxide particles. Mutat. Res. **634,** 205-219.

Kirkland D, Kasper P, Müller L, Corvi R and Speit G (2008). Recommended lists of genotoxic and non-genotoxic chemicals for assessment of the performance of new or improved genotoxicity tests: A follow-up to an ECVAM workshop. Mutat. Res. **653**, 99-108.

Kirkland D and Speit G (2008). Evaluation of the ability of a battery of 3 *in vitro* genotoxicity tests to discriminate rodent carcinogens and non-carcinogens. III. Appropriate follow-up testing *in vivo*. Mutat. Res. **654**, 114-132.

Lorge E, Hayashi M, Albertini S and **Kirkland D** (2008). Comparison of different methods for an accurate assessment of cytotoxicity in the *in vitro* micronucleus test. I. Theoretical aspects. Mutat. Res. **655**, 1-3

Fellows M D, O'Donovan M R, Lorge E and **Kirkland D** (2008). Comparison of different methods for an accurate assessment of cytotoxicity in the *in vitro* micronucleus test. II. Practical aspects with toxic agents. Mutat. Res. **655**, 4-21

Blakey D, Galloway S M, **Kirkland D J** and MacGregor J T (2008). Regulatory aspects of genotoxicity testing: from hazard identification to risk assessment. Mutat. Res. **657**, 84-90.

Dufour E K, Whitwell J, Nohynek G J, **Kirkland D** and Toutain H (2009). Retinyl palmitate is non-genotoxic in Chinese hamster ovary cells in the dark or after pre-irradiation or simultaneous irradiation with UV light. Mutat. Res. **672**, 21-26

Benfenati E, Benigni R, DeMarini D M, Helma C, **Kirkland D**, Martin T M, Mazzatorta P, Ou'edraogo-Arras G, Richard A M, Schilter B, Schoonen W G E J, Snyder R D and Yang C (2009). Predictive Models for Carcinogenicity and Mutagenicity: Frameworks, State-of-the-Art, and Perspectives. J. Env. Sci. Health Part C, **27**, 57-90.

Kirsch-Volders M, Gonzalez L, Carmichael P and **Kirkland D** (2009). Risk assessment of genotoxic mutagens with thresholds: A brief introduction. Mutat. Res. **678**, 72-75.

Eichenbaum G, Johnson M, **Kirkland D**, O'Neill P, Stellar S, Bielawne J, DeWire R, Areia D, Bryant S, Weiner S, Desai-Krieger D, Guzzie-Peck P, Evans D C and Tonelli A (2009). Assessment of the genotoxic and carcinogenic risks of p-nitrophenol when it is present as an impurity in a drug product. Regul. Tox. Pharm. **55**, 33-42.

Pfuhler S, **Kirkland D**, Kasper P, Hayashi M, Vanparys P, Carmichael P, Dertinger S, Eastmond D, Elhajouji A, Krul C, Rothfuss A, Schoening G, Smith A, Speit G, Thomas C, van Benthem J and Corvi R (2009). Reduction of use of animals in regulatory genotoxicity testing: Identification and implementation opportunities—Report from an ECVAM workshop. Mutat. Res.**680**, 31-42.

Kirkland D (2010). Evaluation of different cytotoxic and cytostatic measures for the in vitro micronucleus test (MNVit): Introduction to the collaborative trial. Mutat. Res. **702**, 135-138.

Kirkland D (2010). Evaluation of different cytotoxic and cytostatic measures for the in vitro micronucleus test (MNVit): Summary of results in the collaborative trial. Mutat. Res. **702**, 139-147.

Fowler P, Whitwell J, Jeffrey L, Young J, Smith K and **Kirkland D** (2010). Cadmium chloride, benzo[a]pyrene and cyclophosphamide tested in the in vitro mammalian cell micronucleus test (MNvit) in the human lymphoblastoid cell line TK6 at Covance laboratories, Harrogate UK in support of OECD draft Test Guideline 487. Mutat. Res. **702**, 171-174

Fowler P, Whitwell J, Jeffrey L, Young J, Smith K and **Kirkland D** (2010). Etoposide; colchicine; mitomycin C and cyclophosphamide tested in the in vitro mammalian cell micronucleus test (MNvit) in Chinese hamster lung (CHL) cells at Covance laboratories; Harrogate UK in support of OECD draft Test Guideline 487. Mutat. Res. **702**, 175-180.

Whitwell J, Fowler P, Allars S, Jenner K, Lloyd M, Wood D, Smith K, Young J, Jeffrey L, **Kirkland D** (2010). 5-Fluorouracil, colchicine, benzo[a]pyrene and cytosine arabinoside tested in the *in vitro* mammalian cell micronucleus test (MNvit) in Chinese hamster V79 cells at Covance Laboratories, Harrogate, UK in support of OECD draft Test Guideline 487. Mutat. Res. **702**, 230-236.

Whitwell J, Fowler P, Allars S, Jenner K, Lloyd M, Wood D, Smith K, Young J, Jeffrey L, **Kirkland D** (2010). 2-Aminoanthracene, 5-fluorouracil, colchicine, benzo[a]pyrene, cadmium chloride and cytosine arabinoside tested in the in vitro mammalian cell micronucleus test (MNvit) in Chinese hamster ovary (CHO) cells at Covance Laboratories, Harrogate UK in support of OECD draft Test Guideline 487. Mutat. Res. **702**, 237-247.

Kirkland D and Fowler P (2010). Further analysis of Ames-negative rodent carcinogens that are only genotoxic in mammalian cells in vitro at concentrations exceeding 1 mM, including retesting of compounds of concern. Mutagenesis **25**, 539-553.

Dearfield K L, Thybaud V, Cimino M C, Custer L, Czich A, Harvey J S, Hester S, Kim J H, **Kirkland D**, Levy D D, Lorge E, Moore M M, Ouédraogo-Arras G, Schuler M, Suter W, Sweder K, Tarlo K, van Benthem J, van Goethem F and Witt K L (2011). Follow-up actions from positive results of *in vitro* genetic toxicity testing. Environ. Mol. Mutagen. **52**, 177-204.

Kirkland D, Reeve L, Gatehouse D and Vanparys P (2011). A core *in vitro* genotoxicity battery comprising the Ames test plus the *in vitro* micronucleus test is sufficient to detect rodent carcinogens and *in vivo* genotoxins. Mutat. Res. **721,** 27-73.

Bowen D E, Whitwell J H, Lillford L, Henderson D, Kidd D, McGarry S, Pearce G, Beevers C and **Kirkland D J** (2011). Evaluation of a multi-endpoint assay in rats, combining the bone-marrow micronucleus test, the Comet assay and the flow-cytometric peripheral blood micronucleus test. Mutat. Res. **722**, 7-19.

Galloway S, Lorge E, Aardema M J, Eastmond D, Fellows M, Heflich R, **Kirkland D**, Levy D D, Lynch A M, Marzin D, Morita T, Schuler M and Speit G (2011). Workshop summary: Top concentration for in vitro mammalian cell genotoxicity assays; and report from working group on toxicity measures and top concentration for in vitro cytogenetics assays (chromosome aberrations and micronucleus). Mutat. Res. **723**, 77-83.

Rothfuss A, Honma M, Czich A, Aardema M J, Burlinson B, Galloway S, Hamada S, **Kirkland D**, Heflich R H, Howe J, Nakajima M, O'Donovan M, Plappert-Helbig U, Priestley C, Recio L, Schuler M, Uno Y and Martus H-J (2011). Improvement of *in vivo* genotoxicity assessment: Combination of acute tests and integration into standard toxicity testing. Mutat. Res. **723**, 108-120.

Kirkland D J, Hayashi M, Jacobson-Kram D, Kasper P, Gollapudi B, Müller L and Uno Y (2011). Summary of major conclusions from the 5th IWGT, Basel, Switzerland, 17–19 August 2009, Mutat. Res. **723**, 73-76.

Felter SP, Conolly RB, Bercu JP, Bolger PM, Boobis AR, Bos PMJ, Carthew P, Doerrer NG, Goodman JI, Harrouk WA, **Kirkland DJ**, Lau SS, Llewellyn GC, Preston RJ, Schoeny R, Schnatter AR, Tritscher A, van Velsen F, and Williams GM (2011). A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens. Crit. Rev. Toxicol. **41**, 507-544.

Kirkland D, Ballantyne M, Harlfinger S, Will O, Jahnel U, Kraus A and van Dorp C (2011). Further investigations into the genotoxicity of 2,6-xylidine and one of its key metabolites. Regul. Toxicol. Pharmacol.**62**, 151-159.

Kirkland D (2011). Improvements in the reliability of *in vitro* genotoxicity testing. Expert Opin. Drug Metab. Toxicol. **7**, 1513-1520.

Fowler P, Smith K, Young J, Jeffrey L, **Kirkland D**, Pfuhler S and Carmichael P (2012). Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. I. Choice of cell type. Mutat. Res. **742**, 11-25

McKeon M, Xu Y, **Kirkland D**, Schmuck G, Krebsfänger N, Avlasevich S L and Dertinger S D (2012). Cyclophosphamide and etoposide canine studies demonstrate the cross-species potential of the flow cytometric peripheral blood micronucleated reticulocyte endpoint. Mutat. Res. **742**, 79-83.

Fowler P, Smith R, Smith K, Young J, Jeffrey L, **Kirkland D**, Pfuhler S, Carmichael P (2012). Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. II. Importance of accurate toxicity measurement. Mutat. Res. **747**, 104-117.

Kier L D, **Kirkland D J** (2013). Review of genotoxicity studies of glyphosate and glyphosate-based formulations. Crit. Rev. Toxicol. **43**, 283-315.

Fowler P, Smith R, Smith K, Young J, Jeffrey L, Carmichael P, **Kirkland D**, Pfuhler S (2014). Reduction of misleading ("false") positive results in mammalian cell genotoxicity assays. III. Sensitivity of human cell types to known genotoxic agents, Mutat. Res. **767**, 28-36.

Kirkland D, Zeiger E, Madia F, Gooderham N, Kasper P, Lynch A, Morita T, Ouedraogo G, Parra Morte J M, Pfuhler S, Rogiers V, Schulz M, Thybaud V, van Benthem J, Vanparys P, Worth A, Corvi R (2014). Can *in vitro* mammalian cell genotoxicity test results be used to complement positive results in the Ames test and help predict carcinogenic or *in vivo* genotoxic activity? I. Reports of individual databases presented at an EURL ECVAM Workshop, Mutat. Res.**775-776**, 55-68.

Kirkland D, Zeiger E, Madia F, Corvi R (2014). Can *in vitro* mammalian cell genotoxicity test results be used to complement positive results in the Ames test and help predict carcinogenic or *in vivo* genotoxic activity? II. Construction and analysis of a consolidated database, Mutat. Res. **775-776**, 69-80.

Kirkland D, Edwards J, Woehrle T, Beilstein P (2015). Investigations into the genotoxic potential of olive extracts. Mutat. Res. **777**, 17-28.

Martus H-J, Hayashi M, Honma M, Kasper P, Gollapudi B, Müller L, Schoeny R, Uno Y, **Kirkland D J** (2015). Summary of major conclusions from the 6th International Workshop on Genotoxicity Testing (IWGT), Foz do Iguaçu, Brazil. Mutat. Res. **783**, 1-5.

Whitwell J, Smith R, Jenner K, Lyon H, Wood D, Clements J, Gollapudi B, **Kirkland D**, Lorge E, Pfuhler S, Tanir J, Thybaud V (2015). Relationship between p53 status, apoptosis and induction of micronuclei in different human and mouse cell lines in vitro: implications for improving existing assays. Mutat. Res.**789-790**, 7-27.

Kirkland D, Brock T, Haddouk H, Hargeaves V, Lloyd M, Mc Garry S, Proudlock R, Sarlang S, Sewald K, Sire G, Sokolowski A, Ziemann C (2015). New investigations into the genotoxicity of cobalt compounds and their impact on overall assessment of genotoxic risk. Regul. Toxicol. Pharmacol. **73**, 311-338.

Kirkland D, Gatehouse D (2015). Aspartame: a review of genotoxicity data. Food Chem. Toxicol. **84**, 161-168.

SCIENTIFIC PRESENTATIONS AND INVITED LECTURES
Too numerous to list.

Marsh

Curriculum Vitae

June 2015

GARY M. MARSH, Ph.D., F.A.C.E.

Business Address: A410 Crabtree Hall
Graduate School of Public Health
130 DeSoto Street
Pittsburgh, PA 15261

Telephone: [redacted]
Fax: [redacted]
E-Mail: gmarsh@cobe.pitt[redacted]
www.publichealth.pitt.edu/home/directory/gary-m-marsh

Home Address: [redacted]
McMurray, PA [redacted]

Telephone: [redacted]
Fax: [redacted]

EDUCATION AND TRAINING

1969-73	University of Pittsburgh Pittsburgh, Pennsylvania	B.S. (Honors)	Mathematics 1973
1973-74	University of Pittsburgh Graduate School of Public Health	M.S. (Hyg.)	Biostatistics 1974
1975-77	University of Pittsburgh Graduate School of Public Health	Ph.D.	Biostatistics 1977

APPOINTMENTS AND POSITIONS

1974-75	Wesley Institute Bethel Park, Pennsylvania	Mathematics Instructor
1977-78	University of Pittsburgh Graduate School of Public Health (GSPH)	Research Associate
1978-84	University of Pittsburgh, GSPH	Assistant Professor of Biostatistics
1981-83	University of Pittsburgh School of Health Related Professions	Adjunct Assistant Professor of Health Related Professions
1983-92	University of Pittsburgh Center for Environmental Epidemiology	Assistant Director
1984	University of Minnesota School of Public Health	Faculty, Graduate Summer Session in Epidemiology
1984-91	University of Pittsburgh, GSPH	Associate Professor of Biostatistics
1991-date	University of Pittsburgh, GSPH	Professor of Biostatistics
2008-date	University of Pittsburgh, GSPH	Founder and Director, Center for Occupational Biostatistics and Epidemiology
2007, 09-10	University of Pittsburgh, GSPH	Interim Chairman, Department of Biostatistics
2010-date	University of Pittsburgh, Center for Clinical and Translational Science	Professor of Clinical and Translational Science
2010-date	University of Pittsburgh, GSPH	Professor of Epidemiology

MEMBERSHIP IN PROFESSIONAL ORGANIZATIONS AND SCIENTIFIC SOCIETIES

1974-date	American Statistical Association -Secretary, Vice President, President-Pittsburgh Chapter, 1979-82 -National Council Representative, 1981-1982
1974-date	Biometric Society
1978-date	Society for Occupational and Environmental Health -National Governing Council, 1986-1989
1979-date	Society for Epidemiological Research
1986-date	Pennsylvania Public Health Association -Member, Board of Directors, 1989-92
1988-date	International Society for Environmental Epidemiology
1996-date	International Commission on Occupational Health
1997-date	American College of Epidemiology - Fellowship, 1997
2001-2010	British Occupational Hygiene Society

HONORS and AWARDS

1973	B.S., Cum Laude
1981	Adolf G. Kammer Merit in Authorship Award - Best Publication in Field of Occupational Health, American Occupational Medical Association
1985	Delta Omega, Public Health Honorary Society
1986	Tenure, University of Pittsburgh, Department of Biostatistics
1994	Outstanding Teacher Award, Graduate School of Public Health
1997	Biographical Entry in *Who's Who in Science and Engineering*
1997	Fellowship, American College of Epidemiology
1999	50 at 50 Award, Graduate School of Public Health (selected as one of 50 outstanding contributors in field of public health in 50 year history of school)
2002	Biographical Entry in *Who's Who in Medicine and Healthcare*
2003	Biographical Entry in *2000 Outstanding Scientists of the 21st Century*
2004	Biographical Entry in *Who's Who in America*
2005	Biographical Entry in *Who's Who in American Education*

2006, 08, 09, 13 University of Pittsburgh Innovator Award for work on OCMAP software package

PUBLICATIONS

1. Articles

a. Published Refereed Articles

1. Cohen J and **Marsh GM**: Testing for the Communicability of Economic Ideas Via the Federal Reserve Bank, Reviews: A Learning Experiment. Journal of Economics Education 8:104-107, 1977.

2. **Marsh GM** and Enterline PE: A Method for Verifying the Completeness of Cohorts Used in Occupational Mortality Studies. Journal of Occupational Medicine 21:665-670, 1979.

3. **Marsh GM** and Preininger ME: OCMAP: A User-Oriented Occupational Cohort Mortality Analysis Program. American Statistician 34:245-246, 1980.

4. Enterline PE and **Marsh GM**: Mortality Studies of Smelter Workers. American Journal of Industrial Medicine 1:251-259, 1980.

5. Summers WK, Viesselman JO, and **Marsh GM**: The Use of THA in the Treatment of Alzheimer-Like Dementia. Biological Psychiatry 16:145-153, 1981.

6. Summers WK, Munoz R, Reed M, and **Marsh GM**: The Psychiatric Physical Examination: Findings in 75 Unselected Patients. Journal of Clinical Psychiatry 42:99-102, 1981.

7. Linn JG, Stuart JC, Warnicki JW, Sinclair RA, and **Marsh GM**: Endothelial Morphology in Long-Term Keratonconus Corneal Transplants. Ophthalmology 88:761-770, 1981.

8. Enterline PE and **Marsh GM**: Mortality among Nickel Workers in a Nickel Refinery and Manufacturing Plant in West Virginia. Journal of the National Cancer Institute 68:925-933, 1982.

9. **Marsh GM**: Computerized Approach to Verifying Study Population Data in Occupational Epidemiology. Journal of Occupational Medicine 24:596-601, 1982.

10. Enterline PE and **Marsh GM**: Missing Records in Occupational Disease Epidemiology. Journal of Occupational Medicine 24:677-680, 1982.

11. Enterline PE and **Marsh GM**: Cancer among Workers Exposed to Arsenic and other Substances in a Copper Smelter. American Journal of Epidemiology 116:895-911, 1982.

12. **Marsh GM**: Proportional Mortality Patterns among Chemical Plant Workers Exposed to Formaldehyde. British Journal of Industrial Medicine 39:313-322, 1982.

13. **Marsh GM**: Mortality among Workers from a Plastics Producing Plant: A Matched Case Control Study Nested Within a Cohort Study. Journal of Occupational Medicine 25:219-230, 1983.

14. John LR, **Marsh GM**, and Enterline PE: Evaluating Occupational Hazards Using Only Information Known to Employers: A Comparative Study. British Journal of Industrial Medicine 40:346-352, 1983.

15. Enterline PE, **Marsh GM**, and Esmen NA: Respiratory Disease among Workers Exposed to Mineral Fiber. American Review of Respiratory Disease 128:1-7, 1983.

16. **Marsh GM**: A Critical Review of Epidemiologic Studies Related to Ingested Asbestos. Environmental Health Perspectives 53:49-56, 1983.

17. Summers WK, **Marsh GM**, Chiong B, Bugoyne RM, Swenson SW, and Walker NR: The General Adult In-Patient Psychiatric Assessment Scale (GAIPAS). Psychiatry Research 10:217-236, 1983.

18. **Marsh GM**: Commentary: Additional Thoughts on the Review of Epidemiologic Studies Related to Ingested Asbestos. Environmental Health Perspectives 53:185-187, 1983.

19. Caplan RJ, **Marsh GM**, and Enterline PE: A Generalized Effective Exposure Modeling Program for Assessing Dose-Response in Epidemiologic Investigations. Computers and Biomedical Research 16:587-596, 1984.

20. Helmkamp J, Talbott E, and **Marsh GM**: Whole Body Vibration-A Critical Review. American Industrial Hygiene Association Journal 45:162-167, 1984.

21. Stehr PA, Gloninger MF, Kuller LH, **Marsh GM**, Radford EP, and Weinberg G: Vitamin A Deficiencies as a Predisposing Factor in the Development of Stomach Cancer. American Journal of Epidemiology 121:65-79, 1985.

22. Rao BR, **Marsh GM**, and Winwood J: Sidak-Type Simultaneous Prediction Intervals for the Measures $RSRR_i$ About the Corresponding $SePMR_i$ for Several Competing Risks of Death in an Epidemiologic Study. Journal of Statistical Planning and Inference 12:311-329, 1985.

23. Rao BR, **Marsh GM**, and Winwood J: Sidak-Type Simultaneous Confidence Intervals for the Measures $RSMR_i$ in Proportional Mortality Analyses Involving Competing Risks of Death. Communications in Statistics-Theory and Methods 15:515-536, 1986.

24. **Marsh GM**, Ehland J, Paik M, Preininger M, Caplan R: OCMAP/PC: A User Oriented Cohort Mortality Analysis Program for the IBM PC. The American Statistician 40:308-309, 1986.

25. Summers WK, Majowski LJ, **Marsh GM**, Tachiki K, and Kling A: Use of Oral THA in Long-Term Treatment of Senile Dementia, Alzheimer's Type. New England Journal of Medicine 315:1241-1245, 1986.

26. **Marsh GM**, Winwood J, and Rao BR: Prediction of the Standardized Risk Ratio Via Proportional Mortality Analysis. Biometrical Journal 29:355-368, 1987.

27. Enterline PE, Henderson VL, and **Marsh GM**: Exposure to Arsenic and Respiratory Cancer: A Re-Analysis. American Journal of Epidemiology 125:929-938, 1987.

28. **Marsh GM**: A Strategy for Merging and Analyzing Work History Data in Industry-wide Occupational Epidemiology Studies. American Industrial Hygiene Association Journal 48:414-419, 1987.

29. Rao BR, **Marsh GM**: Approximate Methodologies for Proportional Mortality Analyses in Epidemiologic Studies Involving Competing Risks of Death Regardless of Their Covariance Structure. Biometrical Journal 29:525-540, 1987.

30. Enterline PE, **Marsh GM**, Esmen NA, Henderson VL, Callahan C, and Paik M: Some Effects of Cigarette Smoking, Arsenic, and SO_2 on Mortality among U.S. Copper Smelter Workers. Journal of Occupational Medicine 29:831-838, 1987.

31. Enterline PE, **Marsh GM**, Henderson V, and Callahan C: Mortality Update of a Cohort of U.S. Man-Made Mineral Fiber Workers. The Annals of Occupational Hygiene 31:625-656, 1987.

32. Rao BR and **Marsh GM**: Approximate Simultaneous Inferential Procedures for Overall Risk Assessment of Several Competing Risk Factors in Biomedical and Epidemiologic Studies. Journal of Statistical Inference and Planning 18:323-344, 1988.

33. **Marsh GM**, Sachs DPL, Callahan C, Leviton LC, Ricci E, and Henderson V: Direct Methods of Obtaining Information on Tobacco Use in Occupational Studies. American Journal of Industrial Medicine 13:71-104, 1988.

34. Rao BR and **Marsh GM**: Approximate Variance Formulas and Asymptotic Joint Sampling Distribution of Standardized Risk Ratios in the Presence of Competing Risks in Cohort Studies. Communications in Statistics-Theory and Methods 17:745-777, 1988.

35. **Marsh GM**, Costantino JP, Lyons EE, Logue JN, and Fox JM: Health Effects of Exposure to the Drake Chemical Company Superfund Site: Morbidity Patterns among Former Employees. Journal of Environmental Health 50:389-394, 1988.

36. Summers WK, Kobhler AL, **Marsh GM**, Tachiki R, Kling A: Long Term Hepatoxicity of Tetrahydroaminoacridine. Lancet 8640, April 1:729, 1989.

37. Rao BR, **Marsh GM**, and Winwood J: Asymptotic Interval Estimation of Some Cause-Specific Mortality Risk Measures in Epidemiologic Studies. Biometrical Journal 31:461-475, 1989.

38. Collins JJ, Swaen G, **Marsh GM**, Utidjian HMD, Caporossi JC, Saipher JN, et al: Mortality Patterns among Workers Exposed to Acrylamide. Journal of Occupational Medicine 30:614-617, 1989.

39. **Marsh GM**, Co-Chien H, Rao BR, and Ehland J: OCMAP: Module 6 - A New Computing Algorithm for Proportional Mortality Analysis. American Statistician 43:127-128, 1989.

40. Lilienfeld DE, Chan E, Ehland J, Godbold J, Landrigan PJ, Letz R, **Marsh GM**, Perl DP: Increasing Mortality from Motor Neuron Disease. Lancet 8640, April 1:710-713, 1989.

41. Mazumdar S, Redmond CK, Enterline PE, **Marsh GM**, Costantino JP, Zhou SY, Patwardhan RN: Multistage Modeling of Lung Cancer Mortality among Arsenic Exposed Copper Smelter Workers. Risk Analysis 9:551-563, 1989.

42. Rao BR and **Marsh GM**: Simultaneous Statistical Inference Concerning the SMR's of Several Strata in an Epidemiologic Study. Biometrical Journal 32:107-123, 1990.

43. **Marsh GM**, Enterline PE, Stone RA, Henderson VL: Mortality among a Cohort of U.S. Man-Made Mineral Fiber Workers: 1985 Follow-Up. Journal of Occupational Medicine 32:594-604, 1990.

44. Enterline PE, Henderson V, and **Marsh GM**: Mortality among Workers Potentially Exposed to Epichlorohydrin. British Journal of Industrial Medicine 47:269-276, 1990.

45. Summers WK, Kobhler AL, **Marsh GM**, Tachiki R, Kling A: Comparison of Seven Psychometric Instruments Used for Evaluation of Treatment Effect in Alzheimers Patients. Neuroepidemiology 9:193-207, 1990.

46. Lilienfeld DE, Chan E, Ehland J, Godbold J, **Marsh GM**, Landrigan PJ, and Perl DP: Two Decades of Increasing Mortality from Parkinson's Disease among the United States Elderly. Archives of Neurology 47:731-734, 1990.

47. **Marsh GM**, Callahan C, Pavlock D, Leviton LC, Talbott E, Hemstreet G: A Protocol for Bladder Cancer Screening and Medical Surveillance among High Risk Groups: The Drake Health Registry Experience. Journal of Occupational Medicine 32:881-886, 1990.

48. Lilienfeld DE, Sekkor D, Simpson S, Perl DP, Ehland J, **Marsh GM**, Chan E, Godbold JH, Landrigan PJ: Parkinsonism Death Rates by Race, Sex and Geography. A 1980's Update. Neuroepidemiology 9:243-247, 1990.

49. Collins JJ, Swaen GMH, **Marsh GM**, Hofsteenge E, von Bedaf A: Mortality among Workers Exposed to Acrylamide. Tijdschrift voor toegepaste Arbowetenschap 3:54-58, 1990.

50. **Marsh GM**, Leviton LC, Talbott E, Callahan C, Pavlock D, Hemstreet G, Logue JN, Fox J, Schulte, P: The Drake Chemical Workers Health Registry Study: I. Notification and Medical Surveillance of a Group of Workers at High Risk of Developing Bladder Cancer. American Journal of Industrial Medicine 19:291-302, 1991.

51. Leviton LC, **Marsh GM**, Talbott E, Callahan C, et al: The Drake Chemical Workers Health Registry Study: II. Coping with Community Tension in Health Protection. American Journal of Public Health 81:689-693, 1991.

52. Lilienfeld DE, Chan E, Ehland J, Godbold J, Landrigan PJ, **Marsh GM**: Mortality from Pulmonary Embolism in the United States: 1962-1984. Chest 47:731-734, 1991.

53. **Marsh GM**, Enterline PE, and McCraw D: Mortality Patterns among a Cohort of Petroleum Refinery and Petrochemical Plant Workers. American Journal of Industrial Medicine 19:29-42, 1991.

54. **Marsh GM**, Day R: A Model Standardized Risk Assessment Protocol for Use with Hazardous Waste Sites. Environmental Health Perspectives 90:199-208, 1991.

55. Day R, Talbott EO, **Marsh GM**, Case B: A Comparative Ecologic Study of Selected Cancers in Kanawha County, WV. American Journal of Industrial Medicine 21:235-251, 1992.

56. Rao BR, Day R, **Marsh GM**: Estimation of Relative Risks from Individual and Ecological Correlation Studies. Communications in Statistics-Theory and Methods 21:241-268, 1992.

57. **Marsh GM**, Stone RA, Henderson V: A Reanalysis of the National Cancer Institute Study on Mortality among Industrial Workers Exposed to Formaldehyde. Journal of Occupational Medicine 34:42-44, 1992.

58. Talbott EO, Day RD, **Marsh GM**, Haile-Cattledge GT, McKenna M, Case BW: Trends in Cancer Mortality in Kanawha County, West Virginia, 1950-1984. Science of the Total Environment 127:139-154, 1992.

59. **Marsh GM**, Stone RA, Henderson V: Lung Cancer Mortality among Industrial Workers Exposed to Formaldehyde: A Poisson Regression Analysis of the National Cancer Institute Study. American Industrial Hygiene Association Journal 53:681-691, 1992.

60. Leviton LC, Chen HT, **Marsh GM**, Talbott EO: Evaluation Issues in the Drake Chemical Workers Notification and Health Registry Study. American Journal of Industrial Medicine 23:197-204, 1993.

61. **Marsh GM**, Stone RA, Esmen NA, Henderson VL: Mortality Patterns among Chemical Plant Workers Exposed to Formaldehyde and Other Substances. Journal of the National Cancer Institute 86:384-385, 1994.

62. Stone RA, **Marsh GM**, Henderson VL, Owens AD, Smith TJ: Statistical Power to Detect Occupationally Related Respiratory Cancer in a Cohort of Female Employees in the U.S. MMVF Industry. Journal of Occupational Medicine 36:899-901, 1994.

63. Craun GF, Bull RJ, Clark RM, Doull J, Grabow W, **Marsh GM**, Okun DA, Regli S, Sobsey MD, Symons JM: Balancing Chemical and Microbial Risks of Drinking Water Disinfection. Part I, Benefits and Potential Risks. AQUA 43:192-199, 1994.

64. Craun GF, Bull RJ, Clark RM, Doull J, Grabow W, **Marsh GM**, Okun DA, Regli S, Sobsey MD, Symons JM: Balancing Chemical and Microbial Risks of Drinking Water Disinfection. Part II, Stategies to Manage Risk. Aqua 43:207-218, 1994.

65. Enterline PE, Day RD, **Marsh GM**: Cancers Related to Arsenic Exposure at a Copper Smelter. Occupational and Environmental Medicine 52:28-32, 1995.

66. Stone RA, **Marsh GM**, Youk AO, Quinn M: Statistical Estimation of Exposures to Fibers for Which No Direct Measurements are Available. Occupational Hygiene 3:91-101, 1996.

67. **Marsh GM**, Stone RA, Youk AO, Smith TS, Quinn MM, Henderson VL, Schall LC, Wayne LA, Lee KY: Mortality among United States Rock Wool and Slag Wool Workers: 1989 Update. Journal of Occupational Health and Safety - Australia and New Zealand 12(3):297-312, 1996.

68. **Marsh GM**, Stone RA, Esmen NA, Henderson VH, Lee KY: Mortality Patterns among Chemical Workers in a Factory Where Formaldehyde Was Used. Occupational and Environmental Medicine 53:613-617, 1996.

69. Esmen NA, **Marsh GM**: Applications and Limitations of Air Dispersion Modeling in Environmental Epidemiology, Journal of Exposure Analysis and Environmental Epidemiology 6:339-353, 1996.

70. Massoudi BL, Talbott EO, Day RD, Swerdlow SH, **Marsh GM**, Kuller LH: A Case-Control Study of Hematopoietic and Lymphoid Neoplasms: The Role of Work In the Chemical Industry. American Journal of Industrial Medicine 31:21-27, 1997.

71. Esmen NA, **Marsh GM**, Stone RA, Gula MJ, Gause CK: Quantifying Individual Residential Exposure to Smelter Emissions in Four Arizona Copper Smelting Communities: Exposure Estimation Procedures and Results. Toxicology and Industrial Health 13:247-258, 1997.

72. Schall LS, **Marsh GM**, Henderson VL: A Two-Stage Protocol for Verifying Vital Status in Large Historical Cohort Studies. Journal of Occupational and Environmental Medicine 39:1097-1102, 1997.

73. **Marsh GM**, Stone RA, Esmen NA, Gula MJ, Gause CK, Petersen NJ, Meaney FJ, Rodney S, Prybylski D: A Case-Control Study of Lung Cancer Mortality in Six Gila Basin, Arizona Smelter Towns. Environmental Research 75:56-72, 1997.

74. **Marsh GM**, Stone RA, Esmen NA, Gula MJ, Gause CK, Petersen NJ, Meaney FJ, Rodney S, Prybylski D: A Case-Control Study of Lung Cancer Mortality in Four Rural Arizona Smelter Towns. Archives of Environmental Health 53:15-28, 1998.

75. **Marsh GM**, Youk AO, Stone RA, Sefcik S, Alcorn C: OCMAP-PLUS, A New Program for the Comprehensive Analysis of Occupational Cohort Data. Journal of Occupational and Environmental Medicine 40:351-362, 1998.

76. Lear D, Schall LC, **Marsh GM**, Liu KS, Yao Y: Identification and Case Management of Patients at Risk of Preterm Labor in an HMO. American Journal of Managed Care 4:865-871, 1998.

77. Jain AB, Yee LD, Nalesnik M, Youk AO, **Marsh GM**, Reyes J, Rakela J, Irish W, Fung JJ: *De Novo* Non-Lymphoid Malignancies Following Liver Transplantation Under Tacrolimus. Transplantation, 66:1193-1200, 1998.

78. **Marsh GM**, Lucas L, Youk AO, Schall LC: Mortality Patterns among Workers Exposed to Acrylamide: 1994 Follow-Up. Occupational and Environmental Medicine, 56:181-190, 1999.

79. Esmen NA, Hall TA, Stone RA, **Marsh GM**, Gula MJ, Gause CK: An Investigation of Secondary Exposure Misclassification Effects of Lifelong Occupational History in Exposure Estimation. American Industrial Hygiene Association Journal 60:175-181, 1999.

80. **Marsh GM**, Gula MJ, Youk AO, Schall LC: Mortality among Chemical Plant Workers Exposed to Acrylonitrile and Other Substances. American Journal of Industrial Medicine, 36:423-436, 1999.

81. Schall LC, Buchanich JM, **Marsh GM**, Bittner G: Utilizing Multiple Vital Status Tracing Services Optimizes Mortality Follow-Up in Large Cohort Studies. Annals of Epidemiology , 11:292-296, 2001.

82. **Marsh GM**, Youk AO, Collins J: A Reevaluation of Lung Cancer Risk in the NCI/NIOSH Acrylonitrile Cohort Study. Scandinavian Journal of Work, Environment and Health 27:5-13, 2001.

83. **Marsh GM,** Youk AO, Stone RA, Buchanich JM, Gula MJ, Smith TJ, Quinn MM: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Production Workers. I. 1992 Fiber Glass Cohort Follow-Up-Initial Findings. Journal of Occupational and Environmental Medicine 43:741-756, 2001.

84. **Marsh GM,** Gula MJ, Youk AO, Buchanich JM, Churg A, Colby TV: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Production Workers. II. Mortality from Mesothelioma. Journal of Occupational and Environmental Medicine 43:757-766, 2001.

85. Youk AO, **Marsh GM**, Stone RA, Buchanich JM, Smith TJ: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Production Workers. III. Analysis of Exposure-Weighted Measures of Respirable Fibers and Formaldehyde in the Nested Case-Control Study of Respiratory System Cancer. Journal of Occupational and Environmental Medicine 43:767-778, 2001.

86. Stone RA, Youk AO, **Marsh GM**, Buchanich JM, McHenry MB, Smith TJ: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Production Workers. IV. Quantitative Exposure-Response Analysis of the Nested Case-Control Study of Respiratory System Cancer. Journal of Occupational and Environmental Medicine 43:779-792, 2001.

87. Buchanich JM, **Marsh GM**, Youk AO: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Production Workers. V. Tobacco Smoking Habits. Journal of Occupational and Environmental Medicine 43:793-802, 2001.

88. **Marsh GM**, Buchanich JM, Youk AO: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Production Workers. VI.Respiratory System Cancer SMRs Adjusted for the Confounding Effect of Cigarette Smoking. Journal of Occupational and Environmental Medicine 43:803-808, 2001.

89. Smith TJ, Quinn MM, **Marsh GM**, Youk AO, Stone RA, Buchanich JM, Gula MJ: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Production Workers. VII. Overview of the Exposure Assessment. Journal of Occupational and Environmental Medicine 43:809-823, 2001.

90. Quinn MM, Smith TJ, Youk AO, **Marsh GM,** Stone, RA, Buchanich JM, Gula MJ: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Glass Production Workers VIII. Exposure-Specific Job Analysis. Journal of Occupational and Environmental Medicine 43:824-834, 2001.

91. Schall LC, **Marsh GM**, Holleran MK, Ruhl LS: Methodology to Improve Data Quality from Chart Review in the Managed Care Setting. American Journal of Managed Care 8:787-793, 2002.

92. **Marsh GM,** Youk AO, Stone RA, Buchanich JM, Gula MJ, Smith TJ, Churg A, Colby T: Does Fiber Glass Pose a Respiratory Cancer Risk in Man? Findings from the Latest Update of the U.S. Cohort Study of Man-Made Vitreous Fiber Workers. Annals of Occupational Hygiene 46(Supp.1): 110-114, 2002.

93. **Marsh GM**, Gula MJ, Youk AO, Cassidy LD: Bladder Cancer among Chemical Workers Exposed to Nitrogen Products and Other Substances. American Journal of Industrial Medicine 42:286-295, 2002.

94. **Marsh GM**, Youk AO, Buchanich JM, Cassidy LD, Lucas LJ, Esmen NA, Gathuru I. Pharyngeal Cancer Mortality among Chemical Plant Workers Exposed to Formaldehyde. Toxicology and Industrial Health, 18:257-268, 2003.

95. **Marsh GM**, Cassidy LD: The Drake Health Registry Study: Findings from Fifteen Years of Continuous Bladder Cancer Screening. American Journal of Industrial Medicine, 43:142-148, 2003.

96. Lin CJ, Lave JR, Chang CC, **Marsh GM**, LaValee CP, Jovanovic Z:Factors Associated with Medicaid Enrollment for Low-Income Children in the United States. Journal of Health and Social Policy, 16:35-51, 2003.

97. **Marsh GM**, Gula MJ, Roggli V, Churg A: The Role of Smoking and Asbestos Exposure in a Questionable Case of Mesothelioma. Industrial Health, 41:332-334, 2003.

98. Cassidy LD, Youk AO, **Marsh GM**. The Drake Health Registry Study: Cause-Specific Mortality among Workers with Probable Past Exposure to Beta-naphthylamine, American Journal of Industrial Medicine, 44:282-290, 2003.

99. Bloemen LJ, Youk AO, Bradley TD, Bodner KM, **Marsh GM**, Collins JJ: Lympho-Hematopoietic Cancer among Chemical Workers Exposed to Benzene, Occupational and Environmental Medicine, 61:270-274, 2004.

100. Youk AO, Stone RA, **Marsh GM**.: A Method for Imputing Missing Data in Longitudinal Studies. Annals of Epidemiology, 14:354-361, 2004.

101. Starr T, Gause C, Youk AO, Stone RA, **Marsh GM**, Collins JJ. A Risk Assessment for Occupational Exposure to Acrylonitrile Using Epidemiology Data, Risk Analysis, 24:587-601, 2004.

102. Stone RA, Youk AO, **Marsh GM**, Buchanich JM, Smith TJ, Quinn MM.: Historical Cohort Study of U.S. Man-Made Vitreous Fiber Production Workers IX: Summary of 1992 Mortality Study Follow-Up and Analysis of Respiratory System Cancer among Female Workers, Journal of Occupational and Environmental Medicine, 46:55-67, 2004.

103. Dolan D, **Marsh GM**, Youk AO, Buchanich J. A 50-Year Retrospective Study of Workers Employed in a Pharmaceutical Company. Journal of Occupational and Environmental Medicine, 46:161-166, 2004.

104. **Marsh GM**, Youk AO. Reevaluation of Mortality Risks from Leukemia in the Formaldehyde Cohort Study of the National Cancer Institute. Regulatory Toxicology and Pharmacology, 40:113-124, 2004.

105. **Marsh GM**, Youk AO, Buchanich JM, Esmen NA. Mortality Patterns among Workers in a U.S. Pharmaceutical Production Plant. Annals of Epidemiology, 15:112-122, 2005.

106. Catov J, **Marsh GM**, Youk AO. Asthma Management Outcome Evaluation in a Medicaid Health Plan: How Do the Findings Change with an External Control Group. Disease Management, 8:178-187, 2005.

107. Buchanich JM, Dolan DG, **Marsh GM**, Madrigano J. Under-Ascertainment of Deaths Using Social Security Records: A Recommended Solution to a Little-Known Problem. American Journal of Epidemiology, 162:193-194, 2005.

108. Kirman CR, Gargas, ML, **Marsh GM**, Strother DE, Collins JJ, Deskin R. Reassessment of the Cancer Potency of Acrylonitrile for Human Health Risk Assessment Based Upon Rodent Brain Tumor Incidence: Use of Epidemiology, Mode of Action and Pharmacokinetic Data. Regulatory Toxicology and Pharmacology 43:85-103, 2005.

109. **Marsh GM**, Youk AO. Reevaluation of Mortality Risks from Nasopharyngeal Cancer in the Formaldehyde Cohort Study of the National Cancer Institute. Regulatory Toxicology and Pharmacology, 42:275-283, 2005.

110. **Marsh GM**, Gula MJ. Employment as a Welder and Parkinson's Disease among Heavy Equipment Manufacturing Workers. Journal of Occupational and Environmental Medicine, 48:1031-1045, 2006.

111. **Marsh GM**, Youk AO, Buchanich JM, Cunningham M, Esmen NA, Hall TA, Phillips ML. Mortality Patterns among Industrial Workers Exposed to Chloroprene and Other Substances: I. General Mortality Patterns. Chemico-Biological Interactions 166:285-300, 2007.

112. **Marsh GM,** Youk AO, Buchanich JM, Cunningham M, Esmen NA, Hall TA, Phillips ML. Mortality Patterns among Industrial Workers Exposed to Chloroprene and Other Substances: II. Mortality in Relation to Exposure. Chemico-Biological Interactions 166:301-316, 2007.

113. Esmen NA, Hall TA, Phillips ML, **Marsh GM.** Chemical Process Based Reconstruction of Exposures for an Epidemiology Study: I. Theoretical and Methodological Issues. Chemico-Biological Interactions 166:254-263, 2007.

114. Esmen NA, Hall TA, Phillips ML, Jones PE, Basara H, **Marsh GM**, Buchanich JM. Chemical Process Based Reconstruction of Exposures for an Epidemiology Study: II. Estimated Exposures to Chloroprene and Vinyl Chloride. Chemico-Biological Interactions 166:264-276, 2007.

115. Hall TA, Esmen NA, Jones PE, Basara H, Phillips ML, **Marsh GM**, Youk AO, Buchanich JM, Leonard R. Chemical Process Based Reconstruction of Exposures for an Epidemiological Study: III. Analysis of Industrial Hygiene Samples. Chemico-Biological Interactions 166:277-284, 2007.

116. Esmen NA, Kennedy KJ, Hall TA, Phillips ML, **Marsh GM** Classification of Worker Exposures Chemico-Biological Interactions 166:245-253, 2007.

117. Leonard RC, Lineker GA, Kreckmann KH, **Marsh GM**, Buchanich J, Youk A. Comparison of Standardized Mortality Ratios (SMRs) Obtained from Use of a Reference Population Based on Company-Wide Registry Cohort to SMRs Calculated against Local and National Rates. Chemico-Biological Interactions 166:317-322, 2007.

118. **Marsh GM,** Youk AO, Morfeld P. Mis-Specified and Non-Robust Mortality Risk Models for Naspharyngeal Cancer in the National Cancer Institute Formaldehyde Worker Cohort Study. Regulatory Toxicology and Pharmacology 47:59-67, 2007.

119. **Marsh GM**, Youk AO, Buchanich JM, Kant IJ, Swaen G. Mortality among Workers Exposed to Acrylamide: Updated Follow-up. Occupational and Environmental Medicine 49:82-95, 2007.

120. **Marsh GM**, Youk AO, Buchanich JM, Erdal S, Esmen NA. Work in the Metal Industry and Nasopharyngeal Cancer Mortality among Formaldehyde-Exposed Workers. Regulatory Toxicology and Pharmacology 48:308-319, 2007.

121. Magnuson BA, Burdock G, Doull J, Kroes RM, **Marsh GM**, Pariza M, Spencer PS, Waddell WJ, Walker R, Williams GW. Aspartame: A Safety Evaluation Based on Current Use Levels, Regulations, Toxicological and Epidemiological Studies. Critical Reviews in Toxicology 37:629-727, 2007.

122. Lippert J, Lacey S, Esmen N, Kennedy K, Hancock R, **Marsh GM**, Buchanich J, Youk A, Cunningham M, Lieberman F, Magnetic field exposure in a non-destructive testing operation. Archives of Environmental and Occupational Health 62:187-193, 2007.

123 Fong J, **Marsh GM**, Stokan L, Ruhl L, Vinson C. The Hospital Quality Performance Report: An Application of Composite Scoring. American Journal of Medical Quality 23:287-295, 2008.

124. Kheifets L, Bowman J, Checkoway H, Feychting M, Harrington M, , Kavet R, **Marsh GM**, Mezei G, Renew J, van Wijngaarden E. Future Needs of Occupational ELF EMF Epidemiology. Occupational and Environmental Medicine 66:72-80, 2009, Online version September 19, 2008.

125. Cassidy L, Buchanich J, **Marsh GM.** Proposed Sampling Plan for a National Trauma Registry for Children. Journal of Registry Management 35:113-119, 2008.

126. **Marsh GM**, Buchanich J, Youk A, Cunningham M, Kennedy K, Lacey S, Hancock R, Esmen N. Long-Term Health Experience of Jet Engine Manufacturing Workers: I. Mortality from Central Nervous System Neoplasms. Journal of Occupational and Environmental Medicine 50:1099-1116, 2008.

127. **Marsh GM**, Buchanich J, Youk A, Cunningham M, Kennedy K, Lacey S, Hancock R, Esmen N. Long-Term Health Experience of Jet Engine Manufacturing Workers: II. Total and Cause-Specific Mortality excluding Central Nervous System Neoplasms. Journal of Occupational and Environmental Medicine 50:1117-1129, 2008.

128. Youk AO, Buchanich JM, **Marsh GM**, Esmen NA. Pharmaceutical Production Workers and the Risks of Mortality from Respiratory System Cancer and Lymphatic and Hematopoeitic Tissue Cancers. Journal of Occupational and Environmental Medicine 51:903-915, 2009.

129. Buchanich JM, Youk AO, **Marsh GM**, Bornemann Z, Lacey SE, Kennedy KJ, Hancock RP, Esmen NA, Lieberman FL. Methodological Issues in United States Retrospective Cancer Incidence Studies. American Journal of Epidemiology 170:112-119, 2009.

130. **Marsh GM**, Esmen NA, Buchanich JM, Youk AO. Mortality Patterns among Workers Exposed to Arsenic, Cadmium and Other Substances in a Copper Smelter. American Journal of Industrial Medicine 52:633-644, 2009.

131. Summers W, Cunningham M, **Marsh GM**. Complex Antioxidant Blend Improves Memory in Community-Dwelling Seniors. Journal of Alzheimer's Disease 19:429-439, 2010.

132. **Marsh GM**, Buchanich J, Youk A, Cunningham M, Kennedy K, Lacey S, Hancock R, Esmen N, Lieberman FL, Fleissner ML. Long-Term Health Experience of Jet Engine Manufacturing Workers: III. Incidence of Malignant Central Nervous System Neoplasms. Neuroepidemiology 35:123-141 2010.

133. **Marsh GM**, Morfeld P, Youk AO, Collins JJ, Symons M. Incomplete follow-up in the National Cancer Institute's formaldehyde worker study and the impact on subsequent reanalyzes and causal evaluations. Regulatory Toxicology and Pharmacology 58:233-236, 2010.

134. Buchanich J, Youk A, **Marsh GM**, Kennedy K, Lacey S, Hancock R, Esmen N, Cunningham M, Lieberman FL, Fleissner ML. Long-Term Health Experience of Jet Engine Manufacturing Workers: IV. Comparison of Incidence and Mortality Rates of Central Nervous System Neoplasm. Annals of Epidemiology 20:759-765, 2010.

135. Shire J, **Marsh GM,** Talbott E, Sharma R. Recent Advances and Current Themes in Occupational Health and Environmental Public Health Surveillance. Invited Review in Annual Reviews of Public Health 32: 21;1-24, 2010.

136. Cassidy LD, **Marsh GM**, Talbott EO, Kelsey SF. Initial and Continued Adherence with Bladder Cancer Screening in an Occupationally Exposed Cohort. Journal of Occupational and Environmental Medicine 53:455-460, 2011.

137. **Marsh GM**, Buchanich JM, Youk AO. Fiber Glass and Human Respiratory Cancer Risk: Lack of Evidence Persists Since 2001 IARC Re-evaluation. Regulatory Toxicology and Pharmacology 60:84-92, 2011.

138. **Marsh GM**, Youk AO, Roggli VL. Asbestos Fiber Concentrations in the Lungs of Brake Repair Workers: Commercial Amphiboles Levels are Predictive of Chrysotile Levels. Inhalation Toxicology 23:681-688, 2011.

139. Buchanich JM, Youk AO, **Marsh GM**, Lacey SE, Kennedy KJ, Hancock RH, Esmen NA, Lieberman FS, Fleissner ML. Long-Term Health Experience of Jet Engine Manufacturing Workers: V. Issues with the Analysis of Non-Malignant Central Nervous System Neoplasms, Journal of Registry Management 38(3): 115-119, 2011.

140. Hesterberg T, Bunn B, Chase J, Jankousky A, McClelland RO, **Marsh GM.** Product Stewardship and Science: Safe Manufacturers and Use of Fiber Glass. Regulatory Toxicology and Pharmacology Regulatory Toxicology and Pharmacology 62: 257-277, 2012.

141. Youk AO, Buchanich JM, **Marsh GM**, Fryzek J. A Study of Cancer Mortality Rates in High Altitude Counties of the United States. High Altitude Medicine & Biology Journal 13:98-104, 2012.

142. Liu Y, Chang, C H, **Marsh GM**, Wu F. Population Attributable Risk of Aflatoxin-Related Liver Cancer: Systematic Review and Meta-Analysis. European Journal of Cancer 48:2125-2136, 2012.

143. Castle T, Cunningham M, **Marsh GM.** Antidepressant Medication Adherence via Interactive Voice Response Most Effective in Older Patients. American Journal of Managed Care 18(9):e346-e355, 2012.

144. **Marsh GM**, Youk AO, Buchanich JM, Cunningham M, Xu H, Downing S, Kennedy KJ, Esmen NA, Hancock RH, Lacey SE, Fleissner ML. Long-Term Health Experience of Jet Engine Manufacturing Workers: VI. Incidence of Malignant Central Nervous System Neoplasms in Relation to Estimated Workplace Exposures. Journal of Occupational and Environmental Medicine 55:654-675, 2013.

145. Kennedy KJ, Esmen NA, Hancock RH, Lacey SE, **Marsh GM**, Buchanich JM, Youk AO, Cunningham M, Fleissner ML. Long-Term Health Experience of Jet Engine Manufacturing Workers: VII. Occupational Exposures. Journal of Occupational and Environmental Medicine 55:676-689, 2013.

146. **Marsh GM**, Youk AO, Buchanich JM, Downing S, Kennedy KJ, Esmen NA, Hancock RH, Lacey SE, Fleissner ML. Long-Term Health Experience of Jet Engine Manufacturing Workers: VIII. Incidence of Malignant Central Nervous System Neoplasms in Relation to Workplace Experience with Parts and Processes. Journal of Occupational and Environmental Medicine 55:690-708, 2013.

147. Youk AO, **Marsh GM**, Buchanich JM, Downing S, Kennedy KJ, Esmen NA, Hancock RH, Lacey SE. Long-Term Health Experience of Jet Engine Manufacturing Workers: IX. Further Investigation of General Mortality Patterns in Relation to Workplace Exposures. Journal of Occupational and Environmental Medicine 55:709-721, 2013.

148. **Marsh** GM, Buchanich JM, Youk AO, Downing SC, Esmen NE, Kennedy KJ, Lacey SE, Hancock RP, Fleissner ML, Lieberman FS. Long-Term Health Experience of Jet Engine Manufacturing Workers: Results from a 12-Year Exploratory Investigation. Journal of Occupational and Environmental Medicine 55:652, 2013.

149. Talbott EO, Brink LL, Sharma RK, **Marsh GM**, Rager JR. Ecological Study of the Potential Association Between County-level Air Lead and Childhood Blood Lead Levels: County-Based Results. Journal of Environment and Public Health 2013:1-8, http://dx.doi.org/10.1155/2013/278042, 2014.

150. **Marsh GM,** Morfeld P, Collins J, Symons M. Issues of Methods and Interpretation in the NCI Formaldehyde Worker Cohort Study. Commentary. Journal of Occupational Medicine and Toxicology 9:22 DOI: 10.1186/1745-6673-9-22, URL: http://www.occup-med.com/content/9/1/22, 2014.

151. Allen BC, Van Landingham C, Yang Y, Youk AO, **Marsh GM**, Esmen NA, Gentry PR, Clewell H, Himmelstein M. A Constrained Maximum Likelihood Approach to Evaluate the Impact of Dose Metric on Cancer Risk Assessment: Application to Chloroprene. Journal of Regulatory Toxicology and Pharmacology, 70:2013-213, 2014.

152. Johnson R, Johnson T, Heasley C, Downing SC, **Marsh GM**, Garcia-Dominic O. Impact of P4P and Best Practice/Patient Outcome Interventions among Participating Pennsylvania Highmark Network Provider Serving Minority Patients. Journal of Racial and Ethnic Health Disparities, Online DOI 10.10.1007/s40615-014-0057-8, October 2, 2014.

153. **Marsh GM**, Zimmerman SD. Mortality among Chemical Workers Exposed to Acrylonitrile: 2011 Follow-Up, Journal of Occupational and Environmental Medicine 57:134-145, 2015.

154. Zimmerman SD, **Marsh GM**, Youk AO, Talbott EO. Adjustment for Confounding by Smoking in the Presence of Misclassified Smoking Data in a Cohort Study of Workers Exposed to Formaldehyde. Journal of Occupational and Environmental Medicine 57:146-151, 2015.

155. Ferguson A., Bilonick R, **Marsh GM**, Fisher A. How Well Do Raters Agree on the Development Stage of Caenorhabditis elegans? PLOS One, In Press, 2015.

b. Manuscripts Submitted or in Preparation

1. Gathuru I, Dolan D, Buchanich J, **Marsh GM.** Health Hazards in the Pharmaceutical Industry, Submitted.

2. Dolan D, Gathuru I, Buchanich J, **Marsh GM.** Challenges in the Occupational Epidemiology of Pharmaceutical Workers. Commentary, Submitted.

3. Brink L, Talbott O, Sharma R, **Marsh, GM**, Rager J, Wu W, Benson S, Menager H. Revisiting Non-Residential Environmental Exposures and Childhood Lead Poisoning in the US -- findings from Kansas, 2000-2005, Submitted

4. Summers WK, Martin RL, Liu Y, Pea B, **Marsh GM**. Complex Antioxidant Single Blind Study for Memory, Submitted.

5. Benson S, Talbott EO, Brink LA, Wu C, Sharma R. **Marsh GM.** Environmental contribution to childhood blood lead levels in U.S. Children, NHANES 1999-2006., Submitted.

6. Dabass A, Talbott E, Venkat A, Rager J, **Marsh GM**, Sharma R, Holguin F. Association of exposure to particulate matter and biomarkers of cardiovascular disease risk in adult NHANEs participants. Submitted.

7. Benson S, **Marsh GM**, Talbott EO, Brink LA, Wu C, Sharma R. Benson S, et al. Are Children who live near airports more likely to have elevated blood lead levels? , In Preparation.

8. Benson S, Talbott EO, Brink LA, Wu C, Sharma R. **Marsh GM.** Elevated blood lead levels in Pennsylvania and New Jersey (2003-2008): Are urban children still at highest risk?, In Preparation.

2. Books and Book Chapters

1. Enterline PE, Sussman N, and **Marsh GM**: "Asbestos and Cancer. The First Thirty Years" Philip Enterline, 1978.

2. Enterline PE and **Marsh GM**: Environment and Mortality of Workers from a Fibrous Glass Plant. In Dusts and Disease, Editors: R. Lemen and J.C. Dement: Pathotox Publishers, Inc. New York City, NY, 1979.

3. Enterline PE and **Marsh GM**: Mortality of Workers in the Man-Made Mineral Fiber Industry. In Biological Effects of Mineral Fibers, Volume 2, Editor: J.C. Wagner, World Health Organization, International Agency for Research on Cancer, Lyon, France, 1980.

4. Enterline PE and **Marsh GM**: Mortality among Workers in a Nickel Refinery and Manufacturing Plant in West Virginia, USA. In Nickel Toxicology, Editors: S.S. Brown and F.W. Sunderman, Jr., Academic Press, Inc. (London) Ltd., 1980.

5. **Marsh GM**: Proportional Mortality among Chemical Workers Exposed to Formaldehyde. In Formaldehyde Toxicity, Editor: J.E. Gibson, Hemisphere Publishing, Washington, D.C., 1983.

6. **Marsh GM** and Caplan RJ: The Feasibility of Conducting Epidemiologic Studies of Populations Residing Near Hazardous Waste Disposal Sites. In Environmental Epidemiology, Editors: F.C. Kopfler and G.F. Craun, Lewis Publishers, Inc., Chelsea, Michigan, 1986.

7. **Marsh GM** and Caplan RJ: Evaluating Health Effects of Exposure to Hazardous Waste Sites: A Review of the State-of-the-art with Recommendations for Future Research. In Health Effects from Hazardous Waste Sites, Editors: J.B. Andelman and D.W. Underhill, Lewis Publishers, Inc. Chelsea, MI, 1987.

8. Summers WK, Majovski LV, **Marsh GM**, Tachiki K and Kling A: Tacrine, Back to the Future? In Current Research in Alzheimer Therapy: Cholinesterase Inhibitors, Editors: E. Giacabini and R. Becker, Taylor and Francis, New York, 1988.

9. **Marsh GM**: Occupational Epidemiology. In Environmental and Occupational Medicine, Second Edition, Editor: W.N. Rom, Little, Brown, and Company, Boston, MA, 1992.

10. **Marsh GM**: Statistical Issues in the Design, Analysis and Interpretation of Environmental Epidemiological Studies. In Environmental Epidemiology Methods, Editor: G. Craun and E. Talbott, CRC Press, Boca Raton, FL, 1995.

11. **Marsh GM**: Basic Occupational Epidemiologic Measures. In Occupational Medicine: State of the Art Reviews. Occupational Epidemiology Issues, Editor: Ki Moon Bang, Hanley & Belfus, Inc., Medical Publishers, Philadelphia, PA, Vol. 11, No. 3, July-September 1996.

12. Heenan MT, **Marsh GM**: NIOSH Investigations. In Workplace Safety and Health, Para. 33, 700 et seq., Clark Boardman Callaghan, 1997.

13. **Marsh GM:** Epidemiology of Occupational Diseases. In Environmental and Occupational Medicine, Third Edition, Editor: W.N. Rom, Little, Brown, and Company, Boston, MA, 1998.

14. **Marsh GM:** Epidemiology of Occupational Diseases. In Environmental and Occupational Medicine, Fourth Edition, Editor: W.N. Rom, Wolters Kluwer/ Lippincott Williams and Wilkins, Philadelphia, PA, 2007.

15. Buchanich JM, Songer TJ, Cassidy LD, **Marsh GM**, Ford HR. A Clinical Decision-Making Rule for Mild Head Injury in Infants and Toddlers. VDM Verlag Dr. Muller Aktiengesellschaft & Co., Saarbrucken, Germany, 2008.

3. Reviews, Invited Published Papers, Proceedings of Conferences and Symposia, Monographs and Letters

1. Enterline PE, **Marsh GM**: Mortality among Workers in a Nickel Refinery and Manufacturing Plant in West Virginia, USA. Proceeding of the Second International Conference on Nickel Toxicology, Swansea, Wales, September 3-5, 1980.

2. Stubbs HK, **Marsh GM**, and Preininger ME: A Misallocation Obscures. Letter to the Editor. Journal of Occupational Medicine 23:226-227, 1981.

3. Enterline PE and **Marsh GM**: Mortality among Workers Exposed to Arsenic and Other Substances in a Copper Smelter. Proceedings of the Arsenic Symposium, Gaithersburg, Maryland, November 5, 1981.

4. Enterline PE and **Marsh GM**: The Health of Workers in the United States Mineral Fiber Industry. Proceedings of the WHO-EURO Occupational Health Conference, Biologic Effects of Man-Made Mineral Fibers, Copenhagen, Denmark, April 20, 1982.

5. **Marsh GM**: The Feasibility of Conducting Epidemiologic Studies of Populations Residing Near Hazardous Waste Disposal Sites. Proceedings of the 1985 American Chemical Society Symposium on Exposure Measurements and Evaluation Methods for Epidemiology Studies, Chicago, IL, September 10, 1985.

6. Enterline PE, **Marsh GM**, and Henderson VL: Mortality Update of a Cohort of U.S. Man-Made Mineral Fiber Workers. Proceedings of the International Symposium on Man-Made Mineral Fibers in the Working Environment, Copenhagen, Denmark, October 28, 1986.

7. **Marsh GM**: The University of Pittsburgh Epidemiology Studies of Man-Made Mineral Fiber Workers. Proceedings of the 1992 Toxicology Forum Annual Winter Meeting, Washington, DC., February 17-19, 1992.

8. Stone RA, **Marsh GM**, Lee KY, Smith, TJ, Quinn MM, Wilcox MA: Assessing Joint Effects of Multiple Time-Dependent Exposures. Proceedings of the 9th ICOH International Symposium on Epidemiology in Occupational Health, Cincinnati, OH, September, 23-25, 1992.

9. **Marsh GM**, Stone RA, Henderson VL, Smith TJ, Quinn MM, Wilcox MA: An Evaluation of New Fiber and Co-Exposure Data for the U.S. Cohort of Fiber Glass Production Workers. Proceedings of the 9th ICOH International Symposium on Epidemiology in Occupational Health, Cincinnati, OH, September, 23-25, 1992.

10. Smith TJ, Quinn MM, Wilcox MA, Yu RC, Schneider T, **Marsh GM**: Extrapolation of Past Fiber Exposures in the Production of Man Made Vitreous Fibers. Proceedings of the 9th ICOH nternational Symposium on Epidemiology in Occupational Health, Cincinnati, OH, September, 23-25, 1992.

11. **Marsh GM**, Day R, Youk J: An Expert System for a Standardized Risk Assessment Protocol Used at Hazardous Waste Sites. Proceedings of the 1993 ATSDR International Congress on the Health Effects of Hazardous Waste, Atlanta, GA, May 3-6, 1993.

12. **Marsh GM**, Leviton LC, Talbott EO, Schall LS, Pavlock D, Hemstreet G, Logue J, Fox J, Schulte P: The Drake Chemical Workers Health Registry Study: Notification and Medical Surveillance of a Group of Workers at High Risk of Developing Bladder Cancer. Proceedings of the 1993 ATSDR International Congress on the Health Effects of Hazardous Waste, Atlanta, GA, May 3-6, 1993.

13. Stone RA, **Marsh GM**, Owens AO, Smith TJ: Propagation of Errors Using Retrospective Exposure estimates in the Cox Model. Proceedings of the 10th ICOH Annual International Congress on Occupational Health, Nice, France, September 12-16, 1993.

14. Stone RA, **Marsh GM**, Youk AO, Quinn MM, Smith TJ: Retrospective Estimation of Airborne Fiber Exposure: Statistical Aspects. American Statistical Association, 1994 Proceedings of the Section on Epidemiology, Pittsburgh, PA 152.127-132.

15. **Marsh, GM**, Stone RA, Henderson VL, Esmen NA: Misclassification of Nasopharyngeal Cancer. Letter, Journal of the National Cancer Institute, 86:1556-1558, 1994.

16. Esmen NA, **Marsh GM**, Stone RA, Gula MJ, Gause CK: Quantifying Individual Residential Exposure to Smelter Emissions in Four Arizona Copper Smelting Communities: Exposure Estimation Procedures and Results. Proceedings of the 1995 ATSDR International Conference on Hazardous Waste: Impact on Human and Ecological Health, Atlanta, GA, June 5-8, 1995.

17. Stone RA, **Marsh GM**, Gula MJ, Gause CK, Esmen NA: Quantifying Individual-Level Lifetime Residential Exposure to Smelter Emissions in Four Arizona Copper Smelting Communities: Missing Data Issues. Proceedings of the 1995 ATSDR International Conference on Hazardous Waste: Impact on Human and Ecological Health, Atlanta, GA, June 5-8, 1995.

18. **Marsh GM**, Stone RA, Youk AO, Smith TJ: Comments on IARC 1990 Follow-Up of European MMVF Worker Study. Epidemiology 9:218, 1998.

19. Casanova M, Cole P, Collins JJ, Connolly R, Delzell E, Heck Hd HA, Leonard R, Lewis R, **Marsh GM**, Ott MG, Sorahan T, Axten C. Comments on, "Mortality from Lymphohematopoietic Malignancies among Workers in Formaldehyde Industries, Journal of the National Cancer Institute Jun 16;96(12): 966-967; Author Reply 967-968, 2004.

20. **Marsh GM.** Overview of Formaldehyde Epidemiology. Proceedings of the 2005 European Toxicology Forum, Brussels, Belgium, November 8-10, 2005.

21. **Marsh GM**. EMF-ELF Exposure Potentials among Magnetic Particle Inspections Workers. Proceedings of the International Workshop to Evaluate Future Needs of Occupational ELF Epidemiology, Edinburgh, Scotland, September 14-15, 2006.

22. Marsh GM, Youk AO, Roggli VL: Letter to the editor in response to Finkelstein et al. (2012). Inhalation Toxicology. 24: 141-142, 2012.

4. Published Abstracts

1. **Marsh GM**, Stone RA, Henderson V, Smith TJ, Hallock MF, Quinn MM: The Potential Impact of Exposure Misclassification and Confounding on the Lung Cancer Mortality Experience of U.S. Mineral Wool Fiber Workers. (Abstract) Revue D'epidemiologie et de Sante Publique 40:S71, 1992.

2. **Marsh GM**, Smith TJ, Stone RA, Hallock MF, Quinn MM: L'Impact des Erreurs de Classification et des Facteurs Confusion sur la Mortalite des Travailliers dans la Fabrication de Fibre de Verre Synthetique. Archives des Maladies Professionnelles 53:547, 1992.

3. Smith TJ, Quinn M, **Marsh GM**, Hallock MF: Extrapolation des Expositions Passees pour les Travailleurs de la Production de Laine de Verre: Une Approche Integree pour L'Epidemiologie. Archives des Maladies Professionnelles 53:552, 1992.

4. **Marsh GM**, Stone R, Owens AD, Henderson V, Smith T, Quinn M. A descriptive analysis of the new fiber and co-exposure data for the U.S. cohort study of man-made vitreous fiber production workers. The 24th International Congress on Occupational Health, Nice, France; 1993.

5. Stone RA, **Marsh GM**, Owens AD, Smith TJ, Quinn MM. Statistical estimation of fiber exposures assigned to unmeasured jobs. I.A.R.C. Conference on Retrospective Assessment of Occupational Exposures in Epidemiology, Lyon, France; 1994.

6. **Marsh GM**, Stone RA, Youk AO, Henderson VL, Smith TJ, Quinn MM. 1989 update of the U.S. cohort mortality study of rock and slag wool workers. Symposium on the Health Effects of Fibrous Materials Used in Industry, Sydney, Australia; 1995.

7. Stone RA, **Marsh GM**, Gula MJ, Esmen NA, Gause CK: Quantifying Individual-Level Lifetime Exposures to SO2 Emissions in Gila River Basin Arizona Copper Smelter Communities. Epidemiology 6:S44, July 1995.

8. Stone RA, **Marsh GM**, Youk AO, Enterline PE: Modelling the Combined Effects of Exposure and Cigarette Smoking on Respiratory Cancer Risk for Copper Smelter Workers: Methodological Issues. Epidemiology 6:S114, July 1995.

9. Esmen NA, Stone RA, **Marsh GM**, Gula MJ: An Investigation of Secondary Exposure Misclassification Effects of Lifelong Occupational History in Exposure Estimation. Paper No. 325 American Industrial Hygiene Conference, Washington, D.C., May 1996 (extended abstract).

10. Rohay JM, **Marsh GM**, Sereika S, Mazumdar S, Dunbar-Jacob: The Effects of Aggregation on Medication Compliance History in Repeated Measures ANOVA: A Simulation Study. Controlled Clinical Trials 15 (suppl. 3) 98, 1994.

11. Youk AO, Stone RA, **Marsh GM**: Assessing a Method for Allocating Partially Classified Person-Time: A Simulation Study. Annals of Epidemiology 9:458, 1999.

12. Schall LC, **Marsh GM**, Buchanich JM, Bittner, G: A Comparison of Three National Vital Status Tracing Services for Large Scale. Annals of Epidemiology 9:457-458, 1999.

13. **Marsh GM**, YOUK AO, Stone RA, Buchanich JM, Gula MJ, Smith TJ, Churg A, Colby T. Does fiberglass pose a respiratory system cancer risk in humans? Latest findings from the US cohort and nested case-control studies. Annals of Occupational Hygiene, Inhaled Particles IX Supplement.

14. **Marsh GM**, Youk AO, Buchanich JM, Cassidy LD, Lucas LJ, Esmen NA, Gathuru I. Formaldehyde Exposure and Respiratory Tract Cancer among Chemical Plant Workers: An Updated Cohort Study and New Nested Case-Control Study. Annals of Occupational Hygiene 2003.

15. **Marsh GM**, Youk AO, Buchanich JM, Esmen NA. Mortality Patterns among Pharmaceutical Production Workers at One U.S. Site. Annals of Occupational Hygiene. 2004.

16. **Marsh GM**, Youk AO, Buchanich JM, Esmen NA. Mortality Patterns among Workers Exposed to Chloroprene and Other Substances. Annals of Occupational Hygiene 2005.

17. **Marsh GM**, Buchanich JM, Lieberman FS, Youk AO, Bornemann Z, Esmen NE, Lacey SE, Kennedy K, Hancock R. An epidemiological study of brain cancer mortality and incidence among a cohort of jet engine manufacturing workers. Society of Neuro-Oncology 2006 MeetingProceedings.

18. **Marsh GM**, Buchanich JM, Lieberman FS, Youk AO, Bornemann Z, Esmen NE, Lacey SE, Kennedy K, Hancock R. An epidemiological study of brain cancer mortality and incidence among a cohort of jet engine manufacturing workers: Year 5 Study Update. Society of Neuro-Oncology 2007 Meeting Proceedings.

19. Esmen NA, Hancock RP, Lacey SE, Kennedy KJ, **Marsh GM**, Buchanich JM. Exposure to Aerosol Generated in High Temperature Alloy Surface Grinding. Annals of Occupational Hygiene 2007.

20. Lacey S, Horvatin S, Alcazar T, Kennedy K, Hancock R, Esmen N, Buchanich J, Youk A, Cunningham M, **Marsh GM**, Myers D. Examination of Worker Ability to Recall Personal Occupational History. Annals of Occupational Hygiene 2008.

21. Esmen NE, Kennedy KJ, **Marsh GM**, Buchanich JM. Exposure to lead and arsenic in copper smelting. Annals of Occupational Hygiene 2008

22. Lacey S, Kennedy K, Hancock R, Esmen N, Buchanich J, Youk A, Cunningham M, **Marsh GM**, Lieberman F. Exposure reconstruction to inform an epidemiologic study of brain cancer mortality among a cohort of jet engine manufacturing workers: an update on findings to date. Society of Neuro-Oncology 2008 Meeting Proceedings.

23. **Marsh GM**, Buchanich J, Youk A, Cunningham M, Lieberman F, Kennedy K, Lacey S, Hancock R, Esmen N. An epidemiological study of brain cancer mortality and incidence among a cohort of jet engine manufacturing workers: total and cause specific mortality with emphasis on CNS neoplasms. Society of Neuro-Oncology 2008 Meeting Proceedings.

24. Kennedy K, Esmen N, Buchanich J, Lacey S, **Marsh GM**, Youk A, Hancock R. Occupational hygiene considerations in a large retrospective epidemiology study: job dictionary. Annals of Occupational Hygiene 2009.

25. Lacey S, Gundi V, Kennedy K, Hancock R, Esmen N, Buchanich J, Youk A, **Marsh GM**. Application of GIS in occupational exposure reconstruction. Annals of Occupational Hygiene 2009.

26. Buchanich JM, **Marsh GM**, Esmen NA, Youk AO, Kennedy KJ. Cerebrovascular Mortality among Arsenic-Exposed Copper Smelter Workers. Annals of Occupational Hygiene 2009.

27. Esmen NA, Hall TA, Phillips ML, **Marsh GM**: Chemical Process Based Reconstruction of Exposures: Estimation of Task Based Exposures Method Selection, Annals of Occupational Hygiene, 2010.

28. Esmen NA, Broda TA, Hall TA, Phillips ML, **Marsh GM**: Chemical Process Based Reconstruction of Exposures: Estimation of Task Based Exposures. A Case Study. Annals of Occupational Hygiene, 2010.

29. Rohay J, **Marsh GM**, Anderson S, Dunbar-Jacobs J, Arena V. Statistical Assessment of Medication Adherence Data: A Technique to Analyze the J-Shaped Curve. Abstract: 35th Annual Meeting of the Society for Clinical Trials, May 18-21, 2014, Philadelphia, PA.

29. Sharma RK, Talbott EO, **Marsh GM**, Brink L, Zborowski J. Spatial Data Analytic Tools for Linking Environmental Surveillance Data to Health Outcomes: Application to Data from a Local Health Department. American Journal of Public Health, 2010.

30. Youk AO, Buchanich JM, **Marsh GM**, Fryzek J. A Study of Cancer Mortality Rates in High Altitude Counties of the United States. Society for Epidemiological Research, Annual Meeting, 2010.

31. Summers W, Martin RL, Liu Y, **Marsh GM.** Memory Improvement in Aging Community Dwelling Seniors: A Single-Blinded Study of Two Antioxidant Supplements. Society for Neuroscience (www.sfn.org), Annual Meeting, November 15-19 ,2014, Washington, D.C.

32. Rohay J, **Marsh GM,** Anderson S, Arena V, Youk A, Dunbar-Jacob J. A Statistical Assessment of Medication Adherence Data: A Technique to Analyze the J-Shaped Curve. Society for Clinical Trials Annual Meeting, May 18-21, 2014, Philadelphia, PA.

33. Marsh GM, Buchanich J, Zimmerman S, Kennedy K, Esmen N, Moshammer H, Morfeld P, Erren T, Svartengren M, Westberg H, McElvenny D, Cherrie J. An International historical cohort study of workers in the hard-metal industry: mid-study epidemiology update. Occupational Environmental Medicine2014 Jun;71 Suppl 1:A96-7. doi: 10.1136/oemed-2014-102362.302.

34. Kennedy K, Esmen N, Marsh GM, Buchanich J, Zimmerman S, Moshammer H, Morfeld P, Erren T, Svartengren M, Westberg H, McElvenny D, Cherrie J. An international historical cohort study of workers in the hard-metal industry: exposure assessment. Occupational and Environmental Medicine 06/2014; 71 Suppl 1:A65. DOI: 10.1136/oemed-2014-102362.203.

5. Other Publications

1. **Marsh GM**: Final Report on the Monsanto Company Indian Orchard Plant Mortality Study. Technical Report submitted to the Monsanto Company, December 21, 1979.

2. Enterline PE and **Marsh GM**: Mortality among Man-Made Mineral Fiber Workers in the United States. Technical Report submitted to the Thermal Insulation Manufacturers Association, May 15, 1981.

3. **Marsh GM**: Proportional Mortality among Chemical Workers Exposed to Formaldehyde. Technical Report submitted to the Monsanto Company, May 15, 1981.

4. **Marsh GM**: A Case-Control Study of Digestive System Cancer and Genito-Urinary System Cancer within a Cohort of Chemical Plant Workers. Technical Report submitted to the Monsanto Company, October 15, 1981.

5. **Marsh GM** and Preininger ME: OCMAP: Occupational Cohort Mortality Analysis Program-User Manual, Version September 1980. Copyright 1981, University of Pittsburgh, Pittsburgh, PA.

6. Enterline PE and **Marsh GM**: Mortality and Morbidity among Workers in a Nickel Refinery and Alloy Manufacturing Plant in Huntington, West Virginia. Technical Report submitted to Huntington Alloys, Inc. (INCO Limited), April 30, 1982.

7. **Marsh GM**, Costantino JP, and Lyons EE: Statistical Analysis of the Drake Superfund Site Occupational Health Survey. Technical Report submitted to the Pennsylvania Department of Health, Division of Environmental Epidemiology, September 30, 1985.

8. Enterline PE, **Marsh GM**, Esmen NA, Henderson V, and Ricci E: Mortality among Copper and Zinc Smelter Workers in the United States. Technical Report submitted to the Smelter Environmental Research Association, January 31, 1986.

9. **Marsh GM** and Enterline PE: The Deer Park Mortality Study. Mortality Patterns among a Cohort of Refinery and Chemical Plant Workers. Technical Report submitted to the Shell Oil Company, July 31, 1987.

10. **Marsh GM**, Leviton LC, Talbott EO, Callahan C and LaValley M: Health Registry and Epidemiologic Study of Former Drake (Kilsdonk) Chemical Company Workers. Annual Technical Reports submitted to the Pennsylvania Department of Health, Division of Environmental Health, 1987-date.

11. Enterline PE, **Marsh GM**, Henderson V, and Callahan C: Mortality among Man-Made Mineral Fiber Workers in the United States: Mortality Update 1978-82, Technical Report submitted to the Thermal Insulation Manufacturers Association, January, 1988.

12. **Marsh GM** and Day R: Decision Making and Quality Control Criteria for Conduct of Pilot and Epidemiology Studies by ATSDR Under SARA Section 110. Technical Report submitted to the Chemical Manufacturers Association, July 1988.

13. **Marsh GM**, Preininger M, Ehland J, Beardon A, CoChien H and Paik M. OCMAP, OCMAP/PC Version 2.0 User Manual, Copyright 1989, University of Pittsburgh, Pittsburgh, PA.

14. **Marsh GM** and Day R: PITT/ACC Coronary Heart Disease Study, Final Report on Prevalence Data for the Wallingford, CT and Wayne, NJ Study Cohorts, Technical Report submitted to the American Cyanamid Company, December 1989.

15. **Marsh GM** and Day R: PITT/ACC Coronary Heart Disease Study: Final Report on the Study of Fatal Coronary Heart Disease Events. Technical Report submitted to the American Cyanamid Company, December 1989.

16. **Marsh GM**, Stone RA, Henderson V: A Reanalysis of the National Cancer Institute Study on Mortality among Industrial Workers Exposed to Formaldehyde. Technical Report submitted to the Formaldehyde Institute, March 1990.

17. **Marsh GM**, Stone RA, Henderson V: Additional Analysis of the National Cancer Institute Study on Mortality among Industrial Workers Exposed to Formaldehyde. Technical Report Submitted to the Formaldehyde Institute, May 1991.

18. Day R, **Marsh GM**, Ramlow J: A Review and Critique of Ecologic Analysis as an Epidemiologic Research Method. Technical Report Submitted to the Chemical Manufacturers Association, July 15, 1991.

19. Day R, **Marsh GM**, Ramlow J: Evaluating Disease Clusters: A Practical Guidance Document. Technical Report to the Chemical Manufacturers Association, August 1991.

20. Trauth J, Ramlow J, **Marsh GM**, DeCamp R, Day R: Responding to Community Concerns about Chemical Exposures: A Manual for DuPont Company Plant Managers. Technical Report Submitted to the DuPont Company, February 17, 1992.

21. Stone RA, **Marsh GM**, Lee KY, Smith TJ, Quinn MM, Wilcox MA: Assessing Joint Effects of Multiple Time-Dependent Exposures. Proceedings of the 9th ICOH International Symposium on Epidemiology in Occupational Health, Cincinnati, OH, September 23-25, 1992.

22. **Marsh GM**, Stone RA, Henderson VL, Smith TJ, Quinn MM, Wilcox MA: An Evaluation of New Fiber and Co-Exposure Data for the U.S. Cohort of Fiber Glass Production Workers. Proceedings of the 9th ICOH International Symposium on Epidemiology in Occupational Health, Cincinnati, OH, September 23-25, 1992.

23. Smith TJ, Quinn MM, Wilcox MA, Yu RC, Schneider T, **Marsh GM**: Extrapolation of Past Fiber Exposures in the Production Man Made Vitreous Fibers. Proceedings of the 9th ICOH international Symposium on Epidemiology in Occupational Health, Cincinnati, OH, September 23-25, 1992.

24. **Marsh GM**, Stone RA, Henderson V: The Wallingford Cohort Study: Mortality Patterns among Chemical Plant Workers Exposed to Formaldehyde and Other Substances. Technical Report Submitted to the American Cyanamid Company, May 1, 1992.

25. **Marsh GM**, Stone RA, Esmen NA, Gula MJ, Gause CK, Petersen NJ, Meaney FJ, Rodney S, Prybylski D: A Population-Based Case-Control Study of Lung Cancer Mortality in Four Arizona Smelter Towns. Technical Reported Submitted to Agency for Toxic Substances Disease Registry, August, 1995.

26. **Marsh GM**, Stone RA, Esmen NA, Gula MJ, Gause CK, Petersen NJ, Meaney FJ, Rodney S, Prybylski D: A Population-Based Case-Control Study of Lung Cancer Mortality in Gila Basin Smelter Towns. Technical Reported Submitted to the Arizona Department of Health Services, December, 1995.

27. **Marsh GM**, Stone RA, Youk AO, Henderson VL, Schall LC, Wayne LA, Lee KY: Mortality Patterns among Mineral Wool Workers, 1989 Update. Technical Report Submitted to the North American Insulation Manufacturer's Association, January 1996.

28. Stone RA, **Marsh GM**: A Review of the Proposed G-Null and G-Estimation Procedures to Control Bias in Occupational Cohort Studies, Report Submitted to the American Industrial Health Council, June 1996.

29. **Marsh GM**, Youk AO, Buchanich JM: Cohort Mortality Study of the Wallingford, Connecticut Plant. Additional Investigations of Pharyngeal Cancers. Technical Report Submitted to Cytec Industries, Inc., March 2001.

30. **Marsh GM**, Gula MJ, Youk AO, Schall LC: Bladder Cancer among Employees of the BP Chemicals Lima Ohio, Facility. Technical Report Submitted to BP Chemicals, May 2001.

31. **Marsh GM**, Youk AO, Buchanich JM: Cohort Mortality Study of Workers of the GenCorp Lawrence, Massachusetts Plastics Producing Plant. Technical Report Submitted to TERRA, Inc., May 2001.

32. **Marsh GM**, Cassidy LD, Youk AO: Evaluation of the Coordinated Care Network: The Gateway Health Plan Experience. Technical Report Submitted to Gateway Health Plan, September 2002.

33. **Marsh GM**, Youk AO, Morfeld P. Mis-Specified and Non-Robust Mortality Risk Models for Naspharyngeal Cancer in the National Cancer Institute Formaldehyde Worker Cohort Study Technical Report Submitted to the European Chemical Industry Council (CEFIC), February 2006.

34. **Marsh GM**, Buchanich JM, Youk AO. Mortality Patterns among a Cohort of U.S. Petroleum Refinery Workers: Updated Follow-Up. Technical Report Submitted to BP, April 2006.

35. **Marsh GM**, Esmen NA, Buchanich JM, Youk AO. Copperhill Cohort Mortality Study Update - Final Report- Phase IV. Technical Report Submitted to NIOSH, April 2006.

36. **Marsh GM**, Buchanich J, Cunningham M. Evaluation of Confounding by Smoking in Studies of Transportation Workers Exposed to Diesel Exhaust, Technical Report Submitted to International Truck and Engine Corporation, May 2008.

37. Esmen NA, Youk AO, **Marsh GM.** Evaluation of Exposure Misclassification in the NCI-NIOSH Diesel Exhaust in Miners Study and its Impact on Risk Estimates and Exposure-Response Relationships. Technical Report Submitted to the Mining Awareness Resources Group, February 1, 2012.

PROFESSIONAL ACTIVITIES

1. Teaching (post-1990)

a. Courses Taught

BIOS 2016 - Sampling Design and Analysis, 3 credits, 12 students (current)

BIOS 2017 - Advanced Sampling Methods, 2 credits

BIOS 2011 - Principles of Statistical Reasoning, 2 credits, 50 students

BIOS 2087 - Biostatistics Consulting Practicum (Co-Director), 1 credit, 12 students

b. Other Teaching (guest lecturer)

EPID 2022 - Environmental Epidemiology, 2 credits, 15 students (current)

EPID 2019 – Advanced Topics in Epidemiological Methods, 2 credits, 20 students (current)

BIOS 2019 - Vital and Medical Care Statistics, 2 credits, 15 students

EPID 2018 - Epidemiologic Methods I, 2 credits, 20 students

EOH 2180 - Introduction to the Risk Sciences, 2 credits, 7 students

c. Directed Graduate Student Essays, Theses, and Dissertations:

Jeffrey Rohay, M.S. (Bios) 1993, The Use of Computer Simulation to Explore Statistical Techniques to Analyze Adherence to Medication Regimens. .

Laura Schall, M.S. (Bios) 1994, Assessing the Diagnostic Specificity and Sensitivity of Bladder Cancer Screening Modalities.

Leslie Wayne, M.S. (Bios) 1997, A Reanalysis of the U.S. Fibrous Glass Worker Cohort Data Using a Job Exposure Category Approach to Assess Exposure-Response.

Richard Mierzejewski, M.S. (Bios) 2000, An Analysis of the Drake Health Registry Study Screening Data.

Jennifer Barkin, M.S. (Bios) 2002, The Impact of Matching Criteria on Estimated Odds Ratios in an Occupational Case-Control Study.

Weilian Sang, M.S. (Bios) 2004, Comparison of Two Population Estimates and Its Effect on Standardized Mortality Ratio (SMR) Calculation.

Michael Cunningham, M.S. (Bios) 2006, Reanalysis of Smoking and Lung Cancer in the National Cancer Institute Acrylonitrile Worker Cohort Study.

Song-Won Seo M.S. (Bios) 2006, A Review and Comparison of Methods for Detecting Outliers in Univariate Data Sets.

Jeff Rohay, Ph.D. (Bios) 2009, Statistical Assessment of Medication Adherence Data: a Technique to Analyze the J-shaped Curve.

Jiawai Huang, M.S. (Bios) 2011, Comparing Methods of FRED System.

Dan Lans, M.S. (Bios) 2013, Assessment of Biomarkers and Clinical Characteristics to Determine Coronary Artery Disease among Symptomatic Patients.

Yimeng Liu, M.S. (Bios) 2013, Statistical Analysis of Data with Detection Limits.

Sarah Downing, M.S. (Bios) 2013, Monte Carlo Simulation Study to Assess Impact of Confounding by Smoking in a Cohort of Chemical Workers.

Annabel Ferguson, M.S. (Bios) 2014, Comparison of Methods to Assess Inter-rater Reliability

d. Service on Masters and Doctoral Committees:

Barbara Salthouse, Ph.D. (Epid), 1994
Deborah Landon, Ph.D. (Epid), 1996
Ada Youk, Ph.D. (Bios), 1996
Maureen McGuire, Ph.D. (Epid), 1997
Laura Schall, Ph.D. (Epid), 2000
Christine Gause, Ph.D. (Bios), 2001
Patricia Documet, Dr.P.H. (HSA), 2001
Mary Yee Chow, M.P.H. (EOH), 2001
Jeff Lang, Ph.D. (EOH), 2004
Jeanine Buchanich, Ph.D. (Epid), 2007
Karen Singleton, M.P.H. (EOH), 2008
John Zeiner, M.S. (Bios), 2009
Jeffrey Rohay, Ph.D. (Bios), 2009
Hui Xu, M.S. (Bios), 2009
Lan Liu, Ph.D. (EOH), 2011
Jiawei Huang, M.S. (Bios), 2011
Dan Lans, M.S. (Bios), 2013
Sarah Zimmerman, M.S.. (BIOS), 2013
Annabel Furgeson, M.S. (Bios), 2013
Pornsri Khlangwiset, Ph.D. (EOH), 2013
Fangfang Chen, M.S. (Bios), 2013
Stacy Benson, Ph.D. (Epid), 2014
Yimeng Liu, M.S. 2013, Ph.D. (Bios), ongoing
Chengli Shen, M.S. 2014, Ph.D. (Bios), ongoing
Matthew Glover, M.S. (Bios), ongoing
Xuan Li, M.S. (Bios), ongoing
Quinheng Ma, M.S. (Bios), ongoing
Zhongying Xu, M.S. (Bios), ongoing
Arvind Dabass, Ph.D. (Epid), ongoing
Liane Ong, Ph.D. (BCHS), ongoing

e. Supervision of Post-Doctoral Students:

Jonathan Ramlow, Ph.D. Post-Doctoral Fellow, 1990-1992

2. Research and Training

a. Grants and Contracts Received

1974-81 Co-Principal Investigator, Contract: "Mortality among Man-Made Mineral Fiber Workers in the United States," Sponsor: Thermal Insulation Manufacturers Association, 6/1/74 - 5/31/81, $232,055.

1977-81 Co-Principal Investigator, Contract: "Mortality and Morbidity among Workers in a Nickel Refinery and Manufacturing Plant in West Virginia, USA," Sponsor: INCO Limited, 6/1/77 - 5/31/81, $67,880.

1978-79 Principal Investigator, Contract: "The Monsanto Company Indian Orchard Plant Mortality Study," Sponsor: The Monsanto Company, 9/1/78 - 12/31/79, $63,548.

1979-date Principal Investigator, Development of Statistical/Epidemiological Computer Software Package, "OCMAP: A User-Oriented Occupational Cohort Mortality Analysis Program," Copyright, 1981, University of Pittsburgh.

1980-date Principal Investigator, Development of Statistical/Epidemiological Data Base, "MPDS: United States Mortality and Population Data System".

1980-81	Principal Investigator, Contract: "Proportional Mortality among Chemical Workers Exposed to Formaldehyde," Sponsor: The Monsanto Company, 1/1/80 -4/30/81, $7,050.
1980-81	Principal Investigator, Contract: "A Case-Control Study of Digestive System Cancer and Genito-Urinary System Cancer within a Cohort of Chemical Workers," Sponsor: The Monsanto Company, 1/1/80 - 4/30/81, $7,050.
1980-81	Co-Principal Investigator, Contract: "Cancer in Arsenic Exposed Populations," Sponsor: National Cancer Institute, 1/1/80 - 6/30/81, $315,870.
1981-86	Co-Principal Investigator, Contract: "Factors Associated with Mortality among Smelter Workers," Sponsor: Smelter Environmental Research Association, 6/1/82 - 3/31/86, $485,000.
1982-85	Co-Principal Investigator, Contract: "Mortality among Petroleum Refinery Workers," Sponsor: Mobil Oil Corporation, 6/1/82 - 6/30/85, $100,000.
1983-87	Principal Investigator, Contract: "Investigation of Cause-Specific Mortality among Employees of the Shell Oil Company's Refinery and Chemical Plant at Deer Park, Texas, "Sponsor: Shell Oil Company, 3/1/83 - 6/30/87, $507,550.
1984-87	Co-Principal Investigator, Contract: "Update of the Man-Made Mineral Fiber Worker Study," Sponsor: Thermal Insulation Manufacturers Association, 12/1/84 - 6/30/87, $195,000.
1984-87	Co-Principal Investigator, Contract: "A Generalized Computer Program for Multistage Modeling with Time Dependent Dose Patterns with Applications to Arsenic-Exposed Smelter Worker Mortality Data." Sponsor: U.S. Environmental Protection Agency, Office of Research and Development, 10/1/84 - 12/31/87, $80,000.
1985-86	Co-Principal Investigator, Contract: "Update of the Mortality and Morbidity Study of Workers in a Nickel Refinery and Manufacturing Plant in West Virginia, USA," Sponsor: U.S. Environmental Protection Agency/Program Resources, Inc., 7/1/85 - 12/31/86, $20,000.
1985	Principal Investigator, Contract: "Statistical Analysis of the Drake Superfund Site Occupational Health Survey," Sponsor: Pennsylvania State Health Department/Lock Haven Hospital, 5/1/85 - 8/31/85, $15,699.
1985-87	Principal Investigator, Contract: "1977-82 Update of the Monsanto Company Indian Orchard Plant Mortality Study," Sponsor: The Monsanto Company, 6/1/85 - 12/31/87, $55,394.
1986-96	Principal Investigator, Contract: "Health Registry and Epidemiologic Study of Former Drake-Kilsdonk Chemical Workers," Sponsor: Pennsylvania State Health Department/National Institute for Occupational Safety and Health, 8/1/86 - 6/30/96, $1,355,500.
1986-92	Principal Investigator, Contract: "Mortality Patterns among Chemical Plant Workers Exposed to Formaldehyde and Other Substances," Sponsor: American Cyanamid Company, 10/1/86 - 2/28/91, $165,891.
1987-93	Principal Investigator, Contract: "Mortality Surveillance Program for the U.S. Fiberglass and Mineral Wool Worker Cohort," Sponsor: Thermal Insulation Manufacturers Association, 5/1/87 - 3/31/93, $2,300,000.

1987	Developer/Coordinator, The Monsanto Company Graduate Grant Program. Two-Year Fellowship Program for Students in Biostatistics with Interest in Occupational/ Environmental Health. 9/1/87-8/31/89, $24,560.
1987	Co-Principal Investigator, Contract: "Factors Associated with Reported Medical Problems in a Community Exposed to Hazardous Waste Site Materials," Sponsor: DuPont Company, 5/1/87 - 10/31/87, $51,000.
1988	Principal Investigator, Contract: "Development of Decision and Quality Control Criteria for Conduct of Pilot and Epidemiology Studies by ATSDR and SARA Section 110", Sponsor: Chemical Manufacturers Association, 2/1/88 - 6/30/88, $20,000.
1988-89	Principal Investigator, Contract: "Coronary Heart Disease Patterns among Employees of a Chemical Manufacturing Facility," Sponsor: American Cyanamid Company, 9/1/88 - 8/31/89, $86,000.
1989-91	Principal Investigator, Grant: "A Mortality Update and Case-Control Study of Workers Exposed to Arsenic in a Copper Smelter", Sponsor: U.S. Environmental Protection Agency, 1/1/89 - 7/31/91, $57,000.
1989	Principal Investigator, Contract: "A Review and Critique of Ecologic Analyses as an Epidemiologic Research Method", Sponsor: Chemical Manufacturers Association, 1/1/89 - 6/30/89, $21,000.
1989-91	Principal Investigator, Contract: "A Reanalysis of the National Cancer Institute Study on Mortality among Industrial Workers Exposed to Formaldehyde," Sponsor: Formaldehyde Institute, 8/15/89 - 2/28/91, $41,355.
1990-93	Recipient, The DuPont Company Educational Aid Grant Award, 9/1/90-8/31/93, $45,000.
1990-95	Co-Principal Investigator, Contract: "Program for Biostatistical Support for West Penn Hospital Research Activities", Sponsor: The Western Pennsylvania Hospital, 5/1/90 - 4/30/91, $128,272.
1990-92	Principal Investigator, Contract: "Post-Doctoral Research Fellowship Program in Occupational and Environmental Health", Sponsor: DuPont Company, 5/1/90 - 4/30/92, $167,336.
1991-94	Principal Investigator, Contract: "Enhancement, Modification and Update of an Occupational and Ecological Mortality and Population Data System", Sponsor: DuPont Company, 1/1/91 - 12/31/92, $130,000.
1991-92	Principal Investigator, Contract: "A Model Program for Assessing Health Risks among Communities Near Hazardous Waste Sites", Sponsor: DuPont Company, 1/1/91 - 12/31/91, $30,000.
1991-93	Principal Investigator, Contract: "An Expanded Nested Case-Control Study of Respiratory System Cancer among U.S. Man-Made Mineral Fiber Workers", Sponsor: Thermal Insulation Manufacturers Association, 1/1/91 - 1/31/93, $88,000.
1991-92	Principal Investigator, Contract: "Identifying and Responding to Human Disease Clusters: A Practical Guidance Document", Sponsor: Chemical Manufacturers Association, 1/15/91 - 5/15/91, $20,000.

1991-95	Principal Investigator, Contract: "A Population-Based Case-Control Study of Lung Cancer Mortality in Gila Basin Smelter Towns", Sponsor: Arizona Department of Health Services, 12/1/91 - 11/30/93, $250,000.
1992-95	Principal Investigator, Contract: "A Population-Based Case-Control Study of Lung Cancer Mortality in Four Arizona Smelter Towns", Sponsors: Agency for Toxic Substances and Disease Registry/Arizona Department of Health Services, 11/1/92 - 10/31/94, $154,000.
1993-94	Principal Investigator, Contract: "Continuation of the Mortality Surveillance Program for the U.S. Man-Made Mineral Fiber Industry", Sponsor: North American Insulation Manufacturer's Association, 4/1/93-3/31/94, $342,000.
1994-96	Principal Investigator, Contract: "A Program of Biostatistical Support for the Research and Clinical Audit Activities of HealthAmerica of Pittsburgh", Sponsor: HealthAmerica of Pittsburgh, 1/1/94-6/30/96, $220,000.
1994-99	Principal Investigator, Contract: "Continuation and Expansion of the Mortality Surveillance Program for the U.S. Man-Made Mineral Fiber Industry", Sponsor: North American Insulation Manufacturer's Association, 4/1/94-3/31/99, $2,549,377.
1996-2006	Principal Investigator, Contract: "Maintenance of the Drake Health Registry Program", Sponsor: Pennsylvania Cancer Control Program, 7/1/96-6/30/06, $2,000,000.
1996-2009	Principal Investigator, Contract: "Mortality Patterns among Pharmaceutical Workers at the Eli Lilly & Company, Clinton, IN Plant", Sponsor: Eli Lilly & Company, 9/1/96-7/31/05, $355,342.
1997-2004	Principal Investigator, Grant: "A Program of Epidemiological and Biostatistical Support for the Acrylonitrile Group", Sponsor: The Acrylonitrile Group, 12/1/97-11/30/03, $180,000.
1998-99	Principal Investigator, Contract: "Evaluation of the Community Health Project", Sponsor, Pennsylvania Department of Health, 10/1/98-12/31/99, $100,000.
1998-2014	Principal Investigator, Contract: "A Program of Biostatistical Support for the Research and Quality Improvement Activities of Highmark Blue Cross Blue Shield", Sponsor: Highmark Blue Cross Blue Shield, 3/1/98-12/31/13, $1,5000,000.
1999-2009	Principal Investigator, Contract: "Mortality Patterns among Pharmaceutical Workers at the Eli Lilly & Company, Clinton, IN Plant: Additional Investigations of Lung and Hematopoietic Tissue Cancer," Sponsor: Eli Lilly & Company, 2/1/99-7/31/03, $34,668.
1999-2003	Principal Investigator, Contract: "A Collaborative Program of Biostatistical and Epidemiological Support for Solutia, Inc.," Sponsor: Solutia, Inc., 3/1/99-2/28/02, $218,688.
1999-2009	Principal Investigator, Contract: "Mortality Patterns among Pharmaceutical Workers at the Eli Lilly & Company, Lafayette, IN Plant," Sponsor: Eli Lilly & Company, 9/1/99-7/31/03, $86,272.
1999-03	Principal Investigator, Contract: "Supplemental Funding for the Mortality Surveillance Program for the U.S. Man-Made Mineral Fiber Industry," Sponsor: North American Insulation Manufacturer's Association, 4/1/99-3/31/03, $706,250.
2000-05	Principal Investigator (Subcontract with University of Oklahoma Health Sciences Center): Contract: "Mortality Patterns among Workers Exposed to Chloroprene," Sponsor: International Institute of Synthetic Rubber Producers, 2/1/00-1/31/03, $631,957.

2002-date	Principal Investigator, Contract: "Mortality Surveillance and Epidemiologic Support Program for Owens Corning," Sponsor: Owens Corning, 1/1/02-12/31/14 $3,000,000.
2002-13	Principal Investigator, Contract: "Historical Cohort Study of Pratt&Whitney Employees at Seven CT Sites," Sponsor: Pratt&Whitney, 7/15/02-5/31/13, $3,693,701.
2002-05	Co-Investigator, Contract: "Pediatric Injury Surveillance System," Sponsor: Maternal and Child Health Bureau, U.S. Dept. of Health and Human Services, Health Resources and Services Administration, 9/1/02-8/31/04, $238,727.
2003-05	Co-Investigator, Contract: "Creation and Maintenance of an Occupational and Non-occupational Medical Claims Analysis Database for PPG Industries," Sponsor: PPG Industries, Inc., 01/02/03-12/31/07, $465,198.
2005-12	Co-Investigator, Grant, "Academic Partners in Environmental Public Health Tracking Program", Sponsor: U.S. Centers for Disease Control, 07/01/05-06/30/10.
2007-08	Principal Investigator, Contract: "Tungsten Industry Phase 2 Feasibility Study", Sponsor: International Tungsten Industry Association, 10/01/07-10/31/08, $200,000.
2008	Co-Investigator, Contract: "Evaluation of Mortality Rates in High Altitude U.S. Counties", Sponsor: Amgen Corp., 3/1/08-12/31/08, $25,777.
2009-10	Principal Investigator, Grant: "Historical Cohort Study of Workers Exposed to Tungsten Carbide with Cobalt Binder, Phase 3-Part 1", Sponsor: Pennsylvania State Department of Health, 7/1/09-6/30/11, $750,000.
2010	Principal Investigator, Contract: "Literature Review of Health Effects from Exposure to Man-Made Vitreous Fibers", Sponsor: North American Insulation Manufacturers Association, 1/1/10-6/30/10, $30,000.
2010-13	Co-Investigator, Grant: Ecological and Case-Control Study of Ambient Air Levels and Childhood Blood Lead Levels", Sponsor: Centers for Disease Control, 9/15/10-9/14/13, $207,748.
2011-13	Principal Investigator, Contract:" Use of Human Exposure and Epidemiology Data in a Physiologically Based Kinetic Modeling Risk Assessment for Chloroprene", Sponsor: International Institute of Synthetic Rubber Producers, 1/1/11-6/30/11, $43,974.
2011-12	Principal Investigator, Grant: "Historical Cohort Study of Workers Exposed to Tungsten Carbide with Cobalt Binder, Phase 3-Part 2", Sponsor: Pennsylvania State Department of Health, 6/1/11 - 5/31/12, $100,000.
2011	Co-Investigator, Grant: "Updated and Expanded Study of Polycythemia Vera and Other Myeloproliferative Neoplasms in the Tri-County Area", Sponsor: Commonwealth of Pennsylvania, 1/1/2011-9/17/2012, $286,210.
2011	Co-Investigator, Grant: "Evaluation of Commercial Resources for Tracing/Locating NCS Participants", Sponsor: National Institutes of Health, 9/23/2010-9/22/2011, $62,045.
2011-13	Principal Investigator, Contract: "Statistical Methods for Adjusting Risk Estimates for Potential Confounding by Smoking", Sponsor: The Acrylonitrile Group, 9/1/11-8/31/12, $26,466.

2011-12	Principal Investigator, Contract: "Evaluation of Uncertainty Factors in NCI-NIOSH Diesel Exhaust In Miners Study Exposure Assessment and Their Impact on Risk Estimates and Exposure-Response Relationships", Sponsor: Mining Awareness Resource Group, 9/1/11-2/28/12, $30,000.
2011-date	Principal Investigator, Contract: "Historical Cohort Study of Production Workers Exposed to Tungsten Carbide with Cobalt Binder", Sponsor: International Tungsten Industry Association, 11/15/11-11/14/14, $2,332,427.
2012-2015	Principal Investigator, Contract: "Update of the Lima Plant Acrylonitrile Cohort Study", Sponsor: INEOS Nitriles, 1/1/12-06/30/14, $248,000.
2012-date	Principal Investigator, Contract: "Analysis of Pooled Data from the NCI and DuPont Acrylonitrile Worker Cohort Studies-Phase 1-Part 1", Sponsor: The AN Group, 8/1/12-7/31/14, $100,000.
2013-2014	Principal Investigator, Contract: "Commentary on Methodological and Interpretational Issues in the National Cancer Institute Formaldehyde Worker Cohort Study", Sponsor: Research Foundation for Health and Environmental Effects, 11/01/13-03/31/14, $10,000.
2013-2014	Principal Investigator, Contract: "Feasibility Study of Historical Cohort Study of Pharmaceutical Production Workers at the Cosmopolis, Brazil Site, Phase 1: Feasibility Evaluation", Sponsor: Eli Lilly and Company, 11/01/13-03/31/14, $32,441.
2013-date	Principal Investigator, Contract: "Analysis of Pooled Data from the NCI and DuPont Acrylonitrile Worker Cohort Studies-Phase 1-Part 2", Sponsor: The AN Group, 8/1/12-7/31/14, $80,000.
2013-2014	Principal investigator, Subcontract: "Sample Design and Analysis for Child Welfare Project" Sponsor: Department of Social Work, 10/01/13-06/30/14, $10,125.
2014-date	Principal Investigator, Contract:" Additional Reevaluation of the National Cancer Institute Formaldehyde Cohort Data", Sponsor: Research Foundation for Health and Environmental Effects, 02/01/14-03/31/15, $70,000.
2014-date	Principal Investigator, Contract: "Update and Enhancement of the Mortality and Population Database System (MPDS)", Sponsor: GSPH Dean's Office, 10/01/14-09/30/15, $152,724.
2015	Principal Investigator, Contract: "Historical Cohort Study of Workers from the Cytec Aerospace Materials Facility in Havre de Grace, MD", Sponsor: Cytec Aerospace Materials, 01/01/15-06/30/16, $142,915.
2105	Principal Investigator, Contract: "Update of the Clinton Plant Historical Cohort Study", Sponsor: Eli Lilly and Company, 04/30/15-04/30/17, $337,332.

b. Conference Presentations, Invited Lectureships and Major Seminars (post-1990)

"Additional Analysis of the National Cancer Institute Study on Mortality among Industrial Workers Exposed to Formaldehyde". Presented at the 1991 American Industrial Hygiene Conference and Exposition. Salt Lake City, UT, May 23, 1991.

"The Impact of Exposure Misclassification and Confounding on the Mortality Experience of U.S. Man-Made Vitreous Fiber Workers". Presented at the 8th International Congress on Occupational Health (ICOH)-Epidemiology in Occupational Health, Paris, France, September 12, 1991.

"Long-Term Mortality Studies of Man-Made Mineral Fiber Exposure." Presented at the 1991 ICOH/Congrex Symposium on Health Aspects of MMMF. Rotterdam, Netherlands, September 13, 1991.

"The University of Pittsburgh Studies of Man-Made Mineral Fiber Workers". Presented at the 1992 Toxicology Forum, Washington D.C., February 18, 1992.

"Evaluating Health Risks in a Multi-Exposure Environment: The Case of Formaldehyde." Presented at the 1992 Annual Meeting of the American Occupational Health Conference, Washington, D.C., May 8, 1992.

"An Expert Computer System to Accompany the Model Standardized Risk Assessment Protocol for Use with Hazardous Waste Sites". Presented at the ATSDR International Congress on the Health Effects of Hazardous Wastes, Atlanta, GA, May 3, 1993.

"Drake Chemical Company Superfund Site. Notification and Medical Surveillance of Workers at High Risk of Developing Bladder Cancer", Presented at the ATSDR International Congress on the Health Effects of Hazardous Wastes, Atlanta, GA, May 4, 1993.

"A Preliminary Evaluation of New Fiber and Co-Exposure Data for the U.S. Man-Made Vitreous Fiber Worker Cohort", Presented at the 10th International Congress on Occupational Health (ICOH), Nice, France, September 25, 1993.

"OCMAP-PLUS: A New Occupational Cohort Mortality Analysis Program for Multifactor Work History and Exposure-Based Analysis", Presented at the IARC Conference on Retrospective Assessment of Occupational Exposures in Epidemiology, Lyon, France, April 13-15, 1994.

"A Population-Based Case-Control Study of Lung Cancer Mortality in Four Arizona Smelter Towns", Presented at the ATSDR International Congress on Hazardous Waste: Impact on Human and Ecological Health, Atlanta, GA, June 6, 1995.

"Mortality Surveillance Program for the United States Man-Made Mineral Fiber Workers Cohort: Mortality Patterns among Rock/Slagwool Workers 1989 Update", Presented at the Symposium on the Health Effects of Fibrous Materials (excluding asbestos), Sydney, Australia, October 31, 1995.

"A Program of Biostatistical Support for the Research and Quality Improvement Activities of Highmark Blue Cross Blue Shield", Presented at the 1999 Annual Meeting of the Pennsylvania Public Health Association, Pittsburgh, PA, October 25, 1999.

"The Role of Epidemiology in an Integrated Workplace Surveillance Program", Presented at the 1999 Eli Lilly & Company Annual Health Fair, Indianapolis, IN, September 19, 1999.

"Census 2000: Scientifically and Politically Correct?" Symposium Panel Member and Discussant, University of Pittsburgh, Graduate School of Public Health, May 5, 2000.

"Industrial Inorganic Fibres: Assessing and Controlling the Risk to Public Health", Presented at the 26th International Congress on Occupational Health (ICOH): Mini-Symposium on Fibres-State of the Art, Singapore, August 28, 2000.

"Historical Cohort Study of U.S. Fiber Glass Production Workers. I. Initial Findings of 1992 Follow-Up", Presented at the 26th International Congress on Occupational Health (ICOH), Singapore, August 29, 2000.

"Staying Healthy in an Unhealthy World-Occupational and Environmental Health", Presented at the "Mini-Medical School" Seminar Series of the University of Pittsburgh, School of Medicine, December 5, 2000.

"Does Fiber Glass Pose a Respiratory Cancer Risk in Man? Findings from the Latest Update of the U.S. Cohort Study of Man-Made Vitreous Fiber Workers" Ninth Inhaled Particles Conference, British Occupational Hygiene Society, Robinson College, Cambridge, UK, September 2-6, 2001.

"Bladder Cancer among Chemical Workers Exposed to Nitrogen Products and other Substances", 2003 British Occupational Hygiene Society Annual Meeting, London, England, April 8, 2003.

"Pharyngeal Cancer Mortality among Workers Exposed to Formaldehyde", 2004 Toxicology Forum, Washington, D.C., February 2, 2004.

"Mortality Patterns among Pharmaceutical Production Workers at One U.S. Site", 2004 British Occupational Hygiene Society Annual Meeting, Stratford England, April 20, 2004.

"Mortality Patterns among Workers Exposed to Chloroprene and Other Substances", 2005 British Occupational Hygiene Society Annual Meeting, Manchester, England, April 19, 2005.

"Mortality among Industrial Workers Exposed to Chloroprene and Other Substances: I. Methods and Issues", 2005 International Symposium on Butadiene and Chloroprene, Charleston, SC, September 20, 2005.

"Mortality among Industrial Workers Exposed to Chloroprene and Other Substances: II. Results", 2005 International Symposium on Butadiene and Chloroprene, Charleston, SC, September 20, 2005.

"Overview of Formaldehyde Epidemiology", Toxicology Forum, 2005 Annual Meeting, Brussels, Belgium, November 8, 2005.

"EMF-ELF Exposure Potentials among Magnetic Particle Inspections Workers", International Workshop to Evaluate Future Needs of Occupational ELF Epidemiology, Edinburgh, Scotland, September 14-15, 2006.

"Sampling, Statistics and Iraq: Review and Critique of Two Surveys Conducted to Estimate Deaths in Iraq Since 2003." GSPH Doctoral Student Association Invited Seminar, Pittsburgh, PA, December 10, 2006.

"A New Software Tool- *Rapid Assessment and Characterization of Environmental Risks (RACER)*". Presented at the Environmental Summit, sponsored by the GSPH Department of Epidemiology, Pittsburgh, PA, April 18, 2007.

"Formaldehyde and Human Cancer Risk Understanding the Nasopharyngeal Cancer Excess in Plant 1 of the NCI Study," Formaldehyde International Science Conference, Barcelona, Spain, September 20-121, 2007.

"Rapid Assessment and Characterization of Environmental Risk (RACER)" Centers for Disease Control, Public Health Information Network (PHIN) Annual Meeting, Atlanta, GA, August 25, 2008.

"An Epidemiological Study of Mortality among a Cohort of Jet Engine Manufacturing Workers", Society for Neuro-Oncology Annual Meeting, Las Vegas, NV, November 19-22, 2008.

"Rapid Assessment and Characterization of Environmental Risk (RACER)" CDC National Environmental Public Health Tracking Conference, Washington, D.C., February 24-26, 2009.

"Training Workshop: Rapid Assessment and Characterization of Environmental Risk (RACER)" CDC National Environmental Public Health Tracking Conference, New Orleans, LA, April 24-26, 2010.

"Does Formaldehyde Cause Leukemia? Opposing Viewpoint" University of Pittsburgh, Department of Epidemiology Tipping Point Seminar Series, December 2, 2010.

"Formaldehyde and Nasopharyngeal Cancer- What Do We Know from the Epidemiology Studies?" Formaldehyde International Science Conference, Madrid, Spain, April 18-19, 2012.

"An International Historical Cohort Study of Workers in the Hard-Metal Industry", EPICOH Conference, Utrecht, The Netherlands, June 18-21, 2013.

"Evaluating Health Effects of Exposure to Acrylonitrile": A Comprehensive Research Program at the University of Pittsburgh", EPICOH Conference, Utrecht, Netherlands, June 18-21, 2013.

"An International Historical Cohort Study of Workers in the Hard-Metal Industry", EPICOH 2014 Conference, Chicago, IL, June 23-26, 2014.

c. Other Research and Training (post-1990)

Journal Refereeing

Annals of Epidemiology
Lancet
Epidemiology
American Journal of Epidemiology
Journal of Occupational and Environmental Medicine
Occupational and Environmental Medicine (U.K.)
Journal National Cancer Institute
American Industrial Hygiene Association Journal
Cancer Causes and Control
American Journal of Public Health
Journal of Exposure Analysis and Environmental Epidemiology
Archives of Environmental Health
Critical Reviews in Toxicology
Chemico-Biological Interactions
Regulatory Toxicology and Pharmacology
Risk Analysis
Journal of Occupational and Environmental Hygiene
Open Epidemiology Journal

Editorial Boards

1995-date Associate Editor, *Cancer Informatics*

2008-date Associate Editor, *Journal of Environmental and Public Health*

2009-date Associate Editor, *Epidemiology Research International*

2013-date Associate Editor, *Open Access Epidemiology*

d. Service (post-1990)

(1) Departmental

1992-93 Representative, GSPH Accreditation Committee

1995-98 Member, Budget Policies Committee

2004-05 Chair, Committee to Evaluate Master's Comprehensive Examination

2006-07 Chair, Committee to Evaluate Departmental Biostatistics Consulting Practicum

2008 Founder and Director, Center for Occupational Biostatistics and Epidemiology

2007, 09-10 Interim Chairman, Department of Biostatistics

2010-date Member, Curriculum Committee

(2) School

1992-94 President, GSPH Faculty Senate

1992-94	Chair, GSPH Faculty Senate Executive Committee
1992-94	Member, GSPH Strategic Planning Committee
1996	Chair, Ad Hoc Search and Appointment Committees for Associate Professor and Director Occupational Medicine, Department of Environmental & Occupational Health
1997	Member, GSPH Recruitment Committee
1999	Member, GSPH Faculty Advancement Committee
1999-01	Member, Faculty Advancement, Promotion and Tenure Committee
1999-00	Member, GSPH Search Committee for Chair of EOH Department
2000-01	Member, GSPH Committee to Develop MPH Comprehensive Examination
2005-06	Member, GSPH Committee to Evaluate MMPH Program
2007, 09-10	Member GSPH Council
2007, 09-10	Member, Dean's Cabinet
2009-10	Departmental Chair Representative, GSPH Planning and Budget Policy Committee
2012-date	Departmental Representative, GSPH Faculty Advancement, Promotion, Tenure Committee
2014-15	Member, Faculty Search Committee, Department of Epidemiology

(3) University

1990-date	Member, Pittsburgh Cancer Institute
1995	Member, International Committee to Review Graduate Program of the Civil & Environmental Engineering Department
1995-96	Member, Fact-Finding Committee for the Performance Review of Dean Mattison
1997-03	Member, Health Sciences Library Advisory Committee.
1999-00	Member, Search Committee for Dean of GSPH
2000-date	Faculty Associate, Center for Social and Urban Research

(4) US and International

1987-99	Invited Member, National Scientific Advisory Committee, CDC, Center for Environmental Health, Atlanta, GA.
1989-92	Invited Member, Study Section on Safety and Occupational Health, Centers for Disease Control/National Institute for Occupational Safety and Health.

1991-92	Invited Participant, Advisory Committee on ATSDR Sponsored Project, "Community Health Effects of a Hazardous Waste Incinerator", The University of South Carolina, Columbia Campus.
1992-93	Guest Editor, "The First International Conference on the Safety of Water Disinfection: Balancing Chemical and Microbial Risks". International Life Sciences Institute, Health and Environmental Sciences Institute.
1992	Reviewer, "Draft Health Assessment on Inorganic Arsenic", Health and Welfare Canada, May 1992.
1992	Invited Participant, Workshop on Environmental Epidemiology, National Research Council, National Academy of Sciences, Washington, D.C., June 1992.
1994-96	Invited Member, Committee to Review the Health Consequences of Military Service During the Persian Gulf War, National Academy of Sciences, Institute of Medicine, Medical Follow Up Agency.
1997	Invited Member, Site Visit Team, Veterans Health Administration, Office of Public Health and Environmental Hazards, Environmental Epidemiology Service, March 1997, Washington, D.C.
1998	Invited Peer Reviewer, External Peer Review Workshop on Hazard Assessment and Dose-Response Characterization for the Carcinogenicity of Formaldehyde by Route of Inhalation. Health Canada and the U.S. Environmental Protection Agency, Ottawa, Canada, March-December, 1998.
2001	Invited Member, International Agency for Research on Cancer (IARC), Working Group to Re-evaluate the Carcinogenicity of Man-Made Vitreous Fibers, Lyon, France, October 9-16, 2001.
2001-03	Member, NIOSH Scientific Advisory Panel, Proposed NIOSH Study of Health Effects of Exposure to Electromagnetic Fields (EMF), Cincinnati, OH, May 4, 2001.
2002	Member, CDC Scientific Advisory Panel to Review Protocol for Study of Long-Term Health Effects Following Administration of Anthrax Vaccine, Atlanta, GA, May 14-15, 2002.
2006	Invited Member, Butadiene Risk Assessment Expert Panel, Sciences International Inc., Alexandria, VA.
2006	Invited Member, Electromagnetic Field (EMF) Risk Assessment Expert Panel, Energy Networks Association, Edinburgh, Scotland
2006	Invited Member, Expert Panel to Assess Health Effects of Artificial Sweetener, Burdock Group, Washington, D.C.
2008	Invited Charter Member, U.S. Environmental Protection Agency, Science Advisory Board, Asbestos Panel, Washington, D.C.

(5) Private

1990-95	Consultant, HealthAmerica, Pittsburgh, PA.
1993-04	Member, Research Advisory Committee, Showa Denko America, New York, NY.

1994-95	Consultant, PPG Industries, Inc., Pittsburgh, PA.
1994-date	Consultant, Cytec Industries, Inc., West Paterson, NJ.
1994-03	Consultant, Ecology and Environment, Buffalo, NY.
1995-96	Consultant, Group Health Plan, St. Louis, MO.
1995-99	Scientific Reviewer, ARCO Chemical Company, Newtown Square, PA.
1996-07	Consultant, CertainTeed Products Corporation, Valley Forge, PA.
1996-03	Scientific Reviewer, Electric Power Research Institute, Palo Alto, CA.
1996-01	Scientific Reviewer, Chemical Manufacturers Association, Washington, D.C.
1996-01	Consultant, BP Chemicals, Inc., Cleveland, OH.
1997	Scientific Reviewer, American Industrial Health Council, Washington, D.C.
1997	Scientific Reviewer, American Institute of Biological Sciences, Washington, D.C.
1997-98	Consultant, Highmark Blue Cross Blue Shield, Pittsburgh, PA.
1997-98	Consultant, The Mead Corporation, St. Paul, MN.
1997-2005	Consultant, The Acrylonitrile (AN) Group, Washington, D.C.
1998-01	Consultant, Chemical Industry Institute of Toxicology, Research Triangle Park, NC
1998-02	Consultant, National Academy of Sciences, Institute of Medicine, Medical Follow-Up Agency, Washington, D.C.
1998-03	Consultant, TERRA Inc., Tallahassee, FL.
1999	Consultant, Aristech Chemicals Corporation, Pittsburgh, PA.
1999	Consultant (Seminar Presenter), Dow Chemical Company & Dow Corning Corporation, Midland, MI.
1999-02	Consultant, BP Inc., Chicago, IL.
1999-03	Consultant, New Jersey Department of Health and Senior Services, Trenton, NJ.
1999-03	Invited Member, Research Advisory Committee, University of Texas, Houston/Baylor Medical College, Houston, TX.
1999-01	Consultant, Orthopedic & Reconstructive Center, Oklahoma City, OK
2000	Consultant, The Sapphire Group, Bethesda, MD.
2000-01	Consultant, American Smelting and Refining Company, Salt Lake City, UT.
2000-01	Consultant, Dow Chemical Company, Midland, MI.

2001-05	Consultant, Merck & Co., Rahway, NJ.
2001-05	Consultant, Gateway Health Plan, Pittsburgh, PA.
2001-02	Consultant, Coordinated Care Network, Monroeville, PA.
2001-07	Consultant, NIOSH Follow-up Investigations of Suspected Health Effects of Exposure to Effluents from a Copper Smelter, Copperhill, TN.
2001-02	Consultant, Pratt & Whitney Company, Hartford, CT.
2002-09	Consultant, Formaldehyde Council Inc., Washington, D.C.
2003-10	Invited Member, Scientific Advisory Board, Semi-Conductor Industry Association, Washington, D.C.
2003- 08	Consultant, Academy for Educational Development, Washington, D.C.
2004-06	Consultant, Pressley Ridge Child Care Services, Pittsburgh, PA.
2004-2013	Invited Member, Scientific Advisory Board, Dow Chemical Co., Midland, MI.
2005-07	Consultant, PPG Industries, Inc., Pittsburgh, PA
2005-07	Consultant, FormaCare -European Chemical Industry Council (CEFIC), Brussels, Belgium.
2007-11	Consultant, International Truck and Engine Corporation, Chicago, IL
2009	Consultant, North American Insulation Manufacturers Association, Alexandria, VA.
2009-11	Consultant, Rohm and Haas Company, Philadelphia, PA.
2009-11,15	Consultant, American Chemistry Council, Washington, DC.
2009-10	Consultant, United BioSource Corporation, Kansas City, MO.
2010-11	Consultant, Momentive Specialty Chemicals, Inc., Columbus, OH.
2010-11	Consultant, Navistar, Inc., Chicago, IL.
2010-11	Consultant, Honeywell International, Inc., Morristown, NJ.
2010-12	Member, Scientific Advisory Board, ENVIRON International Corporation, Boston, MA.
2012-13	Scientific Advisor, inXsol, Phoenix, AZ.
2013-14	Consultant, Gateway Health Plan, Pittsburgh, PA.
2013-date	Consultant, City of St. Louis, St. Louis, MO.
2015	Consultant, American Chemistry Council

Roberts

Senior Vice President, Food & Nutrition 201-2233 Argentia Road, Mississauga, ON, Canada, L5N 2X7

EXPERIENCE

Senior Vice President, Food & Nutrition Intertek 2014 – Present
Intertek Cantox 2010 – 2013
Cantox Health Sciences, Inc.* 2001 – 2010
Responsibilities: Directing the Food & Nutrition group; responsible for both safety and efficacy related topics on an international basis. Further roles include development and design of scientific research programs for food ingredients, additives, and contaminants. Development of international regulatory strategies for food additives and ingredients. Calculation of qualitative human health risk assessments for food components, contaminants, and foods. Preparation of documents and reports for submission to international regulatory authorities. Has international recognition from both a scientific and regulatory standpoint and has developed strong relationships with regulatory authorities on a global basis.

*Cantox Health Sciences Inc., was acquired by Intertek Group plc in April 2010.

Scientific & Regulatory Affairs Manager Tate & Lyle Specialty Sweeteners 1991 – 2001
Responsibilities: Managed the worldwide safety and regulatory strategy. Designed, developed, and undertook toxicology and clinical safety studies in co-operation with leading toxicologists, academics, hospitals, and contract research organizations throughout Europe and North America. Provided overall data interpretation, toxicological evaluation, safety assessment, and prepared reports specific for the different worldwide regulatory authorities. Wrote detailed scientific position papers in response to specific questions from different regulatory authorities. Presented data and detailed scientific arguments to regulatory authorities, scientific groups, and at scientific meetings throughout the world. Dealt and worked closely with regulatory authorities and government departments throughout the world including Western and Eastern Europe, North America, and the Far East. *Achievements*: Successful undertaking and completion of toxicological scientific data-base and safety evaluation of a major novel food additive which has gained world-wide regulatory approval.

Research Manager, Merthyr Tydfil Simbec Research Ltd. 1989 – 1990
Responsibilities: Managed clinical pharmacology studies of novel and established pharmaceuticals in many therapeutic regions from design and inception through to final reporting. Managed clinical and research staff. Liaised with the world's leading pharmaceutical companies on study design and protocol development. Prepared and presented detailed information to the Ethical Committee to seek approval for the conduct of such studies. Managed and organized staff in the undertaking of the actual experimentation. Undertook data analysis and result interpretation for clients. Undertook the final report writing along with presentation of the results to the clients. *Achievements*: Successful conduct of many studies enabling major pharmaceutical companies to file product license applications. Worked closely on several medicines which have now gained worldwide recognition.

Laboratory Development Manager Peter Hand Animal Health Ltd. 1988 – 1989
Responsibilities: Managing a group of laboratory personnel and secretarial staff. Overall responsibility for development of animal health care products and for providing the technical and scientific information relating to regulatory applications. Development of new veterinary pharmaceutical products. Preparation of study protocols. Analytical method development and sample analysis. Result analysis and data interpretation. Preparation of reports and documents for regulatory authorities, including pharmacology/toxicology expert

reports. Responsible for purchase of latest laboratory technology and recruitment of staff for the laboratory. Achievements: Major involvement in the company being granted two new medicinal product licenses.

Research Fellow Clinical Pharmacology Group, University of Southampton 1985 – 1987
Responsibilities: Undertook pre-clinical research in the areas of metabolism and pharmacokinetics. Took Medical Student Pharmacokinetic lectures and tutorials.

Ph.D. Studentship University of Southampton 1982 – 1985
Provided the opportunity to study mechanisms in toxicity, resulting from the daily administration of cyclohexylamine a toxic metabolite of cyclamate. This research also provided the opportunity to collaborate with Senior Toxicologists from the British Industrial Biological Research Association (BIBRA). The research was sponsored by the Calorie Control Council (USA) and the International Life Sciences Institute European Technical Cyclamate Committee. Additional responsibilities: Demonstrated Pharmacology Practicals to medical students. Supervised MSc and BSc students with final year projects in Toxicology and Clinical Pharmacology. *Achievements*: Awarded a British Pharmacology Society bursary to present my research at the World Toxicology Congress in Japan (1986).

Research Scientist Huntington Research Centre 1980 – 1982
Responsibilities: Developed, conducted, and reported metabolism and pharmacokinetic studies with pharmaceuticals, agrochemicals, and food additives in animals and man. Assisted in the writing of study protocols and reports. Undertook the majority of the experimentation involved in the project and supervise laboratory and animal technicians.

EDUCATION

Ph.D., Clinical Pharmacology/Toxicology 1987 University of Southampton

B.Sc. (Honours), Biochemistry 1980 University of London

PROFESSIONAL SOCIETIES/ASSOCIATIONS

- American Herbal Products Association (AHPA) – Member
- British Industrial Biological Research Association (BIBRA) – Member
- The British Toxicology Society (BTS) – Full Member
- Canadian Institute of Food Science and Technology (CIFST) – Member
- Institute of Food Technologists (IFT) – Regulatory Member
- International Life Sciences Institute (ILSI) – Member of the Acceptable Daily Intake and Food Chemical Intake Task Force
- International Society of Regulatory Toxicology and Pharmacology (ISRTP) – Member
- International Sweeteners Association (ISA) – Past Chairman Elect of the Scientific and Regulatory Committee
- Society of Toxicology (SOT) – Member
- Toxicology Forum – Member
- Food Safety and Quality Program Advisory Board, McGill University – Member

PRESENTATIONS

2018 Safety Evaluation of Glutamic Acid and Related Glutamates Pattaya, Thailand
Presented at the The 8th International Congress of Asian Society of Toxicology (ASIATOX 2018).

2018 Safety Assessment of Food Additives/Ingredients Derived from Genetically Modified Microorganisms Beijing, China
Presented at ILSI China's Workshop on Safety Assessment of Foods Derived from Genetically Modified Microorganisms(GMMs)

2017 Steviol Glycoside Safety Evaluation Istanbul, Turkey
Presented at Low and No-Calorie Sweeteners (Conf. II).

2017 Steviol Glycoside Safety Evaluation Ankara, Turkey
Presented at Low and No-Calorie Sweeteners (Conf. I).

2017 Potential Impact of U.S. Guidance to Reduce the intakes of Added Sugars on Estimated Daily Intakes of Non-Nutritive Sweeteners Naples, Florida
Presented at the Calorie Control Council – 2017 Annual Meeting & Educational Symposium.

2017 Sweetener Safety Festival City, Dubai
Presented at the Dubai Nutrition Conference.

2017 Overview of Stevia Approvals by the Global Safety Authorities Buenos Aires, Argentina
Presented at the ILSI at 21st International Congress of Nutrition (ICN2017) - Sponsored Scientific Symposium: 144/129 – Stevia: An Ally to Support Nutrition and Health. Organized by: International Stevia Council (ISC) (Belgium) & Calorie Control Council (CCC) (USA).

2017 Global Safety and Regulatory Processes for the Evaluation of Low-Calorie Sweeteners Buenos Aires, Argentina
Presented at the ILSI at 21st International Congress of Nutrition (ICN2017).

2017 Approaches to Safety Assessment of Low Calorie Sweeteners & Global Regulatory Development Status New Delhi, India
Presented at ILSI India, Conference on Sweetness: Role of Sugar & Low-Calorie Sweeteners.

2017 Safety Evaluation of Low/No Calorie Sweeteners Beijing, China
Presented at the *Science, Safety and Innovation of Sugars & Sweeteners* Workshop.

2017 The Use of Chemical-Specific Adjustment Factors (CSAF's) in the Derivation of the ADI Using Steviol Glycosides as a Case Example Las Vegas, NV
Presented at IFT 2017 Annual Meeting and Expo; Session: Deriving an Acceptable Daily Intake (ADI) for Steviol Glycosides Utilizing Chemical-Specific Adjustment Factors Food Additive Safety: Using Chemical-Specific Adjustment Factors (CSAFs) when Estimating Acceptable Daily Intakes (ADIs).

2017 Update on Low/No/Reduced Calorie Sweeteners & Possible Impacts on the Microbiome Santiago, Chile
Presented at the Symposium for Sugar reduction in Foods: From Evidence to Action; a joint event with Sochital (the Chilean Society of FS&T) and Sochinut (the Chilean Society of Nutrition).

2017 Update on Low/No/Reduced Calorie Sweeteners & Possible Impacts on the Microbiome Lima, Peru
Presented at Nutrition Congress (XIII Peruvian Congress of Nutrition and XII International Course of Nutrition and Nutrition Update).

2017 Sweeteners: Do They Bear a Carcinogenicity Risk Sao Paulo, Brazil
Presented at ILSI Brazil – IX Updates on Food Safety Sweeteners.

2016 Update on Low/No/Reduced Calorie Sweeteners & Possible Impacts on the Microbiome Clearwater Beach, Florida
Presented at the Calorie Control Council – 2016 Annual Meeting & Education Symposium & 50th Anniversary Celebration.

2016 The Metabolism and Pharmacokinetics of Steviol Glycosides and Their Impact on the ADI Rome, Italy
Presented at Euro Toxicology 2016, 7th Euro-Global Summit on Toxicology and Applied Pharmacology.

2016 Stevia Sweeteners: The Past the Present and the Future; and Do High Intensity Sweeteners Modulate the Gut Microbiome? Buenos Aires, Argentina
Presented at the Symposium on Low and No Calorie Sweeteners: Myths and Realities, organized by the AATA (Argentine Association of Food Technologists) together with the Argentine Nutrition Society (SAN).

2015 Regulatory Overview: Chinese Doing Business in the European Union Paris, France
Presented at Food Ingredients Europe (FI Europe).

2015 Regulatory requirements for food ingredients added to foods for nutritional health purposes; and Regulatory impact of newly reported data on L-arginine Paris, France
Presented at the International Council on Amino Acid Sciences (ICAAS).

2015 Health Claims: Comparing the New Japanese Regulation to that of the US, Australia, and Europe Tokyo, Japan
Presented at Health Ingredients Japan 2015.

2015 The Safety & Regulatory Process for High Intensity Sweetener Approval in the U.S. Purdue University, West Lafayette, Indiana
Presented at the *Workshop on High Intensity Sweeteners: Evolving Science, Exploding Controversy.*

2015 Clarifying the Complexities in the Regulation of New Food Ingredients in Key Global Markets Mississauga, Ontario
Hosted by Intertek Scientific and Regulatory Consultancy *via* webinar.

2014 A Hard Look at FDA's Review of GRAS Notices Washington, DC
Presented at the International Society of Regulatory Toxicology and Pharmacology's Workshop on GRAS Determinations.

2014 Health Claim Comparison Between the EU and China Shanghai, China
Presented at Food Ingredients China 2014.

2013 Analytical and Toxicity Study Requirements for Gaining Regulatory Approval Tokyo, Japan
Presented at Health Ingredients Japan 2013.

2013 Safety Assessment of Caffeine in Foods and Beverages Washington, DC
Presented *via* webcast for The National Academies' Planning Committee on Potential Health Hazards Associated with Consumption of Caffeine in Food and Dietary Supplements – Session: *Safety Assessment of Caffeine in Foods and Beverages.*

2013 Regulatory Procedure of Submission and Approval of US GRAS and EU Novel Food Shanghai, China
Presented at Food Ingredients China 2013.

2012 Analytical and Toxicity Study Requirements for Gaining Regulatory Approval U.S.A. & Switzerland
Presented at the Intertek Cantox Workshop on *Beyond the Great Wall: How to access the food and supplement markets in China.*

2012 Substantiating Immune Health Claims: Perspectives of Scientific/Regulatory Authorities in North America and Europe Las Vegas, Nevada
Presented at IFT Annual Meeting; Session: *Substantiating an Immune Health Claim – Three Perspectives.*

2012 The GRAS Process for Feed Brussels, Belgium
Presented at the Intertek Cantox Workshop – *Regulation of Animal Feed Ingredients in the United States.*

2011 Regulatory Developments for Supplements in the United States and Canada Las Vegas, NV
Presented at SupplySide West.

2011 EU Guidance on the Submission of a Dossier on Food Enzymes and the Latest Position on Health Claims
Presented at the Intertek Cantox Workshop on *The Current Situations of Regulatory Approvals for Functional Food Ingredients in Overseas Market* (Memorial Workshop on the 5th Anniversary of the Intertek Cantox Tokyo Branch Office).

2011 The Use of Animal Toxicological Studies of High Intensity Sweeteners in Predicting Effects on Human Weight Management Washington, DC
Presented at ILSI North America: *Conference on Low-Calorie Sweeteners.*

2010 How to Get Your Food Ingredients to the Marketplace in the U.S.; Regulation of Claims on Foods and Dietary Supplements in the U.S; Regulatory Overview of Food Ingredient Legislation in the EU; and Regulation of Claims in the European Union Seoul, South Korea
Presented at Cantox's Workshop on *Food Ingredients and Supplements: Gaining Access to the U.S., EU., and Korean Markets.*

2010 An Overview of Japanese Food Regulations. Regulatory Processes for Food Product Approval in Japan Webcast
Institute of Food Technologists' webcast: *Global Regulatory Approval for Food Ingredients.*

2010 Progress of Health Claims in Europe: A New Perspective Brussels, Belgium
Cantox Workshop.

2010 Private Sector Experience: What Characterizes an Adequate Package? Washington, DC
Presented at the 35th Annual Winter Meeting of the Toxicology Forum.

2009 New Technologies and Development for Monitoring Safety of Functional Foods for Heart Health Winnipeg, Manitoba
Presented at the *Functional Foods for Heart Health: Continuum Between Science and Commercialization.*

2009 U.S. GRAS/NDI Notifications, and Health Claim Regulations Tokyo, Japan
Hayashi T, **Roberts A**. Presented at: *Food Ingredients and Supplements: Gaining Access to the U.S., E.U., and China Markets.*

2009 Understanding the Latest European Regulations Regarding Food Additives, Novel Foods, Enzymes and Heath Claims Tokyo, Japan
Presented at Cantox's Workshop on *Food Ingredients and Supplements: Gaining Access to the U.S., E.U., and China Markets.*

2009 Regulation of Claims in Europe Rosemont, Illinois
Presented at Health Claims in North America and Europe: Capitalizing on Recent Developments.

2009 How Does 912 Impact the Development of Novel Ingredients; and How to Gain Approval of a Health Claim in Europe Rosemont, Illinois
Presented at IFT – Wellness 09: At the Forefront of Food & Health.

2008 Chinese Food Regulatory Requirements Mississauga, Ontario
Presented at *From Research to Revenue IV: Capturing Business Opportunities in Asia.*

2008 Metabolism and PK Studies and Their Impact on the Safety Evaluation of Rebaudioside A (Rebiana) Aspen, Colorado
Presented at the 34th Annual Summer Meeting of The Toxicology Forum.

2008 How Does 912 Impact the Development of Novel Ingredients? New Orleans, Louisiana
Presented at IFT Annual Meeting & Food Expo.

2007 Canadian Natural Health Products (NHP) Regulations Tokyo, Japan
Presented at Health Ingredients Japan 2007.

2007 Overview of Canada's Natural Health Products and Functional Food Regulations Tokyo, Japan
Presented at the Canadian Functional Foods and Natural Health Products Seminar and Tabletop Networking Reception, Canadian Embassy.

2007 A Global Perspective on Health-Related Claims Permitted on Foods and Food Ingredients Outside of the U.S. and an Overview of Steps to Developing a Global Strategy for Compiling Appropriate Scientific Data and Gaining Regulatory Approval of Such Claims Chicago, Illinois
Presented at 2007 IFT Annual Meeting & Food Expo.

2006 How to Market Your Functional Foods and Nutraceuticals in the US, Canada, Europe and Japan Tokyo, Japan
CANTOX Seminar co-sponsored by the Canadian Embassy held at the Canadian Embassy in Tokyo, Japan.

2006 How Can CANTOX Assist You Towards Marketing Success? Tokyo, Japan
Presented at Health Ingredients Japan 2006.

2006 Safety Evaluation of Ferric Sodium Ethylenediaminetetraacetate (FeNaEDTA) for Use as a Source of Iron in Foods Tokyo, Japan
Presented at Health Food Exposition Japan 2006.

2006 Presentations: 1) US and EU Comparative Case Study; 2) Safety Evaluation of Old Food Ingredients with New Health Benefits in the US and EU; 3) Substantiation of Health Claims in the US and EU and 4) Substantiation of a Health Claim for Soy Protein in the UK and US Washington, DC
Presented at the US & EU *Comparative Case Study Functional Foods and Supplements Workshop*.

2004 Regulation & Safety Data Requirements for Introducing Products into the Health Food and Food Additive Markets in the US & EU Tokyo, Japan
Presented at Health Ingredients Japan 2004 Meeting.

2004 Health Claim Regulations in the US Tokyo, Japan
Presented at BioJapan 2004.

2004 Food Law & Regulatory Processes for Food Product Approval in the European Union University of Toronto, Toronto, Ontario
Presented at the Program in Food Safety.

2003 The Regulatory Evaluation of Functional Foods and Nutraceuticals Tokyo, Japan
Munro IC, **Roberts A.** CANTOX Seminar co-sponsored by the Canadian Embassy.

2003 Regulatory Processes for Food Product Approval in the European Union University of Toronto, Toronto, Ontario
Presented at the Program in Food Safety.

2003 Regulatory Process for Food Product Approval in the European Union Chicago, Illinois
Presented at the IFT Annual Meeting & Food Expo.

2002 Functional Foods and Nutraceuticals -- How to Launch Nutraceuticals on the U.S. Market Paris, France
A workshop conducted by Munro IC and **Roberts A** in association with Archimex.

PAPERS & PUBLICATIONS

Martyn DM, Darch MN, **Roberts A**, Lee HY, Tian YT, Kaburagi N, Belmar P (2018). Low-/no-calorie sweeteners: a review of global intakes. Nutrients 10(3):357 [39pp plus supplemental tables]. DOI:10.3390/nu10030357.

Haighton L, **Roberts A**, Walters B, Lynch B (2018). Systematic review and evaluation of aspartame carcinogenicity bioassays using quality criteria. Regul Toxicol Pharmacol [Epub ahead of print - Jan. 12, 2018]. DOI:10.1016/j.yrtph.2018.01.009.

Martyn D, Lau A.; Richardson P, **Roberts A** (2017). Temporal patterns of caffeine intake in the United States. Food Chem Toxicol 111:71-83. DOI:10.1016/j.fct.2017.10.059.

Lynch BS, West S, **Roberts A** (2017). Safety evaluation of water-soluble palm fruit bioactives. Regul Toxicol Pharmacol 88:96-105. DOI:10.1016/j.yrtph.2017.05.021.

Magnuson BA, **Roberts A**, Nestmann ER (2017). Critical review of the current literature on the safety of sucralose. Food Chem Toxicol 106(Part A):324-355. DOI:10.1016/j.fct.2017.05.047.

Martyn DM, Lau AA, Darch MN, **Roberts AS** (2017). Benzoates intakes from non-alcoholic beverages in Brazil, Canada, Mexico and the United States. Food Addit Contam Part A Chem Anal Control Expo Risk Assess [epub ahead of print – Jun. 8, 2017]. DOI:10.1080/19440049.2017.1338836.

Grotz VL, Pi-Sunyer X, Porte D Jr, **Roberts A**, Trout J (2017). A 12-week randomized clinical trial investigating the potential for sucralose to affect glucose homeostasis. Regul Toxicol Pharmacol 88:22-33. DOI:10.1016/j.yrtph.2017.05.011.

Roberts A (2016). The safety and regulatory process for amino acids in Europe and United States. J Nutr. 146(12):2635S-2642S. DOI:10.3945/jn.116.234591.

Williams GM, Aardema M, Acquavella J Berry C Brusick D, Burns MM, Viana de Camargo JL, Gabarrant D, Greim HA, Kier LD, Kirkland DJ, Marsh G, Solomon KR, Sorahan T, **Roberts A**, Weed DL (2016). A review of the carcinogenic potential of glyphosate by four independent expert panels and comparison to the IARC assessment. Crit Rev Toxicol 46(Supp. 1):3-20.

Roberts A, Haighton LA (2016). A hard look at FDA's review of GRAS notices. Regul Toxicol Pharmacol 79(Suppl. 2):S124-S128.

Roberts A, Lynch B, Rogerson R, Renwick A, Kern H, Coffee M, Cuellar-Kingston N, Eapen A, Crincoli C, Pugh G Jr, Bhusari S, Purkayashtha S, Carakostas M (2016). Chemical-specific adjustment factors (inter-species toxicokinetics) to establish the ADI for steviol glycosides. Regul Toxicol Pharmacol 79:91-102.

Okado N, Hasegawa K, Mizuhashi F, Lynch BS, Vo TD, **Roberts A** (2016). Safety evaluation of nuclease P1 from *Penicillium citrinum*. Food Chem Toxicol 88:21-31.

Purkayastha S, Markosyan A, Prakash I, Bhusari S, Pugh G Jr, Lynch B, **Roberts A** (2016). Steviol glycosides in purified stevia leaf extract sharing the same metabolic fate. Regul Toxicol Pharmacol 77:125-133.

Roberts A (2016). Caffeine: an evaluation of the safety database. In: Gupta RC, editor. *Nutraceuticals - Efficacy, Safety and Toxicity*. San Diego (CA): Academic Press, pp. 417-434.

Roberts A (2016). The safety and regulatory process for low calorie sweeteners in the United States. Physiol Behav 164(Part B):439-444.

Okado N, Suji M, Ueda M, Mizuhashi F, Lynch BS, Vo T, **Roberts A** (2015). Safety evaluation of AMP deaminase from *Aspergillus oryzae*. Food Chem Toxicol 86:342-350.

Hearty A, Lau A, **Roberts A** (2014). Chewing gum intake in Europe: a survey of intakes in France, Germany, Italy, Spain and the UK. Food Addit Contam Part A 31(7):1147-1157.

Nakano M, Takahashi H, Koura S, Chung C, Tafazoli S, **Roberts A** (2014). Acute and subchronic toxicity studies of pyrroloquinoline quinone (PQQ) disodium salt BioPQQ™) in rats. Regul Toxicol Pharmacol 70(1):107-121.

Purkayastha S, Pugh G Jr, Lynch B, **Roberts A**, Kwok D, Tarka SM Jr (2014). *In vitro* metabolism of rebaudioside B, D, and M under anaerobic conditions: comparison with rebaudioside A. Regul Toxicol Pharmacol 68(2):259-268.

Roberts A (2014). Safety signals and surveillance. Safety assessment of caffeine in foods and beverages. Presented at: Pray L, Yaktine AL, Pankevich D, Rapporteurs. *Caffeine in Food and Dietary Supplements: Examining*

Safety: Workshop Summary. Institute of Medicine (IOM), Board on Health Sciences Policy, Food and Nutrition Board (FNB), Planning Committee on Potential Health Hazards Associated with Consumption of Caffeine in Food and Dietary Supplements. Washington (DC): National Academies Press (NAP), pp. 38-50.

Roberts A, Renwick AG (2014). Toxicokinetics (Chapter 5) In: Hayes AW, Kruger CL, editors. *Hayes' Principles and Methods of Toxicology, 6th edition.* Baton Rouge (FL): CRC Press, pp. 215-245.

Roberts A (2013). Safety Assessment of Caffeine in Foods and Beverages. Presented August 5 via webcast for The National Academies' - Session: *Safety Assessment of Caffeine in Foods and Beverages* - Washington, DC, August 5-6.

Kitadate K, Homma K, **Roberts A**, Maeda T (2013). Thirteen-week oral dose toxicity study of Oligonol containing oligomerized polyphenols extracted from lychee and green tea. Regul Toxicol Pharmacol 68(1):140-146.

Konishi T, Aoshima T, Mizuhashi F, Choi SSH, **Roberts A** (2013). Safety evaluation of glucose oxidase from *Penicillium chrysogenum*. Regul Toxicol Pharmacol 66(1):13-23 & [Corrigendum 66(3):300].

Magnuson B, Munro I, Abbot P, Baldwin N, Lopez-Garcia R, Ly K, McGirr L, **Roberts A**, Socolovsky S (2013). Review of the regulation and safety assessment of food substances in various countries and jurisdictions. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 30(7):1147-1220.

Fernstrom JD, Munger SD, Sclafani A, de Araujo IE, **Roberts A**, Molinary S (2012). Mechanisms for sweetness. J Nutr 142(6):1134S-1141S.

Clarke K, Tchabanenko K, Pawlosky R, Carter E, Todd King M, Musa-Veloso K, Ho M, **Roberts A**, Robertson J, Vanitallie TB, Veech RL (2012). Kinetics, safety and tolerability of (*R*)-3-hydroxybutyl (*R*)-3-hydroxybutyrate in healthy adult subjects. Regul Toxicol Pharmacol 63(3):401-408.

Clarke K, Tchabanenko K, Pawlosky R, Carter E, Knight NS, Murray AJ, Cochlin LE, King MT, Wong AW,

Roberts A, Robertson J, Veech RL (2012). Oral 28-day and developmental toxicity studies of (*R*)-3-hydroxybutyl (*R*)-3-hydroxybutyrate. Regul Toxicol Pharmacol 63(2):196-208.

Fujii H, Nishioka N, Simon RR, Kaur R, Lynch B, **Roberts A** (2011). Genotoxicity and subchronic toxicity evaluation of Active Hexose Correlated Compound (AHCC). Regul Toxicol Pharmacol 59(2):237-250.

Lynch B, Simon R, **Roberts A** (2011). Subchronic toxicity evaluation of aloesin. Regul Toxicol Pharmacol 61(2):161-171.

Lynch B, Simon R, **Roberts A** (2011). *In vitro* and *in vivo* assessment of the genotoxic activity of aloesin Regul Toxicol Pharmacol 61(2):215-221.

Tarka SM, **Roberts A** (2011). Letter to the Editor – Stevia: it's not just about calories. Open Obes J 3:85-85.

Uchida M, Tsuboi H, Takahashi Arita M, Nemoto A, Seki K, Tsunoo H, Martyres S, **Roberts A** (2011). Safety of high doses of *Propionibacterium freudenreichii* ET-3 culture in healthy adult subjects. Regul Toxicol Pharmacol 60(2):262-267.

Uchida M, Yoda N, Terahara M, Seki K, Choi SS, **Roberts A** (2011). Safety evaluation of *Propionibacterium freudenreichii* ET-3 culture. Regul Toxicol Pharmacol 60(2):249-261.

Roberts A, Renwick AG (2009). Toxicokinetics (Chapter 6) In: Ballantyne B, Marrs TC, Syversen T, editors. *General and Applied Toxicology: Vol. 1, 3rd edition*. West Sussex, UK: John Wiley & Sons Limited, pp. 147-180.

Bidlack WR, Birt D, Borzelleca J, Clemens R, Coutrelis N, Coughlin JR, Dunaif JE, Ebert A, Hall R, Heimbach JH, Helferich W, Magnuson B, McColl DB, McQuate RS, Munro I, Petersen B, **Roberts A**, Scimeca J, Slayne M, Trautman T, contributors (2009). Making decisions about the risks of chemicals in foods with limited scientific information (An IFT Expert Report). Compr Rev Food Sci Food Safety 8:269-303. DOI:10.1111/j.1541-4337.2009.00081.x.

Day AG, Brinkmann D, Franklin S, Espina K, Rudenko G, **Roberts A**, Howse KS (2009). Safety evaluation of a high-lipid algal biomass from *Chlorella protothecoides*. Regul Toxicol Pharmacol 55(2):166-180.

Roberts A, Munro I (2009). Stevioside and related compounds: therapeutic benefits beyond sweetness [with rebuttal from Varanuj Chatsudthipong and Chatchai Muanprasat]. Pharmacol Ther 122(3):e1-e2, author rebuttal, e3.

Curry LL, **Roberts A** (2008). Subchronic toxicity of rebaudioside A. Food Chem Toxicol 46(Suppl. 7):S11-S20.

Curry LL, **Roberts A**, Brown N (2008). Rebaudioside A: two-generation reproductive toxicity study in rats. Food Chem Toxicol 46(Suppl. 7):S21-S30.

Fujii H, Nishioka H, Wakame K, Magnuson BA, **Roberts A** (2008). Acute, subchronic and genotoxicity studies conducted with Oligonol, an oligomerized polyphenol formulated from lychee and green tea extracts. Food Chem Toxicol 46(12):3553-3562.

Roberts A, Renwick AG (2008). Comparative toxicokinetics and metabolism of rebaudioside A, stevioside, and steviol in rats. Food Chem Toxicol 46(Suppl. 7):S31-S39.

Roberts A, Rogerson R (2008). Chinese approach on regulating food additives, novel foods, functional foods and dietary supplements (Chapter 19). In: Bagchi D, editor. *Nutraceutical and Functional Food Regulations in the United States and Around the World.* (Food Science and Technology International Series). New York (NY)/Toronto (ON): Elsevier, pp. 291-303.

Zhang B, Maniatis T, Song Y, Zhang W, Zhang X, Li N, Chen J, Wong AW, **Roberts A** (2008). Evaluation of magnolia bark extract in chromosomal aberration assays. Mutat Res 654(2):133-137.

Blum R, Kiy T, Tanaka S, Wong AW, **Roberts A** (2007). Genotoxicity and subchronic toxicity studies of DHA-rich oil in rats. Regul Toxicol Pharmacol 49(3):271-284.

Blum R, Kiy T, Waalkens-Berendsen I, Wong AW, **Roberts A** (2007). One-generation reproductive toxicity study of DHA-rich oil in rats. Regul Toxicol Pharmacol 49(3):260-270.

Goodfellow G, Lee-Brotherton V, Daniels J, **Roberts A**, Nestmann E (2007). Assessment of the antibacterial agent, triclosan, under use conditions. Am J Infect Control (UNPUBLISHED).

Li N, Song Y, Zhang W, Wang W, Chen J, Wong AW, **Roberts A** (2007). Evaluation of the *in vitro* and *in vivo* genotoxicity of magnolia bark extract. Regul Toxicol Pharmacol 49(3):154-159.

Liu Z, Zhang X, Cui W, Zhang X, Li N, Chen J, Wong AW, **Roberts A** (2007). Evaluation of short-term and subchronic toxicity of magnolia bark extract in rats. Regul Toxicol Pharmacol 49(3):160-171.

Cremer DR, Rabeler R, **Roberts A**, Lynch B (2006). Long-term safety of α-lipoic acid (ALA) consumption: a 2-year study. Regul Toxicol Pharmacol 46(3):193-201.

Cremer DR, Rabeler R, **Roberts A**, Lynch B (2006). Safety evaluation of α-lipoic acid (ALA). Regul Toxicol Pharmacol 46(1):29-41.

Wolterbeek AP, **Roberts A**, Korte H, Unkila M, Waalkens-Berendsen DH (2004). Prenatal developmental toxicity study with 7-hydroxymatairesinol potassium acetate (HMRlignan) in rats. Regul Toxicol Pharmacol 40(1):1-8.

Roberts A, Renwick AG, Sims J, Snodin DJ (2000). Sucralose metabolism and pharmacokinetics in man. Food Chem Toxicol 38(Suppl. 2):S31-S41.

Sims J, **Roberts A**, Daniel JW, Renwick AG (2000). The metabolic fate of sucralose in rats. Food Chem Toxicol 38(Suppl. 2):S115-S121.

Roberts A (1999). Sucralose and diabetes. FFI J (182):49-52.

Roberts A, Renwick AG (1989). The pharmacokinetics and tissue concentrations of cyclohexylamine in rats and mice. Toxicol Appl Pharmacol 98(2):230-242.

Roberts A, Renwick AG, Ford G, Creasy DM, Gaunt I (1989). The metabolism and testicular toxicity of cyclohexylamine in rats and mice during chronic dietary administration. Toxicol Appl Pharmacol 98(2):216-229.

Roberts A (1987). *The Metabolism and Pharmacokinetics of Cyclohexylamine and Their Relevance to Testicular Toxicity*. [Ph.D. Thesis]. Southampton, England, University of Southampton, Clinical Pharmacology Group Faculty of Medicine.

Angelo MJ, Pritchard AB, Hawkins DR, Waller AR, **Roberts A** (1986). The pharmacokinetics of dichloromethane. I. Disposition in B6C3F1 mice following intravenous and oral administration. Food Chem Toxicol 24(9):965-974. DOI:10.1016/0278-6915(86)90325-X.

Angelo MJ, Pritchard AB, Hawkins DR, Waller AR, **Roberts A** (1986). The pharmacokinetics of dichloromethane: II. Disposition in Fischer 344 rats following intravenous and oral administration. Food Chem Toxicol 24(9):975-980. DOI:10.1016/0278-6915(86)90326-1.

Roberts A, Renwick AG (1985). The effect of saccharin on the microbial metabolism of tryptophan in man. Food Chem Toxicol 23(4&5):451-455. DOI:10.1016/0278-6915(85)90139-5.

Roberts A, Renwick AG (1985). The metabolism of ^{14}C -cyclohexylamine in mice and two strains of rat. Xenobiotica 15(6):477-483.

ABSTRACTS & POSTERS

Purkayastha S, Markosyan A, Prakash I, Bhusari S, Pugh G, Lynch B, **Roberts A** (2016). Steviol glycosides in purified stevia leaf extract sharing the same metabolic fate [55th Society of Toxicology Annual Meeting, New Orleans, LA, Mar. 17]. Toxicol Sci (Toxicologist Suppl.):[Abstract 3789; Poster Board: P481].

Roberts A (2016). The metabolism and pharmacokinetics of steviol glycosides and their impact on the ADI. Presented at: *7th Euro-Global Summit on Toxicology and Applied Pharmacology*, Oct. 24-26, 2016. Rome, Italy.

Aardema M, Acquavella J, Berry C, Brusick D, Burns B, de Camargo JLV, Garabrant D, Greim H, Kier L, Kirkland D, Marsh G, **Roberts A**, Solomon K, Sorahan T, Weed D, Williams G (2015). Expert Panel Review of the Carcinogenic Potential of the Herbicide Glyphosate.

Roberts A, Lynch B (2014). Assessing Potential Interactions of "Active" Ingredients in Food. [presented at the 53rd Society of Toxicology Annual Meeting, Phoenix, Arizona, March 27]. Abstract -343i - Poster Board 572.

Roberts A, Lynch B (2014). Assessing Potential Interactions of "Active" Ingredients in Food. [presented at the 53rd Society of Toxicology Annual Meeting, Phoenix, Arizona, March 27]. Abstract -343i - Poster Board 572.

Choi S, Howse K, **Roberts A** (2011) Approach for determining if data on heterologous strains of similar species would support the safety of a particular strain where data are lacking [SOT 50th annual Meeting, Washington, D.C. presented March 9, 2011, Abstract Number: 2441].

Roberts A (2006). Investigation of the molecular mechanism of hepatotoxicity of a G-protein couples receptor antagonist using toxicogenomics. Toxicologist 90(1, Suppl.):203 [abstract 995].

Thompson C, **Roberts A** (2006). Utility of toxicogenomics in the elucidation of the hepatoxic mechanism of a discontinued drug candidate. Toxicologist 90(1, Suppl.):265-266 [abstract 1300].

Roberts A, Lynch BS, Wolterbeek AB, Korte H, Unkila M, Waalkens-Berendsen DH (2006). Safety assessment of 7-hydroxymatairesinol (HMR) lignan. Toxicologist 90(1, Suppl.):477-478 [abstract 2335].

Goodfellow G, Lee-Brotherton V, Daniels J, **Roberts A**, **Nestmann E** (2003). Antibacterial resistance and triclosan. Toxicol Sci [abstract 1470].

Roberts A (1996). Species differences in pharmacokinetics: An aid to toxicological evaluation. Eur Teratol Soc p. 45.

Renwick AG, **Roberts A**, Sims J (1991). Sucralose metabolism and pharmacokinetics in man. Eurotox. 310.

Roberts A, Renwick AG (1988). The fate of cyclohexylamine in rat and mouse in relation to testicular toxicity. Human Toxicol 7(2):229.

Roberts A, Renwick AG, Creasy DM, Ford GP, Gaunt IF (1988). The DA rat as an aid to toxicological evaluation. Human Toxicol 7(2):228.

Roberts A, Renwick AG, George CF (1985). The pharmacokinetics and tissue distribution of cyclohexylamine in the rat and mouse. Toxicol Lett 31.

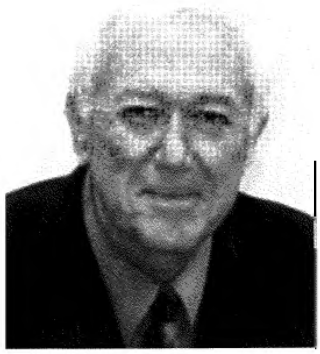
Roberts A, Renwick AG, George CF (1985). Salicylate pharmacokinetics: An undergraduate practical. Br J Clin Pharmacol 20.

Solomon

KEITH R SOLOMON *CURRICULUM VITAE*

May 2015 (printed November 20, 2015)

1 PERSONAL INFORMATION



LAST NAME: Solomon

FIRST NAMES: Keith Ross

BORN: 1944-12-11, Cape Town, South Africa.

Professor Emeritus, School of Environmental Sciences and Director, Centre for Toxicology,
2120 Bovey Building, Gordon Street,
University of Guelph, Guelph,
ON, N1G 2W1, Canada
[redacted]@uoguelph.ca
Tel: [redacted] x [redacted] Fax: [redacted]

STATUS: University Professor Emetirus and Adjunct Graduate Faculty

CITIZENSHIP: Canadian

2 EDUCATION

DEGREE	DEPARTMENT	UNIVERSITY	YEAR/MONTH
Ph.D.	Entomology	University of Illinois	1973/11
M.S.	Entomology	University of Illinois	1972/07
M.Sc.	Zoology	Rhodes University	1971/02
B.Sc.(Hons)	Zoology	Rhodes University	1967/02
B.Sc.	Zoology/Chemistry	Rhodes University	1966/02

3 EXPERIENCE

POSITION	LOCATION	YEAR/MONTH
Professor Emeritus and Associate Graduate Faculty	School of Environmental Sciences, University of Guelph	2010/01-present
Director	Centre for Toxicology, University of Guelph	1992/05-present
Assoc. Director	Canadian Centre for Toxicology, Guelph	1984/01-1992/05
Full Professor	School of Environmental Sciences, University of Guelph	1989/09-2009/31
Associate Professor	Environmental Biology, University of Guelph	1982/09-1989/09
Assistant Professor	Environmental Biology, University of Guelph	1978/08-1982/09
Entomologist/Toxicologist	Tick Control Unit, Vet. Research Institute, S. Africa	1977/07-1978/07
Insect Toxicologist	Biochemistry Div., National Chem. Research Lab, C.S.I.R.	1974/12-1977/06
Biological Chemist	Biochemistry Div., National Chem. Research Lab, C.S.I.R.	1968/01-1970/01
Biological Chemist	Tick Control Unit, Vet. Research Institute, S. Africa	1967/01-1968/01

4 SCHOLARLY AND PROFESSIONAL ACTIVITIES

ROLE	ORGANIZATION	DATE
Co-Chairman	Aquatic Toxicity Workshop Organizing Committee.	1981
Program Co-Chair	14th Annual Aquatic Toxicity Workshop.	1987
Co-Editor	Proceedings of the 14th Annual Aquatic Toxicity Workshop.	1988

ROLE	ORGANIZATION	DATE
Member Board of Directors	North Eastern North American Chapter of the Society of Environmental Toxicology and Chemistry (SETAC).	1986-1989
Program Chair	SETAC.	1985-1986
Publications & Educ. Comm.	SETAC.	1986-1989
Secretary/Treasurer	SETAC.	1986-1989
Co-Convenor	Environmental Toxicology Session at the IUPAC Congress of Pesticide Chemistry, Ottawa.	1986
Co-Convenor	Toxicology session at the XVIII World Congress of Entomology, Vancouver.	1988
Member	Organizing Committee, SETAC '89.	1988-1989
Associate Member	IUPAC Water Chemistry Commission	1991-1993
Member Steering Committee	Aquatic Toxicity Workshop	1980-2001
Associate	Institute of Environmental Studies University of Toronto.	1986-1994

5 SCIENTIFIC MEETINGS

ROLE (last 3 years only)	ORGANIZATION	DATE
Session chair	ACS Meeting, Indianapolis, IN	Sep 09-14 2013
Session chair	SETAC US Meeting, Long Beach, CA	Sep 10-14 2012

6 SCIENTIFIC SOCIETIES

American Association for the Advancement of Science
American Chemical Society (Agrochemicals and Environmental Divisions). Board member for ACS AGRO.
Aquatic Toxicity Workshop.
Society of Environmental Toxicology and Chemistry (SETAC).
Laurentian Chapter of SETAC.

7 AWARDS AND HONORS

Fellow of the Society for Environmental Toxicology and Chemistry (SETAC) 2014-present
The American Chemical Society 2013 Sterling B. Hendricks Memorial Lecturer sponsored by the the U.S. Agricultural Research Service.
Society for Society for Environmental Toxicology and Chemistry (SETAC) Founders Award, November 2006.
Society for Environmental Toxicology and Chemistry (SETAC) Europe Award for Environmental Education, May 2006.
American Chemical Society International Award for Research in Agrochemicals. Agrochemicals Division of the American Chemical Society, April, 2002.
HERA Ecological Risk Assessment Paper of the Year 2001. Presented by the Editorial Board of HERA for the paper Solomon KR, Giesy JP, Kendall RJ, Best LB, Coats JR, Dixon KR, Hooper MJ, Kenaga EE, McMurry ST. 2001. Chlorpyrifos: ecotoxicological risk assessment for birds and mammals in corn agroecosystems. Human and Ecological Risk Assessment 7:497-632.
Fellow of the Academy of Toxicological Sciences (1999-present)
Watkins Visiting Professor, Wichita State University, Wichita, Kansas. February 19-22, 1996
Society for Environmental Toxicology and Chemistry (SETAC) North America Award for Environmental Education. November, 1993

8 POST-DOCTORAL FELLOWS AND RESEARCH ASSOCIATES

J. Bestari (1995-01 to present)
H. Sanderson (2003-09 to 2005-09)
S. Richards (2001-09 to 2003-09)
P. Sibley
R. Robinson
R. Gensemer

M. Sharom

9 GRADUATE STUDENT SUPERVISION

9.1 AS SUPERVISOR

	NAME	YEAR	SUBJECT
M.Sc.			
34	S. Baccus	Sep 2006, WD Sep 2014	Analysis and risk assessment of endocrine active substances in the environment (Co-advised with Mark Hewitt).
33	S. Sturman	Sep 2005, WD Oct 2014	PFCs in the Arctic food web (Co-advised with D. Muir).
32	R. Van Engen	Jan 2009 – Apr 2012	Assessment of the physical and biological effects of mine-related total suspended solids in arctic lakes (Co-advised with Paul Sibley).
31	L. Baxter	Sep 2009 – Apr 2011	Effects of atrazine and phosphorus on growth of aquatic 3 autotrophs and pond snails in outdoor microcosms
30	S. Howard	Withdrew	Effects of forest spraying with glyphosate on frogs
29	J. Rickard	Sep 2005-Dec 2008	Colonization, fecundity and probing behaviour of soybean aphid on susceptible and resistant soybean varieties (Co-advised with R Hallett)
28	M. McDowell	Withdrew	Treatment of pharmaceuticals (Co-advised with N Bunce, Chemistry, U of Guelph).
27	A. Belknap	Sep 2002 - Mar 2005	Identification of hormonally-active compounds in bleached kraft chemical recovery condensates (Co-advised with M Hewitt).
26	M. Smithwick	Jan 2002-Apr 2005	Geographic, biological, temporal trends, and accumulation parameters of polyfluorinated compounds (Co-advised with D Muir).
25	C. Wilson	May 2002-Dec 2004	Pharmaceuticals in the environment: assessment of effects on freshwater ecosystems using microcosms
24	D. Johnson	May 2001-April 2004	Risk assessment of selective serotonin reuptake inhibitors: Comparing methods in tiered environmental risk assessment.
23	A. Gamble	Withdrew	Effects of industrial effluents on fish reproduction.
22	S. Quade	Sep 2001-Sep 2003	Determination of tetrabromobisphenol-A in sediment and sludge (Co-advised with M Alaee).
21	J. Princz	Sep 2001-Mar 2003	Ecotoxicological and chemical evaluation of soils contaminated with motor gasoline, and benzene, toluene, ethylbenzene, and xylenes (BTEX).
20	T. Boudreau	Sep 1999-Dec 2002	Toxicological evaluation of perfluorniated organic acids to selected freshwater primary and secondary trophic levels under laboratory and semi-natural field conditions.
19	J. Luross	Aug 2001	Spatial and temporal distributions of polybrominated diphenyl ethers in lake trout (*Salvinius namaycush*) from the Great Lakes.
18	M. Chappel	Aug 2001	Evaluation of the toxicity of pesticides mixtures to fathead minnows (*Pimephales promelas*) using probabilistic ecological risk assessment and toxic equivalency methods
17	K. Munro	Aug 2001	Population-level and suborganismal responses in fish due to chronic creosote exposure in aquatic microcosms
16	P. Takacs	May 1999	Evaluation of probabilistic ecological risk assessment methodology using aquatic microcosms and azinphos-methyl
15	S. Knutson	Apr 1998	Effects of phytosterols and estradiol on maturation and reproduction in fathead minnows
14	H. Sonnenberg	Aug 1998	Extractable organochlorine (EOCl) in white sucker (*Catostomus commersoni*) exposed to bleached kraft-mill effluents
13	J. Lewis	May 1997	Bioindicators of polycyclic aromatic hydrocarbon PAH exposure in rainbow trout (*Onchorynchus mykiss*) and fathead minnows (*Pimiphales promelas*)

	NAME	YEAR	SUBJECT
12	J. McCann	Feb 1997	The use of growth and membrane integrity assays as bioindicators of creosote effects in *Myriophyllum spicatum* L. growth
11	G. O'Brien	Dec 1996	Penetration and extractability of pesticides into and from plastic used for container manufacture and recycling
10	L. Novak	Sep 1994	Behavioural responses of rainbow trout (*Oncorphynchus mykiss*) to selected pulp and paper mill effluent constituents
9	A. Vandersluis	May 1993	Dislodgeability and leachability of pesticides from products made from recycled plastic pesticide containers
8	G. Fan	Jul 1991	The effect of dissolved organic matter on fenvalerate toxicity to *Daphnia magna*
7	S. Harris	May 1991	Exposure of homeowners, professional applicators and bystanders to 2,4-dichlorophenoxyacetic acid (2,4-D)
6	R. Buchanan	May 1991	Persistence, leaching and availability of chromated-copper-arsenate polyethylene glycol, copper naphthenate and pentachlorophenol wood preservatives from pressure treated utility poles
5	P. Martin	Nov 1990	Effects of carbofuran on mallard ducklings (*Anas platyrynchos*)
4	J. Warner	May 1990	Persistence, leaching, and bioavailability of CCA and pentachlorophenol wood preservatives
3	T. Valdes	Dec 1983	Toxicity and synergism of permethrin to *Trichogramma minutum* Riley and *T. fuentes* Torre (Hymenoptera: Trichogrammatidae)
2	D. Thompson	Apr 1983	Studies on the persistence of two phenoxy herbicides in agricultural, forestry and turfgrass environments
1	S. MacDonald	Jan 1983	The management and mechanisms of resistance to permethrin in a field strain of the house fly, *Musca domestica* L

	NAME	YEAR	SUBJECT
Ph.D.			
29	D. Moore	Sep 2009 in progress	Toxicity of metals to cold-water fish (Co-advised with Paul Sibley)
28	J. Rodrigues	Sep 2009-Aug 2015	Fate and Effects of an Alkylamine Ethoxylate Surfactant Mixture in Aquatic Sys-tems: Pulsed Exposures, Recovery Capacity and the Importance of Sediment. (Co-advised with Mark Hanson, Paul Sibley)
27	A. Morris	Sep 2007-Aug 2015	Current Use Organohalogen Contaminant Distributions in Seawater and Trophodynamics in Marine and Terrestrial Food Chains of the Canadian Arctic. (Co-advised with D. Muir and Richard Manderville)
26	S. Leelachao	May 2009 – Apr 2015	Expression of Anti-Atrazine scFv and Atrazine Chlorohydrolase TrzN in planta for Potential Phytoremediation of Atrazine Contamination (Co-advised with Chris Hall)
25	R. Prosser	May 2011-Oct 2014	Investigation of the Risk that Biosolids-Derived Triclosan and Triclocarban Pose to Plants and Human Health (Advisor Paul Sibley).
24	B. de Jourdan	Sep 2007-Aug 2012	Environmental Fate and Toxicity of Three Brominated Flame Retardants in Aquatic Mesocosms (Co-advised with D. Muir and Mark Hanson)
23	J. Van Geest	May 2007-Sep 2010	Bioaccumulation of sediment-associated contaminants in freshwater organisms: Development and standardization of a laboratory method
22	N. Gantner	Sep 2004-Nov 2008	Effects of climate change on mercury concentrations in arctic char (*Salvelinus alpinus*) in the high arctic (Co-advised with D Muir).
21	R. Frank	Sep 2003-Apr 2008	Fractionation and toxicity of naphthenic acids from oil-sand waste
20	A. Buckman	Sep 2001-Apr 2006	Toxicokinetics and biological effects of PCBs and their hydroxylated metabolites in rainbow trout (Co-advised with Aaron Fisk)
19	M. Houde	Sep 2002-	Emerging organohalogen contaminants in bottlenose dolphins *(Tursiops*

	NAME	YEAR	SUBJECT
		Apr 2006	*truncatus*) (Co-advised with D Muir)
18	R. Brain	May 2002-Apr 2006	Evaluation of the phytotoxic effects of pharmaceuticals in aquatic higher plants
17	L. Lissemore	Sep 2001-Aug 2005	Pharmaceuticals in agricultural surface waters: detection, distribution, exposure and risk
16	G. Stephenson	Sep 1994-Apr 2003	Terrestrial test methods for plants and soil invertebrates.
15	P. Hoekstra	Sep 1998-Mar 2003	Bioaccumulation and biotransformation of persistent organochlorine contaminants in the arctic marine ecosystem (Co-advised with D Muir)
14	M. Hanson	Sep 1997-Sep 2002	*Myriophyllum spp.* in ecological risk assessment: A case study with haloacetic acids.
13	J. Martin	May 1998-May 2002	Environmental (per-)halogenated acids; detection, distribution, sources, and bioaccumulation (Co-advised with D Muir).
12	A. Farwell	Jan 2000	Stable isotope study of riverine benthic food webs influenced by anthropogenic developments.
11	C. Marwood	Jul 1999	Chlorophyll fluorescence as a mechanistic bioindicator of photosynthetic inhibition in aquatic plants.
10	M. Hewitt	Jul 1997	An assessment of the contamination and effects of lampricide formulations of 3-triflurormethyl-4-nitrophenol (TFM).
9	D. Houghton	Apr 1997	Development and validation of fluorescent tracer method to estimate dermal exposure to pesticides used indoors.
8	R. Robinson	Aug 1994	Endocrine effects of pulp mill effluents on non-target aquatic organisms
7	B. Archibald	May 1993	Video imaging as a technique for estimating pesticide exposure in greenhouse chrysanthemum production.
6	D. Thompson	May 1992	The effects of hexazinone and metsulfuron methyl in aquatic ecosystems
5	C. Fortin	Apr 1991	Acute and chronic toxicity of technical and slow-release formulations of methoprene in selected zooplankton.
4	K. Liber	Apr 1990	Persistence and biological effects of a commercial tetrachlorophenol formulation in aquatic ecosystems: Laboratory and limnocorral studies
3	A. Mahdavi	May 1990	Insecticide resistance mechanisms in Ontario strains of the Colorado Potato Beetle.
2	S. Gaul	Apr 1988	Interaction of tridiphane and metribuzin in soybean and tomato.
1	M. Lungle	Feb 1988	Studies of the dissipation and effects of chlorpyrifos in microcosms.

9.2 AS CO-SUPERVISOR

	NAME	YEAR	SUBJECT AND LOCATION
10	Paddy McManus	Sep 2010-Dec 2013	Characterization of efficacy and release patterns in a slow-release formulation of novaluron (Supervisor J C Hall).
9	A. Wojtyniak, M.Sc.	Sep 2004-Withdrew	Effects of veterinary pharmaceuticals on soil microbiological processes (Supervisor Paul Sibley).
8	D. Hillis, Ph.D.	Sep 2004-Dec 2008	Arbuscular mycorrhizal fungi in ecological risk assessment: a case study with selected pharmaceuticals (Supervisor Paul Sibley).
7	E. Dussault, Ph.D.	May 2003-Apr 2008	Effects of pharmaceuticals on benthos (Supervisor Paul Sibley).
6	B. Fraser, M.Sc.	Sep 2003-Dec 2006	Degradation of carbamazepine in STPs. With Nigel Bunce, Chemistry, U of Guelph.
5	G. Everson, M.Sc.	Jan 2004-Jan 2006	Reproduction of *Xenopus laevis* under field conditions (Supervisor, L Du Preez, Potchefstroom University, SA)
4	M. MacDonald, M.Sc.	Jan 2002-Sep 2005	Fluorotelomer acid toxicity to aquatic organisms (Supervisor Paul Sibley).

3	K. Rattan, M.Sc.	May 2002-Jan 2005	Establishing a reference condition to assess the effects of forest harvesting on phytoplankton community structure in boreal lakes (Supervisor Paul Sibley).
2	A. Warne, M.Sc.	Jan 2002-Dec 2004	The effects of antibiotics on the structure and function of freshwater sediment bacterial communities. (Supervisor Paul Sibley).
1	A. Jooste, M.Sc.	Jan 2001-July 2003	Effects of atrazine on *Xenopus laevis* under field conditions. (Supervisor, L Du Preez, Potchefstroom University, SA)

9.3 AS EXTERNAL EXAMINER (Ph.D.)

NAME	YEAR	UNIVERSITY
Karen Fildes	2008	University of Wollongong, Australia
Neil Tripodi	2005	The University of Queensland, Australia
Kerri-Ann Bartley-Hynes	2004	University of the West Indies, Kingston, Jamaica
Tsui Tsk Ki Martin	2002	Chinese University of Hong Kong
Yousef El-alawi	2000	University of Waterloo
U. Klee	1998	University of Waterloo
V. Kimani	1995	University of Nairobi
P.Y. Caux	1988	University of Ottawa, Ontario
M. Rafi Ahamed	1987	Sri Krishnadevaraya University, India
C. Henry	1985	University of the West Indies, Jamaica.
B. Sutherland	1979	Witwaterstrand, S. Africa

9.4 AS COMMITTEE MEMBER (current only)

NAME OF STUDENT	DEGREE	SUPERVISOR	DEPARTMENT
Renésahba Shahmohamadloo	M.Sc.	Paul Sibley	School of Environmental Sciences
Kathleen Stevac	M.Sc.	Paul Sibley	School of Environmental Sciences

10 TEACHING

10.1 GRADUATE COURSES TAUGHT

TOX6530, Ecotoxicological Risk Characterization 1996 - 2011
TOX6000, Advanced Principles of Toxicology 1997 - present
ENVB6720, Advanced Seminar 2006 - 2007
ENVB6700, Seminar 1979 - 1982
ENVB6710, Seminar 1983 - 1984
ENVB6510, Scientific Methods in Biology II (Residue analysis module) 1979 - 1983

10.2 UNDERGRADUATE COURSES TAUGHT

TOX2000, Principles of Toxicology 1982 - 2009
TOX4200, Topics in Toxicology, 1984 - 2010
TOX4550, Ecotoxicological Risk Characterization (Same as TOX6530 above)
ENVB3030, Pesticides in the Environment 1978 - 1994
ENVB4240, Biological Activity of Pesticides 1979 - 1992

10.3 COURSEWORK MATERIAL

Principles of Toxicology, 1st to 21st edition, 1988-2009. Courseware for Principles of Toxicology, TOX-2000. Editor and Chapter author (200 pp).

Chemical and Biological Pesticides in the Environment, 1994-2006. Courseware for Pesticides in the Environment, ENVG-3030. Author with G.R. Stephenson, R. Frank, T. Hsaing (350 pp). Now published as a book in English, Portuguese, and Spanish

Ecotoxicological Risk Characterization. 1996-2011. Courseware for Ecotoxicological Risk Characterization, ENVB-6530/4550 & TOX-6530/4550 (246 pp).

11 RESEARCH FUNDING THROUGH UNIVERSITY OF GUELPH (last 3 years only)

YEAR	TITLE AND RECIPIENTS	AMOUNT	TYPE
2014-2018	DFR for various pesticides on greenhouse vegetables.	$1,409,040	Contract, Agriculture and Agrifood Canada
2014	The response of the salamander *Ambystoma maculatum* and its egg-capsule symbiont (the alga *Oophila sp.*) to the photosystem II inhibitor atrazine under laboratory conditions. Keith Solomon*, Mark Hanson	$38,514.77	Contract from Syngenta Crop Protection, USA
2013	Response of the green alga *Oophila sp.*, a salamander endosymbiont, to a PSII-inhibitor under laboratory conditions Keith Solomon*, Mark Hanson	$14,976	Contract from Syngenta Crop Protection, USA
2011-2012	Developing methods for more realistic assessments of indirect effects of herbicides on threatened and endangered species. Paul Sibley* and Mark Hanson, Keith Solomon	$24,000	Contract from CLA.
2011-2014	CREAT-HERA funding for graduate students. Steve Siciliano*, K Solomon, et al.	$90,860	NSERC subaward via U of SK.
2011	Influence of light intensity, nutrient content, and temperature on the toxicity of atrazine to the green algae *Pseudokirchneriella subcapitata* (formerly *Selenastrum capricornutum*). Mark Hanson*, Keith Solomon.	$60,000	Contract from Syngenta Crop Protection, USA
2010-2011	Testing toxicity of mine effluents in Northern fish. K Solomon*	$35,000	Contract from BHP Billiton Diamonds and Diavik Diamond Mines.
1978-2010	Total funding for research projects at the University of Guelph	$8,405,142	Various sources
	Total funding for network projects	$21,115,000	Federal and provincial governments
* indicates principal investigator.			

12 SUPERVISION OF RESEARCH PERSONNEL (person years at University of Guelph)

Research Associates	24
Technicians	32
Summer students	30

13 SCIENTIFIC AND ADVISORY COMMITTEES

13.1 STANDING COMMITTEES

Member and Secretary of the United Nations Environment Programme (UNEP) Panel on Environmental Effects of Ozone Depletion 2001-present.

Member and Chair of the OAS CICAD Panel on Environmental and Human Health Risk Assessment of the Use of Glyphosate for the Eradication of Illicit Crops. 2004-2008.

Member of the EUFRAM team for pesticide risk assessment 2003-2007.

Member of the Science Advisory Panel to PMRA on risks of the use of 2,4-D for landscape uses 2003-2004.

Member of ILSI Technical Committee on Aggregate Exposure September 2000-2004.

Member of the US EPA Ecological Committee on FIFRA Risk Assessment Methods (ECOFRAM) 1998-2000.

Member of the Science Panel, Centre for Environmental Endocrine Effects, Washington DC 1994-1996.

Member and Chair of the Board of Directors of the Pest Management Alternatives Office, Agriculture Canada.

Member and Vice Chair of the Ontario Pesticides Advisory Committee (OPAC) 1982-1994.

Member of the OPAC Research Sub-committee 1982-1994.

Chairman of the OPAC Classification Review, Classification and Toxicology Sub-committees 1982-1994.

Member of the Associate Committee on Toxicology, NRCC 1984-1986.

Member of the Minneapolis Mosquito Control District Technical Advisory Committee and Scientific Peer Review Panel 1991-1995.

Member of the Ontario Waste Management Classification Sub-committee 1982-1983.Member of the Canadian Centre of Toxicology, Environmental Toxicology Task Force 1982-1986.

Chairman of the NRCC, ACSCEQ Expert Panel on the Environmental Impact of the Pyrethroid Insecticides.

Member of the National Research Council of Canada (NRCC), Associate Committee on Scientific Criteria for Environmental Quality (ACSCEQ), Expert Panel on Pesticide Pollinator Interactions 1986-1986.

Member of the Review Board for D5 Siloxane for Environment Canada, 2010 – 2011.

Member of the CropLife America Sceicne Forum and Panel on Weight of Evidence, May 2012

Member of the International Institute for Life Sciences (ILSI) HESI committee, July 1998-present. Current subcommittees are: Cumulative Risks and Problem Formulation for Cumulative Risks

13.2 WORKSHOP GROUPS AND AD HOC COMMITTEES

Member of the U.S. Environmental Protection Agency Advisory Panel for the Development of a Method to Assess the Impact of Pesticides in Aquatic Ecosystems 1982.

Member of the U.S. Environmental Protection Agency Research Review Panel for the U.S. EPA Regional Laboratory, Gulf Breeze, Florida 1986.

Member of the U.S. National Academy of Science/NRC Board of Environmental Studies and Toxicology Working Group on "Research Needs in Anticipation of Future Environmental Problems 1988.

Consultant to the Prairie Provinces Container Disposal Committee, January, 1990.

Consultant to the B.C. Antisapstain Committee, March, 1990.

Member of the U.S. EPA's Aquatic Risk Assessment and Mitigation Dialogue Group for Pesticides.1992-1994

Chair of the Scientific Advisory Board to review and assess the ecological risks associated with the use of chlorine dioxide for the bleaching of pulp. 1992-1993

Member of the Steering Committee for the SETAC workshop on Environmental Risk Assessment for Organochlorine Chemicals, July 24-29, 1994.

Member of the SETAC workshop on Ecological Risk Assessment Decision Support Systems, Pellston, MI, August 23-28

Member and group leader of the SETAC workshop on Sediment Risk Assessment, Asilomar, CA, April 23-28, 1995

Member of the Atrazine Risk Assessment Panel, TIWET, 1994-1995.

Member of the U.S. EPA workshop on Environmental Risk Assessment of Endocrine Disruptors, Duluth, MN, June 12-13, 1995

Member of the U.S. EPA workshop on Toxicity Thresholds for Superfund Sites, Chicago, IL June 19-20, 1995

Member and group chair of the SETAC Pellston workshop on Multiple Stressors, Pellston, MI, September 1997.

Participant in SETAC/Europe OECD Higher Tier Aquatic Risk Assessment for Pesticides (HARAP) workshop on higher tier methods of toxicity testing in Bordeaux, France, April 1998.

Participant in the SETAC Pellston Workshop of Water Quality Criteria in Fairmont Montana, July 1998.

Participant in the Community Level Aquatic System Studies - Interpretation Criteria (CLASSIC) workshop in Schmallenberg, Germany in May 30-June 2, 1999.

Invited plenary speaker and participant at Workshop on Risk Assessment and Risk Mitigation in the Context of the Authorization for Plant Protection Products (WORMM) workshop in Braunschweig, Germany, Sept 26-30, 1999

Participant and member of organizing committee for ILSI Aggregate Exposure Workshop, Omni Inner Harbour Hotel, Baltimore MD, October 19-21, 1999.

Participant in workshop on "Innovative Exposure Assessment of Pesticide Uses for Appropriate Risk Assessment" The Hague, Netherlands, September 2000

Participant in the WERF PBT Workshop, Washington DC, March 17, 2001

Participant in CCIW Sediment Toxicity Workshop, Cambridge ON, November 23-26, 2001

Participant in Probabilistic Risk Assessment Workshop, June 3-9 2001, Netherlands.

Participant in CNTC Planning Workshop, June 28-29, 2001.

Co-Chair at Intertopic Workshop IW7 "Environmental Risk Assessment: Integrating the Exposure and Effects Information" IUPAC meeting in Basel Switzerland, August 4-9 2002

Participant in Workshop on Assessment Endpoints for PMRA at Far Hills Inn in Quebec. October 4-6, 2002

Participant in EPIF Workshop in Le Croisic, France. October 21, 2003

Participant in DFO Site Specific Risk Assessment Workshop, Ottawa, ON. October 27-28, 2003

Participant in Probabilistic Assessment Methods for Risk Analysis in the Framework of PPP Authorization. Umweltbundesamt Berlin. 25-28 November 2003

Participant in Toward a Monitoring Network: A Technical Workshop for Pharmaceuticals & Personal Care Products in the Environment March 28-30, 2004. Queen's Landing. Niagara-on-the-Lake, Ontario

Participant in SOLEC Workshop, October 8, 2004. Toronto, ON.

Participant in Environment Agency Workshop on Chronic Aquatic Ecotoxicity Testing of Human Pharmaceuticals May 19, 2005, London, UK.

Participant in SOLEC Workshop, November 11, 2005. Windsor, ON.

Participant in Veterinary Pharmaceuticals: A SETAC Pellston Workshop. February 12-15, 2006, Pensacola FL.

Participant in POPs Workshop: A SETAC Pellston Workshop. January 20-26, 2008, Pensacola FL.

Member of the siloxane D5 Board of Review established under the Canada Environmetnal Protection Act Aug 23 2010.

Participant in the LATARAP workshop for Aquatic Risk Assessment in Buenos Aires, October 2012.

Session Chair; Harmonization of Assessment Practices for Chemicals with Persistent, Bioaccumulative, Toxic and Long-range Transport Characteristics. SETAC Meeting, Long Beach, CA, November 2012.

14 EDITORIAL BOARDS

Human and Ecological Risk Assessment (HERA) Ed Board 2001 - present

Chemosphere 2000 – 2012

Environmental Toxicology and Chemistry (2004-2007); 2010 to present as Section Editor.

Pesticide Management Science (Associate editor 2009-present; Exec. Editor 2013-present).

15 PERSONNEL REVIEWS (including P&T) (last 4 years only)

	2011	2012	2013	2014
Total	1	2	1	2

16 COMMUNITY ACTIVITIES

Advocate for bringing science to the public. Advisor to a number of City Councils and Provincial Governments on matters related to pesticides and other environmental issues.

17 PUBLICATIONS

17.1 BOOKS AND CHAPTERS IN BOOKS

49 Solomon KR, Dalhoff K, Volz D, Van Der Kraak G. 2013. Effects of Herbicides on Fish. In: Tierney KB, Farrell AP, Brauner CJ, editors. Organic Chemical Toxicology of Fishes. Vol. 33. Amsterdam, NL: Academic Press. p 369-409.

48 Stephenson GR, Solomon KR, Carazo E. 2013. Plaguicidas y Ambiente. San Juan, Costa Rica, University of Costa Rica Press. 580 pp.

47 Solomon KR, Hanson ML. 2012. Reducing Ecotoxicity. In: Boethling R, Voutchkova A, editors. Green Processes: Designing Safer Chemicals. Vol. 9. Weinheim, Germany: Wiley-VCH Verlag & Co. p 407-452.

46 Solomon KR, Stephenson GR, Correa CL Zambrone FAD. 2010. Praguicidas e o Meio Ambiente. Sao Paulo, Brazil, ILIS Press 473 pp.

45 Solomon KR. 2010. Ecotoxicological Risk Assessment of Pesticides in the Environment. In: Krieger RI, Doull J, van Hemmen JJ, Hodgson E, Maibach HI, Ritter L, Ross J, Slikker W, editors. Handbook of Pesticide Toxicology. Vol. 2, 3 ed. Burlington, MA, USA: Elsevier. p 1191-1217.

44 Solomon KR, Hillis DG, Lissemore L, Sibley PK. 2009. Risks of Agricultural Pharmaceuticals in Surface Waters and Soil. In: Henderson K, Coats JR, eds. *Veterinary Pharmaceuticals in the Environment, ACS Symposium Series 1018*. Washington, DC, USA: American Chemical Society. p 191-204.

43 Solomon KR. 2008. Use of (eco) toxicity data as screening criteria for the identification and classification of PBT / POP compounds. In: Klecka G, Muir DCG, editors. Science-Based Gudance and Framework for the Evauation and Identification of PBTs and POPs: Summary of a SETAC Pellston Workshop. Pensacola, LF, USA: SETAC. p 17-20.

42 Solomon KR, Cooper D. 2008. Probabilistic Assessment of Laboratory-derived Acute Toxicity Data for Triazine Herbicides to Aquatic Organisms. In: LeBaron HM, McFarland JE, Burnside OC, editors, The Triazine Herbicides. 50 Years Revolutionizing Agriculture. Amsterdam, NL, Elsevier, p 425-438.

41 Brock TCM, Maltby L, Hickey C, Solomon KR. 2008. Spatial Extrapolation in Ecological Effect Assessment of Chemicals. In: Solomon KR, Brock TCM, de Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H,

Sibley PK, van den Brink PJ, editors. Extrapolation Practice for Ecotoxicological Effect Characterization of Chemicals. Pensacola, FL, USA: CRC/Taylor and Francis/SETAC Press. p 233-256.

40 Brock TCM, Solomon KR, Van Wijngaarden RPA, Maltby L. 2008. Temporal Extrapolation in Ecological Effect Assessment of Chemicals. In: Solomon KR, Brock TCM, de Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, Van den Brink PJ, editors. Extrapolation Practice for Ecotoxicological Effect Characterization of Chemicals. Pensacola, FL, USA: CRC/Taylor and Francis/SETAC Press. p 187-221.

39 Posthuma L, De Zwart D, Solomon KR, Brock TCM. 2008. Guidance On the Application of Extrapolation Methods in Ecological Exposure and Effects Characterization of Chemicals. In: Solomon KR, Brock TCM, De Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, van den Brink PJ, editors. Extrapolation Practice for Ecotoxicological Effect Characterization of Chemicals. Pensacola, FL, USA: CRC/Taylor and Francis/SETAC Press. p 281-322.

38 Solomon KR, Brock TCM, de Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, van den Brink PJ. 2008. Preface. In: Solomon KR, Brock TCM, de Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, van den Brink PJ, editors. Extrapolation Practice for Ecotoxicological Effect Characterization of Chemicals. Pensacola, FL, USA: CRC/Taylor and Francis/SETAC Press. p xv-xviii.

37 Solomon KR, Brock TCM, de Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, van den Brink PJ. 2008. Extrapolation for Criteria Setting and Risk Assessment. In: Solomon KR, Brock TCM, de Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, van den Brink PJ, editors. Extrapolation Practice for Ecotoxicological Effect Characterization of Chemicals. Pensacola, FL, USA: CRC/Taylor and Francis/SETAC Press. p 1-32.

36 Solomon KR, Brock TCM, de Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, van den Brink PJ. 2008. Conclusions. In: Solomon KR, Brock TCM, de Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, van den Brink PJ, editors. Extrapolation Practice for Ecotoxicological Effect Characterization of Chemicals. Pensacola, FL, USA: CRC/Taylor and Francis/SETAC Press. p 257-267.

35 Solomon KR, Brock TCM, De Zwart D, Dyer SD, Posthuma L, Richards SM, Sanderson H, Sibley PK, van den Brink PJ, editors. 2008. Extrapolation Practice for Ecotoxicological Effect Characterization of Chemicals. Pensacola, FL, USA: CRC/Taylor and Francis/SETAC Press. 368 p

34 Stephenson GR, Solomon KR. 2007. Pesticides and the Environment. Guelph, Ontario, Canada: Canadian Network of Toxicology Centres Press. 427 p.

33 Kennedy IR, Solomon KR, Gee S, Crossan AN, Wang S, Sanchez-Bayo F. 2007. Achieving Rational Use of Agrochemicals: Environmental Chemistry in Action. In: Kennedy IR, Solomon KR, Gee S, Crossan AN, Wang S, Sanchez-Bayo F, editors. Rational Environmental Management of Agrochemicals: Risk Assessment, Monitoring, and Remedial Action. ACS Symposium Series No 966 Washington, DC, USA: American Chemical Society, pp 1-7.

32 Solomon KR, Anadón A, Brain RA, Cerdeira AL, Crossan AN, Marshall AJ, Sanin LH, Smith L. 2007. Comparative Hazard Assessment of the Substances used for Production and Control of Coca and Poppy in Colombia. In: Kennedy IR, Solomon KR, Gee S, Crossan AN, Wang S, Sanchez-Bayo F, editors. Rational Environmental Management of Agrochemicals: Risk Assessment, Monitoring, and Remedial Action ACS Symposium Series No 966 Washington, DC, USA: American Chemical Society, pp 87-99.

31 Giddings JM, Anderson TA, Hall LW, Jr, Kendall RJ, Richards RP, Solomon KR, Williams WM. 2005. A Probabilistic Aquatic Ecological Risk Assessment of Atrazine in North American Surface Waters. Pensacola, FL, USA: SETAC Press. 432 p

30 Solomon KR, Carr JA, du Preez LH, Giesy JP, Gross TS, Kendall RJ, Smith EE, Van Der Kraak GJ. 2005. Ecotoxicological risk assessment of atrazine in amphibians. In: Clark JM, Ohkawa H, editors. Environmental Fate and Safety Management of Agrochemical ACS Symposium Series No 899. Washington, DC, USA: American Chemical Society. p 124-137.

29 Bright DA, Hodson PV, Lehtinen K-J, McKague BA, Rodgers JH Jr, Solomon KR. 2003. Evaluation of Ecological Risks Associated with the Use of Chlorine Dioxide for the Bleaching of Pulp: Scientific Progress Since 1993. In: Aquatic Impacts of Pulp and Paper Effluents. In: Stuthridge T, van den Heuvel M, Marvin N, Slade A, Gifford J (Eds). Environmental Impacts of Pulp and Paper Waste Streams. SETAC Press: Pensacola FL. 552 pp p18-26.

28 Brooks BW, Richards SM, Weston J, Turner PK, K. Stanley JK, La Point TW, Brain R, Glidewell EA, Rene A, Massengale D, Smith W, Blank, CL, Solomon, KR, Slattery M, Foran CM. 2004. Aquatic Ecotoxicology of Fluoxetine: A Review of Recent Research. In: Dietrich D, Webb S, Petry T, Eds, Hot Spot Pollutants: Pharmaceuticals in the Environment. Elsevier. Same paper as Brooks et al. 2003.

27 Moore DRJ, Delos CG, Giddings JM, Hansen DL, Landis WG, Mancini ER, McGee BL, Solomon KR, Toll JE, Wuerthele W, Adams WJ. 2003. Risk Characterization. In: Reiley MC, Stubblefield WA, Adams WJ, Di Toro DM, Hodson PV, Erickson RJ, Keating FJ, Jr, eds. Reevaluation of the State of the Science for Water-quality Criteria Development. Pensacola, FL, USA: SETAC Press. p 119-142

26 Solomon KR. 2003. Distributional risk assessment for agrochemicals: Triazine herbicides. In: Coats JR, Yamamoto H, eds. Environmental Fate and Effects of Pesticides. ACS Symposium Series 853. Washington, DC, USA, American Chemical Society, p 227-240

25 Solomon KR, Takacs P. 2002. Probabilistic risk assessment using species sensitivity distributions. In: Postuma L, Traas T, Suter GW, eds. Species Sensitivity Distributions in Risk Assessment. Boca Raton, FL, USA, CRC Press, p 285- 313.

24 Solomon KR. 2001. Ecotoxicology. In: Krieger RI, ed. Handbook of Pesticide Toxicology. 2nd ed. New York, NY: Academic Press. Volume 1, p 353-374.

23 Marwood CA, Dobson E, Smith REH, Solomon KR, Greenberg BM. 2001. In: Greenberg BM, Hull RN, Roberts, Jr. MH, Gensemer, RW (Eds.) Chlorophyll fluorescence as a bioindicator of photosynthesis inhibition from solar ultraviolet radiation in plants and algae. Environmental Toxicology and Risk Assessment: Science, Policy and Standardization - Implications for Environmental Decisions: Tenth Volume, ASTM STP 1403, West Conshohocken, PA, USA, American Society for Testing and Materials, p 27-39.

22 Gentile JH, Solomon KR, Butcher JB, Harrass M, Landis WG, Power M, Rattner BA, Warren-Hicks WJ, Wenger R. 1999. Linking stressors and ecological responses. In Foran JA, Ferenc SA (Eds.) Multiple stressors in ecological risk and impact assessment. Pensacola, FL, USA, SETAC Press, p 27-50.

21 Sherry J, Gamble A, Hodson P, Solomon K, Hock B, Marx A, Hansen P. 1999. Vitellogenin induction in fish as an indicator of exposure to environmental estrogen. In: Rao SS (Ed) Impact Assessment of Hazardous Aquatic Contaminants: Concepts and Approaches. Boca Raton, FL, USA, Lewis Publishers, p 123-160.

20 Solomon KR. 1999. Integrating environmental fate and effects information: the keys to ecotoxicological risk assessment for pesticides. In: Brooks, GT Roberts, TR (Eds.) Pesticide Chemistry and Bioscience: The Food-Environment Challenge. Special Publication No. 233. London, UK, Royal Society of Chemistry, p 313-326.

19 Stephenson, G.L., A. Kaushik, N.K. Kaushik, K.R. Solomon, T. Steele, R.P. Scroggins. 1998. Development of an avoidance response test to assess the toxicity of contaminated soils to earthworms, pp. 67-82. *In* Advances in Earthworm Ecotoxicology, S. Sheppard, J. Bembridge, M. Holmstrup, and L. Posthuma, (eds.). SETAC Press, Pensacola, FL

18 Parkhurst BR, Christensen S, Goldstein R, Neely B, Solomon KR. 1998. Model selection considerations in fate-and-effects analysis. In: Reinert KH, Bartell SM, Biddinger GR, eds. Ecological Risk Assessment Decision-Support System: A Conceptual Design. Pensacola, FL, USA, SETAC Press, p 15-19.

17 Houghton D, Archibald BA, Solomon KR. 1998. Review of video imaging techniques for estimating dermal exposure to pesticides. In: Ecobichon DJ (Ed) Occupational Hazards of Pesticide Exposure: Sampling, Monitoring, Measuring. Philadelphia, PA, USA, Taylor and Francis, p 135-186.

16 Solomon KR Chappel MJ. 1998. Triazine Herbicides: Ecological Risk Assessment in Surface Waters. In: Ballantine LG McFarland JE Hackett DS. (Eds.) Triazine Risk Assessment. ACS Symposium Series 683. Washington, DC, USA, American Chemical Society, p 357-368.

15 Solomon KR. 1998. Research Needs. In: R. Kendall, R. Dickerson, J. Giesy and W. Suk. (Eds.) Principles and Processes for Evaluating Endocrine Disruption in Wildlife. Pensacola, FL, USA, SETAC Press, p 449-455.

14 Tillitt DE Solomon KR Mihaich EM Cobb G Touart L Kubiak TJ. 1998. Role of exposure assessment in characterizing risk of endocrine-disrupting substances in wildlife. In: R. Kendall, R. Dickerson, J. Giesy and W. Suk. (Eds.) Principles and Processes for Evaluating Endocrine Disruption in Wildlife. Pensacola, FL, USA, SETAC Press, p 39-68.

13 Solomon KR Ankley GT Baudo R Burton GA Ingersoll CG Lick W Luoma SN MacDonald DD Reynoldson TB Swartz RC Warren-Hicks W. 1997. Workgroup Summary Report on Methodological Uncertainty in Conducting Sediment Ecological Risk Assessments with Contaminated Sediments. In: Biddinger,G.R., T. Dillon, and C.G. Ingersoll, (Eds.) Ecological Risk Assessments of Contaminated Sediments. Pensacola, FL, USA, SETAC Press, p 271-296.

12 Ingersoll CG, Ankley GT, Baudo R, Burton GA, Lick W, Luoma SN, MacDonald DD, Reynoldson TB, Solomon KR, Swartz RC, and Warren-Hicks W. 1997. Workgroup Summary Report on an Uncertainty Evaluation of Measurement Endpoints Used in Sediment Ecological Risk Assessments In: Biddinger,G.R., T. Dillon, and C.G. Ingersoll, (Eds.) Ecological Risk Assessments of Contaminated Sediments. Pensacola, FL, USA, SETAC Press, p 297-352.

11 Stephenson GL, Solomon KR, Hale B, Greenberg BM, Scroggins RP. 1997. Development of a suitable test method for evaluating the toxicity of contaminated soils to a battery of plant species relevant to soil environments in Canada In: Dwyer FJ, Doane TR, Hinman ML. (Eds.) Environmental Toxicology and Risk Assessment: Modelling and Risk Assessment 6th Volume, ASTM STP 1317, Philadelphia, American Society for Testing and Materials, p. 474-489

10 Huang X-D, Babu TS, Marwood CA, Gensemer RW, Solomon KR, Greenberg BM. 1997. Inhibition of photosynthesis as an endpoint for the photoinduced toxicity of intact and photomodified PAHs. In: Dwyer, FJ, Doane TR, Hinman ML (Eds.). Environmental Toxicology and Risk Assessment: Modelling and Risk

Assessment (6th Volume) ASTM STP 1317. Philadelphia, PA, USA, American Society for Testing Materials, p 443-455

9 Gensemer RW, Ren L, Day KE, Solomon KR, Greenberg BM. 1996. Fluorescence induction as a biomarker of creosote phototoxicity to the aquatic macrophyte Lemna gibba. In: Bengtson D, Herschel DS, (Eds). Environmental Toxicology and Risk Assessment: Biomarkers and Risk Assessment 5th Vol., ASTM STP 1306, Philadelphia, PA, USA, American Society for Testing and Materials, p 163-176.

8 Hewitt LM, Scott IM, Van Der Kraak GJ, Munkittrick KR, Solomon KR, Servos MR. 1996. Development of TIE procedures for complex mixtures using physiological responses in fish, In: In: Bengtson D, Herschel DS, (Eds). Environmental Toxicology and Risk Assessment: Biomarkers and Risk Assessment 5th Vol., ASTM STP 1306, Philadelphia, PA, USA, American Society for Testing and Materials, p 37-53.

7 Baker JL, Barefoot AC, Beasley LE, Burns L, Caulkins P, Clark J, Feulner R, Gipsy J, Graney R, Griggs R Jacoby H, Laskowski D, Maciorowski A, Maihach E, Nelson H, Parish R, Siefert R, Solomon KR, van der SchalieW. 1994 Aquatic Dialogue Group: Pesticide Risk Assessment and Mitigation. Pensacola, FL, USA, SETAC Press, 220 p.

6 Liber K, Solomon KR, Kaushik NK, Carey JH. 1994. Impact of 2,3,4,6-tetrachlorophenol (DIATOX) on plankton communities in limnocorrals. In: Graney, R.L., J.H. Kennedy and J.H. Rogers (Eds.) Aquatic Mesocosm Studies in Ecological Risk Assessment. Boca Raton, FL, USA, Lewis Publishers, p 257-294.

5 Thompson DG, Holmes SB, Pitt DG, Solomon KR, Wainio-Keizer KL. 1994. Applying Concentration-Response Theory to Aquatic Enclosure Studies. In: Graney RL, Kennedy JH, Rodgers JH, Jr., editors. Aquatic Mesocosm Studies in Ecological Risk Assessment. Boca Ratton, FL, USA: Lewis Publishers. p 129-156.

4 Solomon KR, Harris SA, Stephenson GR. 1993. Applicator and bystander exposure to home garden and landscape pesticides. In: Pesticides in Urban Environments. Fate and Significance. Eds. Racke, KD and Leslie, AR. ACS Symposium Series 522, Washington, DC, USA, American Chemical Society, p 262-274.

3 Solomon KR. 1983 Acaricide resistance in ticks: Advances in Veterinary Science and Comparative Medicine 27:273-296.

2 Solomon KR. 1982. Endocrine mechanisms in ticks: Effects of insect hormones and their mimics on development and reproduction. In: Current Themes in Tropical Science Vol 1: Physiology of Ticks, Ed. Obenchain FD and Galun R, London, UK, Academic Press, p 399-438.

1 Solomon KR. 1981. Pesticide - Pollinator Interactions. Environmental Secretariat Publication No. 18471 Ottawa, ON, Canada, National Research Council of Canada.

17.2 PAPERS IN PRESS, ACCEPTED, SUBMITTED, OR IN PREPARATION FOR PUBLICATION

Accepted or in Press

Giesy JP, Solomon KR, Kacew S, Mackay D, Stobo G, Kennedy S. 2015. The case for establishing a board of review for resolving environmental issues: The science court in Canada. *Integrated Environmental Assessment and Management* Accepted: DOI: 10.1002/ieam.1729

Submitted

17.3 PUBLICATIONS IN REFEREED SCIENTIFIC JOURNAL

288 Baxter L, Brain RA, Hosmer AJ, Nema M, Müller KM, Solomon KR, Hanson ML. 2015. Effects of atrazine on egg masses of the yellow-spotted salamander (*Ambystoma maculatum*) and its endosymbiotic alga (*Oophila amblystomatis*). *Environmental Pollution* 206:324-331

287 Prosser RS, Brain RA, Malia Andrus J, Hosmer AJ, Solomon KR, Hanson ML. 2015. Assessing temporal and spatial variation in sensitivity of communities of periphyton sampled from agroecosystem to, and ability to recover from, atrazine exposure. *Ecotoxicology and Environmental Safety* 118:204-216

286 Currie Z, Prosser RS, Rodriguez-Gil JL, Mahon K, Poirier D, Solomon KR. 2015. Toxicity of Cúspide 480SL® spray mix formulation of glyphosate to aquatic organisms. *Environmental Toxicology and Chemistry* 34:1178-1184.

285 Lutter R, Abbott L, Becker R, Borgert C, Bradley A, Charnley G, Dudley S, Felsot A, Golden N, Gray G, Juberg D, Mitchell M, Rachman N, Rhomberg L, Solomon K, Sundlof S, Willett K. 2014. Improving weight of evidence approaches to chemical evaluations. *Risk Analysis* 35:186–192:

284 Ross JH, Hewitt A, Armitage J, Solomon K, Watkins DK, Ginevan ME. 2015. Exposure to TCDD from base perimeter application of Agent Orange in Vietnam. *Science of the Total Environment* 511:82-90.

283 Armitage JA, Ginevan ME, Hewitt A, Ross JH, Watkins DK, Solomon KR. 2015. Environmental fate and dietary exposures of humans to TCDD as a result of the spraying of Agent Orange in upland forests of Vietnam. *Science of the Total Environment* 506-507:621–630.

282 Madronich S, Shao M, Wilson SR, Solomon KR, Longstreth JD, Tang XY. 2015. Changes in air quality and tropospheric composition due to depletion of stratospheric ozone and interactions with changing climate: implications for human and environmental health. *Photochemical & Photobiological Sciences* 14:149-169

281 Ross JH, Hewitt A, Armitage J, Solomon KR, Watkins DK, Ginevan ME. 2014. Handler, bystander, and reentry exposure to TCDD from application of Agent Orange by C-123 aircraft during the Vietnam War. *Science of the Total Environment* 505:514–525.
280 Van Der Kraak GJ, Hosmer AJ, Hanson ML, Kloas W, Solomon KR. 2014. Effects of atrazine in fish, amphibians, and reptiles: An analysis based on quantitative weight of evidence. Critical Reviews in Toxicology:44(S5):1-66.
279 Rodríguez-Gil JL, Brain RA, Baxter L, Ruffell S, McConkey B, Solomon KR, Hanson ML. 2014. Optimization of culturing conditions for toxicity testing with the alga *Oophila* sp. (Chlorophyceae), an amphibian endosymbiont. *Environmental Toxicology and Chemistry* 33:2566–2575.
278 Carriquiriborde P, Mirabella P, Waichman A, Solomon K, Van den Brink PJ, Maund S. 2014. Aquatic Risk Assessment of Pesticides in Latin America. *Integrated Environmental Assessment and Management* 10:539–542
277 Morris AD, Muir DCG, Solomon KR, Teixeira C, Duric M, Wang X. 2014. Bioaccumulation and trophodynamics of current use pesticides and endosulfan in the vegetation-caribou-wolf food chain in the Canadian Arctic. *Environmental Toxicology and Chemistry* 33:1956–1966.
276 Prosser RS, Lissemore L, Solomon KR, Sibley PK. 2014. Toxicity of biosolids-derived triclosan and triclocarban to six crop species. *Environmental Toxicology and Chemistry* 33:1840-1848.
275 Baxter L, Brain R, Rodriguez-Gil JL, Hosmer A, Solomon K, Hanson M. 2014. Response of the green alga *Oophila sp.*, a salamander endosymbiont, to a PSII-inhibitor under laboratory conditions. *Environmental Toxicology and Chemistry* 33: 1858–1864.
274 Cutler C, Purdy J, Giesy JP, Solomon KR. 2014. Risk to pollinators from the use of chlorpyrifos in North America. *Reviews of Environmental Contamination and Toxicology* 231:219-265.
273 Giddings J, Williams M, Solomon KR, Giesy JP. 2014. Risks to aquatic organisms from the use of chlorpyrifos in the United States. *Reviews of Environmental Contamination and Toxicology* 231:119-162.
272 Giesy JP, Solomon KR, Mackay D, Giddings JM, Williams M, Moore D, Purdy J, Cutler C. 2014. Ecological risk assessment for chlorpyrifos in terrestrial and aquatic systems in the United States – overview and conclusions. *Reviews of Environmental Contamination and Toxicology* 231:1-12.
271 Mackay D, Giesy JP, Solomon KR. 2014. Fate in the environment and long-range atmospheric transport of the organophosphorus insecticide, chlorpyrifos and its oxon. *Reviews of Environmental Contamination and Toxicology* 231:35-76.
270 Moore DRJ, Teed RS, Greer C, Solomon KR, Giesy JP. 2014. Refined avian risk assessment for chlorpyrifos in the United States. *Reviews of Environmental Contamination and Toxicology* 231:163-217.
269 Solomon KR, Williams M, Mackay D, Purdy J, Giddings JM, Giesy JP. 2014. Properties and uses of chlorpyrifos in the United States. *Reviews of Environmental Contamination and Toxicology* 231:13-34.
268 Williams M, Giddings J, Purdy J, Solomon KR, Giesy JP. 2014. Exposures of aquatic organisms to the organophosphorus insecticide, chlorpyrifos resulting from use in the United States. *Reviews of Environmental Contamination and Toxicology* 231:77-118.
267 Martin JW, Mabury SA, Solomon KR, Muir DCG. 2013. Progress toward understanding the bioaccumulation of perfluorinated alkyl acids. *Environmental Toxicology and Chemistry* 32:2421-2423.
266 Armbrust K, Burns M, Crossan AN, Fischhoff DA, Hammond LE, Johnston JJ, Kennedy I, Rose MT, Seiber JN, Solomon K. 2013. Perspectives on Communicating Risks of Chemicals. *Journal of Agricultural and Food Chemistry* 61:4676-4691.
265 Prosser RS, Brain RA, Hosmer AJ, Solomon KR, Hanson ML. 2013. Assessing sensitivity and recovery of field-collected periphyton acutely exposed to atrazine using PSII inhibition under laboratory conditions. *Ecotoxicology* 22:1367-1383.
264 Baxter L, Brain R, Prosser R, Solomon K, Hanson M. 2013. Sensitivity of a green alga to atrazine is not enhanced by previous acute exposure. *Environmental Pollution* 181:325-328
263 de Jourdan BP, Hanson ML, Muir DCG, Solomon KR. 2013. Environmental fate of three novel brominated flame retardants in aquatic mesocosms. *Environmental Toxicology and Chemistry* 32:1060-1068.
262 Kavanagha RJ, Frank RA, Solomon KR, Van Der Kraak G. 2013. Reproductive and health assessment of fathead minnows (*Pimephales promelas*) inhabiting a pond containing oil sands process-affected waters. *Aquatic Toxicology* 130-131: 201–209.
261 Solomon KR, Matthies M, Vighi M. 2013. Assessment of PBTs in the EU: A critical assessment of the proposed evaluation scheme with reference to plant protection products. *Environmental Sciences Europe* 25:1-25.
260 Solomon KR, Giesy JP, Lapoint TW, Giddings JM, Richards RP. 2013. Ecological risk assessment of atrazine in North American surface waters. *Environmental Toxicology and Chemistry* 32:10-11.
259 Baxter LR, Sibley PK, Solomon KR, Hanson ML. 2013. Interactions between atrazine and phosphorus in aquatic systems: Effects on phytoplankton and periphyton. *Chemosphere* 90:1069-1076.
258 Baxter L, Moore D, Sibley PK, Solomon K, Hanson M. 2012. Response to: Rohr JR, Halstead NT, Raffel TR. 2012. The herbicide atrazine, algae, and snail populations. *Environmental Toxicology and Chemistry* 31:973-974; author reply 974-976.

257 Kavanagh RJ, Frank RA, Burnison BK, Young RF, Fedorak PM, Solomon KR, Van Der Kraak G. 2012. Fathead minnow (*Pimephales promelas*) reproduction is impaired when exposed to a naphthenic acid extract. *Aquatic Toxicology* 116-117:34-42.

256 Bjergager M-BA, Hanson ML, Solomon KR, Cedergreen N. 2012. Synergy between prochloraz and esfenvalerate in *Daphnia magna* from acute and subchronic exposures in the laboratory and microcosms. *Aquatic Toxicology* 110-111:17-24.

255 Gilroy ÈB, Balakrishnan VK, Solomon KR, Sverko E, Sibley PK. 2011. Behaviour of pharmaceuticals in spiked lake sediments – effects and interactions with benthic invertebrates. *Chemosphere* [Epub ahead of print] Dec 6 2011

254 Swanton CJ, Mashhadi HR, Solomon KR, Afifi MM, Duke SO. 2011. Similarities between the discovery and regulation of pharmaceuticals and pesticides: in support of a better understanding of the risks and benefits of each. *Pest Management Science* 67:790-797.

253 Van Geest J, Mackay D, Poirier D, Sibley PK, Solomon KR. 2011. Accumulation and depuration of polychlorinated biphenyls from field-collected sediment in three freshwater organisms. *Environmental Science & Technology* 45:7011-7018.

252 Baxter L, Moore DL, Sibley PK, Solomon KR, Hanson ML. 2011. Atrazine does not affect algal biomass or snail populations in microcosm communities at environmentally relevant concentrations. *Environmental Toxicology and Chemistry* 30:1689–1696.

251 Boobis A, Budinsky R, Collie S, Crofton K, Embry M, Felter S, Hertzberg R, Kopp D, Mihlan G, Mumtaz M, Price P, Solomon KR, Teuschler L, Yang R, Zaleski R. 2011. Critical analysis of literature on low dose synergy for use in screening chemical mixtures for risk assessment. *Critical Reviews in Toxicology*, 41:369-83.

250 Van Geest JL, Poirier D, Solomon KR, Sibley PK. 2010. A comparison of the bioaccumulation potential of three freshwater organisms exposed to sediment-associated contaminants under laboratory conditions. *Environmental Toxicology and Chemistry*, 30:939-949.

249 Van Geest JL, Poirier DG, Sibley PK, Solomon KR. 2011. Validation of Ontario's new laboratory-based bioaccumulation methods with in situ field data. *Environmental Toxicology and Chemistry*, 30:950–958.

248 Tang X, Wilson SR, Solomon KR, Shao M, Madronich S. 2011. Changes in tropospheric composition and air quality due to stratospheric ozone depletion and interactions with changes in climate. *Photochemical & Photobiological Sciences* 10:280–291.

247 Bjergager MB, Hanson ML, Lissemore L, Henriquez N, Solomon KR, Cedergreen N. 2011. Synergy in microcosms with environmentally realistic concentrations of prochloraz and esfenvalerate. *Aquatic Toxicology* 101:412-422.

246 Brandsma SH, Smithwick M, Solomon K, Small J, de Boer J, Muir DCG. 2011. Dietary exposure of rainbow trout to 8:2 and 10:2 fluorotelomer alcohols and perfluorooctanesulfonamide: Uptake, transformation and elimination. *Chemosphere* 82:253-258.

245 Kavanagh RJ, Frank RA, Oakes KD, Servos MR, Young RF, Fedorak PM, MacKinnon M, Solomon KR, Dixon G, Van Der Kraak G. 2011. Fathead minnow (*Pimephales promelas*) reproduction is impaired in aged oil sands process-affected waters. *Aquatic Toxicology* 101:214–220.

244 Van Geest J, Poirier D, Solomon KR, Sibley PK. 2011. The effect of organism density on the bioaccumulation of contaminants from sediment in three aquatic test species: A case for standardizing to sediment organic carbon. *Archives of Environmental Contamination and Toxicology* 60:626-635.

243 Van Geest JL, Poirier DG, Sibley PK, Solomon KR. 2010. Measuring bioaccumulation of contaminants from field-collected sediment in freshwater organisms: A critical review of laboratory methods. *Environmental Toxicology and Chemistry* 29:2391-2401.

242 Schreider J, Barrow C, Birchfield N, Dearfield K, Devlin D, Henry S, Kramer M, Schappelle S, Solomon KR, Weed DL, Embry MR. 2010. Enhancing the credibility of decisions based on scientific conclusions: Transparency is imperative. *Toxicological Sciences* 116:5-7.

241 Phillips MM, Dinglasan-Panlilio MJA, Mabury SA, Solomon KR, Sibley PK. 2010. Chronic toxicity of fluorotelomer acids to *Daphnia magna* and *Chironomus dilutus*. *Environmental Toxicology and Chemistry* 29:1123–1131.

240 Gantner N, Muir DCG, Power M, Iqualuk D, Reist JD, Meili M, Borg H, Hammar J, Michaud W, Dempson B, Solomon KR. 2010. Mercury concentrations in landlocked Arctic char (*Salvelinus alpinus*) from the Canadian High Arctic: Part II - Influence of lake biotic and abiotic characteristics on geographic trends in 27 populations. *Environmental Toxicology and Chemistry* 29:633-643

239 Gantner N, Power M, Iqualuk D,Meili M, Borg H, Sundbom M, Solomon KR, Lawson G, Muir DCG. 2010. Mercury concentrations in landlocked Arctic char *(Salvelinus alpinus*) from the Canadian High Arctic: Part I – Insights from trophic relationships in 18 lakes. *Environmental Toxicology and Chemistry*. 29:621-632

238 Frank RA, Sanderson H, Kavanagh R, Burnison BK, Headley JV, Solomon KR. 2010. Use of a (quantitative) structure-activity relationship [(Q)SAR] model to predict the toxicity of naphthenic acids. *Journal of Toxicology and Environmental Health A* 73:319–329.

237 Kavanaugh R, Frank RA, Burnison BK, Solomon KR, Van Der Kraak G. 2009. Detecting oil sands process-affected waters in the Alberta oil sands region using synchronous fluorescence spectroscopy. *Chemosphere* 76:120-126.

236 Weber J, Halsall CJ, Muir DCG, Teixeira C, Small J, Solomon KR, Mark H, Hung H, Bidleman T. 2009. Endosulfan, a global pesticide: a review of its fate in the environment and occurrence in the Arctic. *Science of the Total Environment* 408: 2966-2984.

235 Du Preez HH, Kunene N, Hanner R, Giesy JP, Hosmer AJ, Solomon KR, Van Der Kraak GJ. 2009. Population-specific incidence of testicular ovarian follicles in *Xenopus laevis* from South Africa: A potential issue in endocrine testing. *Aquatic Toxicology* 95:10-16.

234 Solomon KR, Dohmen P, Fairbrother A, Marchand M, McCarty LS. 2009. Use of (eco) toxicity data as screening criteria for the identification and classification of PBT / POP compounds. *Integrated Environmental Assessment and Management* 5:680-696.

233 Houde M, Pacepavicius G, Darling C, Fair PA, Alaee M, Bossart GD, Solomon KR, Muir DCG. 2009. Polybrominated diphenyl ethers (PBDEs) and hydroxylated polybrominated diphenyl ethers (OH-PBDEs) in plasma of bottlenose dolphins (*Tursiops truncatus*) from the U.S. east coast. *Environmental Toxicology and Chemistry* 28:2061-2068.

232 Sanderson H, Laird B, Brain RA, Wilson CJ, Solomon KR. 2009. Detectability of fifteen aquatic micro/mesocosms. *Ecotoxicology* 18:838-845.

231 Bolognesi C, Carrasquilla G, Volpi S, Solomon KR, Marshall EJP. 2009. Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate. Journal of Toxicology and Environmental Health A 72: 986-997.

230 Bernal MH, Solomon KR Carrasquila G. 2009. Toxicity of glyphosate and Cosmo-Flux® to larval and juvenile Colombian frogs 2. Field and laboratory microcosm acute toxicity. Journal of Toxicology and Environmental Health A 72: 966-973.

229 Bernal MH, Solomon KR Carrasquilla G. 2009. Toxicity of glyphosate and Cosmo-Flux® to larval Colombian frogs 1. Laboratory acute toxicity. Journal of Toxicology and Environmental Health A 72: 961-965.

228 Sanin L-H, Carrasquilla G, Solomon KR, Cole DC, Marshall EJP. 2009. Regional differences in time to pregnancy among fertile women from five Colombian regions with different uses of glyphosate. Journal of Toxicology and Environmental Health A 72: 949-960.

227 Brain RA, Solomon KR. 2009. Comparative hazards of glyphosate, other pesticides, and other human activities to amphibians in the production of coca. Journal of Toxicology and Environmental Health A 72: 937-948.

226 Marshall EJP, Solomon KR, Carrasquilla. 2009. Impacts of different adjuvants and glyphosate formulations on the control of coca (Erythroxylum coca). Journal of Toxicology and Environmental Health A 72: 930-936.

225 Hewitt AJ, Solomon KR, Marshall EJP. 2009. Spray droplet size, drift potential, and risks to non-target organisms from aerially-applied glyphosate for coca control in Columbia. Journal of Toxicology and Environmental Health A 72: 921-929.

224a Gomez JG, Solomon KR, Marshall EJP, Carrasquilla G. 2010. Letter to the editor and response. Re: Production of illicit drugs, the environment, and human health, J of Toxicology and Environmental Medicine 2009;72 (15-16). *Journal of Toxicology and Environmental Health A* 73:581; author reply 581-582.

224 Solomon KR, Marshall EJP, Carrasquilla G. 2009. Human health and environmental risks from the use of glyphosate formulations to control the production of coca in Colombia: Overview and conclusions. *Journal of Toxicology and Environmental Health A* 72: 914-920.

223 Kavanagh R, Frank RA, Burnison BK, Solomon KR, Van Der Kraak G. 2009. Detecting oil sands process-affected waters in the Alberta oil sands region using synchronous fluorescence spectroscopy. *Chemosphere* 76: 120-126.

222 Dussault ÈB, Balakrishnan VK, Solomon KR, Sibley PK. 2009. Matrix effects on mass spectrometric determinations of four pharmaceuticals and personal care products in water, sediments and biota. *Canadian Journal of Chemistry*. 87:662-672.

221 Dussault ÈB, Balakrishnan VK, Borgmann U, Solomon KR, Sibley PK. 2008. Bioaccumulation of the synthetic hormone 17β-ethinylestradiol in the benthic invertebrates *Chironomus tentans* and *Hyalella azteca*. *Ecotoxicology and Environmntal Safety* 72:1635–1641.

220 United Nations Environment Programme EEAP. 2009. Environmental effects of ozone depletion and its interactions with climate change: Progress Report 2008. *Photochemical & Photobiological Sciences* 8:13-22.

219 Gantner N, Power M, Babaluk J, Reist JD, Köck G, Lockhart WL, Solomon KR, Muir DCG. 2009. Temporal trends of mercury, cesium, potassium, selenium, and thallium in arctic char (*Salvelinus alpinus*) from Lake Hazen (Nunavut): Effects of trophic position, size and age. *Environmental Toxicology and Chemistry* 28:253-263.

218 Frank RA, Fischer K, Kavanagh R, Burnison BK, Arsenault G, Headley JV, Peru KM, Van Der Kraak G, Solomon KR. 2009. Effect of carboxylic acid content on the acute toxicity of oil sands naphthenic acids. *Environmental Science and Technology* 43:266-271.

217 Dussault ÈB, Balakrishnan VK, Solomon KR, Sibley PK. 2008. Chronic toxicity of the synthetic hormone 17β-ethinylestradiol to *Chironomus tentans* and *Hyalella azteca*. *Environmental Toxicology and Chemistry* 27:2521-2529.

216 Solomon KR, Carr JA, Du Preez LH, Kendall RJ, Smith EE, Van Der Kraak GJ. 2008. Effects of atrazine on fish, amphibians, and aquatic reptiles: A critical review. *Critical Reviews in Toxicology* 38:721–772.

215 Hillis DG, Solomon KR, Sibley PK. 2008. Structural responses of *Daucus carota* root organ cultures and the arbuscular mycorrhizal fungi, *Glomus intraradices*, to 12 pharmaceuticals. *Chemosphere* 73:344-352.

214 McGregor EB, Solomon KR, Hanson ML. 2008. Effects of planting system design on the toxicological sensitivity of *Myriophyllum spicatum* and *Elodea canadensis* to atrazine. *Chemosphere* 73:249-260

213 Frank RA, Kavanagh R, Burnison BK, Arsenault G, Headley JV, Peru KM, Van Der Kraak G, Solomon KR. 2008. Toxicity assessment of collected fractions from an extracted naphthenic acid mixture. *Chemosphere* 72:1309-1314.

212 Solomon KR. 2008. Effects of ozone depletion and UV-B radiation on humans and the environment. *Atmosphere-Ocean* 46:185-202.

211 Frewer LJ, Fischer A, R H, van den Brink PJ, Byrne P, Brock T, Brown C, Crocker J, Goerlitz G, Hart A, Scholderer J, Solomon KR. 2008. Potential for the adoption of probabilistic risk assessments by end-users and decision-makers. *Human and Ecological Risk Assessment* 14:166-178.

210 Du Preez LH, Kunene N, Everson GJ, Carr JA, Giesy JP, Gross TS, Kendall RJ, Smith EE, Solomon KR, Van Der Kraak GJ. 2008. Reproduction, larval growth, and reproductive development in African clawed frogs, (*Xenopus laevis*) exposed to atrazine. *Chemosphere* 71:546–552.

209 Dussault ÈB, Balakrishnan VK, Sverko E, Solomon KR, Sibley PK. 2008. Toxicity of human pharmaceutical and personal care products to benthic invertebrates. *Environmental Toxicology and Chemistry* 27:435-442.

208 United Nations Environment Programme Environmental Effects Assessment Panel. 2008. Environmental effects of ozone depletion and its interactions with climate change: Progress Report 2007. *Photochemistry and Photobiology Sciences* 7:15-27.

207 Buckman AH, Fisk AT, Parrott JL, Solomon KR, Brown SB. 2007. The effect of PCBs and temperature on the thyroid status in rainbow trout (*Oncorhynchus mykiss*). *Aquatic Toxicology* 84:366-378.

206 McGregor EB, Solomon KR, Hanson ML. 2007. Monensin is not toxic to aquatic macrophytes at environmentally relevant concentrations. *Archives of Environmental Contamination and Toxicology* 53:541-551.

205 Brain RA, Solomon KR. 2007. A protocol for conducting 7-day daily renewal tests with *Lemna gibba*. *Nature Protocols* 2:979-987.

204 Brain RA, Hanson ML, Solomon KR, Brooks BW. 2007. Aquatic plants exposed to pharmaceuticals: Effects and risks. *Reviews of Environmental Contamination and Toxicology* 192:67–115.

203 Laird BD, Brain RA, Johnson DJ, Wilson CJ, Sanderson H, Solomon KR. 2007. Toxicity and hazard of a mixture of SSRIs to zooplankton communities evaluated in aquatic microcosms. *Chemosphere* 69, 949-954.

202 Sanderson H, Laird B, Pope L, Brain RA, Wilson C, Johnson D, Bryning G, Peregrine AS, Boxall A, Solomon KR. 2007. Assessment of the environmental fate and effects of ivermectin in aquatic mesocosms. *Aquatic Toxicology* 85:229-240.

201 Phillips MM, Dinglasan-Panlilio MJA, Mabury SA, Solomon KR, Sibley PK. 2007. Fluorotelomer acids are more toxic than perfluorinated acids. Environmental Science and Technology 41: 7159-7163

200 Hillis DG, Lissemore L, Sibley PK, Solomon KR. 2007. Effects of monensin on zooplankton communities in aquatic microcosms. *Environmental Science and Technology* 41:6620-6626.

199 Buckman AH, Brown SB, Small J, Muir DCG, Parrott JL, Solomon KR, Fisk AT. 2007. The role of temperature and enzyme induction in the biotransformation of PCBs and bioformation of OH-PCBs by rainbow trout (*Oncorhynchus mykiss*). *Environmental Science and Technology* 41:3856-3863.

198 Johnson DJ, Sanderson H, Brain RA, Wilson CJ, Solomon KR. 2007. Toxicity and hazard of selective serotonin reuptake inhibitor antidepressants fluoxetine, fluvoxamine, and sertraline to algae. *Ecotoxicology and Environmental Safety* 67:128-139.

197 Wilson SR, Solomon KR, Tang X. 2007. Changes in tropospheric composition and air quality due to stratospheric ozone depletion and climate change. *Photochemical and Photobiological Sciences* 6:301-310.

196 Solomon KR, Anadón A, Carrasquilla G, Cerdeira A, Marshall J, Sanin L-H. 2007. Coca and poppy eradication in Colombia: environmental and human health assessment of aerially applied glyphosate. *Reviews of Environmental Contamination and Toxicology* 190:43-125.

195 Houde M, Pacepavicius G, Wells RS, Fair PA, Letcher RJ, Alaee M, Bossart GD, Hohn AA, Sweeney J, Solomon KR, Muir DCG. 2006. Polychlorinated biphenyls (PCBs) and hydroxylated polychlorinated biphenyls (OH-PCBs) in plasma of bottlenose dolphins (*Tursiops truncatus*) from the Western Atlantic and the Gulf of Mexico. *Environmental Science and Technology* 40: 40:5860-5866.

194 Thompson DG, Solomon KR, Wojtaszek BF, Edginton AN, Stephenson GR. 2006. The impact of insecticides and herbicides on the biodiversity and productivity of aquatic communities. Letter to the Editor. *Ecological Applications* 16:2022-2027.

193 Murphy MB, Hecker M, Coady KK, Tompsett AR, Jones PD, Solomon KR, Van Der Kraak G, Carr JA, Smith EE, Kendall RJ, Giesy JP. 2006. Sediment TCDD-EQs and EROD and MROD activities in Ranid frogs from agricultural and nonagricultural sites in Michigan (USA). *Archives of Environmental Contamination and Toxicology* 51:467-477.

192 Belknap AM, Hewitt ML, Solomon KR, Dubé MG, MacLatchy DL. 2006. Identification of compounds associated with testosterone depressions in fish exposed to bleached kraft pulp and paper mill chemical recovery condensates. *Environmental Toxicology and Chemistry* 25:2322–2333.

191 Brain RA, Rietsma TS, Lissemore LI, Bestari KT, Sibley PK, Solomon KR. 2006. Herbicidal effects of statin pharmaceuticals in *Lemna gibba*. *Environmental Science and Technology* 40:5116-5123

190 Houde M, Balmer BC, Brandsma S, Wells RS, Row T, Solomon KR, Muir DCG. 2006. Perfluorinated alkyl compounds in relation to life-history and reproductive parameters in bottlenose dolphins (*Tursiops truncatus*) from Sarasota Bay, Florida, USA. *Environmental Toxicology and Chemistry* 25:2405-2412.

189 Lissemore L, Hao C, Yang P, Sibley PK, Mabury SA, Solomon KR. 2006. An exposure assessment for selected pharmaceuticals within a model watershed in Southern Ontario. *Chemosphere* 64:717-729.

188 Frank RA, Kavanaugh R, Burnison BK, Headley JV, Peru KM, Van Der Kraak G, Solomon KR. 2006. Diethyaminoethyl-cellulose clean-up of a large volume naphthenic acid extract. *Chemosphere* 64:1346-1352.

187 Houde M, Bujas TAD, Small J, Wells RS, Fair PA, Bossart GD, Solomon KR, Muir DCG. 2006. Biomagnification of perfluoroalkyl compounds in the bottlenose dolphin (*Tursiops truncatus*) food web. *Environmental Science and Technology* 40:4138-4144.

186 Hecker, MH, Murphy MB, Coady KK, Villeneuve DL, Jones PD, Carr JA, Solomon KR, Smith EE, Van Der Kraak GJ, Gross T, du Preez LH, Kendall RJ, Giesy JP. 2006. Terminology of gonadal anomalies in fish and amphibians resulting from chemical exposures. *Reviews in Environmental Contamination and Toxicology* 187:103-132.

185 Park J-W, Hecker M, Murphy MB, Jones PD, Solomon KR, Van Der Kraak G, Carr JA, Smith EE, du Preez L, Kendall RJ and Giesy JP. 2006. Development and optimization of a highly sensitive Q RT RT-PCR technique to determine CYP19 gene expression in testis of *Xenopus laevis*: Comparisons with aromatase enzyme activity. *Comparative Biochemistry and Physiology B* 144:18-28

184 Buckman AH, Wong CS, Chow EA, Brown SB, Solomon KR, Fisk AT. 2006. Biotransformation of polychlorinated biphenyls (PCBs) and biotransformation of hydroxylated PCBs in fish. *Aquatic Toxicology* 78:176-185.

183 Houde M, Martin JW,Letcher RJ, Solomon KR, Muir DCG. 2006. Biological monitoring of polyfluoroalkyl compounds: A review. *Environmental Science and Technology* 40:3463-3473.

182 United Nations Environment Programme, Environmental Effects Assessment Panel. 2006. Environmental effects of ozone depletion and its interactions with climate change: Progress report, 2005. *Photochemical & Photobiological Sciences* 5:13-24.

181 Smithwick M, Norstrom RJ, Mabury SA, Solomon K, Evans TJ, Stirling I, Taylor MK, Muir DCG. 2006. Temporal trends of perfluoroalkyl contaminants in polar bears (*Ursus maritimus*) from two locations in the North American Arctic, 1972-2002. *Environmental Science and Technology* 40:1139-1143.

180 Hao C, Lissemore L, Nguyen B, Kleywegt S,Yang P, Solomon KR. 2006. Detection and identification of pharmaceuticals in agricultural surface waters by liquid chromatography coupled to electrospray ionization tandem mass spectrometry. *Analytical and Bioanalytical Chemistry* 384:505–513.

179 Brain RA, Sanderson H, Sibley PK, Solomon KR. 2006. Probabilistic ecological hazard assessment; Evaluating pharmaceutical effects on aquatic higher plants as an example. *Ecotoxicology and Environmental Safety* 68:128-135.

178 Sherry J P, Whyte JJ, Karrow NA, Gamble A, Boermans HJ, Bols NC, Dixon DG, Solomon KR. 2005. The effect of creosote on vitellogenin production in rainbow trout (*Oncorhynchus mykiss*). *Archives of Environmental Contamination and Toxicology* 50:65-68.

177 Murphy MB, Hecker M, Coady KK, Tompsett AR, Jones PD, Solomon KR, Van Der Kraak G, Carr JA, Smith EE, du Preez L, Kendall RJ and Giesy JP. 2005. Gross morphology and gonad histology of ranid frogs collected from atrazine-exposed agricultural ponds in Michigan. *Aquatic Toxicology* 76:230-245

176 Sanderson H, Ingerslev F, Brain RA, B H-S, Bestari JK, Wilson CJ, Johnson DJ, Solomon KR. 2005. Determination and characterization of dissipation of oxytetracycline, chlortetracycline, tetracycline and doxycycline under aquatic semi-field microcosm conditions using HPLC-UV and LC-MS-MS. *Chemosphere* 60:618-629.

175 Solomon KR, Houghton D, Harris SA. 2005. Nonagricultural and residential exposures to pesticides. Scandinavian *Journal of Work, Environment & Health* 31 suppl 1: 74-81.

174 Brain RA, Wilson CJ, Johnson DJ, Sanderson H, Bestari KT, Hanson ML, Sibley PK, Solomon KR. 2005. Effects of a mixture of tetracyclines to *Lemna gibba* and *Myriophyllum sibiricum* evaluated in aquatic microcosms. *Environmental Pollution* 138:426-443.

173 Hecker M, Park J-W, Murphy MB, Jones PD, Solomon KR, Van Der Kraak G, Carr JA, Smith EE, du Preez L, Kendall RJ and Giesy JP. 2005. Effects of atrazine on CYP19 gene expression and aromatase activity in testes and on sex steroid concentrations in plasma of male African clawed frogs (*Xenopus laevis*). *Toxicological Science* 86:273–280.

172 Hanson ML, Small J, Sibley PK, Boudreau TM, Brain RA, Mabury SA, Solomon KR. 2005. Microcosm evaluation of the fate, toxicity, and risk to aquatic macrophytes from perfluorooctanoic acid (PFOA). *Archives of Environmental Contamination and Toxicology* 48:329-337.

171 Coady KK, Murphy MB, Villeneuve DL, Hecker M, Carr JA, Solomon KR, Van Der Kraak GJ, Smith EE, Kendall RJ, Giesy JP. 2005. Effects of atrazine on metamorphosis, growth, laryngeal and gonadal development, aromatase activity, and plasma sex steroid concentrations in *Xenopus laevis*. *Ecotoxicology and Environmental Safety* 62:160-173.

170 Johnson DJ, Sanderson H, Brain RA, Wilson CJ, Bestari KT, Solomon KR. 2005. Exposure assessment and microcosm fate of selected selective serotonin reuptake inhibitors. Regulatory Toxicology and Pharmacology 42:313–323

169 Houde M, Wells RS, Fair PA, Bossart GD, Hohn AA, Rowles T, Solomon KR, Muir DCG. 2005. Perfluoroalkyl compounds in free-ranging bottlenose dolphins (*Tursiops truncatus*) from Eastern U.S. waters. Environmental Science and Technology 39, 6591-6598.

168 Smithwick M, Mabury SA, Solomon KR, Sonne C, Martin JW, Born EW, Dietz R, Derocher AE, Letcher RJ, Evans TJ, Gabrielson GW, Nagy J, Stirling I, Taylor MK, Muir DCG. 2005. Circumpolar study of perfluoroalkyl contaminants in polar bears (*Ursus maritimus*). Environmental Science and Technology 39, 5517-5523.

167 Jooste AM, Du Preez LH, Carr JA, Giesy JP, Gross TS, Kendall RJ, Smith EE, Van Der Kraak GJ, Solomon KR. 2005. Gonadal development in *Xenopus laevis* larvae and juveniles exposed to atrazine in semi-natural microcosms. *Environmental Science and Technology*, 39, 5255-5261

166 Du Preez LH, Solomon KR, Carr JA, Giesy JP, Gross TS, Kendall RJ, Smith EE, Van Der Kraak GJ, Weldon C. 2004. Population structure characterization of the clawed frog (*Xenopus laevis*) in corn-growing versus non-corn-growing areas in South Africa. *African Journal of Herpetology*, 54:61-68.

165 Smith EE, du Preez LH, Gentles BA, Solomon KR, Tandler B, Carr JA, Van Der Kraak GJ, Kendall RJ, Giesy JP, Gross TS. 2004. Stereological assessment of testicular cell types in *Xenopus laevis* inhabiting agricultural and non-agricultural areas of South Africa. *African Journal of Herpetology*, 54:69-76.

164 Hanson ML, Sibley PK, Brain RA, Mabury SA, Solomon KR. 2005. Microcosm evaluation of the toxicity and risk to aquatic macrophytes from perfluorooctane sulfonic acid. *Archives of Environmental Toxicology and Chemistry* 48:329-337

163 Hecker M, Kim WJ, Park J-W, B MM, Villeneuve D, Coady KK, Jones PD, Solomon KR, Van Der Kraak GJ, Carr JA, Smith EE, du Preez LH, Kendall RJ, Giesy JP. 2004. Plasma concentrations of estradiol and testosterone, gonadal aromatase activity and ultrastructure of the testis in *Xenopus laevis* exposed to estradiol or atrazine. *Aquatic Toxicology* 72:383-396.

162 Oakes KS, Sibley PK, Martin JW, MacLean DD, Solomon KR, Mabury SA, Van Der Kraak GJ. 2005. Short-term exposures of fish to perfluorooctane sulfonate (PFOS): effects on fatty acyl-CoA oxidase activity, oxidative stress, and circulating sex steroids. *Environmental Toxicology and Chemistry* 24:1172-1181.

161 Hao C, Headley JV, Peru KM, Frank R, Yang P, Solomon KR. 2005. Characterization and pattern recognition of oil–sand naphthenic acids using comprehensive two-dimensional gas chromatography/time-of-flight mass spectrometry. *Journal of Chromatography A* 1067: 277-284

160 Van den Brink PJ, Tarazona JV, Solomon KR, Knacker T, Van den Brink NW, Brock TCM, Hoogland JPH. 2005. The use of terrestrial and aquatic microcosm and mesocosms for the ecological risk assessment of veterinary pharmaceuticals. *Environmental Toxicology and Chemistry* 24:820–829.

159 Smithwick MM, Muir DCG, Mabury SA, Solomon KR, Sonne C, Dietz R, Born EW. 2005. Perfluorinated acids in liver tissue from East Greenland polar bears (*Ursus maritimus*) 1999-2001. *Environmental Toxicology and Chemistry* 24:981–986.

158 Du Preez LH, Jansen van Rensburg PJ, Jooste AM, Carr JA, Giesy JP, Gross TS, Kendall RJ, Smith EE, Van Der Kraak G, Solomon KR. 2005. Seasonal exposures to triazine and other pesticides in surface waters in the western Highveld corn-production region in South Africa. *Environmental Pollution*, 135:131-141.

157 United Nations Environment Programme, Environmental Effects Assessment Panel. 2005. Environmental effects of ozone depletion and its interactions with climate change: Progress report, 2004. *Photochemical & Photobiological Sciences* 4 177-184.

156 Houde M, Hoekstra PF, Solomon KR, Muir DCG. 2005. A review of persistent organohalogen contaminants in delphinoid cetaceans. *Reviews in Environmental Contamination and Toxicology*, 184:1-57.

155 Brain RA, Bestari KT, Sanderson H, Hanson ML, Wilson CJ, Johnson DJ, Sibley PK, Solomon KR. 2005. Aquatic microcosm assessment of the effects of tylosin to *Lemna gibba* and *Myriophyllum spicatum*. *Environmental Pollution* 133:389-401.

154 Wilson CJ, Brain RA, Sanderson H, Johnson DJ, Bestari KT, Sibley PK, Solomon KR. 2004. Structural and functional responses of plankton to a mixture of four tetracyclines in aquatic microcosms. *Environmental Science and Technology* 38:6430-6439.

153 Hecker M, Giesy JP, Jones PD, Jooste AM, Carr JA, Solomon KR, Smith EE, Van der Kraak GJ, Kendall RJ, Du Preez LH. 2004. Plasma sex steroid concentrations and gonadal aromatase activities in African clawed frogs frogs (*Xenopus laevis*) from the corn-growing region of South Africa. *Environmental Toxicology and Chemistry* 23:1996-2007.

152 Brain RA, Johnson DJ, Richards SM, Hanson ML, Sanderson H, Lam MW, Mabury SA, Sibley PK, Solomon KR. 2004. Ecotoxicological evaluation of th effects of an eight pharmaceutical mixture to the aquatic macrophytes *Lemna gibba* and *Myriophyllum sibiricum* exposed in aquatic microcosms. *Aquatic Toxicology*, 70:23-40.

151 Sibley PK, Harris ML, Bestari KT, Steele TA, Robinson RD, Gensemer RW, Day KE, Solomon KR. 2004. Response of zooplankton and phytoplankton communities to creosote-impregnated Douglas-fir pilings in freshwater microcosms. *Archives of Environmental Contamination and Toxicology*. 47:56-66.

150 Sanderson H, Brain RA, Johnson DJ, Wilson CJ, Solomon KR. 2004. Toxicity classification and evaluation of four pharmaceuticals classes; antibiotics, antineoplastics, cardiovascular, and sex hormones. *Toxicology* 203:27-40.

149 MacDonald M, Sibley PK, Warne A, Stock NL, Mabury SA, Solomon KR. 2004. Toxicity of perfluorooctane sulfonic acid (PFOS) and perfluorooctanoic acid (PFOA) to *Chironomus tentans*. *Environmental Toxicology and Chemistry*. 23:2116-2123.

148 Oakes KD, Sibley PK, Solomon KR, Mabury SA, Van Der Kraak, GL. 2004. Impact of perfluorooctanoic acid (PFOA) on fathead minnow (*Pimephales promelas*) fatty acyl-CoA oxidase activity, circulating steroids, and reproduction in outdoor microcosms. *Environmental Toxicology and Chemistry*, 23:1912-1919.

147 Buckman AH, Brown S, Hoekstra PF, Solomon KR, Fisk AT. 2004. Toxicokinetics of three PCB Aroclor mixtures in rainbow trout (*Oncorhynchus mykiss*). *Environmental Toxicology and Chemistry*, 23, 1725-1736.

146 Coady KK, Murphy MB, Villeneuve DL, Hecker M, Jones PD, Carr JA, Solomon KR, Smith EE, Van Der Kraak GJ, Kendall RJ, Giesy JP. 2004. Effects of atrazine on metamorphosis, growth, and gonadal development in the green frog (*Rana clamitans*). *Journal of Toxicology and Environmental Health A* 67:941-957.

145 Martin JW, Muir DCG, Moody CA, Ellis DA, Kwan WC, Solomon KR, Mabury SA. 2004. Collection of airpborne fluorinated organics and analysis by gas chromatography/chemical ionisation mass spectroscopy. *Analytical Chemistry* 74:584-590.

144 Lam MW, Young CJ, Brain RA, Johnson DJ, Hanson MA, Wilson CJ, Richards SM, Solomon KR, Mabury SA. 2004. The aquatic persistence of eight pharmaceuticals in outdoor microcosms monitored by HPLC-UV and LC-MS-MS using electrospray ionization. *Environmental Toxicology and Chemistry*, 23, 1431-1440.

143 Hanson ML, Solomon KR. 2004. Haloacetic acids in the aquatic environment I: Macrophyte toxicity. Archives of *Environmental Pollution* 130:371-383.

142 Hanson ML, Solomon KR. 2004. Haloacetic acids in the aquatic environment II: Ecological risk assessment for aquatic macrophytes. *Environmental Pollution* 130:385-401.

141 Sanderson H, Boudreau TM, Mabury SA, Solomon KR. 2004. Effects of perfluorooctane sulfonate and perfluorooctanoic acid on the zooplanktonic community. Ecotoxicology and Environmental Safety 58:68-76.

140 Richards SM, Wilson CJ, Johnson DJ, Castle DM, Lam M, Mabury SA, Sibley PK, Solomon KR. 2004. Effects of pharmaceuticals in aquatic ecosystems. *Environmental Toxicology and Chemistry*, 23:23:1035-1042.

139 Sanderson H, Johnson DJ, Rietsma T, Brain RA, Wilson CJ, Solomon KR. 2004. Ranking and prioritization of environmental risks of pharmaceuticals in surface waters. *Regulatory Toxicology and Pharmacology* 39:158-183

138 United Nations Environment Programme Environmental Effects Assessment Panel. 2004. Environmental effects of ozone depletion and its interactions with climate change: Progress Report 2003. *Photochemistry and Photobiology Science* 3:1-5.

137 Brain RA, Johnson DJ, Richards SM, Sanderson H, Sibley PK, Solomon KR. 2004. Effects of 25 pharmaceutical compounds to *Lemna gibba* using a 7-day static renewal test. *Environmental Toxicology and Chemistry*, 23:371-382

136 Ganassin J. Parrott J, Solomon KR, Sherry J. 2003. Effects of exposure to various sites within the Hamilton Harbour on *Oncorhynchus mykiss* pronephros macrophage function and B cell numbers. Journal of Great Lakes Research 29, 280-295

135 George TK, Liber K, Solomon KR, Sibley PK. 2003. Assessment of the probabilistic ecological risk assessment-toxic equivalent combination approach for evaluating pesticide mixture toxicity to zooplankton in outdoor microcosms. *Archives of Environmental Contamination and Toxicology* 45:453-461.

134 Boudreau TM, Wilson CJ, Cheong WJ, Sibley PK, Mabury SA, Muir DCG, Solomon KR. 2003. Response of the zooplankton community and environmental fate of perfluorooctane sulfonic acid (PFOS) in aquatic microcosms. *Environmental Toxicology and Chemistry* 22:2739–2745.

133 Hoekstra PF, O'Hara TM, Karlsson H, Solomon KR, Muir DCG. 2003. Enantiomer-specific biomagnification of a-hexachlorocyclohexane and selected chiral chlordane-related compounds within an arctic marine food web. *Environmental Toxicology and Chemistry*, 22:2482–2491 (SETAC Best Student Paper Award (2003).

132 Marwood CA, Smith REH, Charlton MN, Solomon KR, Greenberg BM. 2004. Photoinduced toxicity to Lake Erie phytoplankton assemblages from intact and photomodified polycyclic aromatic hydrocarbons. *Journal of Great Lakes Research* 29:558-565

131 Hanson ML, Sanderson H, Solomon, KR. 2003. Variation, replication, and power analysis of *Myriophyllum* spp. microcosm toxicity data. *Environmental Toxicology and Chemistry* 22:1318–1329.

130 Sanderson H, Johnson DJ, Wilson CJ, Brain RA, Solomon, KR. 2003. Probabilistic hazard assessment of environmentally occurring pharmaceuticals toxicity to fish, daphnids, and algae by ECOSAR screening. *Toxicology Letters* 144:385-395.

129 Martin JW, Mabury SA, Wong CS, Noventa F, Solomon KR, Alaee M, Muir DCG. 2003. Airborne haloacetic acids. *Environmental Science and Technology* 37:2889-2897

128 Karrow NA, Bennie DT, Boermans HJ, Bols NC, Dixon DG, Gamble A, Ganassin R, Parrott Joanne, Solomon KR, Sherry JP. 2003. Effect of exposure to various sites within Hamilton Harbour on *Onchorynchus mykiss* pronephros macrophage function and B cell numbers. *Journal of Great Lakes Research*, 29:280-295.

127 Hoekstra PF, O'Hara TM, Solomon KR, Muir DCG. 2003. Trophic transfer of organochlorine contaminants within an Arctic marine food web from the southern Beaufort-Chukchi Seas near Barrow, Alaska. *Environmental Pollution*, 124:509-522.

126 Boudreau TM, Sibley PK, Mabury SA, Muir DCG, Solomon, KR. 2003. Laboratory evaluation of the toxicity of perfluorooctane sulfonate (PFOS) on *Selenastrum capricornutum, Chlorella vulgaris, Lemna gibba, Daphnia magna,* and *Daphnia pulicaria. Archives of Environmental Contamination and Toxicology*, 44:307-313

125 Hanson ML, Sibley PK, Mabury SA, Muir DCG, Solomon KR. 2003. Field level evaluation and risk assessment of the toxicity of dichloracetic acid to the aquatic macrophytes *Lemna gibba, Myriophyllum spicatum*, and *Myriophyllum sibericum. Ecotoxicology and Environmental Safety* 55:46-63

124 Marwood CA, Bestari KT, Gensemer RW, Solomon KR, Greenberg BM. 2003. Chlorophyll fluorescence as a bioindicator of creosote toxicity to plant growth in aquatic microcosms. *Environmental Toxicology and Chemistry* 22:1075-1085

123 Brooks BW, Foran CM, Richards SM, Weston J, Turner PK, Stanley JK, Solomon KR, Slattery M, La Point TW. 2003. Aquatic Ecotoxicology of fluoxetine. *Toxicology Letters* 142:169-183

122 Sanderson H, Boudreau TM, Mabury SA, Solomon KR. 2003. Impact of perfluorooctanoic acid on the structure of the zooplankton community in indoor microcosms. *Aquatic Toxicology* 62:227-234

121 Solomon KR, Thompson DG. 2003. Ecological risk assessment for aquatic organisms from over-water uses of glyphosate. *Journal of Toxicology and Environmental Health B*, 6:211-246

120 Solomon KR, Tang X, Wilson SR, Zanis P, Bais AF. 2003. Changes in tropospheric composition and air quality due to stratospheric ozone depletion. *Photochemistry and Photobiological Science* 2:62-67.

119 Hoekstra PF, Braune BM, O'Hara TM, Elkin B, Solomon KR, Muir, DCG. 2003. Organochlorine contaminant and stable isotope profiles in arctic fox (*Alopex lagopus*) from the Alaskan and Canadian Arctic. *Environmental Pollution* 122:423-433.

118 Carr JA, Gentles A, Smith, EE, Goleman WA, Urquidi LJ, Thuett K, Kendall, RJ, Giesy JP, Gross TS, Solomon KR, Van Der Kraak GL. 2003. Response of larval *Xenopus laevis* to atrazine: assessment of growth, metamorphosis, and gonadal and laryngeal morphology. *Environmental Toxicology and Chemistry* 22:396–405.

117 Martin JW, Mabury SA, Solomon KR, Muir DCG. 2003. Bioconcentration and tissue distribution of perfluorinated acids in rainbow trout (*Oncorhynchus mykiss*). *Environmental Toxicology and Chemistry* 22:196-204

116 Martin JW, Mabury SA, Solomon KR, Muir, DCG. 2003. Dietary accumulation of perfluorinated acids in juvenile rainbow trout (*Oncorhynchus mykiss*). *Environmental Toxicology and Chemistry*, 22:189-195

115 Grapentine L, Anderson J, Boyd D, Burton GA, DeBarros C, Johnson G, Marvin C, Milani D, Painter S, Pascoe T, Reynoldson T, Richman L, Solomon K, Chapman PM. 2002. A decision-making framework for sediment assessment developed for the Great Lakes. *Human and Ecological Risk Assessment* 8:1641-1655

114 Martin JW, Muir DCG, Moody CA, Ellis DA, Kwan WC, Solomon KR, Mabury SA. 2002. Collection of airborne fluorinated organics and analysis by gas chromatography/chemical ionization mass spectroscopy. *Analytical Chemistry* 74:584-590.

113 Sanderson H, Boudreau TM, Mabury SA, Cheong W-J, Solomon KR. 2002. Ecological impact and environmental fate of perfluorooctane sulfonate on the zooplankton community in indoor microcosms. *Environmental Toxicology and Chemistry* 21:1490–1496

112 Hanson ML, Solomon KR. 2002. New technique for estimating thresholds of toxicity in ecological risk assessment. *Environmental Science and Technology* 36:3257-3264

111 Chapman PM, Ho KT, Munns WR, Solomon K, Weinstein MP. 2002. Issues in sediment toxicity and ecological risk assessment. *Marine Pollution Bulletin* 44:271-278.

110 Solomon KR, Sibley, PK. 2002. New concepts in ecological risk assessment: Where do we go from here? *Marine Pollution Bulletin* 44:279-285

109 Hoekstra PF, O'Hara TM, Gallant SJ, Solomon KR, Muir DCG. 2002. Bioaccumulation of organochlorine contaminants in bowhead whales (*Balaena mysticetus*) from Barrow, Alaska. *Archives of Environmental Contamination and Toxicology* 42:497-507.

108 Hanson ML, Sibley PK, Ellis D, Fineberg N, Mabury SA, Solomon KR, Muir DCG. 2002. Trichloroacetic acid (TCA) fate and toxicity to the macrophytes *Myriophyllum spicatum* and *Myriophyllum sibiricum* under field conditions. *Aquatic Toxicology* 56:241-255

107 Hanson ML, Sibley PK, Mabury SA, Solomon KR, Muir DCG. 2002. Trichloroacetic acid (TCA) and trifluoroacetic acid mixture toxicity to the macrophytes *Myriophyllum spicatum* and *Myriophyllum sibiricum* in aquatic microcosms. *Science of the Total Environment* 285:247-259

106 Hoekstra PF, Wong, CC, O'Hara TM, Solomon KR, Mabury SA, Muir DCG. 2002. Enantiomer-specific accumulation of PCB atropisomers in the bowhead whale (*Balaena mysticetus*). *Environmental Science and Technology* 36:1419-1425.

105 Hoekstra PF, Dehn LA, George JC, Solomon KR, Muir DCG, O'Hara TM. 2002. Trophic ecology of bowhead whales (*Balaena mysticetus*) compared to other arctic marine biota as interpreted from carbon-, nitrogen-, and sulphur-isotope signatures. *Canadian Journal of Zoology* 80:223-231.

104 Luross JM, Alaee M, Sergeant DB, Cannon CM, Whittle DM, Solomon KR, Muir DCG. 2002. Spatial distribution of polybrominated diphenyl ethers and polybrominated biphenyls in lake trout from the Laurentian Great Lakes. *Chemosphere* 46:665-672

103 Ritter L, Solomon KR, Sibley PK, Hall K, Mattu G, Keen P, Linton B. 2002. Sources, Pathways and Relative Risks of Contaminants in Surface Water and Groundwater: A Perspective Prepared for the Walkerton Inquiry. *Journal of Toxicology and Environmental Health A* 65:1-142.

102 Sibley PK, Harris ML, Bestari KT, Steele TA, Robinson RD, Gensemer RW, Day KE, Solomon KR. 2001. Response of phytoplankton communities to liquid creosote in freshwater microcosms. *Environmental Toxicology and Chemistry* 20:2785–2793

101 Hanson ML, Sibley PK, Solomon KR, Mabury SA, Muir DCG. 2001. Chlorodifluoroacetic acid fate and toxicity to the macrophytes *Lemna gibba*, *Myriophyllum spicatum* and *Myriophyllum sibiricum* in aquatic microcosms. *Environmental Toxicology and Chemistry*. 20:2758–2767

100 Stephenson GR, Bowhey CS, Lang SR, Solomon KR. 2001. Homeowner-applicator and bystander exposure to chlorpyrifos applied to turfgrass. International Turfgrass Society Research Journal 9:45-49

99 Solomon KR, Giesy JP. 2001. Overview—Ecological Risk Assessment of Pesticides. Guest Editorial. *Human and Ecological Risk Assessment* 7:493-496

98 Solomon KR, Giesy JP, Kendall RJ, Best LB, Coats JR, Dixon KR, Hooper MJ, Kenaga EE, McMurry ST. 2001. Chlorpyrifos: ecotoxicological risk assessment for birds and mammals in corn agroecosystems. *Human and Ecological Risk Assessment* 7:497-632

97 Marwood CA, Bestari KT, Gensemer RW, Solomon KR, Greenberg BM. 2001. Chlorophyll fluorescence as a bioindicator of effects on growth in aquatic macrophytes from mixtures of polycyclic aromatic hydrocarbons. *Environmental Toxicology and Chemistry* 20:890-898

96 Solomon KR, Giddings JM, Maund SJ. 2001. Probabilistic Risk Assessment of Cotton Pyrethroids: I. Distributional Analyses of Laboratory Aquatic Toxicity Data. *Environmental Toxicology and Chemistry* 20:652-659

95 Giddings JM, Solomon KR, Maund SJ. 2001. Probabilistic Risk Assessment of Cotton Pyrethroids: II. Aquatic Mesocosm and Field Studies. *Environmental Toxicology and Chemistry* 20:660-668

94 Maund SJ, Travis KZ, Hendley P, Giddings JM, Solomon KR. 2001. Probabilistic Risk Assessment of Cotton Pyrethroids: V. Combining Landscape-level Exposures and Ecotoxicological Effects Data to Characterize Risks. *Environmental Toxicology and Chemistry* 20:687-692

93 Sibley PK, Harris ML, Bestari KT, Steele TA, Robinson RD, Gensemer RW, Day KE, Solomon KR. 2001. Response of zooplankton communities to liquid creosote in freshwater microcosms. *Environmental Toxicology and Chemistry* 21:394-405.

92 Giddings JM, Hall LWJ, Solomon KR. 2000. An ecological risk assessment of diazinon from agricultural use in the Sacramento-San Joaquin River basins, California. *Risk Analysis* 20:545-572.

91 Solomon KR, Giesy, JP, Jones P. 2000. Probabilistic risk assessment of agrochemicals in the environment. *Crop Protection* 19:649-655.

90 Stephenson GL, Koper N, Atkinson GF, Solomon KR, Scroggins RP. 2000. Use of nonlinear regression techniques for describing concentration-response relationships for plant species exposed to contaminated site soils. *Environmental Toxicology and Chemistry* 19:2968-2981.

89 Ellis DA, Hanson ML, Sibley PK, Shahid T, Fineburg NA, Solomon KR, Muir DCG, Mabury SA. 2001. The fate and persistence of trifluoroacetic and chloroacetic acids in pond waters. Chemosphere 42:309-318.

88 McCann JH, Solomon KR. 2000. The effect of creosote on membrane ion leakage in *Myriophyllum spicatum* L. Aquatic Toxicology 50:275–284

87 McCann JH, Greenberg BM, Solomon KR. 2000. The effect of creosote on the growth of an axenic culture of *Myriophyllum spicatum* L. Aquatic Toxicology 50:265–274

86 Sibley PK, Chappel MJ, George TK, Solomon KR, Liber K. 2000. Integrating effects of stressors across levels of biological organization: Examples using organophosphorus insecticide mixtures in field-level exposures. *Journal of Aquatic Ecosystem Stress and Recovery* 7:117-130.

85 Bright DA, Hodson PV, Lehtinen K-J, McKague B, Rodgers J, Solomon K. 2000. Use of chlorine dioxide for bleaching pulp: A re-evaluation of ecological risks based on scientific progress since 1993. *Pulp and Paper Canada* 101:53-55.

84 Giesy JP, Dobson S, Solomon KR. 2000. Ecotoxicological risk assessment for Roundup® herbicide. *Reviews in Environmental Contamination and Toxicology* 167:35-120.

83 Marwood CA, Smith REH, Furgal JA, Charlton MN, Solomon KR, Greenberg, BM. 2000. Photoinhibition of natural Lake Erie phytoplankton populations exposed to solar radiation. *Canadian Journal of Fisheries and Aquatic Sciences* 57:371-379.

82 Marwood CA, Smith REH, Solomon KR, Charlton MN, Greenberg BM. 1999. Intact and photomodified polycyclic aromatic hydrocarbons inhibit photosynthesis in natural assemblages of Lake Erie phytoplankton exposed to solar radiation. *Ecotoxicology and Environmental Safety* 44:322-327.

81 Martin JW, Franklin J, Hanson ML, Mabury SA, Ellis DA, Scott BF, Muir DCG, Solomon KR. 2000. Detection of chlorodifluoroacetic acid in precipitation: a possible product of fluorocarbon degradation. *Environmental Science and Technology*. 34:274-281.

80 Hall, LW Jr, Giddings, JM, Solomon, KR, Balcomb R. 1999. An ecological risk assessment for the use of Irgarol 1051 as an algaecide for antifoulant paints. *Critical Reviews in Toxicology*, 29:367-437.

79 Karrow NA, Boermans HJ, Dixon DG, Hontella A, Solomon KR, Whyte JJ, Bols NC. 1999. Characterizing the immunotoxicity of creosote to rainbow trout (*Oncorynchus mykiss*): a microcosm study. *Aquatic Toxicology* 45:223-239.

78 Sherry J, Gamble A, Fielden M, Hodson P, Burnison B, Solomon K. 1999. An ELISA for brown trout (*Salmo truta*) vitellogenin and its use in bioassays for environmental estrogen. *The Science of the Total Environment* 225:13-31.

77 Giesy JP, Solomon KR, Coates JR, Dixon KR, Giddings JM, Kenaga EE. 1999. Chlorpyrifos: Ecological risk assessment in North American aquatic environments. *Reviews in Environmental Contamination and Toxicology* 160:1-129.

76 Bestari KTJ, Robinson RD, Solomon KR, Steele TS, Day KE, Sibley PK. 1998. Distribution and composition of polycyclic aromatic hydrocarons within microcosms treated with liquid creosote. *Environmental Toxicology and Chemistry*, 17: 2359-2368.

75 Bestari KTJ, Robinson RD, Solomon KR, Steele TS, Day KE, Sibley PK. 1998. Distribution and composition of polycyclic aromatic hydrocarons within microcosms treated with creosote-impregnated douglas fir pilings. *Environmental Toxicology and Chemistry*. 17: 2369-2377

74 Hewitt LM, Carey JC Munkittrick KR Parrott JL Solomon KR Servos MR. 1998. Identification of chloro-nitro-trifluoromethyl-substitited dibenzo-p-dioxins in lampricide formulations of 3-fluoromethyl-4-nitrophenol: Assessment to induce mixed function oxidase activity. *Environmental Chemistry and Toxicology*, 17:941-950. (SETAC Best Student Paper Award)

73 Solomon KR. 1998. Endocrine Modulating substances in the environment: The wildlife connection. *International Journal of Toxicology*, 17:159-172.

72 Hewitt LM, Tremblay L, Van Der Kraak GJ, Solomon KR, Servos MR. 1998. Identification of the lampricide 3-trifluoromethyl-4-nitrophenol as an agonist for the rainbow trout estrogen receptor. *Environmental Toxicology and Chemistry* 17:425-432.

71 Fan GT, Burnison BK, Solomon KR. 1997. The partitioning of fenvalerate to natural dissolved organic matter. *Water Research* 31:2429-2434.

70 Faber MJ, Smith LMJ, Boermans HJ, Stephenson GR, Thompson DG, Solomon KR. 1997. Cryopreservation of fluorescent marker-labeled algae *(Selenastrum capricornutum)* for toxicity testing using flow cytometry. *Environmental Toxicology and Chemistry*, 16:1059-1067.

69 Liber K, Solomon KR, Carey JH. 1997. Persistence and fate of 2,3,4,6-tetrachlorophenol and pentachlorophenol in limnocorrals. *Environmental Toxicology and Chemistry*, 16:293-305.

68 Solomon KR, Bergman H, Huggett RJ, Mackay D, McKague B. 1996. A review and assessment of the ecological risks associated with the use of chlorine dioxide for the bleaching of pulp. *Pulp and Paper Canada* 97:T345-T354

67 Solomon KR. 1996. Overview of recent developments in ecotoxicological risk assessment. *Risk Analysis*, 16:627-633.

66 Solomon KR. 1996. Chlorine in the bleaching of pulp and paper. *Pure and Applied Chemistry* 68:1721-1730

65 Hewitt M, Servos M, Van Der Kraak G, Solomon K, Munkittrick K. 1996. Characterization of bioactive lampricide formulation impurities. *Organohalogen Compounds*, 29: 434-438.

64 Hewitt LM, Munkittrick KR, Scott IM, Carey JH, Solomon KR, Servos MR. 1996. Use of a MFO-directed toxicity identification evaluation to isolate and characterize bioactive impurities from a lampricide formulation. *Environmental Toxicology and Chemistry*, 15:894-905.

63 Klaine, SJ, Cobb GP, Dickerson RL, Dixon KR, Kendall RJ, Smith EE, Solomon KR. 1996. An ecological risk assessment for the use of the biocide, dibromonitrilopropionamide (DBNPA) in industrial cooling systems. *Environmental Toxicology and Chemistry*, 15:21-30.

62 Solomon KR, DB Baker, P Richards, KR Dixon, SJ Klaine, TW La Point, RJ Kendall, JM Giddings, JP Giesy, LW Hall, Jr., CP Weisskopf, M Williams. 1996. Ecological risk assessment of atrazine in North American surface waters. *Environmental Toxicology and Chemistry*, 15:31-76.

61 Gaul SO, GR Stephenson, KR Solomon. 1995. Phytoxic interaction of tridiphane and metribuzin sensitive and tolerant soybean (*Glycine max*) and tomato (*Lycopersicon exculentum*). *Weed Science*, 43:358-364.

60 Kells AM, KR Solomon. 1995. Dislodgeability of pesticides from products made with recycled pesticide container plastics. *Archives of Environmental Contamination and Toxicology*. 28:134-138.

59 Kells AM KR Solomon. 1995. Leachability of pesticides from recycled pesticide container plastics. *Environmental Toxicology and Chemistry*. 14:383-388.

58 Archibald BA, KR Solomon, GR Stephenson. 1995. Estimation of pesticide exposure to greenhouse applicators using video imaging and other assessment techniques. *American Industrial Journal of Hygiene*, 56:226-235.

57 Liber K, KR Solomon. 1994. Acute and chronic toxicity of 2,3,4,6-tertrachlorophenol and pentachlorophenol to *Daphnia* and rotifers. *Archives of Environmental Contamination and Toxicology*, 26:212-221.

56 Archibald BA, KR Solomon, GR Stephenson. 1994. Survey of pesticide use by Ontario greenhouse chrysanthemum producers. *Bulletin of Environmental Contamination and Toxicology*, 53:486-492.

55 Archibald BA, KR Solomon, GR Stephenson. 1994. Fluorescent tracer and pesticide penetration through selected protective clothing. *Bulletin of Environmental Contamination and Toxicology*, 53:479-485.

54 Robinson, RD, JH Carey, KR Solomon IR Smith, MR Servos, KR Munkittrick. 1994. Survey of receiving water environmental impacts associated with discharges from pulp mills. *Environmental Toxicology and Chemistry*, 13:1075-1088.

53 Archibald BA, KR Solomon, GR Stephenson. 1994. Estimating pirimicarb exposure to greenhouse workers using video imaging. *Archives of Environmental Contamination and Toxicology*, 27:126-129.

52 Archibald BA, KR Solomon, GR Stephenson. 1994. A new procedure for calibrating the video imaging technique for assessing exposure. *Archives of Environmental Contamination and Toxicology*, 26:398-402

51 Thompson DG, SB Holmes, K Wainio-Keizer, L MacDonald, KR Solomon. 1993. Impact of Hexazinone and metsulfuron methyl on the zooplankton community of a boreal forest lake. *Environmental Toxicology and Chemistry*, 12:1709-1717.

50 Thompson DG, Holmes SB, Thomas D, MacDonald L, Solomon KR. 1993. Impact of hexazinone and metsulfuron methyl on the phytoplankton community of a mixed-wood/boreal forest lake. *Environmental Toxicology and Chemistry*, 12:1695-1707.

49 Carlo GL, Cole P, Miller AB, Munro IC, Solomon KR, Squire RA. 1992. Review of a study reporting an association between 2,4-dichlorophenoxyacetic acid and canine malignant lymphoma: Report of an Expert Panel. *Regulatory Toxicology and Pharmacology* 16:245-252

48 Hodge VA, Fan GT, Solomon KR, Kaushik NK, Leppard GG, Burnison BK. 1993. Effects of the presence and absence of various fractions of dissolved organic matter on the toxicity of fenvalerate to *Daphnia magna*. *Environmental Toxicology and Chemistry*, 12:167-176.

47 Harris SA, Solomon, KR. 1992. Percutaneous penetration of 2,4-dichlorophenoxyacetic acid and 2,4-D dimethylamine salt in human volunteers. *Journal of Toxicology and Environmental Health*, 36:233-240.

46 Liber K, Kaushik NK, Solomon KR, Carey JH. 1992. Experimental designs for aquatic mesocosm studies: A comparison of the "ANOVA" and "regression" design for assessing the impact of tetrachlorophenol on zooplankton populations in limnocorrals. *Environmental Toxicology and Chemistry*, 11:61-77.

45 Harris SA, Solomon KR, Stephenson GR. 1992. Exposure of Homeowners and Bystanders to 2,4-dichlorophenoxyacetic Acid (2,4-D). *Journal of Environmental Sciences and Health B*, 27:23-38.

44 Harris SA, Solomon KR. 1992. Human exposure to 2,4-D following controlled activities on recently sprayed turf. *Journal of Environmental Sciences and Health B*, 27:9-22.

43 Stephenson GL, NK Kaushik, KR Solomon. 1991. Chronic toxicity of a pure and technical grade pentachlorophenol to *Daphnia magna*. *Archives of Environmental Contamination and Toxicology*. 21:388-394.

42 Mahdavi A, Solomon KR, Hubert JJ. 1991. Effect of solanaceous hosts on toxicity and synergism of permethrin and fenvalerate in Colorado Potato Beetle (Coleoptera: Chrysomelidae) larvae. *Environmental Entomology*, 20: 427-432.

41 Martin PA, Solomon KR. 1991. Acute carbofuran exposure and cold stress: interactive effects in mallard ducklings. *Pesticide Biochemistry and Physiology*, 40, 117-127.

40 Martin PA, Solomon KR, Forsyth DJ, Boermans HJ, Westcott ND. 1991. Effects of exposure to carbofuran-sprayed vegetation on the behaviour, cholinesterase activity and growth of mallard ducklings (*Anas platyrhynchos*). *Environmental Toxicology and Chemistry*, 10:901-909.

39 Stephenson GR, Kaushik NK, Solomon KR. 1991. Acute toxicity of pure pentachlorophenol and a technical formulation to three species of *Daphnia*. *Archives of Environmental Contamination and Toxicology*, 20:73-80.

38 Munro IC, (*rapporteur*), Higginson J, Krewski D, Pegg AE, Rosenkranz H, Solomon KR, Weisburger E, Williams GM, Wogan GN. 1990. Safety assessment procedures for indirect food additives: An overview. *Regulatory Toxicology and Pharmacology* 12:2-12

37 Martin PA, Solomon KR, Boermans HJ. 1990. Effects of carbofuran ingestion on mallard ducklings. Journal of *Wildlife Management* 55:103-111.

36 Warner JE, KR Solomon. 1990. Acidity as a factor in leaching of copper, chromium and arsenic from CCA-treated dimension lumber. *Environmental Toxicology and Chemistry*, 9:1333-1339

35 Meru S, K Liber, K Stonefield, KR Solomon, GR Stephenson. 1990. Persistence and lateral movement of 2,4-D and picloram on power line rights-of-way. *Archives of Environmental Contamination and Toxicology*, 19:572-577

34 Stephenson GR, C Bowhey, K Liber, KR Solomon. 1990. Leachability, persistence and lateral movement of triclopyr (Garlon) in Canadian forestry soils. *Journal of Agricultural Food Chemistry,* 38:584-588

33 Solomon KR, GL Stephenson, NK Kaushik. 1989. Effects of methoxychlor on zooplankton in freshwater enclosures: Influence of enclosure size and number of applications. *Environmental Toxicology and Chemistry*, 8:659-670

32 Davis AR, KR Solomon and RW Shuel. 1989 Laboratory studies of honeybee larval growth and development as affected by systemic insecticides. *Journal of Apicultural Research*. 27:146-161.

31 Hamilton PB, GS Jackson, NK Kaushik, KR Solomon, GL Stephenson. 1988. The impact of two applications of atrazine on the plankton communities of in situ enclosures. *Aquatic Toxicology*, 13:124-140

30 Solomon KR, CS Bowhey, K Liber, GR Stephenson. 1988 Persistence of hexazinone (Velpar), triclopyr (Garlon) and 2,4-D in a northern Ontario aquatic environment. *Journal of Agricultural and Food Chemistry*, 36:1314-1318

29 Day KE, NK Kaushik, KR Solomon. 1987 The impact of fenvalerate on enclosed freshwater planktonic communities and its effects on in situ rates of filtration. *Canadian Journal of Fisheries and Aquatic Sciences,* 44:1714-1728.

28 Hamilton PB, GS Jackson, NK Kaushik, KR Solomon. 1987 The impact of atrazine on lake periphyton communities, including carbon uptake dynamics using track autoradiography. *Environmental Pollution*, 46:83-103.

27 Johnston AM, J Lohr, J Moes, KR Solomon, ER Zaborski. 1986. Toxicity of synergised and unsynergised nitromethylene heterocycle insecticide (SD 35651) to susceptible and resistant strains of *Musca domestica* L, [Diptera: Muscidae]. *Journal of Economic Entomology*, 79:1439-1442.

26 Herman D, NK Kaushik, KR Solomon. 1986. Impact of atrazine on periphyton in freshwater enclosures and some ecological consequences. *Canadian Journal of Fisheries and Aquatic Science*, 43:1917-1925.

25 Stephenson GL, NK Kaushik, KR Solomon, KE Day, P Hamilton. 1986. Impact of methoxychlor on freshwater plankton communities in limnocorrals. *Environmental Toxicology and Chemistry*, 5:587-603.

24 Solomon KR, JY Yoo, D. Lean, NK Kaushik, KE Day, GL Stephenson. 1986. Methoxychlor distribution, dissipation and effects in freshwater limnocorrals. *Environmental Toxicology and Chemistry*, 5:577-586.

23 Kaushik NK, Solomon KR, Stephenson GL, Day KE. 1986. Use of Limnocorrals in Evaluating the Effects of Pesticides on Zooplankton Communities. In: Cairns J, Jr., editor. *Community Toxicity Testing*. Vol. ASTM STP 920. Philadelphia, PA, USA: Society for Testing and Materials..

22 Kaushik NK, GL Stephenson, KR Solomon, KE Day. 1985. Impact of permethrin on zooplankton communities using limnocorrals. *Canadian Journal of Fisheries and Aquatic Science*, 42:77-85.

21 Solomon KR, JY Yoo, D Lean, NK Kaushik, KE Day, GL Stephenson. 1985. Dissipation of permethrin in limnocorrals. *Canadian Journal of Fisheries and Aquatic Science*, 42:70-76.

20 MacDonald RS, KR Solomon, GA Surgeoner, CR Harris. 1985. Laboratory studies on the mechanisms of resistance to permethrin in a field-selected strain of house flies. *Pesticide Science*, 16:10-16.

19 Jackson GS, P Hamilton, KR Solomon, NK Kaushik. 1984. A computerized plankton counter. *Hydrobiologia*, 118:225-228.

18 Stephenson GL, P Hamilton, NK Kaushik, JB Robinson KR Solomon. 1984. The effect of enclosure size on the spatial distribution of zooplankton. *Canadian Journal of Fisheries and Aquatic Science*, 41:1048-1054.

17 Thompson DG, GR Stephenson, KR Solomon, AV Skelpasts. 1984. Persistence of (2,4-dichlorophenoxy)acetic acid and 2-(2,4-dichlorophenoxy)propionic acid in agricultural and forest soils of Northern and Southern Ontario. *Journal of Agricultural Food Chemistry*, 32:578-581.

16 MacDonald RS, GA Surgeoner, KR Solomon CR Harris. 1983. Field studies on development of resistance to permethrin and dichlorvos by the house fly (Diptera: Muscidae) following continuous and alternating selection pressure. *Canadian Entomologist,* 115:1555-1561.

15 MacDonald RS, GA Surgeoner, KR Solomon, CR Harris. 1983. Effect of four spray regimes on the development of permethrin and dichlorvos resistance, in the laboratory, by the house fly (Diptera: Muscidae). *Journal of Economic Entomology*, 76:417-422.

14 Solomon KR, K Smith, GL Stephenson. 1982. Depth integrating samplers for use in limnocorrals. *Hydrobiologia* 94:71-75.

13 Sharom, M, Solomon KR. 1982. The influence of adsorption on glass, pH and temperature on the disappearance of permethrin in aqueous systems. *Environmental Pollution, B*, 4:269-279.

12 Sharom MS, Solomon KR. 1981. The adsorption-desorption degradation and distribution of permethrin in aqueous systems. *Journal of Agricultural Food Chemistry*, 29:1122-1125.

11 Sharom MS, Solomon KR. 1980. Adsorption and desorption of permethrin and other pesticides on glass and plastic materials used in bioassay procedures. *Canadian Journal of Fisheries and Aquatic Science*, 38:199-204.

10 Brill JH, Solomon KR. 1979. A bioassay method for the pheromones of the Bont Tick *Amblyomma hebraeum* Koch. *Onderstepoort Journal of Veterinary Research*, 46:59-60.

9 Solomon KR, Baker MK, Heyne H, van Kleef J. 1979. The use of frequency diagrams in the survey of resistance to pesticides in ticks in Southern Africa. *Onderstepoort Journal of Veterinary Research*, 46:171-177.

8 Solomon KR, Evans AA. 1978. Activity of juvenile hormone mimics in larval *Amblyomma hebraeum* Koch. (Acarina: Metastriata: Ixodidae). *Onderstepoort Journal of Veterinary Research*, 45:39-42.

7 Solomon KR Evans AA. 1977. Neurosecretion in *Ornithodoros savignyi* (Adouin) (Ixodoidea, Argaside). I. The distribution of neurosecretory cells in the brain. Onderstepoort Journal of Veterinary Research, 44:127-130.

6 Solomon KR, Kuhn P. 1976. A photoelectric counter for tick larvae and small insects. *Journal of Economic Entomology*, 69:17-20.

5 Solomon KR. 1975. The activity and metabolism of the juvenile hormone mimic Altosid^{R} in *Tenebrio molitor* L. and *Oncopeltus fasciatus* (Dallas) in relation to possible practical applications. *Proc. II Congress of the Entomological Society of South Africa*, 53-61.

4 Solomon KR, Walker WF. 1974. Juvenile hormone synergists: a possible case of hasty conclusion? *Science* 185:461-462.

3 Solomon KR, Metcalf, RL. 1974. The effect of piperonyl butoxide and triorthocresyl phosphate on the activity of metabolism of Altosid^{R} (isopropyl, 11-methoxy,3,7,11-trimethyldodeca-2,4-dienoate) in *Tenebrio molitor* L. and *Oncopeltus fasciatus* (Dallas). *Pesticide Biochemistry and Physiology*, 4:127-234.

2 Solomon KR, Bowlus SB, Metcalf, RL, Katzenellenbogen JA. 1973. The effect of piperonyl butoxide and triorthocresyl phosphate on the activity of juvenile hormone mimics and their sulphur isosteres in *Tenebrio molitor* L. and *Oncopeltus fasciatus* (Dallas). *Life Science* 13:733-742.

1 Solomon KR, Allanson BR. 1968. The effects of exposure to low temperatures on the serum proteins of *Tilapia mossambica* Peters. *Comparative Biochemistry and Physiology* 25:485-492.

17.4 PAPERS IN CONFERENCE PROCEEDINGS

17 Solomon KR. 2009. North American Perspective. Workshop on Probabilistic Approaches for Marine Hazard Assessment. ECETOC Workshop Report No. 15 p 12-14.

16 Gantner N, Muir DCG, Power M, Psenner R, Solomon KR. 2006. Effects of climate change on mercury concentrations in landlocked Arctic char (*Salvelinus alpinus*) in the Canadian high Arctic. Proceedings of the COE International Symposium. Ehime University. p 47-50

15 Belknap A, Shaughnessy K, MacLatchy D, Solomon KR, Hewitt M. 2004. Method development for the identification of hormonally active components in bleached kraft chemical recovery condensates. In Borton DL, Hall TH, Fisher RP, Thomas JF (Eds). Method development for the identification of hormonally active components in bleached kraft chemical recovery condensates. DEStech Publishers, Inc., Lancaster, PA, USA. pp 374-383.

14 Solomon KR. 2001. Probabilistic risk assessment of pesticides. Forster E, Streloke M. (Eds) Proceedings of the Workshop on Risk Assessment and Risk Mitigation Measures in the Context of the Authorization of Plant Protection Products 28-29 September, 1999. Heft 383, (2001) Parey Buchverlag, Berlin, FRG, pp 6-16.

13 Solomon, KR, Bergman H, Mackay D, McKague B. 1995. Chlorine dioxide for the bleaching of pulp: characterizing the ecotoxicological risks. Preprints of papers presented at the 210th American Chemical Society Meeting, Chicago, IL, August 20-24, 1995 Vol 35 No. 2, pp 350-353.

12 Solomon KR, Bergman H, Mackay D, McKague B. 1994. A review and assessment of the ecological risks associated with the use of chlorine dioxide for the bleaching of pulp. Proceedings of the 1994 International Pulp Bleaching Conference, Vancouver, June 13-16, 1994. Canadian Pulp and Paper Association, Montreal, PQ, Canada pp 340-348

11 Solomon KR. 1992. Assessing Pesticide Impacts in Lentic Systems Using Limnocorrals. Effects of pesticides on aquatic organisms. 74th table ronde Roussel UCLAF. Maison de la chimie - Paris, France, December 3-4, 1992.

10 Solomon, KR, Kaushik NK, Herman D, Stephenson GL, Day KE, Hamilton P, Jackson G. 1992. Use of enclosures for assessing effects of pesticides in freshwater aquatic ecosystems. Marine ecosystem enclosed experiments: Proceedings of a Symposium held in Beijing People's Republic of China, 9-14 May 1987. International Development Research Centre, Ottawa, ON, Canada pp 87-105.

9 Buchanan RD, Solomon KR. 1990. Leaching of CCA-PEG and CuNap Wood Preservatives from Pressure Treated Utility Poles, and its Associated Toxicity to the Zooplankton, *Daphnia magna*. Proceedings of the 11th Annual Meeting of the Canadian Wood Preservation Association, CITW, Vancouver, BC Canada pp130-143

8 Solomon KR, Liber K. 1988. Fate of pesticides in aquatic mesocosm studies -An overview of methodology. Proceedings of the Brighton Crop Protection Conference, Brighton, England, November pp. 139-148.

7 Munro IC, Solomon KR. 1987. Mechanistic Factors in the Interpretation of Carcinogen Risk Assessment. Ed. R.S. McColl. University of Waterloo Press, Waterloo, ON, Canada pp 83-94.

6 Munro IC, Solomon KR, Lock JD. 1985. Toxicological evaluation of Great Lakes drinking water. Proceedings of the Ontario Ministry of the Environment Technology Transfer Conference, Dec. 11-12, 1985.

5 Solomon KR. 1983. Report of the questionnaire workshop on Training of Aquatic Toxicologists. Canadian Technical Reports of Fisheries and Aquatic Science, 1151: 213-216.

4 Yoo JY, Solomon KR. 1983. Persistence of permethrin, atrazine and methoxychlor in a natural lake system. Canadian Technical Reports of Fisheries and Aquatic Science, 1151: 164-167

3 Solomon KR, Kaushik NK, Smith K, Guest G, Yoo JY. 1980. Use of limnocorrals in studying the effects of pesticides in aquatic ecosystems. Canadian Technical Reports of Fisheries and Aquatic Science, 975:1-11.

2 Solomon, KR, Heyne H, van Kleef J. 1980. The use of a population approach in the survey of resistance to pesticides in ticks in Southern Africa. Recent Advances in Acarology Vol. II (Ed. J.C. Rodriques), pp 65-70.

1 Solomon KR. 1975. The activity and metabolism of the juvenile hormone mimic Altosid (R) in *Tenebrio molitor* L. and *Oncopeltus fasciatus* (Dallas) in relation to possible practical applications. Proceedings of the First Congress of the Entomological Society of Southern Africa, 53-61.

17.5 PUBLICATIONS IN NON-REFEREED SCIENTIFIC JOURNALS

3 Sanderson H, Solomon KR. 2003. Precautionary limits to environmental science and risk management - three types of error. The Journal of Transdisciplinary Environmental Studies 2:1-5.

2 Solomon KR, Giddings JM, Hall LW, Jr. 2001. Olfactory measures of effect, population endpoints in endangered salmon, and probabilistic risk assessment. SETAC Globe 2001, Volume 2, Number 3 pages 21-22.

1 Solomon KR, MacDonald, S, Surgeoner G, Harris CR. 1991. Housefly resistance to pyrethroids. Pyrethrum Post, 17: 1-7.

17.6 PUBLICATIONS IN NON-REFEREED TRADE AND TECHNICAL JOURNALS

1 Archibald B., Solomon KRS, Stephenson GR. 1993. Estimation de L'Exposition aux Pesticides dans les serres. Les Production Option Serre. Option Serre, March 1993. Quebec.

17.7 BOOK REVIEWS

3 Inorganic Contaminants of Surface Water: Research and Monitoring Priorities. By James W. Moore. Springer-Verlag: New York. 1991. Published in the Journal for the American Chemical Society, Vol. 113, No. 18, 1991.

2 Environments at Risk: Case Histories of Impact Assessment. Derek Ellis. Springer-Verlag, New York, 1989. Published in American Zoologist (1990).

1 Experimental Toxicology: The Basic Principles. Edited by D. Anderson and D. M. Conning, Royal Society of Chemistry, London. Published in Pesticide Biochemistry and Physiology, 37: 99-100 (1990).

17.8 THESES

61 De Jourdan, B. 2012. Environmental fate and toxicity of three brominated flame retardants in aquatic mesocosms. Ph.D. Thesis, School of Environmental Sciences, University of Guelph, September 2012

60 Vanengen, R. 2012. Assessment of the physical and biological effects of mine-related total suspended solids in arctic lakes. M.Sc. Thesis, School of Environmental Sciences, University of Guelph, April 2012

59 Baxter, L. 2011. Effects of atrazine and phosphorus on growth of aquatic 3 autotrophs and pond snails in outdoor microcosms. M.Sc. Thesis, School of Environmental Sciences, University of Guelph, April 2011.
58 Van Geest, JL. 2010. Bioaccumulation of sediment-associated contaminants in freshwater organisms: Development and standardization of a laboratory method. Ph.D. Thesis, School of Environmental Sciences, University of Guelph, September 2010
57 Hillis, D. 2008. Arbuscular mycorrhizal fungi in ecological risk assessment: a case study with selected pharmaceuticals. Ph.D. Thesis, Department of Environmental Biology, University of Guelph, December 2008.
56 Gantner N. 2008. Effects of climate change on mercury concentrations in arctic char (Salvelinus alpinus) in the high arctic. Ph.D. Thesis, Department of Environmental Biology, University of Guelph, December 2008.
55 Rickard J. 2008. Colonization, fecundity and feeding behaviour of soybean aphid, on susceptible and resistant soybean varieties. M.Sc. Thesis, Department of Environmental Biology, University of Guelph, December 2008.
54 Dussault EAM. 2008. Effects of Pharmaceuticals and Personal Care Products in Benthic Invertebrates. Ph.D. Thesis. University of Guelph, April 2008
53 Frank RA. 2008. Fractionation and toxicity of naphthenic acids from oil-sand waste. Ph.D. Thesis, University of Guelph, April 2008
52 Fraser B. 2006. Environmental chemistry and toxicology of carbamazepine. M.Sc. Thesis, University of Guelph, November 2006.
51 Houde M. 2006. Emerging organohalogen contaminants in bottlenose dolphins (*Tursiops truncatus*). Ph.D. Thesis, University of Guelph, April 2006.
50 Buckman A. 2006. Toxicokinetics and biological effects of PCBS and their hydroxylated metabolites in rainbow trout. Ph.D. Thesis, University of Guelph, April 2006
49 Brain RAB. 2006. Evaluation of the phytotoxic effects of pharmaceuticals in aquatic higher plants. Ph.D. Thesis, University of Guelph, March 2006.
48 MacDonald M. 2005 Fluorotelomer acid toxicity to aquatic organisms. M.Sc. Thesis, University of Guelph, September 2005.
47 Lissemore L. 2005. Pharmaceuticals in agricultural surface waters: detection, distribution, exposure and risk. Ph.D. Thesis, University of Guelph, September 2005.
46 Smithwick M. 2005. Geographical, biological, temporal trends, and accumulation parameters of polyfluourinated compounds. M.Sc. Thesis, University of Guelph, March 2005.
45 Belknap AM. 2005. Identification of hormonally-active compounds in bleached kraft chemical recovery condensates. M.Sc. Thesis, University of Guelph, March 2005.
44 Rattan K. 2005. Establishing a reference condition to assess the effects of forest harvesting on phytoplankton community structure in boreal lakes. M.Sc. Thesis, University of Guelph, January 2005
43 Warne A. 2004. The effects of antibiotics on the structure and function of freshwater sediment bacterial communities. M.Sc. Thesis, University of Guelph, December 2004
42 Wilson CJ. 2004. Pharmaceuticals in the environment: assessment of effects on freshwater ecosystems using microcosms. M.Sc. Thesis, University of Guelph, December 2004.
41 Johnson DJ. 2004. Risk assessment of selective serotonin reuptake inhibitors: Comparing methods in tiered environmental risk assessment. M.Sc. Thesis, University of Guelph, April 2004.
40 Quade SC. 2003. Determination of tetrabromobisphenol A in sediment and sludge. M.Sc. Thesis, University of Guelph, September 2003.
39 Stephenson GL. 2003. Terrestrial test methods for plants and soil invertebrates. Ph.D Thesis, University of Guelph, April, 2003.
38 Princz J. 2003. Ecotoxicological and chemical evaluation of soils contaminated with motor gasoline, and benzene, toluene, ethylbenzene, and xylenes (BTEX). M.Sc. Thesis University of Guelph, March, 2002
37 Hoekstra PF. 2003. Bioaccumulation and biotransformation of persistent organochlorine contaminants in the arctic marine ecosystem. Ph.D Thesis, University of Guelph, March, 2003.
36 Boudreau TM. 2002. Toxicological evaluation of perfluorinated organic acids to selected freshwater primary and secondary trophic levels under laboratory and semi-natural field conditions. M.Sc. Thesis University of Guelph, December, 2002
35 Hanson, ML. 2002. *Myriophyllum spp.* in ecological risk assessment: A case study with haloacetic acids. Ph.D Thesis, University of Guelph, September 2002
34 Martin JW. 2002. Environmental (per-)halogenated acids; detection, distribution, sources, and bioaccumulation. Ph.D Thesis, University of Guelph, April 2002
33 Luross JM. 2001. Spatial and temporal distributions of polybrominated diphenyl ethers in lake trout (*Salvinius namaycush*) from the Great Lakes. MSc Thesis, University of Guelph, August 2001
32 Munro, KA. 2001. Population-level and suborganismal responses in fish due to chronic creosote exposure in aquatic microcosms. MSc Thesis, University of Guelph, August 2001. 201 p

31 Chappel, MJ. 2001. Evaluation of the toxicity of pesticides mixtures to fathead minnows (*Pimephales promelas*) using probabilistic ecological risk assessment and toxic equivalency methods. MSc Thesis, University of Guelph, August 2001. 219 p.
30 Farwell A. 2000. Stable isotope study of riverine benthic food webs influenced by anthropogenic developments. PhD Thesis, University of Guelph, January 2000. 192 p
29 Marwood CA. 1999. Chlorophyll fluorescence as a mechanistic bioindicator of photosynthetic inhibition in aquatic plants. PhD Thesis, University of Guelph, July 1999. 288 p
28 Takacs P. 1999. Evaluation of probabilistic ecological risk assessment methodology using aquatic microcosms and azinphos-methyl. MSc Thesis, University of Guelph, May 1999. 240 p.
27 Sonnenberg HE. 1998. Extractable organochlorine (EOCl) in white sucker (*Catostomus commersoni*) exposed to bleached kraft mill effluents. MSc Thesis, University of Guelph, August 1998. 141 p.
26 Knutson S. 1998. Effects of phytosterols and estradiol on maturation and reproduction in fathead minnows. MSc Thesis, University of Guelph, 1998. 100 p.
25 Hewitt, LM. 1997. An assessment of the contamination and effects of lampricide formulations of 3-triflurormethyl-4-nitrophenol (TFM). PhD Thesis, University of Guelph, July 1997. 228 p.
24 Houghton D. 1997. Development and validation of fluorescent tracer method to estimate dermal exposure to pesticides used indoors. PhD Thesis, University of Guelph, 1997. 462 p.
23 Lewis J. 1997. Bioindicators of polycyclic aromatic hydrocarbon PAH exposure in rainbow trout (*Onchorynchus mykiss)* and fathead minnows (*Pimiphales promelas*). MSc Thesis, University of Guelph, May 1997. 81 p.
22 McCann J. 1997. The use of growth and membrane integrity assays as bioindicators of creosote effects in *Myriophyllum spicatum* L. growth. MSc Thesis, University of Guelph, February 1997. 165 p.
21 Wisner B. Individual and population-level effects of liquid creosote on fathead minnows (Pimephales promelas). Diploma-Biologic an der Mathematisch-Naturwissenschaftlichen Fakultät der Rheinisch-Westphälischen Technischen Hochschule Aachen, FRG, July 1997. 108 p.
20 O'Brien GM. 1996. Penetration and extractability of pesticides into and from plastic used for container manufacture and recycling. M.Sc Thesis, University of Guelph, December 1996. 118 p.
19 Novak L. 1994. Behavioural responses of rainbow trout (*Oncorphynchus mykiss*) to selected pulp and paper mill effluent constituents. M.Sc. Thesis, University of Guelph, September 1994. 111 p.
18 Robinson R. 1994. Endocrine effects of pulp mill effluents on non-target aquatic organisms. Ph.D. Thesis, University of Guelph, August 1994. 150 p.
17 Archibald BA. 1993. Video Imaging as a Technique for Estimating Pesticide Exposure in Greenhouse Chrysanthemum Production. Ph.D. Thesis, University of Guelph, May 1993. 119 p.
16 Vandersluis (Kells) AM. 1993. Dislodgeability and leachability of pesticides from products made from recycled plastic pesticide containers. M.Sc. Thesis, University of Guelph, May 1993. 102 p.
15 Thompson DG. 1992. The effects of hexazinone and metsulfuron methyl in aquatic ecosystems. Ph.D. Thesis, University of Guelph, May 1992. 163 p.
14 Fan GT. 1991. The effect of dissolved organic matter on fenvalerate toxicity to *Daphnia magna*. M.Sc. Thesis, University of Guelph, July 1991. 62 p.
13 Buchannan RD. 1991. Persistence, leaching and availability of chromated-coper-arsenate polyethylene glycol, copper naphthenate and pentachlorophenol wood preservatives from pressure treated utility poles. M.Sc Thesis, University of Guelph, May 1991. 92 p.
12 Harris SA. 1991. Exposure of homeowners, professional applicators and bystanders to 2,4-dichlorophenoxyacetic acid (2,4-D). M.Sc. Thesis, University of Guelph, May 1991. 85 p.
11 Fortin C. 1991. Acute and chronic toxicity of technical and slow-release formulations of methoprene in selected zooplankton. Ph.D. Thesis, University of Guelph, April 1991. 141 p.
10 Martin PA. 1990. Effects of Carbofuran on Mallard Ducklings (*Anas platyrynchos*). M.Sc. Thesis, University of Guelph, November 1990. 104 p.
9 Liber K. 1990. Persistence and biological effects of a commercial tetrachlorophenol formulation in aquatic ecosystems: Laboratory and limnocorral studies. Ph.D. Thesis, University of Guelph, 1990. 184 p.
7 Warner JE. 1990. Persistence, leaching, and bioavailability of CCA and pentachlorophenol wood preservatives. M.Sc. Thesis, University of Guelph, May 1990. 87 p.
6 Mahdavi A. 1990. Insecticide resistance mechanisms in Ontario strains of the Colorado Potato Beetle. Ph.D. Thesis, University of Guelph, May 1990. 120 p.
5 Gaul SO. 1988. Interaction of tridiphane and metribuzin in soybean and tomato. Ph.D. Thesis, University of Guelph, April 1988. 156 p.
4 Lungle ML. 1988. Studies of the dissipation and effects of chlorpyrifos in microcosms. Ph.D. Thesis, University of Guelph, February 1988. 315 p.
3 Valdes MT. 1983. Toxicity and synergism of permethrin to *Trichogramma minutum* Riley and *T. fuentes* Torre (Hymenoptera: Trichogrammatidae) M.Sc. Thesis, University of Guelph, December 1983. 85 p.

2 Thompson DG. Studies on the persistence of two phenoxy herbicides in agricultural, forestry and turfgrass environments. M.Sc. Thesis, University of Guelph, April 1983. 108 p

1 MacDonald RS. The management and mechanisms of resistance to permethrin in a field strain of the house fly, *Musca domestica* L. (Diptera: Muscidae) M.Sc. University of Guelph, January 1983. 58 p

17.9 AUTHOR OR CONTRIBUTING AUTHOR OF THE FOLLOWING SCIENTIFIC REPORTS AND PAPERS

104 Bestari KT, Solomon KR, Henriquez N. 2013. Determination of Dislodgeable Pesticide Residues from Composite Bricks made from Recycled Plastic Pesticide Containers. September 20, 2013

103 Bestari KT, Solomon KR, Henriquez N. 2013. Preliminary Screening Study Determination of Dislodgeable Tralopyril Residues from Themoplastic Polyurethane (TPU Treated with 3% and 4.5% ECONEA® Brand Tralopyril Antifoulant. August 1, 2013.

102 Bestari KT, Solomon KR, Henriquez N. 2013. Determination of Dissipation and Dislodgeability of Greenhouse-Applied Pesticide (Flonicamid) and the Potential Chronic Exposure of Workers in Ornamental Greenhouse Plants (Chrysanthemums). January 13, 2013.

101 Bestari KT, Solomon KR, Henriquez N. 2013. Determination of Dissipation and Dislodgeability of Greenhouse-Applied Pesticide (Propamocarb.HCl) and the Potential Chronic Exposure of Workers in Ornamental Greenhouse Plants (Chrysanthemums). January 30, 2013.

100 Bestari KT, Solomon KR, Henriquez N. 2013. Determination of Dissipation and Dislodgeability of Greenhouse-Applied Pesticide (Pyridalyl) and the Potential Chronic Exposure of Workers in Ornamental Greenhouse Plants (Chrysanthemums). April 19, 2013.

99 Bestari KT, Solomon KR, Henriquez N. 2013. Determination of Dissipation and Dislodgeability of Greenhouse-Applied Pesticide (Novaluron) and the Potential Chronic Exposure of Workers in Ornamental Greenhouse Plants (Chrysanthemums). April 19, 2013.

98 Bestari KT, Solomon KR, Henriquez N. 2012. Determination of Dissipation and Dislodgeability of Greenhouse-Applied Pesticide (Myclobutanil) and the Potential Chronic Exposure of Workers in Ornamental Greenhouse Plants (Chrysanthemums). November 7, 2012.

97 Bestari KT, Solomon KR, Henriquez N. 2012. Determination of Dislodgeable Tebuconazole residues from Spruce and Southern Yellow Pine (SYP) Boards Pressure Treated with Formulation JJT 4929-1. February 15, 2012

96 Bestari KT, Solomon KR, Henriquez N. 2012. Determination of Dislodgeable Triadimefon residues from Spruce and Southern Yellow Pine (SYP) Boards Pressure Treated with Formulation JJT 4929-1. February 15, 2012

95 Bestari KT, Solomon KR, Henriquez N. 2012. Determination of Dislodgeable Imidacloprid residues from Spruce and Southern Yellow Pine (SYP) Boards Pressure Treated with Formulation JJT 4929-1. February 15, 2012

94 Giesy JP, Solomon KR, Kacew S. 2011. Report of the Board of Review for Decamethylcyclopentasiloxane (Siloxane D5). Environment Canada, Ottawa, ON, Canada October 20, 2011. 83 p.

93 Bestari KT, Solomon KR, Henriquez N. 2012. A Preliminary Determination of Dislodgeable Pesticide Residues from Refuse Plastic Bags Manufactured in Swaziland. June 4, 2012

92 Bestari KT, Solomon KR, Henriquez N. 2011. Leachability of Pesicides from 100-m Long Tile drains. February 7, 2011

91 Bestari KT, Solomon KR, Henriquez N. 2010. Leachability of Pesicides from Multiple Sources of Tile drains. August 11, 2010.

90 Bestari KT, Solomon KR, Henriquez N. 2009. Determination of Dislodgeable Tebuconazole Residues from Spruce and Southern Yellow Pine (SYP) Boards Pressure Treated with Formulation AWP-0911-4. December 7, 2009

89 Bestari KT, Solomon KR, Cahill S. 2008. Field Monitoring and Re-Evaluation of Workers' Dermal Exposures to Didecyldimethylammonium Chloride (DDAC) Used in the Protection of Cut Lumber (Field Study). Work for Sapstain Industry Group (SIG), September 22, 2008.

88 Bestari KT, Solomon KR, Cahill S. 2007. Determination of ADBAC Air Concentrations Used in Household Humidifiers. Report to Lonza, Inc. April 12, 2007.

87 Bestari KT, Solomon KR, Cahill S. 2007. Wipe Study to Define Dislodgeable Residues in Wood Pressure treated with an ACQ Type C Formulation (Outdoor Study). Report to Chemical Specialties, Inc. and Timber Specialties, Co. March 23, 2007.

86 Bestari KT, Solomon KR, Cahill S. 2006. ADMIRE 240F - Determination of Dermal and Inhalation Exposure of Workers during On-Farm Seed Piece Treatment of Potatoes. Report to Bayer CropScience. May 17, 2006.

85 Bestari KT, Solomon KR, Rietzma T, Henriquez N. 2006. Determination of Dislodgeable Carboquat residues from Heartwood Boards Pressure treated with an Ammoniacal Copper Quat (ACQ) Formulation (Outdoor Study). Report to Lonza Inc. March 28, 2006

84 Bestari KT, Solomon KR, Rietzma T. 2006. Determination of Dislodgeable Carboquat residues from Sapwood Boards Pressure treated with an Ammoniacal Copper Quat (ACQ) Formulation (Outdoor Study). Report to Lonza Inc. February 16, 2006.

83 Bestari KT, Solomon KR, Rietzma T. 2006. Determination of Dislodgeable Bifenthrin Residues from Bifenthrin-Impregnated Plastic Films. Report to FMC Corp. January 30, 2006

82 Bestari KT, Solomon KR, Henriquez N. 2005. Analysis of Dislodgeable ADBAC Residues from Wooden Boards Treated with ACQ-C. Report to Lonza Inc. December 19, 2005.

81 Bestari KT, Solomon KR, Henriquez N. 2005. Analysis of Dislodgeable Carbo NT (Carboquat) Residues from Wooden Boards Treated with ACQ-D. Report to Lonza Inc. November 29, 2005.

80 Bestari KT, Solomon KR, Rietzma T. 2005. Comparison of Dislodgeable Residues from Carboquat Pressure Treated Lumber Using Hand Rubbing Versus Rubbing with Wet and Dry Polyester Wipes. Report to Lonza Inc. July 25, 2005.

79 CICAD/OAS. 2005. The Toxicology of Selected Chemicals Used in the Production and Refining of Cocaine and Heroin: A Tier-two Assessment. Washington, DC, USA: CICAD, Organization of American States. OAS/CICAD 2005-01, July 31, 2005. x + 35 + 427 p (Editor). http://www.cicad.oas.org/Desarrollo-Alternativo/ENG/Projects%20By%20Country/Colombia/OAS-CICAD-Tier-2-Hazard-Assessment-July-2005%5B1%5D.pdf.

78 Bestari KT, Solomon KR, Rietzma T. 2005. Method Development and Validation of Methods to Extract and Analyze Carboquat Residues from the Palm of the Human Hand and from Dry and Wet Polyester Wipes. Report to Lonza Inc. April 6, 2005.

77 Solomon KR, Anadón A, Cerdeira A, Marshall J, Sanin L-H. 2005. Environmental and human health assessment of the aerial spray program for coca and poppy control in Colombia. Washington, DC, USA: Inter-American Drug Abuse Control Commission (CICAD) section of the Organization of American States (OAS). 121 p, March 31, 2005.

76 Bestari KT, Solomon KR, Rietzma T. 2005. Dislodgeable carboquat residues from ACQ Treated lumber by rubbing with dry polyester wipes. Report to Georgia-Pacific. March 15, 2005

75 CICAD/OAS. 2004. The Toxicology of Chemicals Used in the Production and Refining of Cocaine and Heroin: A Tier-one Assessment. Washington, DC, USA: CICAD, Organization of American States. OAS/CICAD 2004-01, November 2004. 536 p. (Editor).

74 Bestari KT, Solomon KR, Rietzma T. 2004. Wipe samples of surface dislodgeable bifenthrin residues from plastic sheet. Report to FMC Corp. November 22, 2004.

73 Bestari KT, Solomon KR, Rietzma T. 2004. Method development and determination of dislodgeable isothiazolin derivatives (RH-573 and RH-651) and copper from treated lumber by rubbing with dry polyester wipes. Report to Georgia-Pacific. September 21, 2004.

72 Bestari KT, Solomon KR. 2004. Sampling of water used to wash pesticide recycling plastic chips at the EnviroTech plastics recycling facility in Windsor, Ontario. Report to CropLife Canada. September 8, 2004

71 Bestari KT, Solomon KR, Rietzma T. 2004. Method development and dislodgeability of sample wipe test analysis of bifenthrin from treated wood. Report to FMC Corp. July 14, 2004

70 Bestari KT, Solomon KR, Rietzma T. 2004. Method development of DDAC extraction and analysis from fish. Report to Lonzagroup (Lonza Inc.). June 1, 2004.

69 Bestari KT, Solomon KR, Henriquez N. 2004. Method development of analysis of carboquat from water and sediment (LC-MS). Report to Lonzagroup (Lonza Inc.). May 2004.

68 Bestari KT, Solomon KR, Henriquez N. 2004. Hydrolytic stability of FMB AO-8 (CAS # 2605-78-9) as a function of pH (OECD 111). Report to Lonzagroup (Lonza Inc.) through Stantec. GLP (Study # 62773911-03). April 20, 2004.

67 Bestari KT, Solomon KR, Henriquez N. 2004. Method development of dislodgeability of carboquat and copper from treated lumber using dry polyester wipes. Report to Lonzagroup (Lonza Inc.). February 2004.

66 Ritter L, Arbuckle T, Dawson J, Infante-Rivard C, Solomon KR. 2004. Report of the 2,4-D Science Advisory Panel. Report to the PMRA, January 2004.

65 Bestari KT, Solomon KR, Henriquez N. 2003. Method development: Extraction of carboquat from algal culture medium. Report to Lonzagroup (Lonza Inc.). December 6, 2003.

64 Bestari KT, Solomon KR, Henriquez N. 2003. Method development: Extraction of carboquat from sediment. Report to Lonzagroup (Lonza Inc.). December 6, 2003.

63 Bestari KT, Solomon KR, Henriquez N. 2003. Method development of DDAC extraction and analysis in fruit. Report to ICA Laboratories, South Africa, November 6, 2003.

62 Solomon KR, Bestari KT, Henriquez N. 2003. Measurement of 2,4-D in urine of pesticide container collectors. Report to CropLife Canada September 16, 2003.

61 Bestari KT, Solomon KR, Henriquez N. 2003. Measurement of pesticide residues in air inside the plant at Everwood Agricultural Products International Inc. in Tillsonburg, Ontario. Report to CropLife Canada May, 2003.

60 Bestari KT, Solomon KR, Henriquez N. 2003. Method development for the extraction and analysis of DDAC as low as 1 ppb in water using derivatization of DDAC with Orange II to form an ion pair. Report to Lonzagroup (Lonza Inc.), November 22, 2002.
59 Solomon KR, Tang X, Wilson SR, Zanis P, Alkiviadis F Bais. 2003. Chapter 6: Changes in tropospheric composition and air quality due to stratospheric ozone depletion. In: Environmental Effects of Ozone Depletion and its Interactions with Climate Change: 2002 Assessment. United Nations Environmental Programme. Nairobi, March 2003.
58 Bestari KT, Solomon KR, Henriquez N. 2002. Third study to determine the effect of dermally administered IPBC on serum free iodide levels in human volunteers. Report to Lonzagroup (Lonza Inc.), November 22, 2002.
57 Bestari KT, Solomon KR, Henriquez N. 2002. Method validation: Extraction and quantitation of iodide as the 2-iodoethanol derivative in human urine. Report to Lonzagroup (Lonza Inc.), October, 2002.
56 Bestari KT, Solomon KR, Henriquez N. 2002. Method validation: Extraction and quantitation of iodide as the 2-iodoethanol derivative in human serum. Report to Lonzagroup (Lonza Inc.), October, 2002.
55 Bestari KT, Solomon KR, Henriquez N. 2002. Study to determine the effect of adding 100 g of iodide to the diet of human volunteers on serum free iodide levels. Report to Lonzagroup (Lonza Inc.), October 24 2002.
54 Bestari KT, Solomon KR, Henriquez N. 2002. Determination of the rate and extent of deiodination of IPBC in urine of human volunteers. Report to Lonzagroup (Lonza Inc.), September 24 2002.
53 Bestari KT, Solomon KR, Henriquez N. 2002. Determination of the rate and extent of deiodination of IPBC in serum of human volunteers. Report to Lonzagroup (Lonza Inc.), September 24 2002.
52 Bestari KT, Solomon KR, Henriquez N. 2002. Determination of the rate and extent of deiodination of IPBC in deionized water. Report to Lonzagroup (Lonza Inc.), September 19 2002.
51 Bestari KT, Solomon KR, Henriquez N. 2002. Determination of the effect of dermally administered IPBC/cyclodextrin complex on serum free iodide levels in human volunteers. Report to Lonzagroup (Lonza Inc.), September 6 2002.
50 Bestari KT, Solomon KR, Henriquez N. 2002. Bioavailability of polycyclic aromatic hydrocarbons (PAHs) in soil. Report to Dillon Consulting, August 12 2002.
49 Bestari KT, Solomon KR, Henriquez N. 2002. Preliminary study to determine the effect of dermally administered IPBC on serum free iodide levels in human volunteers. Report to Lonzagroup (Lonza Inc.), August 9 2002.
48 Solomon KR, 2002. Quality control program for products made from recycled plastic pesticide containers. Report to Croplife Canada, July 24, 2002.
47 Bestari KT, Solomon KR, Henriquez N. 2001. Preliminary study to determine the effect of dermally administered IPBC on serum free iodide levels in human volunteers. Report to Lonzagroup (Lonza Inc.) June 19 2002.
46 Maguire RJ, Sibley PK, Solomon KR, Delorme P. 2001. Pesticides. Chapter 3 (pages 9-12) in Threats to sources of drinking water and aquatic ecosystem health in Canada. NWRI Scientific Assessment Report Series No. 1. National Water Research Institute, Environment Canada, Burlington, ON, 72 p.
45 Bestari KT, Henriquez N, Solomon KR. 2001. Determination of Active Ingredient Transfer Factor for Repel Essential Aerosol and Pump Spray products to Arms and Legs Under Simulated Use Conditions. Report to WPC Brands, November 7 2001.
44 Bestari KT, Henriquez N, Solomon KR. 2001. Method Validation: Extraction and Analysis of Propiconazole in Water. Report to Lonzagroup (Lonza Inc.) November 23, 2001
43 Bestari KT, Henriquez N, Solomon KR. 2001. Wood Leaching Screening Study: Determination of the Leachability of Barlox 12, Barlox 1216, and Barlox 16S from Treated Wood. Report to Lonzagroup (Lonza Inc.) September 13, 2001.
42 Bestari KT, Henriquez N, Solomon KR. 2001. Method validation: Extraction and analysis of active ingredients of Bardac 2280, Bardac 22C, and Bardap 26 in water. Report to Lonzagroup (Lonza Inc.) September 6, 2001.
41 Solomon KR, 2001. Quality control program for products made from recycled plastic pesticide containers. Report to Croplife Canada, July 24, 2001.
40 Bestari KT, May RD, Nikiforov AI, Solomon KR. 2001. Measurement and assessment of Citroflex® A-4 migration from a custom molded ball and two commercial toys into saliva of adult human volunteers. Report to Morflex, June 1, 2001.
39 Bestari KT, Henriquez N, Solomon KR. 2001. Determination of the Leachability of Bardac 26 from Treated Wood. Report to Lonzagroup (Lonza Inc.), June 1, 2001.
38 Bestari KT, Henriquez N, Solomon KR. 2001. Determination of the Leachability of Bardac 22C from Treated Wood. Report to Lonzagroup (Lonza Inc.), June 1, 2001.
37 Bestari KT, Henriquez N, Solomon KR. 2001. Determination of the Leachability of Bardac 2280 from Treated Wood. Report to Lonzagroup (Lonza Inc.), June 1, 2001.
36 Solomon KR, Bestari J, Nelson H, Anderson K. 2000. Measurement and assessment of pesticide residues in condensation from greenhouses in Southern Ontario. OMAFRA Project Report. August 24, 2000. 16 p.

35 Solomon KR, Bestari KT, Henriquez N. 2000. Measurement and assessment of dermal and inhalation exposures to 3-iodo-2-propenyl-N-butyl carbamate (IPBC) in a joinery mill. Report to Troy Corporation and PPG, May 15 2000. 89 p plus appendices.

34 Solomon KR, 2001. Quality control program for products made from recycled plastic pesticide containers. Report to Croplife Canada, March 17, 2001.

33 Solomon KR, 2000. Quality control program for products made from recycled plastic pesticide containers. Report to Croplife Canada, February 26, 2000.

32 Bestari KT, Macey K, Solomon KR, Towner, N. 1999. Measurement and assessment of dermal and inhalation exposures to didecyldimethylammonium chloride (DDAC) used in the protection of cut lumber. Report to the Antisapstain Industry Consortium, Phase III, October 25, 1999, 136 p plus appendices.

31 Solomon KR, Bestari KT. 1998 Measurements of Pesticide Residues in Air at Everwood Agricultural Products in Aylmer, Ontario. Report to the Crop Protection Institute of Canada, September 14, 1998.

30 Macey K, Bestari KT, Solomon KR. 1997. Antisapstain use in British Colubian sawmills, planer mills and shipping terminals. Report to the Antisapstain Industry Consortium, October 20, 1997, 6 p plus appendices.

29 Bestari KT, France L, Solomon KR. 1997. Measurement and assessment of the toxicological significance of dermal exposure to antisapstain products used in the protection of cut lumber: Phase I Bridging Study. Report to the Antisapstain Industry Consortium, October 20, 1997. 33 p plus appendices.

28 Bestari KT, France L, Solomon KR. 1997. Measurement and Assessment of the Toxicological Significant of Dermal Exposure to Antisapstain Products used in the Protection of Cut Lumber Phase I. Report to the Antisapstain Industry Consortium, January 15, 1997.

27 Ritter L, Solomon KR, Forget J, Stemeroff M, O'Leary C. 1995. Persistent organic pollutants: A Review of Selected Persistent Organic Pollutants. Interorganization Programme for the Sound Management of Chemicals (IPCS). UNEP, ILO, FAO, UNIDO and OECD. WHO, Geneva November 1995. 240 p.

26 Ritter L, Solomon KR, Forget J, Stemeroff M, O'Leary C. 1995. Persistent organic pollutants: An assessment report on aldrin, chlordane, DDT, dieldrin, dioxins and furans, endrin, heptachlor, hexachlorobenzene, mirex, polychlorinated biphenyls, and toxaphene. Interorganization Programme for the Sound Management of Chemicals. (IPCS) UNEP, ILO, FAO, UNIDO and OECD. WHO, Geneva November 1995. 48 p.

25 Solomon KR, Hale B, Hall JC, Stephenson GR. 1994. A critical review of the proposed guidelines for registration of chemical pesticides: nontarget plant testing and evaluation. . For Crop Protection Institute of Canada. (1994) 23 p

24 Solomon KR, Ritter L, Harris SA. 1994. The measurement of biological and dermal exposure to 2,4-D in pesticide container collectors and assessment of toxicological significance. . For Crop Protection Institute of Canada. (1994) 24 p plus appendices.

23 A review and assessment of the ecological risks associated with the use of chlorine dioxide for the bleaching of pulp. 1993. Prepared for the Association for Environmental Technology by a scientific advisory board. Keith Solomon, Harold Bergman, Robert Huggett, Donald Mackay and Bruce McKague. Association for Environmental Technology, Erin ON. (1993).

22 Preliminary review of the U.S. EPA standards for the use and disposal of sewage sludge final rule document. 1993. Prepared for Agriculture Canada. Prepared by G. Farquhar, L. Haworth, J.H. Shortreed, K. Solomon, L. Crag and D. Del Bel Belluz. Institute for Risk Research University of Waterloo, Waterloo, Ontario. (1993).

21 Critical assessment of the discussion document on the registration status of fenitrothion insecticide. Agriculture Canada D93-01. Prepared for the Forest Pest Management Caucus. with G.A. Surgeoner, June 1993.

20 Canadian Network Of Toxicology Centres: Réseau Canadien Des Centres De Toxicologie. Research Planning Document April 19, 1993

19 Report of the research planning and priority setting workshop on quantitative (probabilistic) risk assessment. Delta Meadowvale Inn, Mississauga, Ontario, February 7-9, 1993

18 Report of the research planning and priority setting workshop on mining and metallurgy. Delta Meadowvale Inn, Mississauga, January 17 to 21, 1993

17 Report of the research planning and priority setting workshop on pulp and paper. Cranberry Inn, Collingwood, December 11 to 14, 1992

16 Mycotoxin Program Review Ontario Ministry of Agriculture and Food, Agricultural and Food Laboratory Services Branch. Report of a Workshop Held on December 7-8, 1992 at the College Inn, Guelph, Ontario

15 Report of the research planning and priority setting workshop on agroecosystems Cranberry Inn, Collingwood, October 31 to November 3, 1992

14 Report of the research planning and priority setting workshop on agroecosystems. Cranberry Inn, Collingwood, October 31 to November 3, 1992

13 Assessment of the environmental impact of fenitrothion in forest environments in Canada. March, 1992. with Rob Currie, Richard Frank, Michael Hooper, and Gord Surgeoner.

12 Toxicology Education in Canada. 1990. Associate Committee on Toxicology, National Research Council of Canada, Ottawa (1990)

11 Summary evaluation of the potential environmental hazard of anti-sapstain chemicals. 1990. Report to the B.C. Stakeholder Forum on Sapstain Control.

10 Possible Hazards Associated with Recycling of Metal Pesticide Containers: A Background Document on the Establishment of an Interim Maximum Allowable Concentration. 1990. Report to the Alberta Special Waste Management Corporation. With: Drs B. Schiefer and D. Irvine.

9 Evaluation of procedures for the disposal, recycling and handling of pesticide containers. 1989. Report to the Crop Protection Institute of Canada.

8 Panel Report on Carcinogenicity of 2,4-D. Prepared for the Ontario Pesticide Advisory Committee of the Ontario Ministry of the Environment. With: K. Crump, R. Squire, A. Miller, I.C. Munro and M.V. Anders, March, 1987

7 The Toxicology and Carcinogenic Potential of 3-amino-1,2,4-triazole: A review of the scientific literature. Prepared for the Ontario Pesticides Advisory Committee. With D. Thompson and G.R. Stephenson, 1985.

6 Dichloraniline based herbicides: Their contaminants, toxicology and carcinogenic potential. Prepared for the Ontario Pesticides Advisory Committee. With: D. Thompson and G.R. Stephenson, 1985

5 Acaricide Resistance in Ticks. A position paper prepared for the WHO Expert Committee on Resistance of Vectors and Reservoirs of Disease to Pesticides. May, 1985.

4 Proposal for the Development of the Canadian Centre for Toxicology. Proposal prepared for the Governments of Ontario and Canada. With: I.C. Munro, F.L. McEwen, March, 1985.

3 Pyrethroids: Their effects on aquatic and terrestrial ecosystems. National Research Council of Canada, Associate Committee on Scientific Criteria for Environmental Quality. NRCC No. 24376. Ottawa, 1986. With: Atkins L, Ruzo L, Coats JR, Plowright CJ, Roberts R.

2 Formaldehyde Risk Assessment. Report to the Ontario Ministry of Labour. With: Munro IC, Golberg L, Farber E, January, 1985.

1 Agricultural Chemicals and Farm Health and Safety. Canadian Centre for Toxicology report to the Ontario Task Force on Health and Safety in Agriculture. With: IC Munro, J Clarke and D Muir, December, 1984.

18 PAPERS PRESENTED AT SCIENTIFIC MEETINGS (last 3 years only)

1102 Solomon KR. 2015. Weighing scientific evidence in risk assessment for pesticides: An example with atrazine. LAPRW Santiago Chile 2015 05 13. **Invited Platform.**

1101 Solomon KR, Bridges J. 2015. Problem Formulation for Risk-Based Ecological Assessments. SETAC Meeting, Barcelona, 2015 05 04, **Invited Platform.**

1100 Baxter L, Brain RA, Hosmer A, Solomon KR, Hanson ML. 2015. Exposure of Yellow Spotted Salamander (*Ambystoma maculatum*) Egg Masses to a PSII Inhibitor. SETAC Meeting, Barcelona, 2015 05 04 **Poster**

1099 Matthies M, Solomon KR, Vighi M, Gilman A, Tarazona JV. 2015. On the origin of the criteria for PBT and POP assessment and the evolution of cut-off values. SETAC Meeting, Barcelona, 2015 05 04 **Poster**

1098 Solomon KR. 2014. Handling of Mixtures in the Environment and Ecological Implications American Chemical Society/IUPAC Meeting, San Francisco 2014 98 10 **Invited Platform**

1097 Solomon KR. 2014. Measuring and Modeling Pesticide Fate in Soil, Water, and Atmosphere at Micro- to Macro-Scales. American Chemical Society/IUPAC Meeting, San Francisco 2014 98 10 **Invited Platform**

1096 Solomon KR, Giesy JP, Mackay D Anderson J. 2014. Bioaccumulation Risk Assessment: Problems and Possibilities. American Chemical Society/IUPAC Meeting, San Francisco 2014 98 10 **Invited Platform**

1095 Solomon KR. 2014. Arriving at the truth: Weight of evidence for assessing risks of chemicals. 23rd IUPAC International Conference on Chemistry Education, Toronto, ON, 2014 07 14. **Invited Platform.**

1094 Solomon KR. 2014. Weight of evidence (WoE) for PBT/ POP assessment. Japan Expert Workshop, Silicone Industry Association. Tokyo, 2014 07 02. **Invited Platform**.

1093 Solomon KR. 2014. Environmental exposure to chemicals: Pathways and importance to assessing risks from chemicals. ICCA-LRI & JRC Workshop, Lugano, CF 2014 06 16. **Invited Platform**.

1092 Solomon KR. 2014. Molecular structures and toxicology, the search for green poisons. Next Steps in Green Chemistry Research. A Workshop by the Green Chemistry Initiative, University of Toronto. 2014 05 22. **Invited Platform**.

1091 Rodriguez-Gil JL, Brain RA, Ruffell S, McConkey B, Solomon KR, Hanson ML 2014. Culturing conditions for toxicity testing with *Oophila* sp., an amphibian symbiont. SETAC Meeting in Basel, CF. 2014 05 14. **Poster**

1090 Rodriguez-Gil JL, Lissemore L, Hanson ML, Solomon KR. 2014. Community responses to the interactive effect of surfactant exposure and water depth in a microcosm set-up. SETAC Meeting in Basel, CF. 2014 05 14. **Platform**

1089 Solomon KR, Giesy JP, Mackay D, Anderson J, Poletika, N. 2014. PBT classification under EC 1107/2009: Practical issues and a case example of chlorpyrifos. SETAC Meeting in Basel, CF. 2014 05 14. **Platform.**

1088 Solomon KR, Van der Kraak, G, Hanson, ML, Kloas W, Hosmer A. 2014. Use of weight of evidence for characterizing adverse outcome pathways in risk assessment. SETAC Meeting in Basel, CF. 2014 05 12. **Platform.**

1087 Solomon K R. 2014. Use of weight of evidence for characterizing adverse outcome pathways in risk assessment. SETAC FTM on Endocrine Disrupting Chemical Testing, Risk Assessment Approaches and Implications, RTP, NC. 2014 02 05. **Invited Platform**

1086 Solomon K R. 2014. Arriving at the truth: Weight of evidence for assessing risks of agrochemicals. ACS Webinar 2014 02 02.

1085 Solomon KR, 2013. Classification of plant protection products as PBTs, is there a role for science? Fresenius Conference, Cologne, Germany, December 12 2013. **Platform.**

1084 Solomon KR, 2013. Ecotoxicological risk characterization. Lecture at the Univerisdad de Costa Rica, San Jose, Costa Rica December 04 2013. **Platform.**

1083 Solomon KR, 2013. Ecotoxicological risk characterization. Lecture at the Univerisdad de Molina, Lima, Peru November 25 2013. **Platform.**

1082 Rodríguez-Gil JL, Ross A, Sibley P, Hanson ML Solomon KR. 2013. Environmental fate of a POEA surfactant. Effect of sediment organic matter and water depth. SETAC NA Meeting, Nashville November 20 2013. **Poster**

1081 Baxter LR, Brain RA, Prosser RS, Solomon KR, Hanson ML. 2013 Sensitivity of an alga to atrazine is not enhanced by previous acute exposure. SETAC NA Meeting, Nashville November 20 2013. **Platform.**

1080 Solomon KR. 2013. Assessment of risks in the jungle: Case example of the use of herbicide to control coca. SETAC NA Meeting, Nashville November 20 2013. **Platform.**

1079 Morris AD, Muir DC, Solomon KR, Teixeira C, Duric M. 2013. Current use pesticide and polybrominated diphenyl ether bioaccumulation in a Canadian Arctic vegetation-caribou-wolf food chain. SETAC NA Meeting, Nashville November 20 2013. **Platform.**

1078 Van der Kraak GJ, Hanson ML, Hosmer A, Kloas W, Solomon KR. 2013. A quantitative approach to weight of evidence in ecotoxicological risk assessment. SETAC NA Meeting, Nashville November 20 2013. **Platform.**

1077 Solomon K R. Arriving at the truth: Weight of evidence for assessing risks of agrochemicals. Stirling B Hendricks Memorial Lecture. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1076 Solomon KR, Wilks M, Moretto A, Boobis A, Philips R, Pastoor T, Embry M. 2013. Cumulative risk assessment for human health: asking the right questions. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1075 Solomon KR, Williams WM, Mackay D, Purdy J, Giddings JM, Giesy JP. 2013. Properties and uses of chlorpyrifos in the United States. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1074 Mackay D, Giesy JP, Solomon KR. 2013. Towards a model of the environmental fate and long-range atmospheric transport of chlorpyrifos and its oxon. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1073 Moore DR, Teed RS, Solomon KR, Giesy JP. 2013. Refined avian risk assessment for agricultural uses of granular chlorpyrifos in the United States. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1072 Moore DR, Teed RS, Solomon KR, Giesy JP. 2013. Refined avian risk assessment for agricultural uses of flowable chlorpyrifos in the United States. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1071 Williams WM, Giddings JM, Purdy J, Solomon KR, Giesy JP. 2013. Exposures to aquatic organisms from the use of chlorpyrifos in North America. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1071 Giddings JM, Williams WM, Giesy JP, Solomon KR. 2013. Risks to aquatic organisms from the use of chlorpyrifos in North America. ACS Meeting, Indianapolis September 09 2013. **Invited Platform**

1070 Purdy J, Cutler GC, Giesy JP, Solomon KR. 2013. Ecological risk assessment for chlorpyrifos in terrestrial systems in North America – the conceptual model for pollinators. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1069 Cutler GC, Purdy J, Giesy JP, Solomon KR. 2013. Risks of chlorpyrifos to pollinators: Risk assessment. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1068 Giesy JP, Cutler GC, Giddings JM, Mckay D, Moore D, Williams WM, Purdy J, Solomon KR. 2013. Ecological tisk assessment for chlorpyrifos in terrestrial and aquatic systems in North America-overview and conclusions. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1067 Solomon K, Poletika N, Anderson J, Giesy J 2013. Pesticides as POPs and PBTs: An assessment of chlorpyrifos. ACS Meeting, Indianapolis September 09 2013. **Invited Platform.**

1066 Prosser R, Brain R, Hosmer A, Solomon K, Hanson, M. 2013. Field-derived periphyton communities recover from an acute herbicide exposure. SETAC EU Meeting, May 11, 2013, Glasgow. **Poster**

1065 Solomon K. 2013. The environmental chemistry of single malt: from *Hordeum vulgare* to the turbinates. SETAC EU Meeting, May 11, 2013, Glasgow. **Invited Platform.**

1064 Solomon K. 2013. POPs: Have we achieved our objectives and where do we go from here? SETAC EU Meeting, May 11, 2013, Glasgow. **Invited Platform.**

1063 Brain R, Andrus M, Prosser R, Hanson M, Hosmer A, Solomon K. 2013. Lines of evidence for establishing an aquatic level of concern for the herbicide atrazine in North American surface waters. SETAC EU Meeting, May 11, 2013, Glasgow. **Platform.**

1062 de Jourdan B, Hanson M, Solomon K, Muir D. 2013. The bioaccumulation, environmental persistence, and degradation of severalthree novel brominated flame retardants in aquatic mesocosms. SETAC EU Meeting, May 11, 2013, Glasgow. **Platform.**

1061 Solomon KR. 2013. Background and history of bioaccumulation criteria. ECHA Worshop, March 11, 2013, Helsinki. **Platform Invited.**

1060 Solomon KR. 2012. Background and current requirements for groundwater (Res. 2115). CLLA Worshop, December 4, 2012, Bogota. **Platform Invited.**

1059 Solomon KR. 2012. Toxicological risk assessment of pesticides: General scientific concepts. CLLA Worshop, December 4, 2012, Bogota. **Platform Invited.**

1058 Solomon KR. 2012. Effects at realistic exposures, weight of evidence, and implications for environmental risk assessment. 12th International Fresenius ECOTOX Conference, Mainz, November 27, 2012. **Platform Invited.**

1057 Solomon KR, Wilks MF. 2012. Problem formulation for risk assessment of combined exposures to chemicals and other stressors. 12th International Fresenius ECOTOX Conference, Mainz, November 26, 2012. **Platform Invited**.

1056 Sousa Oliveira V, Hanson M, Solomon K, Bestari K, Lima J. 2012. The response of three macrophytes to fomesafen and thiamethoxam in microcosms: The benefits of testing multiple species simultaneously. SETAC NA Meeting, Long Beach, CA. November 2012. **Poster**.

1055 Prosser R, Brain, R, Hosmer, A, Hanson, M. Use of PAM fluorometry in assessing field-derived periphyton community sensitivity to, and recovery from, herbicide exposure. SETAC NA Meeting, Long Beach, CA. November 2012. **Poster**.

1054 Van der Kraak Hanson ML, Hosmer A, Kloas W, Solomon KR. 2012. A methodological approach to weight of evidence in ecotoxicological risk assessment. SETAC NA Meeting, Long Beach, CA. November 2012. **Platform.**

1053 Solomon KR, Matthies, M, Vighi, M. 2012. Assessment of PBTs in the EU: A critical review and proposed evaluation scheme with reference to plant protection products. SETAC NA Meeting, Long Beach, CA. November 2012. **Platform.**

1052 Solomon KR, Hall JC. 2012. Fifty years of POPs: Have we achieved our objectives? SETAC NA Meeting, Long Beach, CA. November 2012. **Platform**.

1051 Leelacho S, Solomon KR, Hall JC. 2012. Phytoremediation of atrazine-contaminated water by expression of anti-atrazine antibody fragment (scFv) in duckweed (*Lemna minor*). SETAC NA Meeting, Long Beach, CA. November 2012. **Invited Platform**.

1050 Solomon KR. 2012. Frameworks for Risk Assessment: Global to Local. LATARP Workshop, Buenos Aires, October 10, 2012. **Platform.**

1049 Solomon KR. 2012. POPs on the cusp: The case of endosulfan. ACS Meeting, Philadelphia, PA, July 25, 2012. **Invited Platform.**

1048 Solomon KR, Matthies M, Vighi M. 2012. Assessment of PBTs in the EU: A critical review and proposed evaluation scheme with reference to plant protection products. SETAC Meeting, Berlin, Germany, 2012 05 21. **Poster.**

19 SHORT COURSES (last 3 years only)

Overview of the Regulatory Risk Assessment Frameworks. IUPAC Ecological Risk Assessment Workshop, Santiago, Chile; 2015 05 9-10.

Overview of International Testing Requirements. IUPAC Ecological Risk Assessment Workshop, Santiago, Chile; 2015 05 9-10.

Exposure Assessment. IUPAC Ecological Risk Assessment Workshop, Santiago, Chile; 2015 05 9-10.

Ecotoxicology and Ecological Risk Assessment. Advanced Principles of Toxicology. Course at University of Guelph, 2014 04 08-09, 1.5 days of lectures.

Three-day short course on Risk Assessment for Pesticides. Dow AgroSciences, Zionsville, IN. 2013 09 15-18.

Ecotoxicology and Ecological Risk Assessment. Advanced Principles of Toxicology. Course at University of Guelph. 2013 05 08-09, 1.5 days of lectures.

Ecotoxicology and Ecological Risk Assessment. Advanced Principles of Toxicology. Course at University of Guelph. 2012 05 10-11, 1.5 days of lectures.

20 GUEST LECTURES AND EXTENSION TALKS (last 3 years only)

Solomon KR. 2014. Cumulative risk assessment for human health: Asking the right questions. Invited lecture at Baylor University, Waco, Texas. March 28, 2014

Solomon KR. 2014. Pesticides: Weighing the Risks. Guest lecture in Turf Managers course, University of Guelph. January 2014

Solomon KR. 2013. Pesticides: Weighing the Risks. Guest lecture in Turf Managers course, University of Guelph. January 2013

Solomon KR. 2013. Ecotoxicological Risk Assessment. Three guest lectures in STAT3510, University of Guelph. January 2013.

Solomon KR. 2012. Risk assessment of pesticides. CropLife Latin America. Bogota 2012 12 04-06

21 PAPERS PRESENTED AT PUBLIC MEETINGS (last 3 years only)

Sorahan

CURRICULUM VITAE

TOM SORAHAN

1st May, 2015

CONTENTS

Curriculum Vitae

TOM SORAHAN PhD, DSc, FFOM (Hon)

Present Position: Professor of Occupational Epidemiology
Institute of Occupational and Environmental Medicine
University of Birmingham
Edgbaston
Birmingham
B15 2TT, UK

Date of Birth: 7th May 1950

Nationality: British

Education:

University	Degree
Birmingham	B.Sc. Physics (1970)
Birmingham	Ph.D. Social Medicine (1982)
Birmingham	D.Sc. Occupational Health (1999)

Membership of Professional Societies:

Honorary Fellow, Faculty of Occupational Medicine

Major Interests: Identification and quantification of occupational and environmental cancer hazards

ACADEMIC CAREER - UNIVERSITY OF BIRMINGHAM

Research Assistant: Department of Social Medicine, (Cancer Registry), 1971-1974

I commenced my career in epidemiology as a research assistant to Dr. Pat Prior. I worked on a number of cohort studies relating to multiple primary tumours and cancers following chronic disease.

Research Associate: Department of Social Medicine, (Cancer Registry), 1974-1981

I developed a particular interest in epidemiological methodology as applied to the detection of cancer hazards in industry, writing a Ph.D. thesis on this topic. I enlarged an existing study of some 200 cadmium workers from a local nickel-cadmium battery factory into a full-scale cohort mortality study of some 3,000 current and ex-employees from the same factory. This study has played a prominent role in the debate on the carcinogenicity of cadmium in humans. Other projects included a cohort mortality study of workers employed in a factory manufacturing chlorinated toluenes, the generation of data in the form of industrial cohorts by means of a computer programme, and analyses of cancer incidence data from 'Cancer Incidence in Five Continents'.

Research Fellow : Department of Social Medicine, (Cancer Epidemiology Research Unit), 1981-1991

Projects included the development of a series of occupational cohort studies, and in particular studies of -

(1) nickel-cadmium battery workers,
(2) workers employed in a factory manufacturing chlorinated toluenes,
(3) semiconductor workers,
(4) rubber workers,
(5) nickel/chrome platers
(6) steel foundry workers,
(7) chemical production workers, and
(8) workers employed in the manufacture of polyurethane foam.

Other occupational studies included the analysis of cancer registry data, both in terms of the recorded occupations of cancer patients and those of their spouses. Concurrently, I developed a number of case-control studies investigating possible associations between -
(1) melanoma and exposure to fluorescent lighting,
(2) urothelial cancer and the use of dyed maggots by anglers, and
(3) salivary gland tumours and prior dental radiography.

Studies on ionising radiation included the early work on cancer among participants in the U.K. nuclear weapon tests in the Pacific, further analyses of the mortality experience of British radium luminisers, selection effects in Japanese A-bomb survivors, and reanalysis of the large cohort mortality studies of US radiation workers.

Senior Research Fellow: Department of Public Health and Epidemiology, (Cancer Epidemiology Research Unit), 1991-93

I became the Director of the Cancer Epidemiology Research Unit in October, 1991. My prime objective for C.E.R.U. was to maintain and improve its position regarding high quality research output as judged both by International standing and publications in peer-reviewed scientific journals. Important new work was carried out into the aetiology of moles, parental smoking and childhood cancer, paternal exposure to ionising radiation and childhood cancer, and cancer among workers engaged in the manufacture of flexible foam.

Senior Lecturer: Institute of Occupational Health, 1993-97

I joined the IOH in December, 1993. My responsibilities included the design and delivery of the epidemiology module on the taught M.Med.Sc. programme, the supervision of staff registered for postgraduate degrees, oversight of on-going epidemiology projects and development of my own research programme. The latter included work on cadmium exposure and lung cancer, chrome exposure and lung cancer, paternal exposure to ionising radiation and childhood cancer, and methodology concerning misclassification of exposure.

Reader in Occupational Epidemiology: Institute of Occupational Health, 1997-2000

New research projects included studies of lung cancer in carbon black workers, lung cancer in a recently re-discovered cohort of chrome platers, bladder cancer in workers exposed to 2-mercaptobenzothiazole (MBT), cancer in the offspring of sewing machinists and other occupations attracting exposures to electromagnetic fields (EMF), and leukaemia risks and EMF exposures in a cohort of electricity production workers. The feasibility of carrying out a cancer mortality study in the European titanium dioxide industry was examined and funding was secured for a European case-control study into brain cancer risks in relation to the use of mobile telephones.

Professor of Occupational Epidemiology: Institute of Occupational Health, 2000-present

New research projects included risks of respiratory cancer in relation to nickel exposure, analyses of brain tumour risks and cardiovascular disease risks in relation to magnetic field exposure (electricity production workers), and leukaemia risks in relation to benzene exposure (petroleum industry).

TEACHING EXPERIENCE

(1) Medical Statistics and Epidemiological Methods

I have taught introductory courses on statistics and epidemiological methods to medical students. The latter course included the following topics: comparative trials, evaluation of screening, cause and effect, standardisation and life tables.

(2) Projects and Theses

I have supervised medical students working on individual essay projects in epidemiology and public health, and postgraduate students working on M.Sc. and Ph.D. dissertations. I am the departmental tutor for post graduate studies.

(3) M.Sc. Programme

I was the module tutor from 1997-2010 for a course of lectures and tutorials on statistics and occupational epidemiology, delivered as part of the taught M.Sc. programme in Occupational Health. In that period, I also provided an introductory lecture on epidemiology to M.Sc Toxicology students and a lecture on advanced methodological topics to M.P.H. students from the Department of Public Health and Epidemiology.

FUNDED RESEARCH PROGRAMME (1985 - 2012)

1. IDENTIFICATION AND QUANTIFICATION OF OCCUPATIONAL CANCER HAZARDS

1.1 Cancer Mortality among a Cohort of Nickel/Chromium Platers.

Sponsor: The Colt Foundation

Award: £4,550

1.2 Cancer Mortality in the British Rubber Industry.

Sponsor: The British Rubber Manufacturers' Association

Award: £38,500

1.3 An Investigation into the Mortality and Cancer Morbidity of Production Workers in the U.K. Flexible Polyurethane Foam Industry.

Sponsor: The International Isocyanates Institute Inc.

Award: £51,200

1.4 Cancer Mortality among a Cohort of U.K. Steel Foundry Workers.

Sponsor: The Colt Foundation

Award: £11,100

1.5 Epidemiology at Monsanto, Ruabon.

Sponsor: Monsanto plc

Award: £16,960

1.6 Cancer Mortality and Morbidity among Semiconductor Workers.

Sponsor: Lucas Industries plc

Award: £5,000

1.7 International Collaborative Case-Control Study on Cadmium and Cancer.

Sponsor: International Lead Zinc Research Organisation (ILZRO)

Award: £98,791

1.8 Cancer mortality among U.K. steel foundry workers.

Sponsor: Health and Safety Executive

Award: £12,555

1.9 Parental exposure to ionising radiation and childhood cancer: linkage study.

Sponsor: Department of Health.

Award: £65,183

1.10 A regional case-control study into the aetiology of urothelial tumours.

Sponsor: Health and Safety Executive.

Award: £86,057

1.11 Epidemiology at Monsanto, Ruabon: an update.

Sponsor: Monsanto plc

Award: £34,021

1.12 Titanium dioxide and respiratory cancer: a feasibility study.

Sponsor: Titanium Dioxide Manufacturing Association

Award: £34,150

1.13 Leukaemia risks in relation to EMF exposure.

Sponsor: Electricity Association

Award: £150,000

1.14 Lung cancer risks in relation to carbon black exposure.

Sponsor: International Carbon Black Association (ICBA)

Award: £130,013

1.15 Maintenance of cohorts of oil refinery and distribution workers.

Sponsor: Institute of Petroleum

Award: £68,622

1.16 Maternal occupational exposure to electromagnetic fields in relation to risks of childhood cancer.

Sponsor: Health and Safety Executive

Award: £27,489

1.17 Mortality and cancer morbidity of production workers in the UK flexible polyurethane foam industry: an updated analysis.

Sponsor: International Isocyanates Institute

Award: £53,189

1.18 Mortality of nickel refinery workers.

Sponsor: INCO Ltd and Special Metals Ltd

Award: £58,070

1.18 Brain tumour risks in relation to magnetic field exposure.

Sponsor: National Grid Company plc

Award: £36,658

1.19 Cardiovascular disease risks in relation to magnetic field exposure

Sponsor: National Grid Company plc

Award: £35,764

1.20 Cancer risks in UK oil refinery and petroleum distribution workers

Sponsor: Institute of Petroleum

Award: £42,997

1.21 Cancer risks in an historical UK cohort of benzene-exposed workers

Sponsor: Institute of Petroleum

Award: £52,080

1.22 A study into airwave patterns of use

Award: £27,512

Sponsor: Police Information Technology Organisation

1.23 The National Register of workers exposed to radio-frequency (RF) radiation

Award: £65,337

Sponsor: Health & Safety Executive

1.24 Cancer risks in UK oil refinery and petroleum distribution workers

Sponsor: Energy Institute

Award: £73,500

1.25 Maintenance of cohort of electricity supply industry workers

Sponsor: various companies in electricity supply industry

Award: £121,000

1.26 Updated analysis of cancer risks in semiconductor workers.

Sponsor: Health and Safety Executive

Award: £23,000

1.27 EXASRUB (exposure estimation in the European rubber industry)

Sponsor: EU

Award: £13,236

2. IDENTIFICATION AND QUANTIFICATION OF ENVIRONMENTAL CANCER HAZARDS

2.1 Coarse Fishing and Urothelial Cancer: a Case-Control Study.

Sponsor: Cancer Research Campaign

Award: £47,266

2.2 The Aetiology of Salivary Gland Tumours: a Regional Case-Control Study.

Sponsor: West Midlands Regional Health Authority

Award: £6,400

2.3 The Aetiology of Moles.

Sponsor: Cancer Research Campaign

Award: £46,158

2.4 The Oxford Survey of Childhood Cancers.

Sponsor: Childhood Cancer Research Institute

Award: £8,819

2.5 UK Study into the Aetiology of Adult Brain Tumours

Sponsor: EU and others

Award: £128,528 (West Midlands Components)

PUBLICATIONS

1. Stokes PL, Prior P, Sorahan TM, McWalter RJ, Waterhouse JAH, Cooke WT.
   Malignancy in relatives of patients with coeliac disease.
   Brit J Prev Soc Med 1976;30:17-21.

2. Holmes GK, Stokes PL, Sorahan TM, Prior P, Waterhouse JAH, Cooke WT.
   Coeliac disease, gluten free diet, and malignancy.
   GUT 1976;17:612-619.

3. Sorahan TM.
   Healthy worker effect-fact.
   J Occ Med 1980;21:521.

4. Sorahan TM.
   A comparison of the methods of standardised mortality ratios and regression models in life-tables as used in industrial mortality studies. (abstract).
   J Epid Comm Health 1981;35:153.

5. Sorahan TM.
   A mortality study of nickel-cadmium battery workers.
   Edited proceedings of the third international cadmium conference, Miami.
   Cadmium Association, London 1982.

6. Sorahan T, Waterhouse JAH, Cooke MA, Smith EMB, Jackson JR, Temkin L.
   A mortality study of workers in a factory manufacturing chlorinated toluenes.
   Ann Occup Hyg 1983;27:173-182.

7. Sorahan TM, Crombie IK.
   Cancer of the cervix and cancer of the penis.
   Lancet 1981;ii:1419-1420.

8. Sorahan T.
   Length of follow-up in cohort studies.
   Lancet 1982;i:1246.

9. Sorahan T.
   Incidence of malignant melanoma, England and Wales, 1968-77.
   Lancet 1982;ii:562.

10. Sorahan T, Kokoszynska R, Adams RG.
    Trends in mortality from nephritis and nephrosis.
    Lancet 1982;i:567.

11. Sorahan T, Adams RG, Waterhouse JAH.
Analysis of mortality from nephritis and nephrosis among nickel-cadmium battery workers.
J Occ Med 1983;25:609-612.

12. Sorahan T, Waterhouse JAH.
Mortality study of nickel-cadmium battery workers by the method of regression models in life-tables.
Br J Ind Med 1983;40:293-300.

13. Sorahan T, Aston RHR, Waterhouse JAH.
An analysis of recorded husbands' occupations involving exposure to mineral oils among patients with cancer of the cervix.
IRCS Medical Science 1983;11:243.

14. Knox EG, Sorahan T, Stewart AM.
Cancer following nuclear weapons tests.
Lancet 1983;i:815.

15. Sorahan T, Jones J, Waterhouse JAH.
Cohort studies : effects of written consent.
Lancet 1983;i:1444.

16. Sorahan T, Waterhouse JAH.
The generation of simulated data in the form of industrial cohorts.
Computers and biomedical research 1983;16:260-272.

17. Sorahan T, Waterhouse JAH.
Stillbirth rates in the area around Windscale, 1949-81.
Br Med J 1984;288:148.

18. Knox EG, Sorahan T, Stewart AM.
Cancer following nuclear weapons tests.
Lancet 1983;ii:856.

19. Plant CG, Browne RM, Knibbs PJ, Britton AS, Sorahan T.
Pulpal effects of glass ionomer cements.
International Endodontic Journal 1984;17:51-59.

20. Flanagan NG, Harry DS, Kozlowski T, Sorahan T.
Multiple myeloma on the Fylde coast.
Br Med J 1984;289:1075.

21. Sorahan T, Waterhouse JAH.
Cancer of the prostate among nickel-cadmium battery workers.
Lancet 1985;i:459.

22. Sorahan T.
Cohort studies - power considerations.
J Occ Med 1985;27:177.

23. Sorahan T.
Radium luminisers - selection effects.
J Occ Med 1985;27:7.

24. Sorahan T.
A further study of nickel-cadmium battery workers.
Edited Proceedings Fourth International Cadmium Conference, Munich.
Cadmium Association, London 1984.

25. Sole G, Sorahan T.
Coarse fishing and risk of urothelial cancer.
Lancet 1985;i:1477-1479.

26. Sorahan T, Aston RHR, Waterhouse JAH, Peters D, Roginski C.
Malignant melanoma and occupations involving soldering.
IRCS Med Sci 1985;13:830.

27. Sorahan T, Waterhouse JAH, McKiernan MJ, Aston RHR.
Cancer incidence and cancer mortality in a cohort of semiconductor workers.
Br J Ind Med 1985;42:546-550.

28. Sorahan T, Grimley RP.
The aetiological significance of sunlight and fluorescent lighting in malignant melanoma : a case-control study.
Br J Cancer 1985;52:765-769.

29. Sorahan T, Parkes HG, Veys CA, Waterhouse JAH.
Cancer mortality in the British rubber industry : 1946-80.
Br J Ind Med 1986;43:363-373.

30. Sorahan T, Burges DCL, Waterhouse JAH.
A mortality study of nickel/chromium platers.
Br J Ind Med 1987;44:250-258.

31. Plant CG, Tobias RS, Browne RM, Sorahan T, Rippin JW.
Toxicity testing of inlay cements.
Clinical Materials 1986;1:291-301.

32. Sorahan T.
Radium luminisers.
J Occ Med 1987;29:1202.

33. Al-Fouadi A, Sorahan T, Prior P.
Long-term survival of women diagnosed with breast cancer 1936-50.
Lancet 1987;i:1096-1097.

34. Eisenberg DE, Sorahan T.
Birth weight and childhood cancer deaths.
JNCI 1987;78:1095-1100.

35. Sorahan T.
Mortality from lung cancer among a cohort of nickel-cadmium battery workers: 1946-84.
Br J Ind Med 1987;44:803-809.

36. Sorahan T.
Cancer after nuclear weapons tests.
Br Med J 1988;296:716.

37. Sorahan T.
Suicide, selection, and A-bomb survivors.
Lancet 1988;i:1110-1111.

38. Green A, Sorahan T, Pope D, Siskind V, Hansen M, Hanson L, Leech P, Ball PM, Grimley RP.
Moles in Australian & British schoolchildren.
Lancet 1988;ii:1497.

39. Sorahan T, Parkes HG, Veys CA, Waterhouse JAH, Straughan JK, Nutt A.
Mortality in the British rubber industry, 1946-85.
Br J Ind Med 1989;46:1-11.

40. Sorahan T, Cooke MA.
Cancer mortality in a cohort of United Kingdom steel foundry workers: 1946-85.
Br J Ind Med 1989;46:74-81.

41. Sorahan T, Cathcart M.
Lung cancer mortality among workers in a factory manufacturing chlorinated toluenes: 1961-84.
Br J Ind Med 1989;46:425-427.

42. Sorahan T, Cooke MA, Wilson S.
Incidence of cancer of the scrotum, 1971-84.
Br J Ind Med 1989;46:430-431.

43. Sorahan T, Sole G.
Coarse fishing and urothelial cancer: a regional case-control study.
Br J Cancer 1990;62:138-141.

44. Sorahan T, Ball PM, Grimley RP, Pope D.
Benign pigmented naevi in children from Kidderminster, England: prevalence and associated factors.
J Am Acad Dermatol 1990;22:747-750.

45. Sorahan T.
Epidemiological Studies: International pooling of cadmium data.
Edited Proceedings Sixth International Cadmium Conference, Paris.
Cadmium Association, London 1990, pp 141-142.

46. Kneale GW, Sorahan T, Stewart AM.
Evidence of biased recording of radiation doses of Hanford workers.
Am J Ind Med 1991;20:799-803.

47. Sorahan T, Pope DJ, McKiernan MJ.
Cancer incidence and cancer mortality in a cohort of semiconductor workers: an update.
Br J Ind Med 1992;49:215-216.

48. Pope DJ, Sorahan T, Marsden JR, Ball PM, Grimley RP, Peck IM.
Benign pigmented naevi in children.
Arch Dermatol 1992;128:1201-1206.

49. Sorahan T, Pope DJ.
Mortality and cancer morbidity of production workers in the United Kingdom flexible polyurethane foam industry.
Br J Ind Med 1993;50:528-536.

50. Sorahan T, Roberts PJ.
Childhood cancer and paternal exposure to ionising radiation: preliminary findings from the Oxford Survey of Childhood Cancers.
Am J Ind Med 1993;23:343-354.

51. Sorahan T.
The International collaborative case-control study on cadmium and cancer.
Edited Proceedings Seventh International Cadmium Conference, New Orleans.
Cadmium Association, London 1993, pp 158-159.

52. Sorahan T, Stewart AM.
Retinoblastoma and fetal irradiation.
Br Med J 1993;307:870.

53. Sorahan T, Pope D.
Mortality study of workers employed at a plant manufacturing chemicals for the rubber industry: 1955-86.
Br J Ind Med 1993;50:998-1002.

54. Sorahan T.
Bladder tumours among U.K. rubber workers.
Ann Occup Hyg 1994;38:103-104.

55. Icso J, Szollosova M, Sorahan T.
Lung cancer among iron ore miners in east Sloivakia: a case-control study.
Occup Environ Med 1994;51:642-643.

56. Sorahan T, Lancashire R.
Lung cancer findings from the NIOSH study of United States cadmium recovery workers: a cautionary note.
Occup Environ Med 1994;51:139-140.

57. Sorahan T, Faux AM, Cooke MA.
Mortality among a cohort of United Kingdom steel foundry workers with special reference to cancers of the stomach and lung, 1946-90.
Occup Environ Med 1994;51:316-322.

58. Sorahan T, Lancashire RJ, Sole G.
Urothelial cancer and cigarette smoking: findings from a regional case-controlled study.
Br J Urol 1994;74:753-756.

59. Sorahan T, Gilthorpe MS.
Non-differential misclassification of exposure always leads to an underestimate of risk: an incorrect conclusion.
Occup Environ Med 1994;51:839-840.

60. Fagan DG, Lancashire RJ, Walker A, Sorahan T.
Determinants of fetal haemoglobin in newborn infants.
Arch Dis Child 1995;72:F111-F114.

61. Sorahan T, Lancashire RJ, Temperton DH, Heighway WP.
Childhood cancer and paternal exposure to ionising radiation: a second report from the Oxford Survey of Childhood Cancers.
Am J Ind Med 1995;28:71-78.

62. Sorahan T, Lancashire R, Stewart A, Peck I.
Pregnancy ultrasound and childhood cancer: a second report from the Oxford Survey of Childhood Cancers.
Br J Obstet Gynae 1995;102:831-832.

63. Sorahan T, Lancashire R, Prior P, Peck I, Stewart A.
Childhhod cancer and parental use of alcohol and tobacco.
Annals of Epidemiology 1995;5:354-359.

64. Sorahan T, Lister A, Gilthorpe MS, Harrington JM.
Mortality of copper cadmium alloy workers with special reference to lung cancer and non-malignant diseases of the respiratory system, 1946-92.
Occup Environ Med 1995;52:804-812.

65. Pang D, Burges DCL, Sorahan T.
Mortality study of nickel platers with special reference to cancers of the stomach and lung, 1945-93.
Occup Environ Med 1996;53:714-717.

66. Sorahan T, Lancashire RJ, Hulten MA, Peck I, Stewart AM.
Childhood cancer and parental use of tobacco: deaths from 1953 to 1955.
Br J Cancer 1997;75:134-138.

67. Harrington JM, McBride DI, Sorahan T, Paddle GM, van Tongeren M.
Occupational exposure to magnetic fields in relation to mortality from brain cancer among electricity and transmission workers.
Occup Environ Med 1997;54:7-13.

68. Sorahan T, Lancashire RJ.
Lung cancer mortality in a cohort of workers employed at a cadmium recovery plant in the United States: an analysis with detailed job histories.
Occup Environ Med 1997;54:194-201.

69. Draper GJ, Little MP, Sorahan T, Kinlen LJ, Bunch KJ, Conquest AJ, Kendall GM, Kneale GW, Lancashire RJ, Muirhead CR, O'Connor CM, Vincent TJ, Thomas JM, Goodill AA, Vokes J, Haylock RGE.
Cancer in the offspring of radiation workers - a record linkage study.
NRPB-R298. National Radiological Protection Board, 1997

71. Cross HJ, Faux SP, Sadhra S, Sorahan T, Levy LS, Aw TC, Braithwaite R, McRoy C, Hamilton L, Calvert I.
Criteria document for hexavalent chromium.
International Chromium Development Association, Paris, 1997.

72. Draper GJ, Little MP, Sorahan T, Kinlen LJ, Bunch KJ, Conquest AJ, Kendall GM, Kneale GW, Lancashire RJ, Muirhead CR, O'Connor CM, Vincent TJ.
Cancer in the offspring of radiation workers: a record linkage study.
BMJ 1997;315:1181-1188.

73. Sorahan T, Prior P, Lancashire RJ, Faux SP, Hulten MA, Peck IM, Stewart AM.
Childhood cancer and parental use of tobacco: deaths from 1971 to 1976.
Br J Cancer 1997;76:1525-1531.

74. Gilman EA, Sorahan T, Lancashire RJ, Lawrence GM, Cheng KK.
Seasonality in the presentation of acute lymphoid leukaemia.
Br J Cancer 1998;77:677-678.

75. Sorahan T, Burges DCL, Hamilton L, Harrington JM.
Lung cancer mortality in nickel/chromium platers, 1946-95.
Occup Environ Med 1998;55:236-242.

76. Sorahan T, Hamilton L, Gompertz D, Levy LS, Harrington JM.
Quantitative risk assessments derived from occupational cancer epidemiology: a worked example.
Ann Occup Hyg 1998;42:347-352.

77. Sorahan T, Hamilton L, Wallace DMA, Bathers S, Gardiner K, Harrington JM.
Occupational urothelial tumours: a regional case-control study.
Br J Urol 1998;82:25-32.

78. Sorahan T.
Epidemiology: old ships, new vessels.
In: R McCaig, M Harrington, Eds. The changing nature of occupational health. Sudbury,Suffolk: HSE books,1998;283-294.

79. Sorahan T, Hamilton L, Gardiner K, Hodgson JT, Harrington JM.
Maternal occupational exposure to electromagnetic fields before, during, and after pregnancy in relation to risks of childhood cancers: findings from the Oxford Survey of Childhood Cancers, 1953-81 deaths.
Am J Ind Med 1999;35:348-357.

80. Cross HJ, Beach J, Levy LS, Sadhra S, Sorahan T, McRoy C.
Manufacture, processing and use of stainless steel: a review of the health effects.
Eurofer, Paris, 1999.

81. Sorahan T, Harrington JM.
Lung cancer in Yorkshire chrome platers, 1972-97.
Occup Environ Med 2000;57:385-389.

82. Sorahan T, Hamilton L, Jackson JR.
A further cohort study of workers employed at a plant manufacturing chemicals for the rubber industry, with special reference to the chemicals 2-mercaptobenzothiazole (MBT), aniline, phenyl-β-naphthylamine and ortho-toluidine.
Occup Environ Med 2000;57:106-115.

83. Straughan JK, Sorahan T.
Cohort mortality and cancer incidence survey of recent entrants (1982-91) to the United Kingdom rubber industry: preliminary findings.
Occup Environ Med 2000;57:574-576.

84. Sorahan T, McKinney PA, Mann JR, Lancashire RJ, Stiller CA, Birch JM, Dodd HE, Cartwright RA.
Childhood cancer and parental use of tobacco: findings from the inter-regional epidemiological study of childhood cancer (IRESCC).
Br J Cancer 2001;84:141-146.

85. Sorahan T, Hamilton L, van Tongeren M, Gardiner K, Harrington JM.
A cohort mortality study of UK carbon black workers, 1951-96.
Am J Ind Med 2001;39:158-170.

86. Harrington JM, Nichols L, Sorahan T, van Tongeren M.
Leukaemia mortality in relation to magnetic field exposure: findings from a study of United Kingdom electricity generation and transmission workers, 1973-97.
Occup Environ Med 2001;58:307-314.

87. Sorahan T, Nichols L, van Tongeren M, Harrington JM.
Occupational exposure to magnetic fields relative to mortality from brain tumours: updated and revised findings from a study of United Kingdom electricity generation and transmission workers, 1973-97.
Occup Environ Med 2001;58:626-630.

88. Sorahan T, Nichols L, Harrington JM.
Mortality of United Kingdom oil refinery and petroleum distribution workers, 1951-1998.
Occup Med 2002;52:333-339.

88. Sorahan T, Nichols L.
Mortality and cancer morbidity of production workers in the UK flexible polyurethane foam industry: updated findings, 1958-98.
Occup Environ Med 2002;59:751-758.

89. Lancashire RJ, Sorahan T.
Breastfeeding and childhood cancer risks: OSCC data.
Br J Cancer 2003;88:1035-1037.

90. Sorahan T, Haylock RGE, Muirhead CR, Bunch KJ, Kinlen LJ, Little MP, Draper GJ, Kendall GM, Lancashire RJ, English MA.
Cancer in the offspring of radiation workers: an investigation of employment timing and a re-analysis using updated dose information.
Br J Cancer 2003;89:1215-1220.

91. Sorahan T, Nichols L.
Mortality from cardiovascular disease in relation to magnetic field exposure: findings from a study of UK electricity generation and transmission workers, 1973-1997.
Am J Ind Med 2004;45:93-102.

92. Sorahan T, Esmen NA.
Lung cancer mortality in UK nickel-cadmium battery workers, 1947-2000.
Occup Environ Med 2004;61:108-116.

93. Sorahan T.
Mortality of workers at a plant manufacturing nickel alloys, 1958-2000.
Occup Med 2004;54:28-34.

94. Sorahan T, Lancashire RJ.
Parental cigarette smoking and childhood cancer risks of hepatoblastoma: OSCC data
Br J Cancer 2004;90:1016-1018.

95. Nichols L, Sorahan T.
Further update of cancer incidence and cancer mortality in a cohort of semiconductor workers.
HSE Books 2004, Sudbury, Suffolk.

96. Sorahan T, Williams SP.
Mortality of workers at a nickel carbonyl refinery
Occup Environ Med 2005;62:80-85.

97. Sorahan T, Kinlen L, Doll R.
Cancer risks in a historical UK cohort of benzene exposed workers
Occup Environ Med 2005;62:231-236.

98. Nichols L, Sorahan T.
Mortality of UK electricity generation and transmission workers, 1973-2002
Occup Med 2005;55:541-548.

99. Sorahan T. (Letter to the editor)
Re: Mortality experience of male workers at a UK tin smelter.
Occup Med 2005;55:579-580.

100. Sorahan T, Kinlen LJ, Doll R. (Authors' reply)
Cancer risks in a UK benzene exposed cohort.
Occup Environ Med 2005;62:905-906.

101. Nichols L, Sorahan T.
Cancer incidence and cancer mortality in a cohort of UK semiconductor workers, 1970-2002
Occup Med 2005;55:625-630.

102. Sorahan T.
Links between paternal smoking and childhood cancer.
In: *Male-mediated Developmental Toxicity (Issues in Toxicology series).*
Anderson D, Brinkworth MH, Eds. RSC Publishing, Cambridge. 2007.

103. Harrington M, Sorahan T.
Occupational epidemiology.
In: *The development of Modern Epidemiology: Personal reports from those who were there.* Holland WW, Olsen J, Florey C du V, Eds. Oxford University Press. 2007.

104. Sorahan T.
Mortality of United Kingdom oil refinery and petroleum distribution workers, 1951-2003.
Occup Med 2007;57:177-185.

105. Dost A, Straughan JK, Sorahan T.
A cohort mortality and cancer incidence survey of recent entrants (1982-91) to the UK rubber industry: findings for 1983-2004.
Occup Med 2007;57:186-190.

106. Sorahan T, Harrington M.
A 'lugged' analysis of lung cancer risks in UK carbon black production workers, 1951-2004.
Am J Ind Med 2007;50:555-564.

107. Sorahan T, Kheifets L.
Mortality from Alzheimer's, motor neurone and Parkinson's disease in relation to magnetic field exposure: findings from the study of UK electricity generation and transmission workers, 1973-2004.
Occup Environ Med 2007;64:820-826.

108. Sorahan T, Pang D, Esmen N, Sadhra S.
Urinary concentrations of toxic substances: an assessment of alternative approaches to adjusting for specific gravity.
J Occup Environ Hyg 2008;5:721-723.

109. Sorahan T.
Bladder cancer risks in workers manufacturing chemicals for the rubber industry.
Occup Med 2008;58:496-501.

110. Sorahan T.
Cancer risks in chemical production workers exposed to 2-mercaptobenzothiazole.
Occup Environ Med 2009;66:269-273.

111. Sorahan T.
Lung cancer mortality in arsenic-exposed workers from a cadmium recovery plant.
Occup Environ Med 2009;59:264-266.

112. Dost A, Straughan JK, Sorahan T.
Cancer incidence and exposure to 4,4`-methylene-bis-ortho-chloroaniline (MbOCA).
Occup Med 2009;59:402-405.

113. Hara T, Hoshuyama T, Takahashi K, Delgermaa V, Sorahan T.
Cancer risk among Japanese chromium platers, 1976-2003
Scand J Work Environ Health 2010;36:216-221.

114. Sorahan T.
Cadmium, arsenic and lung cancer: the bigger picture.
Occup Med 2010;60:236.

115. Ward EM, Schulte PA, Straif K.....Sorahan T.....Zeise L, Cogliano VJ.
Research recommendations for selected IARC-classified agents.
Environ Health Perspect 2010;118:1355-1362

116. Park EK, Takahashi K, Hoshuyama T, Cheng TJ, Delgermaa V, Le GV, Sorahan T.
Global magnitude of reported and unreported mesothelioma.
Environ Health Perspect 2011;119:514-518.

117. Delgermaa V, Takahashi K, Park EK, Le GV, Hara T, Sorahan T.
Global mesothelioma deaths reported to the World Health Organisation: 1994-2008.
Bull World Health Organ 2011;89:716-724C.

118. Sorahan T.
Cancer incidence in UK electricity generation and transmission workers, 1973-2008.
Occup Med 2012;62:496-505.

119. Sorahan T.
Magnetic fields and brain tumour risks in UK electricity supply workers.
Occup Med 2014;64:157-165.

120. Sorahan T.
Magnetic fields and leukaemia risks in UK electricity supply workers.
Occup Med 2014;64:150-156.

121. Sorahan T, Mohammed N.
Neurodegenerative disease risks and magnetic field exposures in UK electricity supply workers.
Occup Med 2014;64:454-460.

122. Sorahan T.
Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study (AHS) data.
Int J Environ Res Public Health 2015;12:1548-1559.

123. Sorahan T.
Incidence of myelodysplastic syndrome (MDS) in UK petroleum distribution workers.
Leuk Res 2015;39(suppl 1):S18 (abstract).

PRESENTATIONS AT MEETINGS AND CONFERENCES

(1) A comparison of the method of standardised mortality ratios and regression models in life-tables as used in industrial mortality studies.

Annual Meeting of the Society for Social Medicine. Cambridge, 1980.

(2) Cancer of the cervix and cancer of the penis.

Meeting of the West Midlands Oncology Association.
Birmingham, 1981.

(3) A mortality study of nickel-cadmium battery workers.

Third International Cadmium Conference.
Miami, 1982.

(4) An analysis of mortality from diseases of the circulatory system among nickel-cadmium battery workers.

B.O.H.S. Annual Conference.
Edinburgh, 1983.

(5) A further mortality study of nickel-cadmium battery workers.

Fourth International Cadmium Conference.
Munich, 1984.

(6) Skin cancer among semiconductor workers, rubber workers, cadmium workers and nickel-chromium platers.

Second Symposium on Skin Carcinogenicity.
Rouen, 1984.

(7) Cancer of the prostate among nickel-cadmium battery workers.

Annual B.A.C.R. Meeting.
York, 1984

(8) A mortality study of nickel-chromium platers.

International Meeting on Epidemiology in Occupational Health.
Como, 1985.

(9) Fluorescent light and malignant melanoma : a case-control study.

C.I.E. Technical Group Meeting.
Budapest, 1986

(10) A stomach cancer risk in the rubber industry : how good is the evidence?

International Meeting on Occupational Health in the Rubber Industry.
Trelleborg, 1987.

(11) The International collaborative case-control study on cadmium and cancer.

Sixth International Cadmium Conference.
Paris, 1989.

(12) A lung cancer risk in the rubber industry : how good is the evidence?

International Meeting on Occupational Health in the Rubber Industry.
Paris, 1990

(13) Epidemiology and data from industry.

Monsanto Europe and Africa, Medicine and Environmental Health.
Stratford-upon-Avon, 1990.

(14) Cancer risks and low-level radiation.

Open meeting on Environmental Radioactivity,
The Institute of Radiation Protection.
London, 1990.

(15) Childhood cancer and paternal exposure to ionising radiation:
Findings from the Oxford Survey of Childhood Cancers.

Society for Radiological Protection.
Kiel, 1992.

(16) The International collaborative case-control study on cadmium and cancer.

Seventh International Cadmium Conference.
New Orleans, 1992.

(17) Childhood cancer and paternal exposure to ionising radiation: Preliminary findings from the Oxford Survey of Childhood Cancers.

9th ISEOH Meeting.
Cincinnati, 1992.

(18) Childhood cancer and paternal exposure to ionising radiation:
A second report from the Oxford Survey of Childhood Cancers.

10th ISEOH Meeting.
Como, 1994.

(19) Mortality of copper-cadmium alloy workers.

Society of Occupational Medicine, Annual Scientific Meeting.
Birmingham, 1996.

(20) Occupational cancers in the rubber industry.

Health and Safety Commission's Rubber Industry Advisory Committee (RUBIAC) meeting 'Good Health is Good Business in the Rubber Industry'
Birmingham, 1997

(21) Mortality study of cadmium recovery workers using detailed job histories.

12th ISEOH Meeting.
Harare, 1997.

(22) Childhood cancer and parental exposure to ionising radiation before the child's conception: recent UK epidemiological findings.

International Congress on Effects of Low Doses of Ionising Radiation
Munster, 1998.

(23) Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study data.

EuroTox 2012
Stockholm, 2012

(24) Magnetic field exposures and brain tumour and leukaemia risks in UK electricity generation and transmission workers, 1973-2010.

Epicoh 2014
Chicago, 2014

(25) Incidence of myelodysplastic syndrome (MDS) in UK petroleum distribution workers.

MDS 2015
Washington DC, 2015

ORGANISATION OF MEETINGS

International Conference: Ionising Radiation and Cancer Epidemiology

University of Birmingham, July 12th-13th, 1989

I organised the above meeting, attended by some 180 delegates from seventeen countries, as a forum for radiation epidemiologists concerned with studies related to medical exposures, the Japanese A-bomb survivors, occupational exposures, and the consequences of releases of radioactive materials into the environment.

Guidelines for how the conference was organised included the following: (1) all papers to be given in plenary sessions, (2) no poster papers, (3) open call for papers (no invited papers), (4) all papers allocated twenty minutes, (5) no sponsorship of speakers, (6) unified artwork for all conference publicity, brochures and documentation, and (7) a modest conference fee.

Leukaemia Risks in Relation to Benzene Exposure

Institute of Petroleum, London, 22nd October, 2002.

I organised the above one-day workshop attended by 45 delegates from the UK, USA, Holland, Australia, France and Germany, as a forum for epidemiologists to present recent findings from a number of cohort studies involving benzene exposure. A meeting report comprising the eight original scientific presentations and closing remarks by Sir Richard Doll has been published by the Institute of Petroleum.

WORKING PARTIES AND OTHER GROUPS

1. Invited Observer at the International Agency for Research on Cancer (IARC) for Evaluation carried out for Vol 58 of IARC Monographs. Lyon, 1992.

2. Member of the Task Group to finalise the monograph 'Environmental Health Criteria 202: Selected Non-heterocyclic Polycyclic Aromatic Hydrocarbons', carried out as part of the WHO's International Programme on Chemical Safety. Hannover, 1995. Monograph published by WHO, Geneva, 1998.

3. Member of WHO Consultation Meeting: Strengthening of health surveillance of working populations. Geneva, 1998.

4. Member of Advisory Group on Ionising Radiation. National Radiological Protection Board, UK. 1998-2000.

5. Member of the International Agency for Research on Cancer (IARC) Working Group for Vol 87 of the IARC Monographs on inorganic and organic lead compounds (the Working Group met in 2004 and the Monograph was published in 2006).

6. Member of the International Agency for Research on Cancer (IARC) Working Group for Vol 99 of the IARC Monographs on aromatic amines (the Working Group met in 2007 and the Monograph was published in 2010).

Weed

CURRICULUM VITAE

Douglas L. Weed, M.D., M.P.H., Ph.D.
[redacted]
Salt Lake City, UT [redacted]

Phone [redacted] Fax: [redacted]
Email: douglaslweed[redacted]

Education:

1982 – Ph.D., Epidemiology, University of North Carolina

1980 – M.P.H., Epidemiology, University of North Carolina

1977 – M.D., The Ohio State University

1974 – B.Sc., Engineering, *summa cum laude*, The Ohio State University

Experience:

Dr. Weed is an independent scientific consultant. He is a physician-epidemiologist with 30 years of experience in epidemiological research and research training. Dr. Weed is an internationally recognized scholar and educator in causation, causal inference, and the ethics of epidemiology. He has extensive experience in the methods of general causation, cancer causation, systematic reviews, and weight-of-evidence methods. He holds an academic appointment—adjunct full professor—at the University of Utah School of Medicine. He co-chaired the National Academy of Sciences Committee on the 10th anniversity of the U.S. Supreme Court's *Daubert* decision and was a Visiting Scholar at the Federal Judicial Center (Washington, DC). He maintains an active research program in scientific methods, nutritional epidemiology, occupational epidemiology, and the ethics of research. Recent invited lectures include: American Association for the Advancement of Science, at the World Congress of Epidemiology, and at the National Cancer Institute's Summer Course in Cancer Prevention and Control. Dr. Weed is the Reviews Editor for the Journal of the National Cancer Institute and formerly an Associate Editor at the American Journal of Epidemiology.

Dr. Weed is the founder of DLW Consulting Services, LLC. This scientific consulting company provides expertise in disease causation, the methods of causal inference, weight of evidence methods, epidemiological and clinical research methods, and the ethics of epidemiology and public health. DLW Consulting Services, LLC specializes in providing expert advice and guidance on problems at the interface of science, law, commerce, and public policy. Typical projects include expert testimony and consultation in toxic tort litigation, assessments of health risks from exposure to chemicals, metals, infectious agents, pharmaceuticals, and medical devices, as well as assessments of key methodological and ethical problems facing stakeholders. Examples of such problems include: scientific uncertainty, conflicts of interest, and methods used in legal and regulatory contexts to determine general and specific causation.

Employment:

2008- present	Managing Member, DLW Consulting Services, LLC.
2007-2008	Vice President for Epidemiology and Biostatistics, The Weinberg Group, Washington DC
1990-2007	Chief, Office of Preventive Oncology, National Cancer Institute Director, Cancer Prevention Fellowship Program, Bethesda MD
1982-1989	Senior Staff Fellow, Biometry Branch, National Cancer Institute
1978-1982	Public Health Service Trainee, Department of Epidemiology, University of North Carolina, Chapel Hill, NC.
1978	Research Associate, Environmental Protection Agency, Chapel Hill, NC.
1977	Medical Intern, N. Carolina Memorial Hospital, Chapel Hill, NC.

Professional and Scientific Organizations:

American College of Epidemiology (Fellow)
International Epidemiological Association (Past Member)
Kennedy Institute of Ethics (Member)
Society for Epidemiologic Research (Member)

Elected Positions:

Board of Directors, American College of Epidemiology, 1998-2001
Executive Committee, Society for Epidemiologic Research, 1996-1999

Editorial Positions:

Associate Editor, Journal of the National Cancer Institute, 1994-present
Reviews Editor, Journal of the National Cancer Institute, 1995-present
Associate Editor, American Journal of Epidemiology, 1997-2013
Editor-in-Chief, NCI Division of Cancer Prevention Newsletter, 1999-2002

Reviewer:

American Family Physician
American Journal of Clinical Nutrition
American Journal of Epidemiology
American Journal of Industrial Medicine
American Journal of Preventive Medicine

American Journal of Public Health
Annals of Epidemiology
Cancer
Clinical Trials
Critical Reviews in Toxicology
Emerging Themes in Epidemiology
Environmental Health Perspectives
Epidemiologic Reviews
Epidemiology
Evidence Based Journal
Food and Chemical Toxicology
International Journal of Epidemiology
Journal of the American Medical Association
Journal of Clinical Epidemiology
Journal of Medical Decision-Making
Journal of the National Cancer Institute
Kennedy Institute of Ethics Journal
Nutrition and Cancer
Philosophy and Theory in Biology
Preventive Medicine
Regulatory Toxicology and Pharmacology
Social Science and Medicine
Statistics in Medicine
Theoretical Medicine and Bioethics
Toxicology

Faculty Appointments:

Adjunct Professor, 2014-present
Department of Family and Preventive Medicine
Division of Public Health
School of Medicine
University of Utah
Salt Lake City, UT

Adjunct Professor, 2010 - present
Department of Internal Medicine
Division of Epidemiology and Biostatistics
School of Medicine
University of New Mexico
Albuquerque, NM

Visiting Scholar, 2006
Federal Judicial Center
Washington, D.C.

Visiting Fellow, 2001

National Cancer Center
Tokyo, Japan

Visiting Professor (Oncology), 1999
McGill University and University of Montreal
Montreal, Quebec, Canada

Visiting Professor (Epidemiology), 1998
National School of Public Health
Madrid, Spain

Faculty Affiliate, 2001- 2010
Senior Research Fellow, 1995 – 2001
Visiting Fellow, 1994-5
Kennedy Institute of Ethics
Georgetown University, Washington, D.C.

Faculty member, 1994
Society for Epidemiologic Research
Student Workshop on Epidemiologic Methods, Miami, FL

Adjunct Associate Professor, 1994 - 2010
Department of Preventive Medicine and Biometrics
F. Edward Hebert School of Medicine
Uniformed Services University of the Health Sciences
Bethesda, MD

Associate Faculty, 1989 - 2010
Department of Epidemiology
School of Hygiene and Public Health
Johns Hopkins University, Baltimore, MD

Teaching Assistant and Lecturer (Epidemiology), 1979-80
University of North Carolina, Chapel Hill, NC

Honors and Awards:

Engineering Honor Scholar 1971-1974 (each year)
Phi Eta Sigma (freshman academic honorary) 1971
Alpha Epsilon Delta (pre-med academic honorary) 1973
Tau Beta Pi (engineering academic honorary) 1974
Phi Kappa Phi (general academic honorary) 1974
Alpha Omega Alpha (medicine academic honorary) 1977
Honors in Medicine (clinical) 1977
Honors in Obstetrics and Gynecology (clinical) 1977
On-the-Spot Cash Award (NCI): 1999, 2000
Sustained Superior Performance Cash Award (NCI): 1990-1999 (each year)

Distinguished Alumnus: Ohio State Univ. Preventive Medicine 1994
NIH Merit Award 1995
Commencement Speaker: USUHS M.P.H. Graduation 1996
Quality Step Increase (NCI) 1997, 2000
Keynote Speaker: III Congress of Chilean Society of Epidemiology 1997
Keynote Speaker: Spanish Epidemiologic Society 1998
Advances in Oncology Lecture: McGill University Cancer Center 1999
Samuel C. Harvey Lecture: American Association for Cancer Education 1999
Keynote Speaker: Korean Society for Preventive Medicine 1999
Grand Rounds: Ohio State University Cancer Center 1999
Keynote Speaker: Ethics and Research Integrity Day, University of Alberta, 2000
Keynote Speaker: EPA Conference on Environmental Statistics, 2001
J. Walter Juckett Memorial Lecture, Vermont Cancer Center, 2002
Distinguished Leadership Award, NCI Division of Cancer Prevention, 2002
NIH Merit Award, 2004
Keynote Speaker: Great Lakes Cancer Institute Symposium, 2005
Keynote Speaker: Turkish Society of Internal Medicine, 2005

Board and Committee Memberships

Member, Selection Committee (for Medical School Applicants), University of Utah School of Medicine, 2015 - present

Member, Ethics Committee, American College of Epidemiology, 2014 – present

Member, Admissions Committee, University of Utah School of Medicine, 2014 - 2015

Member, Ohio State University College of Public Health Advisory Board
Columbus, Ohio, 2005 – 2013

Member, Commission on Forensic Science and Public Policy, American Judicature Society, 2005 -- 2007

Co-Chair, National Academy of Sciences Committee, 2005 - 2006
"Alternative Models to the *Daubert* Criteria"
Science, Technology, and Law Program, NAS

Chair, Prevention Working Group, 2001-2007
All-Ireland NCI Cancer Consortium
National Cancer Institute (NCI)

Chair, Scientific Education Committee, 1989- 2007
Division of Cancer Prevention, NCI

Chair, Ethics and Standards of Practice Committee, American College of Epidemiology, 1998-2001.

Member, NIH Committee on Continuing Medical Education (CME), 2000-2005

Cancer Advisory Panel, National Center for Alternative and Complementary Medicine, NIH, 1998-2002

World Health Organization Working Group on the Acceptability of Epidemiologic Evidence for Health Impact Assessment, 1999.

National Cancer Institute Cancer Training Advisory Committee, 1997-9.

Member, Advisory Committee for the National Center for Training in Cancer Prevention and Control, Centers for Disease Control and Prevention, 1995-7.

NIH Epidemiology and Clinical Trials Interest Group, 1985-2000.

NIH Committee on Generic Postdoctoral Research Training, 1994.

NCI Committee on Employee Mentoring, 1994.

Program Planning Committee, American Society of Preventive Oncology, 1991-1993.

American Cancer Society Task Force on Preventive Medicine Training, 1993.

NIH Planning Committee for the Alternative Medicine Technology Assessment Meetings, 1993.

ICCCR International Conference on Cancer Prevention. Bethesda, Maryland, February, 1991. See also: Monographs of the Journal of the National Cancer Institute. NIH Publication 91-3227, p.167, 1992.

American Society of Preventive Oncology Annual Meeting Symposium on Quality of Prevention Research. 1991.

Leader, Roundtable Discussion on Causal Inference. Society for Epidemiologic Research Annual Meeting, 1994.

Panel on Philosophy of Science in Epidemiology. Third Brazilian Congress of Epidemiology, Salvador, Bahia, Brazil, 1995.

Leader, Roundtable Discussion on Methods and Morals in Epidemiology. Society for Epidemiologic Research Annual Meeting, 1995.

NCI Roundtable Discussion on Clinical Trials Auditing, 1995.

Leader, Roundtable Discussion on Preventing Scientific Misconduct. Society for Epidemiologic Research Annual Meeting, 1996.

Education Review Committee, U.T. M.D. Anderson Cancer Center, Cancer Prevention and Education Program, 1996-1998.

Member, Ethics and Standards of Practice Committee, American College of Epidemiology, 1996-1998.

Research Interests:

Disease causation, cancer epidemiology, prevention and control, causal and preventive inference, research synthesis methods (evidentiary methods, meta-analysis, systematic reviews, inferential methods, ethical decision-making methods), philosophy of public health, ethics of biomedical research, professional ethics, medical humanities, research training, science and the law.

Recent Lectures and Invited Seminars

"Best Practices: Interpreting Observational Studies." University of Alabama, Birmingham. July 20, 2015.

"But are you a good epidemiologist?" Society for Epidemiologic Research Graduate Student Workshop. Denver, CO. June 16, 2015.

"Systematic review and meta-analysis of sugar-sweetened beverages and type 2 diabetes." 33rd International Symposium on Diabetes and Nutrition. Toronto, Canada. June 11, 2015.

"Comments on Scientific Question #1 on Butyl Benzyl Phthalate (BBP) and USEPA IRIS Preliminary Materials." United States Environmental Protection Agency (USEPA). Integrated Risk Information System (IRIS) Bimonthly Public Science Meeting. Crystal City, VA. February 26, 2015.

"Meta-Analyses of Observational Studies." International Life Sciences (ILSI) Annual Conference. Phoenix, AZ, January 19, 2015.

"Causality in Public Health and Preventive Medicine." Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT, April 18, 2014.

"On the Utility of Criteria-Based Methods of Causal Inference." Society for Risk Analysis. Baltimore, MD, December 9, 2013.

"What Causes Cancer?" Huntsman Cancer Institute. Salt Lake City, UT, November 13, 2013.

"Does Red Meat Cause Colon Cancer?" Center for Advanced Study at the Norwegian Academy of Science and Letters. Oslo, Norway, November 6, 2013.

"Interpreting Scientific Evidence for Cancer Prevention." National Cancer Institute Summer Curriculum on Cancer Prevention and Control. Rockville, MD, July 10, 2014.

"Conflicts of Interest." University of California, Berkeley. Epidemiology Doctoral Seminar. Berkeley, CA, April 10, 2013.

"On the Utility of Criteria-Based Methods of Causal Inference." International Society for Environmental Epidemiology. Columbia, SC, August 30, 2012.

"How do we make causal conclusions from the 'totality of the evidence' objective and observable?" Conference on "Scientific Approaches to Strengthening Research Integrity in Nutrition and Energetics" sponsored by the University of Alabama, Birmingham. New Paltz, NY, August 2012.

"Standards of Reporting Dietary Supplements Research Studies." National Institutes of Health Office of Dietary Supplements Research Practicum. Bethesda, MD, June 2012.

"Quality of peer-reviewed published reviews: a case study of sugar-sweetened beverages and health outcomes." Institute of Medicine Food Forum. Washington, DC, September 2011.

"Registration of Epidemiological Studies" Pre-Conference Course on Epidemiological Methods, International Epidemiological Association World Congress of Epidemiology. Edinburgh, Scotland, August 2011.

"Comments on Weight of Evidence" AAAS Conference, Washington DC, February 2011.

"The Professional Responsibilities of Epidemiologists." University of California, Berkeley. March, 2010.

"Causal Inference in Cancer Epidemiology." University of California, Berkeley. March, 2010.

"Uncertainty and Weight of Evidence in Risk Assessment." ICNIRP Workshop: Evaluation and Communication of Scientific Evidence and Uncertainty - Towards a Consistent Terminology in Non-ionizing Radiation. Salzburg, Austria, November, 2009.

"Meta-analysis and causal inference: a case study of benzene and non-Hodgkin's lymphoma." Benzene09, Munich, Germany, September, 2009.

"Biological Mechanism and Causal Inference." Institute of Medicine, Washington DC, June 2009.

"A Method for Individual Causation." University of North Carolina, Chapel Hill, NC, May 2008, the American Association of Law Schools Conference on Evidence, Cleveland, Ohio, June 2008, and at Michigan State University, East Lansing, MI, October, 2009.

"Weight of Evidence and Uncertainty Assessments" DIA/FDA Workshop on Risks and Benefits, Bethesda, MD, November 2009 and ICNIRP/WHO Workshop on Risk Assessment and Terminology, Salzburg, Austria, November 2009.

"Cases and Causes" AstraZeneca Wilmington DE, November 2007, and Amgen Inc. Thousand Oaks, CA, March 2008.

"Why should epidemiology bridge the science/law "cultural chasm"? North American Epidemiology Congress plenary session, Seattle, Washington, June 2006.

"Rethinking Epidemiology" Imperial College (London), Division of Epidemiology, London, England, May 2006.

"Weight of Evidence and General Causation" Science for Judges Program, Brooklyn Law School, Brooklyn, NY, March 2006.

"Weight of Evidence: a Review of Concept and Methods." Society for Risk Analysis, Orlando, Florida, December 2005.

"The Future of Cancer Prevention" Keynote Address. Symposium, San Antonio Cancer Institute, San Antonio, Texas, November 2004; and Special Lecture at the 250th Anniversary of the Meath Hospital, Dublin, Ireland, October 2003.

"The End of Epidemiology" Columbia University, Department of Epidemiology, May 2004, University of New Mexico, May 2005 and 2010, Imperial College (London) Department of Epidemiology and Public Health, December 2005.

"Cancer Prevention in the USA" Xi'an Cancer Hospital, Xi'an, China; CICAMS Cancer Hospital, Beijing, China, October 2004.

"Biologic plausibility and other challenges to the primary prevention of cancer." American College of Preventive Medicine, Washington DC, February 2005.

"The Future of Cancer Epidemiology." Michigan State University Department of Epidemiology, East Lansing, MI, April 2005, and the University of New Mexico, Department of Family and Community Medicine, Albuquerque, NM, May 2005.

Advisory Positions

American Health Foundation, 1998-1999.
Australian Cancer Society, 1999.
Health and Environmental Sciences Institute, 2004 – 2005.
International Life Sciences Institute, 2000 – 2003.
World Health Organization, 1999, 2001.
Mead Johnson Nutrition Safety Advisory Panel, 2012 – present.
National Science Teachers Association, 2002-2014.

Brooklyn Law School, 2003, 2006.

Dissertation and Thesis Committees

Vrije University, Brussels, Belgium (Guido Goelen, M.D., Ph.D), 1999-2001

BIBLIOGRAPHY

PUBLICATIONS

Alexander DD, Weed DL, Miller P, Mohamed M. Red meat and colorectal cancer: a quantitative update on the state of the epidemiologic science. 2015. J Am Coll Nutr (in press).

Alexander DD, Bassett JK, Weed DL, Barrett EC, Watson H, Harris W. 2015. Meta-analysis of long-chain omega-3 polyunsaturated fatty acids (LCω-3PUFA) and prostate cancer. Nutrition and Cancer March 31:1-12 [epub ahead of print].

Althuis MD, Weed DL, Frankenfeld CL. 2014. Evidence-based mapping of design heterogeneity prior to meta-analysis: a systematic review and evidence synthesis. Systematic Reviews 3:80.

Miller PE, Alexander DD, Weed DL. 2014. Uncertainty of results in nutritional epidemiology. Nutrition Today 49:147-5.

Oostindjer M, Alexander J, Amdam GV, Andersen G, Bryan NS, Chen D, Corpet DE, De Smet S, Dragsted LO, Haug A, Karlsson AH, Kleter G, de Kok TM, Kulseng B, Milkowski AL, Martin RJ, Pajari A-M, Paulsen JE, Pickova J, Rudi K, Sødring M, Weed DL, Egelandsdal B. The role of red and processed meat in colorectal cancer development: a perspective. Meat Science 2014;97:583-96.

Alexander DD, Weed DL, Chang ET, et al. 2013. A systematic review of multivitamin-multimineral use and cardiovascular disease and cancer incidence and total mortality. J Amer Coll Nutr 32:339-54.

Althuis MD, Weed DL. 2013. Evidence mapping: Methodological foundations and application to intervention and observational research on sugar sweetened beverages and health outcomes. Am J Clin Nutr . doi: 10.3945/ajcn.113.058917.

Weed DL. 2013. The quality of nutrition and cancer reviews: a systematic assessment. Crit Rev Food Sci Nutrition 53:276-86.

Alexander DD, Weed DL, Mink PJ, et al. 2012. A weight-of-evidence review of epidemiologic studies of colorectal cancer in pesticide applicators. Int Arch Occup Environ Health 85:715-45.

Weed DL, Althuis MD, Mink PJ. 2011. Quality of reviews on sugar-sweetened beverages and health outcomes. Am J Clin Nutr 94:1340-7.

Alexander DD, Weed DL, Cushing CA, Lowe KA. 2011. Meta-analysis of prospective studies of red meat consumption and colorectal cancer. Eur J Cancer Prevention 20:293-307.

Navia JL, Byers T, Djordjevic D, Hentges E, King J, Klurfeld D, Llewellyn C, Milner J, Skrypec D, Weed DL. 2010. Integrating the totality of food and nutrition evidence for public health decision making and communication. Crit Rev Food Sci Nutrition 50:1-8.

Schreider J, Barrow C, Birchfield N, Dearfield K, Devlin D, Henry S, Kramer M, Schappelle S, Solomon K, Weed DL, Embry MR. 2010. Enhancing the credibility of decisions based on scientific conclusions: transparency is imperative. Tox Sci doi: 10.1093/toxsci/kfq102.

Weed DL. 2010. Meta-analysis and causal inference: a case study of benzene and non-Hodgkin's lymphoma. Ann Epidemiol 20:347-355.

Weed DL. 2009. Conflicts of Interest. J Epidemiol Commun Health 63:601-602.

Weed DL. 2008. Truth, Epidemiology, and General Causation. Brooklyn Law Review 73:651-665.

Griego FY, Bogen KT, Price PS, Weed DL. 2008. Exposure, epidemiology and human cancer incidence of naphthalene. Reg Tox Pharmacol 51:22-6.

Weed DL. 2007. The nature and necessity of scientific judgment. J Law Policy 15:135-164.

Collins JJ, Bukowski JA, Weed DL, Brent RL, Klein P, Boerstoel-Steefland M, Sprafka JM, Williams AL, Holsapple MP. 2007. Evaluating emerging issues in epidemiology. Regul Toxicol Pharmacol 48(3):296-307.

Dores G, Chang S, Berger VW, Perkins S, Hursting SD, and Weed DL. 2006. Evaluating research training outcomes: experience from the Cancer Prevention Fellowship Program at the National Cancer Institute. Acad Med. 81(6):535-541.

Weed DL. 2006. Commentary: Rethinking epidemiology. Int J Epidemiol. 35(3):583-586.

Parascandola M, Weed DL, and Dasgupta A. 2006. The Surgeon General's Reports on Smoking and Cancer: a historical investigation of the practice of causal inference. Emerg Themes Epidemiol. 3:1-11.

Weed DL. 2006. Evidence synthesis and general causation: key methods and an assessment of reliability. Drake Law Review 54:639-650.

Weed DL. 2006. Vision, values, and verisimilitude: a response. Risk Anal. 26:577.

Weed DL. 2005. Hail the heroes who brave front line. The Times Higher Education Supplement (London) No. 1722:14.

*Weed DL. 2005. Weight of evidence: a review of concepts and methods. Risk Anal. 25:1545-1557.

Chang, S., Hursting, S., Perkins, S., Dores, G., and Weed, D.L. 2005. Adapting postdoctoral training to interdisciplinary science in the 21st century: the Cancer Prevention Fellowship Program at the National Cancer Institute. Acad Med. 80(3):261-265.

Resnik, D.B., Kopelman, L.M., and Weed, D.L. 2004. What is the role of the precautionary principle in bioethics and the philosophy of medicine? J Med Philos. 29(3):255-258.

McKeown, R.E. and Weed, D.L. 2004. Ethical choices in survey research. Soz Praventivmed. 49:67-68.

Weed, D.L. and Dores, G. 2004. Physicians as citizens (letter). JAMA 291:2076.

Kopelman, L.M., Resnick, D., and Weed, D.L. 2004. What is the role of the precautionary principle in the philosophy of medicine and bioethics? J Med Philos. 29:255-258.

Weed, D.L. 2004. Precaution, prevention, and public health ethics. J Med Philos. 29:313-332.

Weed, D.L. and McKeown, R.E. 2003. Science and social responsibility in public health. Environ Health Perspect. 111:1804-1808.

Weed, D.L. 2003. Methodologic implications of the precautionary principle: causal criteria. Eur J Oncolo. 2:103-108.

Weed, D.L. 2003. Causation: an epidemiological perspective. J Law Policy 43:43-53.

Weed, D.L. and McKeown, R.E. 2003. Science, ethics and professional public health practice. J Epidemiol Commun. Health 57:4-5.

McKeown, R.E., Weed, D.L., Kahn, J., and Stoto, M. 2003. American College of Epidemiology Ethics Guidelines: Foundations and Dissemination. Sci Eng. Ethics 9(2):207-214.

*Weed, D.L and Mink, P. 2002. Roles and responsibilities of epidemiologists. Ann Epidemiol. 12:67-72.

Weed, D.L. 2002. Environmental epidemiology: basics and proof of cause-effect. Toxicology 181-182:399-403.

McKeown, R.E. and Weed, D.L. 2002. Glossary of ethics in epidemiology and public health: II. Applied terms. J Epidemiol Commun. Health 56:739-741.

Weed, D.L. 2002. Cancer prevention and the All-Ireland NCI Cancer Consortium. Promoting Health-The Journal of Health Promotion for Northern Ireland 18:26-27.

Weed, D.L. 2001. Methods in epidemiology and public health: does practice match theory? J Epidemiol Commun. Health 55:104-110.

Piniewski-Bond, J.F., Buck, G.M., Horowitz, R.S., Schuster, J.H.R., Weed, D.L., and Weiner, J.M. 2001. Comparison of information processing technologies. J Am Med Informatics Assoc. 8:174-184.

Weed, D.L. 2001. A radical future for public health. Int J Epidemiol. 30:440-441.

Merrill, R.M. and Weed, D.L. 2001. Measuring public health burden of cancer through lifetime and age-conditional risk estimates. Ann Epidemiol. 11:547-553.

Burke, W., Coughlin, S.S., Lee, N.C., Weed, D.L., and Khoury, M. 2001. Application of population screening principles to genetic screening for adult-onset conditions. Genet Test. 5:201-211.

Parascandola, M. and Weed, D.L. 2001. Causation in epidemiology. J Epidemiol Commun. Health 55:905-912.

Weed, D.L. and McKeown, R.E. 2001. Glossary of ethics in epidemiology and public health: I. Technical terms. J Epidemiol Commun. Health 55:855-857.

Weed, D.L. 2001. Theory and practice in epidemiology. Ann NY Acad Sci. 954:52-62.

Stoto, M.A., Hermalin, A.I., Li, R., Martin, L., Wallace, R.B., and Weed, D.L. 2001. Advocacy in epidemiology and demography. Ann NY Acad Sci. 954:76-87.

Weed, D.L. 2000. History of Cancer Prevention: Pioneers of progress: Major Greenwood, Austin Bradford Hill, and the development of the randomized clinical trial (1900-1950). PreventionPost 2:2-3.

Weed, D.L. 2000. The rise and fall of the clinical trial paradigm. PreventionPost 2:1:16.

Weed, D.L. 2000. Interpreting epidemiologic evidence: how meta-analysis and causal inference methods are related. Int J Epidemiol. 29:387-390.

Connor, R.J., Boer, R., Prorok, P.C., and Weed, D.L. 2000. An investigation of design and bias issues in case-control studies of cancer screening using microsimulation. Am J Epidemiol. 151:991-998.

Weed, D.L. 2000. Epidemiologic evidence and causal inference. Hematology/Oncology Clin N America 14:797-807.

Weed, D.L. 2000. History of Cancer Prevention: Joseph Cullen: Champion of Cancer Prevention and Control. PreventionPost 2:2:10.

Weed, D.L. 2000. Heroes and champions. PreventionPost 2:2:12.

Weed, D.L. 1999. Towards a philosophy of public health. J Epidemiol Commun. Health 53:99-104.

Potischman, N. and Weed, D.L. 1999. Causal criteria in nutritional epidemiology. Am J Clin. Nutrition 69(Suppl):1309S-1314S.

Weed, D.L. and Coughlin, S.S. 1999. New ethics guidelines for epidemiology: background and rationale. Ann Epidemiol. 9:277-280.

Weed, D.L. 1999. Book review of: *Philosophy in Epidemiology and Public Health*. Epidemiol. Monitor.

Ratnasinghe, D.D., Weed, D.L., and Shankar, S. 1999. Cancer knowledge and misconceptions among Hispanic El Salvadorian men in the Washington DC area. J Immigrant Health 1:207-213.

Weed, D.L. and Hursting, S.D. 1999. The authors reply (letter). Am J Epidemiol. 150:218-219.

Weed, D.L. 1999. History of Cancer Prevention: Cancer prevention in the "Roaring Twenties." PreventionPost 1:6.

Weed, D.L. 1999. The DCP Newsletter team (editorial). PreventionPost 1:12.

Weed, D.L. 1999. Higher standards for epidemiologic studies-replication prior to publication? (letter). JAMA 282:937.

Weed, D.L. 1998. Preventing scientific misconduct. Am J Public Health 88:125-129.

Weed, D.L. 1998. Beyond black box epidemiology. Am J Public Health 88:12-14.

Breslow, R.A. and Weed, D.L. 1998. Review of epidemiologic studies of alcohol and prostate cancer: 1971-1996. Nutrition and Cancer 30:1-13.

Breslow, R.A. and Ross, S.A., and Weed, D.L. 1998. Quality of reviews in epidemiology. Am J Public Health 88:475-477.

Weed, D.L. and Hursting, S.D. 1998. Biologic plausibility in causal inference: current method and practice. Am J Epidemiol 147:415-425.

Cronin, K.A., Weed, D.L., Prorok, P.C., and Connor, R.J. 1998. Case-control studies of screening: theory and practice. J National Cancer Inst. 90:498-504.

Weed, D.L. and McKeown, R.E. 1998. Epidemiology and virtue ethics. Int J Epidemiol. 27:343-348.

McKeown, R.E. and Weed, D.L. 1998. Authors' response to comment on "Epidemiology and virtue ethics." Int J Epidemiol. 27:348-349.

Huerta, E.E. and Weed, D.L. 1998. "Cuidando su Salud" (Spanish language radio in preventive medicine and public health). Cancer (Suppl) 83:1805-1808.

Weed, D.L. 1997. Methodologic guidelines for review papers. J Nat Cancer Inst. 89:6-7.

Weed, D.L. and Kramer, B.S. 1997. Response to Brind et al. (letter). J Nat Cancer Inst. 89:588.

Bulterys, M., Morgenstern, H., and Weed. D.L. 1997. Quantifying the expected versus potential impact of a risk-factor intervention program. Am J Public Health 87:867-868.

Weed, D.L. 1997. Underdetermination and incommensurability in contemporary epidemiology. Kennedy Institute of Ethics J. 7:107-127.

Weed, D.L. 1997. Meta-analysis under the microscope. J Nat Cancer Inst. 89:904-905.

Weed, D.L. 1997. The behavior-biology interface in cancer prevention and control. Prev Med. 26:S37-S41.

Merrill, R.M., Weed, D.L., and Feuer, E.J. 1997. The lifetime risk of developing prostate cancer in white and black men. Cancer Epidemiol Biom Prev, 6:763-768.

Weed, D.L. 1997. On the use of causal criteria. Int J Epidemiol. 26:1137-1141.

Gerlach, K.K., Marino, C., Weed, D.L., and Hoffman-Goetz, L. 1997. Lack of colon cancer coverage in seven women's magazines. Women & Health 26:57-68.

Weed, D.L. 1996. The sea of person time. Int J Epidemiol 25:1-4.

Weed, D.L. 1996. Book Review of: *The Fight for Public Health: Principles and Practice of Media Advocacy*. Prev Med, 25:86.

Weed, D.L. and Gorelic, L.S. 1996. The practice of causal inference in cancer epidemiology. Cancer Epidemiol Biomark Prev. 5:303-311.

Weed, D.L. 1996. Weed Responds to: The future of epidemiology: a humanist response. Am J Pub Health 86:1029-1030.

Weed, D.L. 1996. Book review of: Changing the Odds: Cancer Prevention through Personal Choice and Public Policy. Oncology 10:1432.

Weed, D.L. and Kramer, B.S. 1996. Induced abortion, bias and breast cancer: why epidemiology hasn't reached its limit. J Nat Cancer Inst. 88:1698-1700.

Weed, D.L. 1995. Epidemiology, the humanities, and public health. Am J Pub Health 85:914-918.

Houn, F., Bober, M.A., Huerta, E.A., Hursting, S., Lemon, S., and Weed, D.L. 1995. The association between alcohol and breast cancer: popular press coverage of research. Am J Pub Health 85:1082-1086.

Weed, D.L. 1994. Science, ethics guidelines, and advocacy in epidemiology. Ann Epidemiol. 4:166-171.

Reprinted by permission in: Coughlin SS (ed.). 1995. Ethics in Epidemiology and Clinical Research. Chestnut Hill, MA: ERI. Pp. 267-272.

Weed, D.L. 1994. Book Review of: Apricots and Oncogenes: On Vegetables and Cancer Prevention. Am J Epidemiol. 139:743-744.

Weed, D.L. 1994. Between science and technology: the case of antihistamines and cancer. J Nat Cancer Inst. 86: 740-741.

Coughlin, S.S., Benichou, J. and Weed, D.L. 1994. Attributable risk estimation in case control studies. Epidemiol Rev. 16:51-64.

Weed, D.L. 1994. Alcohol, breast cancer, and causal inference: where ethics meets epidemiology. Contemporary Drug Problems 21:185-204.

Greenwald, P.G., Kramer, B.K., and Weed, D.L. 1993. Expanding horizons in breast and prostate cancer prevention and early detection. J Cancer Education 8:91-107.

Husten, C., Weed, D.L, and Kaluzny, A.R. 1993. Training researchers in cancer prevention and control: a description and evaluation of NCI's Cancer Prevention Fellowship Program. J Cancer Education 8:281-290.

Pommerenke, F. and Weed, D.L. 1991. Physician compliance: Improving skills in preventive medicine practices. Am Fam Physician 43:560-568.

Weed, D.L. 1991. The merger of bioethics and epidemiology. J Clin Epidemiol. 44:15S-22S.

Cairoli, V.J. and Weed, D.L. 1991. NCI Report on the Cancer Education Program. J Cancer Education 6:65-66.

Connor, R.J., Prorok, P.C., and Weed, D.L. 1991. The case-control design and the assessment of the efficacy of cancer screening. J Clin Epidemiol. 44:1215-1221.

Clark, L.C., Patterson, B.H., Weed, D.L., and Turnbull, B.W. 1991. Design issues in cancer chemoprevention trials using micronutrients: application to skin cancer. Cancer Bulletin 43:519-524.

Koopman, J.S. and Weed, D.L. 1990. Epigenesis theory: A mathematical model relating causal concepts of pathogenesis in individuals to disease patterns in populations. Am J Epidemiol. 132:366-390.

Greenwald, P., Cullen, J.W., and Weed, D.L. 1990. Introduction: cancer prevention and control. Semin Oncol. 17:383-390.

Weed, D.L., Greenwald, P., and Cullen, J.W. 1990. The future of cancer prevention and control. Semin Oncol. 17:504-509.

Weed, D.L., Selmon, M., and Sinks, T. 1988. Links between categories of interaction. Am J Epidemiol. 127:17-27.

Weed, D.L. and Trock, B. 1988. Interactions and public health decisions. J Clin Epidemiol. 41:207-209.

Weed, D.L. 1987. The author replies. (Re: "On the logic of causal inference"). Am J Epidemiol. 126:157-158.

Weed, D.L. 1987. Epidemiology's triple crown. J Chronic Dis. 40:905-906.

Weed, D.L. 1987. The author replies. (Re: "On the logic of causal inference"). Am J Epidemiol. 126:557.

Weed, D.L., Tyroler, H.A., and Shy, C.M. 1987. The healthy worker effect in actively-working communications workers. J Occup Med. 29:335-339.

Weed, D.L. 1986. Historical roots of the healthy worker effect. J Occup Med. 28:343-347.

Weed, D.L. 1986. Lament for an epidemiologist. Pharos 49:43.

Weed, D.L. 1986. On the logic of causal inference. Am J Epidemiol. 123:965-979.

Weed, D.L. and Trock, B.J. 1986. Criticism and the growth of epidemiologic knowledge. (Re: "Popperian refutation in epidemiology"). Am J Epidemiol. 123:1119-1120.

Weed, D.L. 1985. An epidemiological application of Popper's method. J Epidemiol Commun. Health 39:277-285.

Weed, D.L. 1983. Ethics and chemoprevention research. Semin Oncol. 10:355-359.

BOOKS, BOOK CHAPTERS, EDITED JOURNAL ISSUES, DISSERTATION, AND TECHNICAL REPORTS

Weed, D.L. 2009. Towards a Philosophy of Epidemiology. In: Coughlin, S.S., Beauchamp, T.L., and Weed, D.L. (eds). Ethics and Epidemiology. New York:Oxford University Press.

Rockhill, B. and Weed, D.L. 2006. Increasing the contribution of epidemiology to the primary prevention of cancer. In Schottenfeld, D.A. and Fraumeni, J.F. Jr. (eds). Cancer Epidemiology and Prevention. Pp. 1292-1302.

Weed, D.L. 2004. Ethics and philosophy of public health. In Khushf. G. Handbook of Bioethics: A Philosophical Overview. Pp.525-547.

Weed, D.L. 2002. Philosophical basis for public health. In Breslow, L. et al. (ed). Encyclopedia of Public Health. Farmington Hill, Michigan: Macmillan Reference. Pp. 914-917.

Weed, D.L. 2002/2003. Is the Precautionary Principle a principle? IEEE Technology and Society Magazine 21:45-48.

[No authors listed]. American College of Epidemiology Ethics Guidelines. 2000. Ann Epidemiol 10(8):487-497.

WHO Working Group. 2000. Evaluation and use of epidemiological evidence for environmental health risk assessment: guideline document. World Health Organization, EUR/00/5020369, E68940. See also: Environmental Health Perspectives 108:997-1002, 2000.

Weed, D.L. 1999. Ethics and consent. In Kramer, B.S., Gohagan, J., and Prorok, P.C. (eds). Cancer Screening: Theory and Practice. New York: Marcel Dekker. Pp. 89-140.

Douglas Weed and B.S. Kramer, "Breast cancer studies aren't political," Wall Street Journal, Wednesday, 26 Mar 1997, sec. A19.

Weed, D.L. 1996. Epistemology and ethics in epidemiology. In Coughlin, S.S. and Beauchamp, T.L. Ethics and Epidemiology. New York: Oxford. Pp. 76-94.

Weed, D.L. 1995. Causal and preventive inference. In Greenwald, P., Kramer, B., and Weed, D.L. (eds.). Cancer Prevention and Control. New York: Marcel Dekker. Pp. 285-302.

Weed, D.L. and Coughlin, S.S. 1995. Ethics in cancer prevention and control. In Greenwald, P., Kramer, B., and Weed, D.L. (eds). Cancer Prevention and Control. New York: Marcel Dekker. Pp. 497-507.

Weed, D.L. and Husten, C. 1995. Training in cancer prevention and control. In Greenwald, P., Kramer, B., and Weed, D.L. (eds). Cancer Prevention and Control. New York: Marcel Dekker. Pp. 707-717.

Greenwald, P.G., Kramer, B.K., and Weed, D.L. 1995. Cancer Prevention and Control. New York: Marcel Dekker.

Greenwald, P.G., Cullen, J.W., and Weed, D.L. (eds.). Cancer prevention and Control. Seminars in Oncology 17:1990.

Weed, D.L. 1988. Causal criteria and Popperian refutation. In Rothman, K.J. (ed.). Causal Inference. Chestnut Hill: Epidemiology Resources, Inc. Pp. 15-32.

Weed, D.L. 1988. Criticism and its constraints: A self-appraisal and rejoinder. In Rothman, K.J. (ed.). Causal Inference. Chestnut Hill: Epidemiology Resources, Inc. Pp. 201-207.

Weed, D.L. 1982. An investigation of the healthy worker effect. Ph.D. dissertation, University of North Carolina, Chapel Hill, North Carolina.

ABSTRACTS

Kelsh, M.A., Yao, B., Arrindell, D.A., Alexander, D., Acquavella, J., Weed, DL. Evaluation of adverse events of pharmaceutical agents—the impact of effect measure selection on meta-analysis findings. International Society of Pharmacoepidemiology. October, 2014. Taipei, Taiwan.

Weed, D.L., Althuis, M.A. Evaluating Confounding Bias when Designing Meta-analyses of Dietary Risk Factors with Weak Associations: a Systematic Review of Risk Factors for Type 2 Diabetes. International Epidemiology Association World Congress. August, 2014. Anchorage, Alaska.

Weed, D.L. 2012. On the utility of criteria-based methods of causal inference. International Society for Environmental Epidemiology: Conference. August, 2012.

Weed, D.L. 2009. Meta-analysis and causal inference: a case study of benzene and non-Hodgkin's lymphoma. Benzene 2009: Health Effects and Mechanisms of Bone Marrow Toxicity, Implications for t-AML and the Mode of Action Framework. Munich, Germany.

Weed, D.L. 2008. A method for individual causation. Am. J. Epidemiol. 167:S115.

Weed, D.L. 2001. Ethics of precautionary preventive interventions. Am. J. Epidemiol. 153:S7.

Weed, D.L. 2001. Environmental epidemiology: basics and proof of cause-effect. Toxicology 164:29.

Weed, D.L. 2000. Epidemiology, beneficence, and the Precautionary Principle. Am J. Epidemiol. 151: S90.

Marcus, P.M. and Weed, D.L. 1999. Did the chronic disease era of cancer epidemiology start before we think it did? Ann. Epidemiol.

Weed, D.L. 1997. Underdetermination and incommensurability in epidemiology. Am. J. Epidemiol. 145(Suppl):S73.

Weed, D.L. 1993. Bioethical methods in epidemiology. Am. J. Epidemiol. 138:671.

Weed, D.L. 1992. Epidemiology and the humanities: an illustrated example. Am. J. Epidemiol. 136:1006-1007.

Gorelic, L.S., Weed, D.L., Dresser, C., Graubard, B., and Ruiz, E. 1991. Cervical cancer screening practices by Hispanic women. Prev. Med.

Weed, D.L. 1991. Causal inference: A matter of principle. Am. J. Epidemiol. 134:779-780.

Patterson, B.H., Clark, L.C., and Weed, D.L. 1991. Cancer prevention trials using micronutrients: design issues. Cont. Clin. Trials.

Weed, D.L. and Gorelic, L. 1989. Weak associations, bias, and causal inference. Am. J. Epidemiol. 130:819.

Mayer, W.J., Weed, D.L., and Trock, B.J. 1989. Criteria for preventive inference. Am. J. Epidemiol. 130:854.

Chu, K.C. and Weed, D.L. 1989. Validating screening case-control study results with randomized controlled trials for screening. Am. J. Epidemiol. 130:826-827.

Weed, D.L. 1988. Analyzing conflicts of interest in epidemiologic research. Am. J. Epidemiol. 128:943.

Weed, D., Connor, R., and Prorok, P. 1986. Case-control studies of screening: A methodological test. Am. J. Epidemiol. 124:527.

Weed, D. and Trock, B. 1985. Preventive interactions. Am. J. Epidemiol. 122:509-510.

Weed, D. 1985. Causal criteria and Popperian refutation. Am. J. Epidemiol. 122:550.

Trock, B and Weed, D. 1985. Predicting the effects of retinoid chemoprevention. Am. J. Epidemiol. 122:521-522.

Weed, D.L., Selmon, M., and Sinks, T. 1984. Predicting interactions. Am. J. Epidemiol. 120: 464-465.

Weed, D.L. 1983. An epidemiologic application of Popper's method. Am. J. Epidemiol. 118:432.

Weed, D.L. 1982. Age and the healthy worker effect: New findings with old measures. Am. J. Epidemiol. 116:574-575.

PRESENTATIONS:

A Mortality Study in Communications Workers. Society for Epidemiologic Research Student Workshop on Methods, Minneapolis, Minnesota, June, 1980.

Age and the healthy worker effect: new findings with old measures. 15th Meeting of the Society for Epidemiologic Research, Cincinnati, Ohio, June, 1982.

Absolute and relative measures of effect. National Cancer Institute, Division of Cancer Prevention and Control, Bethesda, Maryland, November, 1982.

An epidemiologic application of Popper's method. National Cancer Institute, Division of Cancer Prevention and Control, Bethesda, Maryland, May, 1983.

An epidemiologic application of Popper's method. 16th Meeting of the Society for Epidemiologic Research, Winnipeg, Manitoba, Canada, June, 1983.

Ethics and chemoprevention. National Cancer Institute, Division of Cancer Prevention and Control, Bethesda, Maryland, July, 1983.

Epidemiology and the engineer. 36th Annual Conference on Engineering in Medicine and Biology, Columbus, Ohio, September, 1983.

Disease models and inference in epidemiology. National Meeting of the Operations Research Society of America, Orlando, Florida, November, 1983.

Disease models and epidemiologic inference. Department of Preventive Medicine, Cornell University, Ithaca, New York, November, 1983.

Popper and epidemiology. Division of Preventive Medicine, Walter Reed Army Institute of Research, Washington, D.C., April, 1984.

Some issues in predicting interactions. National Cancer Institute, Division of Cancer Prevention and Control, Bethesda, Maryland, May, 1984.

Predicting interactions. 17th Meeting of the Society for Epidemiologic Research, Houston, Texas, June, 1984.

Cancer control epidemiology. Ohio State Comprehensive Cancer Center, Columbus, Ohio, August, 1984.

Modelling disease interactions. 37th Annual Conference on Engineering in Medicine and Biology, Los Angeles, California, September, 1984.

Causal Criteria and Popperian Refutation. 18th Annual Meeting of the Society for Epidemiologic Research, Chapel Hill, North Carolina, June, 1985.

Preventive Interactions. 18th Annual Meeting of the Society for Epidemiologic Research, Chapel Hill, North Carolina, June, 1985.

Case-control studies of screening: A methodologic test. 19th Annual Meeting of the Society for Epidemiologic Research, Pittsburgh, Pennsylvania, June, 1986.

Speaking in Tongues: A Mega-analysis of a debate. National Cancer Institute, Division of Cancer Prevention and Control, Bethesda, Maryland, July, 1987.

The Analysis of Debates and Other Forms of Epidemiologic Reasoning. University of Pennsylvania School of Medicine, Clinical Epidemiology Unit, Philadelphia, Pennsylvania, January, 1988.

The Analysis of Medical Reasoning. Southern Illinois University School of Medicine, Springfield, Illinois, February, 1988.

Interaction. Uniformed Services University of the Health Sciences, Division of Preventive Medicine and Biometrics, Bethesda, Maryland, May, 1988.

Modelling Interactions in Epidemiologic Research. University of Michigan, School of Public Health, Department of Epidemiology, Ann Arbor, Michigan, May, 1988.

Analyzing Conflicts of Interest in Epidemiologic Research. 21st Annual Meeting of the Society for Epidemiologic Research, Vancouver, British Columbia, Canada, June, 1988.

Analyzing Conflicts of Interest. Office of Protection from Research Risks, Office of the Director, NIH, Bethesda, Maryland, July, 1988.

Epidemiology and the Ethics of Prevention. The Johns Hopkins University, School of Hygiene and Public Health, Department of Epidemiology, Baltimore, Maryland, November, 1988.

Ethical Problems in Cancer Prevention. The Johns Hopkins University, School of Hygiene and Public Health, Department of Epidemiology, Baltimore, Maryland, January, 1989 and June, 1989.

The Future of Cancer Prevention and Control. The University of North Carolina, Lineberger Cancer Center, Chapel Hill, North Carolina, March, 1989.

On the Merger of Bioethics and Epidemiology. IEF Conference on Ethics in Epidemiology, Birmingham, Alabama, June, 1989.

Weak Associations, Bias, and Causal Inference. 22nd Annual Meeting of the Society for Epidemiologic (SER), Birmingham, Alabama, June, 1989.

Criteria for Preventive Inference. Centers for Disease Control, Atlanta, Georgia, September, 1989.

Causal Inference. University of Virginia, College of Medicine, Charlottesville, Virginia, October, 1989.

Uniformed Services University of the Health Sciences, Bethesda, Maryland, May, 1991, May, 1992, April 1993, April 1994.

Ethics in Epidemiology. University of Maryland at Baltimore, College of Medicine, Baltimore, Maryland, December, 1989.

Science, Ethics and the Prevention of Cancer. Fox Chase Cancer Center, Philadelphia, Pennsylvania, December 1989.

Ethics and Cancer Prevention. National Cancer Institute, Bethesda, Maryland, December, 1989.

Common Sense in Epidemiology. The Johns Hopkins University, School of Hygiene and Public Health, Department of Epidemiology, Baltimore, Maryland, January, 1990.

Centers for Disease Control, National Institute of Occupational Safety and Health, Robert A. Taft Laboratories, Cincinnati, Ohio, February, 1990.

Yale University School of Medicine, Department of Epidemiology and Public Health, New Haven, Connecticut, April, 1990.

University of Virginia, College of Medicine, Division of Epidemiology and Virology, Charlottesville, Virginia, October, 1990.

University of North Carolina, School of Public Health, Department of Epidemiology, Chapel Hill, North Carolina, November, 1991.

Harvard University, School of Public Health, Department of Epidemiology, Boston, Massachusetts, December, 1991.

Case Studies in Epidemiological Ethics. Yale University School of Medicine, Department of Epidemiology and Public Health, New Haven, Connecticut, April, 1990.

Inferential Issues in the Study of Alcohol and Breast Cancer. AMC Cancer Research Center, Denver, Colorado, December, 1990.

Epidemiology and the Humanities. Society for Health and Human Values, St. Louis, Missouri, October, 1991.

Bringing Ethics into Causal Inference in Epidemiology. University of Virginia, College of Medicine, Division of Epidemiology and Virology, Charlottesville, Virginia, April, 1992.

Training Programs for Cancer Prevention and Control Researchers. NCI Cancer Center Directors' Workshop, Buffalo, New York, June 1992.

Science, Ethics, and Public Policy: The Case of Alcoholic Beverages and Breast Cancer. American College of Epidemiology, Bethesda, Maryland, September 1992.

Cancer Prevention Training in the Preventive Oncology Branch. American Cancer Society Board of Directors Meeting, Atlanta, Georgia, November 1992.

Ethical Issues in Prophylactic Mastectomy. American Society of Preventive Oncology, Tucson, Arizona, March 1993.

Ethical Considerations in Moderate Alcohol Drinking. Addiction Research Foundation International Symposium, Toronto, Ontario, May 1993.

Ethics in Epidemiology. PHS Epidemiology Training Program Seminar, Bethesda, Maryland, August 1993, and Uniformed Services University of the Health Sciences, Basic Epidemiology I, Bethesda, Maryland, November 1993, November 1994, November 1995.

Alcohol and Breast Cancer. University of Hawaii Cancer Center, Honolulu, Hawaii, September 1993.

Public Health Posters from the National Library of Medicine. Society for Health and Human Values, Rosslyn, Virginia, November 1993.

Untangling Decisions in Health Matters: The Case of Cancer Prevention. Baltimore Ethical Society, Baltimore, Maryland, April 1994.

Evidence-based Cancer Prevention: How Do We Know What to Do? Ohio State University Preventive Medicine Alumni Conference, Columbus, Ohio, September 1994.

Preventive Medicine and the Press: A Case Study. Ohio State University Preventive Medicine Alumni Conference, Columbus, Ohio, September 1994.

Causal Inference in Cancer Epidemiology: A Methodologic Review. Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, September 1994.

Division of Cancer Prevention and Control, NCI, Bethesda, Maryland, September 1994.

Department of Epidemiology, University of Washington School of Public Health and Community Medicine, Seattle, Washington, September 1995.

Epidemiology, Humanities, and Public Health. Department of Epidemiology and Preventive Medicine, University of Maryland, Baltimore, Maryland, September 1994.

Should Epidemiologists be Advocates? Centers for Disease Control and Prevention Course on Government Employees and Public Policy, Atlanta, Georgia, January 1995.

A New Ethic for Epidemiology? Third Brazilian Congress of Epidemiology, Salvador, Bahia, Brazil, April 1995.

Causality, Data and Inference. George Washington University School of Medicine, Washington D.C., May 1995.

The Future of Epidemiology. Uniformed Services University of the Health Sciences, Bethesda, MD, August 1995, August 1996, August 1997.

Beyond Black Box Epidemiology: Behavior and Biology. American College of Epidemiology Annual Meeting, St. Louis, MO, September 1995.

Causal Conclusions, Public Health Recommendations and Methods of Ethical Reasoning: A Practical Approach. American Public Health Association Annual Meeting, San Diego, CA, October 1995.

Biologic Evidence and Human Cancer Causation. Department of Epidemiology, MD Anderson Cancer Center, Houston, TX, March 1996.

Epidemiology Branch, National Institute for Environmental Health Sciences, Research Triangle Park, NC, July 1996.

American Health Foundation, Valhalla, NY, January 1998. Department of Oncology, McGill University, Montreal, QC, Canada, February 1999.

Preventing Scientific Misconduct. Department of Epidemiology and Biostatistics, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, March 1996.

Preventive Medicine Residency Program, Centers for Disease Control and Prevention, Atlanta, GA, March 1996.

Department of Chemistry, University of Maryland, College Park, MD, April 1996.

University of Hawai'i at Manoa, Honolulu, HI, August 1996.

Department of Biometrics and Preventive Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, November 1996 and November 1997.

MD Anderson Cancer Center, Houston, TX, July 1998.

Department of Oncology, Royal Victoria Hospital, McGill University, Montreal, QC, Canada, February 1999.

Office of Research Integrity, U.S. Public Health Service, Rockville, Maryland, September 2000.

Epidemiology and Virtue Ethics. XIVth Congress of the International Epidemiological Association, Nagoya, Japan, August 1996.

Association or Causation: Myths and Legends. NIH Research Festival Workshop, Bethesda, MD, September 1996.

On the Need for Ethics in the Community of University Scholars. University of South Carolina, Columbia, SC, March 1997.

Communicating Cancer Information: an American Perspective. German Cancer Research Center, Heidelberg, Germany, April 1997.

Annual Meeting of the European Association for Cancer Education, Brussels, Belgium, April 1997.

Women's Health and the Media: The Role of the Medical Journal. Healthy Women 2000 Conference, Washington DC, June 1997.

Principles and Practice of Cancer Prevention and Control. NCI Medical Oncology Lecture Series, Bethesda, MD, August 1997.

Ethics and Cancer Screening. Cancer Conference: Integrating Public Health Programs for Cancer Control, Atlanta, GA, September 1997.

NIH Research Festival. Bethesda, MD, October 1997.

University of Puerto Rico, San Juan, Puerto Rico, February 1998.

Pavilion du Chum, University of Montreal, Montreal, QC, Canada, February 1999.

Publishing and Authorship. Cancer Prevention Fellows Data Club Meeting, Bethesda, MD, September 1997.

Towards a Philosophy of Epidemiology. Department of Social and Preventive Medicine, SUNY-Buffalo, Buffalo, NY, September 1997.

Causal Criteria in Nutritional Epidemiology. ILSI Conference on the Role of Epidemiology in making Nutritional Recommendations. Washington, D.C., October 1997.

Philosophical Foundations for the Practice of Epidemiology. III Congress of the Chilean Society of Epidemiology. Vina del Mar, Chile, October 1997.

16th Meeting of the Spanish Society of Epidemiology. Sevilla, Spain, October 1998.

Determining Causality from Epidemiological Studies.

III Congress of the Chilean Society of Epidemiology. Vina del Mar, Chile, October 1997.

Department of Epidemiology and Biostatistics, Boston University School of Public Health, Boston, MA, December 1997.

University of Puerto Rico, San Juan, Puerto Rico February 1998.

Department of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada, February 1999.

End of the Era of Weak Associations? An Historical Study of Epidemiologic Discovery. NIH Historical Office Symposium on Evidence and Action: How epidemiologists make decisions about science and the public's health. NIH Clinical Center, Bethesda, MD, March 1998.

Department of Epidemiology. School of Public Health. University of North Carolina, Chapel Hill, NC, April 1998.

Center for Clinical Epidemiology and Biostatistics. University of Pennsylvania Medical Center, Philadelphia, PA, May 1998.

MD Anderson Cancer Center. Houston, TX, July 1998.

Department of Epidemiology and Biostatistics, Yale University, New Haven, CT, November 1998.

Department of Epidemiology, University of California, Berkeley, Berkeley, CA, March 1999.

Channing Lab, Harvard University, May 1999.
Department of Health Evaluation Sciences, University of Virginia, Charlottesville, VA, January 2000.

Department of Epidemiology, Michigan State University, East Lansing, MI, February 2000.

Department of Epidemiology, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, April 2000.

Epidemiology at a Crossroads. Seminar for the Cosmetics, Fragrance, and Toiletries Association. Morristown, NJ, April 1998.

Epidemiologists and Risk: Theory, Method, and Practice. Workshop on Epidemiology and Toxicology. Washington, DC, May 1998.

The Interpretation of Meta-Analyses with reference to Causal Inference and Public Health Decisionmaking. Society for Epidemiologic Research Symposium on the Methods and Applications of Meta-Analysis. Chicago, IL, June 1998.

Roles and Responsibilities of Epidemiologists. Department of Epidemiology, University of North Carolina, Chapel Hill, NC, March 1999.

Causation and Biology. Society for Epidemiologic Research Symposium on the Future of Causes in Epidemiology. Baltimore, MD, June 1999.

Epidemiologic Evidence and the Precautionary Principle. International Society for Environmental Epidemiology. Athens, Greece, September 1999.

Improving Cancer Screening: An American Perspective. Symposium on Cancer Screening. Catholic University of Korea Cancer Center. Seoul, Korea, October 1999.

Causality and Inference in Cancer Epidemiology: We've Got Some Problems.

Ohio State University James Cancer Hospital. Columbus, OH, October 1999.

Department of Food Science and Human Nutrition. Michigan State University, East Lansing, MI, February 2000.

Department of Epidemiology. Tulane University School of Public Health and Tropical Medicine, New Orleans, LA, April 2000.

Our future is not epidemiology.calm. American Public Health Association Special 70th Anniversary for the Epidemiology Section. Chicago, IL, November 1999.

American College of Epidemiology Ethics Guidelines: Foundations and Dissemination. AAAS Conference on Research Integrity, Washington, DC, April 2000.

Teaching Ethics and Public Health: Curriculum Content. ASPH/HRSA Workshop on Ethics and Public Health, Washington, DC, May 2000.

Science, Ethics and the Future of Preventive Oncology. Seminars in Clinical and Molecular Oncology, National Cancer Institute, Bethesda, MD, July 2000.

Precautionary Principle and the Philosophy of Public Health. WHO Workshop on the Precautionary Principle, Rome, Italy, May 2001.

Science, Ethics and the Future of Epidemiology.

International Epidemiological Association Regional Asia Meeting, Kitakyushu, Japan, September 2001.

Kyoto University School of Public Health, Kyoto, Japan, September 2001.

National Cancer Center, Tokyo, Japan, September 2001.

Cancer Prevention in the 21st Century Istituto Superiore di Sanita, Rome, Italy, May 2002.

Roles and Responsibilities of Epidemiologists Istituto Superiore di Sanita, Rome, Italy, May 2002.

Promoting Research Integrity Cleveland Clinic Foundation, Cleveland, Ohio, May 2002.

Scope and Importance of Public Health World Bank/WHO Conference on Public Health Challenges in the Middle East and North Africa, Beirut, Lebanon, June 2002.

The Precautionary Principle and the Philosophy of Public Health International Society of Environmental Epidemiology, Vancouver, BC, August 2002.

Williams

7/13/2018

CURRICULUM VITAE
GARY MURRAY WILLIAMS, M.D.

EDUCATION: Washington and Jefferson College,
Washington, Pennsylvania. B.A. 1963; Magna Cum Laude

University of Pittsburgh School of Medicine,
Pittsburgh, Pennsylvania. M.D., 1967

SUBSEQUENT TRAINING AND POSITIONS;

1967-1969	Intern and Resident in Pathology, Department of Pathology, Massachusetts General Hospital and Instructor in Pathology, Harvard University Medical School, Boston, Massachusetts.
1969-1971	Staff Associate, National Cancer Institute, Experimental Pathology Branch, Chemical Carcinogen Screening Unit, Bethesda, Maryland.
1971-1972	Visiting Scientist, Wenner-Gren Institute, Department of Cell Physiology, Stockholm, Sweden.
1971-1975	Assistant Professor, Department of Pathology, and Member, Fels Research Institute, Temple University School of Medicine, Philadelphia, Pennsylvania.
1975-1979	Research Associate Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1979-1999	Research Professor, Department of Pathology, New York Medical College, Valhalla, New York.
1999 - present	Professor of Pathology, Department of Pathology, Director of Environmental Pathology and Toxicology, Head, Program on Medicine, Food and Chemical Safety, New York Medical College, Valhalla, New York; Professor of Clinical Public Health, School of Health Sciences and Practice, New York Medical College, Valhalla, New York.

CERTIFICATIONS:

1974	American Board of Pathology
1975	Physician, State Education Department, State of New York
1981	American Board of Toxicology, Recertified, 2007-2011.
1984	Expert in Toxicology, Ministere des Affaires Sociales et de la Solidarite Nationale, Direction de la pharmacie et du medicament, Republic Francais
2000	Fellow in Toxicologic Pathology, International Academy of Toxicologic Pathology
2002	Fellow of the Royal College of Pathologists

AWARDS AND HONORS:

1963	Phi Beta Kappa, Washington and Jefferson College
1967	Sheard-Sandford Award, American Society of Clinical Pathologists
1967	Alpha Omega Alpha, University of Pittsburgh School of Medicine
1971	Research Training Fellowship, International Agency for Research on Cancer
1980	Association of University Pathologists
1982	Arnold J. Lehman Award, Society of Toxicology
1987	Citation Classics: Cancer Lett. 1:231, 1976 and Cancer Res. 37:1845, 1977. Institute for Scientific Information, Current Contents, Vol. 30, No.36, September 7, 1987
1988	Citation Classics: In Vitro 12:521, 1976; 12:821, 1976; 13:809, 1977, 14:824, 1978. Institute for Scientific Information. Current Contents, Vol. 32, No. 9, February 27, 1989
1989	Featured on cover of Cancer Research, Volume 49, November 1

1995	Featured on cover of Cancer Research, Volume 55, April 15
1996	Awards Lecture, Society of Toxicology
1997	Top 10 Most Frequently Cited Articles in 25 years of Toxicologic Pathology Toxicologic Pathology 10:3-10, 1982; Toxicologic Pathology 26:452, 1998
2001	Ambassador in Toxicology Award, Mid-Atlantic Chapter of the Society of Toxicology.
2002	Enhancement of Animal Welfare Award, Society of Toxicology.
2005	Distinguished Scientist Award, Westchester Chemical Society, American Chemical Society, New York Section, Inc.
2006	New York Medical College Dean's Distinguished Research Award, 2005.
2006	Food and Agriculture Organization / World Health Organization Joint Expert Committee on Food Additives. 50th Anniversary Medal (5 years service.)
2009	Merit Award, Society of Toxicology
2011	Honorary Member, American College of Veterinary Pathologists

RECOGNITION:

1996-11	Who's Who in America 50th-65th Editions (1996-2011)
1996-06	Who's Who in the East 26th-34th Editions (1998-2006)
1996-12	Who's Who in Science and Engineering 3rd-11th Editions (1995-2012)
1997/1998	American Men and Women of Science Directory of American Research & Technology
1998-05	Official American Board of Medical Specialties Directory of Board Certified Medical Specialists 30th-38th Editions (2006)
2005-07	Who's Who in American Education 6th-7th Editions (2005-2007)

2005-07	Who's Who in Medicine and Healthcare 6th – 7th Editions (2006-2010)

SOCIETIES:

1974	American Association for Cancer Research
1978	Society of Toxicology
1981	Society of Toxicologic Pathologists
1991	International Society of Regulatory Toxicology and Pharmacology
2011	American College of Veterinary Pathologists (Honorary)
2015	Environmental Mutagenesis and Genomics Society

EDITORIAL RESPONSIBILITIES:

1980	Co-Editor, Differentiation and Carcinogenesis in Liver Cell Cultures. Vol. 349. New York Academy of Sciences.
1980-1981	Consulting Reviewer, Oncology Overviews, International Cancer Research Data Bank.
1980-1986	Reviewing Editor, In Vitro.
1980	Co-editor, The Predictive Value of In Vitro Short-term Screening Tests in Carcinogenicity Evaluation. Elsevier/North Holland Biomedical Press.
1981-1983	Editorial Board, Fundamental and Applied Toxicology.
1981-1989	Editorial Board, Toxicology and Applied Pharmacology.
1981-1999	Editorial Board, Nutrition and Cancer.
1982	Meeting Report: Carcinogenesis and Gene Expression in Liver Cultures. Cancer Research 42:2462-2464, 1982.
1982	Consulting Reviewer, Oncology Overview, International Cancer Research Data Bank Program, National Cancer Institute.
1982-1993	Editorial Board, Mutation Research, Genetic Toxicology Testing Section.

1983	Co-Editor, Colon Carcinogenesis. CRC Press.
1983	Co-Editor, Cellular Systems for Toxicity Testing. Vol. 407. New York Academy of Sciences.
1983	Co-Editor, Tests Courts de Cancerogenese/Short-term Tests for Carcinogenesis, Elsevier Science Publishers BV, Amsterdam.
1983-1992	Editorial Board, Chemico-Biological Interactions.
1983-1996	Editorial Board, Toxicologic Pathology.
1984-present	Founding Editor, Cell Biology and Toxicology.
1987	Meeting Report: Causative and Modifying Factors in Digestive Tract Cancer. Cancer Research 47:922-923, 1987
1988-present	Editorial Board, Archives of Toxicology; Associate Editor 2008-present
1987	Editor, Sweeteners: Health Effects, Princeton Scientific Publishing Company.
1988	Editorial Board, Complex Mixtures and Cancer Risk, IARC Scientific Publications, International Agency for Research on Cancer
1989	Meeting Report: American Health Foundation 20th Anniversary International Symposium on Causes and Prevention of Cancer. Preventive Medicine, in 20:534-547, 1991
1991-2008	International Advisory Board, European Journal of Cancer Prevention
1992	Proceedings of the Second International Conference on Longevity and Aging: Environmental and Nutritional Influences on Aging and Cancer Experimental Gerontology, Volume 27, Special Issue, 1992
1993	Editor-in-Chief, Antioxidants Chemical, Physiological, Nutritional and Toxicological Aspects, Princeton Scientific Publish. Co.
1994-2008	Area Editor for Carcinogenesis, Drug and Chemical Toxicology.
1997	Co-Editor, Reducing Dietary Fat: Putting Theory into Practice, Journal of The American Dietetic Association, Volume 97, Supplement 1, 1997

2001	Co-Editor, Toxicology, Special Issue, Volume 166, Number 3, Festschrift J.H. Weisburger.
2002	Guest Editor, International Symposium on Antimutagenesis and Anticarcinogenesis, European Journal of Cancer Prevention, Volume 11, Supplement 2.
2003-2007	Editorial Board, Toxicologic Pathology, Associate Editor 2005-2007.
2005-2012	International Editorial Board, Food and Chemical Toxicology. Associate Editor 2009-2012.

MEETINGS ORGANIZED:

1980	Conference on Differentiation and Carcinogenesis in Liver Cell Cultures. New York Academy of Sciences. New York, NY.
1980	Workshop on the Predictive Value of in vitro Short Term Screening Tests in the Evaluation of Carcinogenicity. Scientific Council of the Netherlands Cancer Society. Dalen, The Netherlands.
1982	Quo Vadis Symposium on Short Term Tests in Carcinogenesis and Mutagenesis. Research Center Clin-Midy. Montpellier, France.
1983	Conference on Carcinogenesis and Gene Expression in Liver Cultures United States-Japan Cooperative Cancer Research Program. Honolulu, Hawaii.
1984	Conference on Cellular Systems for Toxicity Testing, New York Academy of Sciences, New York, NY.
1986	Conference on Causative and Modulating Factors for Digestive Tract Cancer United States-Japan Cooperative Cancer Research Program. Tokyo, Japan.
1986	International Conference on Cancer Research. Theories of Carcinogenesis. The Norwegian Cancer Society, Oslo, Norway.
1986	Conference on Non-Mutagenic Carcinogens: How Much Risk to Man? The Robens Institute, University of Surrey, Guildford, England.
1987	Conference on Sweeteners: Health Effects. American Health Foundation, New York.

1987	International Symposium in Genetic Toxicology, National Science Foundation (U.S.) and Council of Scientific and Industrial Research (India), University of Calcutta, Calcutta, India.
1988	International Symposium on Causes and Prevention of Cancer, American Health Foundation in cooperation with American Cancer Society and National Cancer Institute, New York, NY.
1989	International Conference on Environmental and Nutritional Influences on Aging and Cancer, American Health Foundation in cooperation with National Institute on Aging, New York, NY.
1990	Conference on Cancer Prevention for Black Americans, Metropolitan Life Insurance, Company, New York, NY.
1991	International Conference on Antioxidants: Chemical, Physiological, Nutritional and Toxicological Aspects, American Health Foundation, Tarrytown, NY.
1991	Second International Conference on Theories of Carcinogenesis. Norwegian Cancer Society, Oslo, Norway.
1992	1st International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.
1993	2nd International Short Course on Preclinical Drug and Chemical Safety, Tarrytown, NY.
1993	American Health Foundation, 25th Anniversary Conference and Celebration, Toward Optimal Health: Examining Goals for Nutrition and the Environment, Tarrytown, NY.
1994	3rd International Course on the Safety Assessment of Pharmaceuticals, Tarrytown, NY.
1995	International Congress on Hepatocytes-Applications in Cell Biology, Toxicology and Medicine, Tubingen, Germany.
1996	Conference, Reducing Dietary Fat: Putting Theory Into Practice, American Health Foundation, New York, NY.
1996	4th International Course on the Safety Assessment of Pharmaceuticals, Part I, White Plains, NY.

1996	4th International Course on the Safety Assessment of Pharmaceuticals, Part II, San Francisco, CA.
1997	5th International Course on the Safety Assessment of Medicines, Part I, White Plains, NY.
1998	6th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2000	7th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2001	8th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2002	International Symposium on Antimutagenesis and Anticarcinogenesis, New York Medical College, Valhalla, NY
2002	10th International Course on the Safety Assessment of Medicines, Advanced Course, Hyéres, Var, France.
2002	International Symposium on Agricultural Exposures and Cancer, Oxford, England.
2003	Symposium, Chemical Safety Assessment: Contribution of Toxicological Pathology and Mechanistic Investigations, New York Medical College, Valhalla, NY.
2004	11th International Course on the Safety Assessment of Medicine. Basic and Regulatory Aspects, White Plains, NY.
2005	12th International Course on the Safety Assessment of Medicine Basic and Regulatory Aspects, White Plains, NY.
2006	Symposium "Current Issues in Safety Assessment of Medicines, New York Medical College, Valhalla, NY.
2006	13th International Course on the Safety Assessment of Medicines, White Plains, NY.
2007	14th International Course on the Safety Assessment of Medicines, White Plains, NY.

2008	Workshop on the Biological Significance of DNA Adducts: Part II, European Centre for Ecotoxicology and Toxicology of Chemicals, Cavtat, Croatia
2008	15th International Course on the Safety Assessment of Medicines, White Plains, N.Y.
2009	16th International Course on the Safety Assessment of Medicines, White Plains, N.Y.

NATIONAL AND INTERNATIONAL RESPONSIBILITIES

1975	Consultant, Pesticides, Toxic Substance and Solid Waste Management, United States Environmental Protection Agency.
1975-1978	Member, Epidemiology Committee, Breast Cancer Task Force, NationalCancer Institute.
1976-1977	Member, Program Committee, American Association for Cancer Research.
1976	Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man: Some Miscellaneous Pharmaceutical Substances, International Agency for Research on Cancer.
1976-1978	Co-Chairperson, Subcommittee on Rat Liver Tumors, Committee on Histologic Classification of Laboratory Animal Tumors, Institute of Laboratory Animal Resources, National Research Council.
1977-1978	Member, Panel on Kepone/Mirex, Scientific and Technical Assessments of Environmental Pollutants, Environmental Studies Board, Commission on Natural Resources, National Research Council.
1979-1980	Member, Panel on Unscheduled DNA Synthesis, Gene-Tox Program, U.S. Environmental Protection Agency.
1980-1981	Member, Panel of Experts Associated with Technical Report Review Subcommittee, National Toxicology Program, Department of Health and Human Services.
1980	Member, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Man-Antineoplastic and Immunosuppressive Drugs,

International Agency for Research on Cancer.

1980-1986	Panel of Reviewers, Netherlands Cancer Foundation.
1981	Advisor, Technical Committee, Society of Toxicology.
1981-1982	Member, Task Group on the Differentiation Between Genotoxic and Epigenetic Carcinogens, International Commission on Protection Against Environmental Mutagens and Carcinogens.
1982	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Chemicals and Industrial Processes Associated with Cancer in Humans, IARC Monographs Volumes 1 to 29, International Agency for Research on Cancer.
1982-1983	Consultant, Office of Health and Environmental Assessment, Reproductive Effects Assessment Group, U.S. Environmental Protection Agency.
1982-1983	Member, International Expert Committee to the Nutrition Foundation on the Relevance of Mouse Liver as a Model for Assessing Carcinogenic Risk, Nutrition Foundation, Incorporated.
1982-1983	Coordinator, Assays of DNA Damage, Collaborative Study on Short-Term Tests for Genotoxicity and Carcinogenicity. International Programme on Chemical Safety, World Health Organization.
1983	Member, Working Group on the Mechanisms of Chemical Carcinogenesis, International Agency for Research on Cancer.
1983-1984	Member, Expert Committee on Pathology/Toxicology and Expert Committee on Short-Term Testing, International Life Sciences Institute.
1984-1987	Assessor, National Health and Medical Research Council Panel of Independent Assessors, National Health and Medical Research Council, Commonwealth of Australia.
1984-1985	Member, Committee on the Carcinogenicity of Cyclamates, Food and Nutrition Board, Commission on Life Sciences, National Research Council.
1984-1985	Member, Task Group of DNA Repair, Subcommittee on Genetic Toxicology, American Society for Testing and Materials.

1985-1987	Member, Toxicology Study Section, National Institutes of Health.
1985	Vice-Chairman, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Naturally Occurring Substances, Food Additives and Amino Acid Pyrolysates in Food, International Agency for Research on Cancer.
1985-1986	Member, Awards Committee, Society of Toxicology.
1986	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Genetic and Related Effects: An Updating of Selected IARC Monographs from Volumes 1 to 42, International Agency for Research on Cancer.
1987	Member, Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42, International Agency for Research on Cancer.
1988	Participant, Tox-90s Conference, Society of Toxicology.
1989	Organizing Committee, Workshop on the Effects of Pesticides on Human Health, Task Force on Environmental Cancer and Heart and Lung Disease.
1989	Chairman, Working Group and Chairman, Subgroup on Animal Carcinogenicity, Working Group on Evaluation of Carcinogenic Risk of Chemicals to Humans: Some Pharmaceutical Drugs, International Agency for Research on Cancer.
1989	Participant and Member of Editorial Board, Workshop on Complex Mixtures and Cancer Risk, International Agency for Research and Cancer.
1989	Participant, Working Group on Short-Term In Vitro and In Vivo Tests, Workshop on Research to Improve Predictions of Long-Term Chemical Toxicity, National Research Council.
1990-1998	Member, Subcommittee on Education, International Federation of Societies of Toxicologic Pathologists.
1991	Member, Working Group on Approaches to Classifying Carcinogens According to Mechanisms of Action, International Agency for Research on Cancer.

1993-1999	Member, Committee on Evaluation of the Research Program "Cancer Risk Factors and Prevention," German Cancer Center.
1993-2005	Member, Board of Trustees, International Life Sciences Institute, Health and Environmental Sciences Institute. Chair, Membership Development Committee, 2002-2003.
1993-1998	Member, Subcommittee on Carcinogenicity, International Federation of Societies of Toxicologic Pathologists.
1995-1996	Consultant, International Life Sciences Institute, North America Antioxidant Technical Committee.
1995-1997	Member, Committee on Research Opportunities and Priorities for EPA, Commission on Geosciences, Environment, and Resources, National Research Council.
1996	Reviewer, U.S. Environmental Protection Agency (EPA), PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures.
1996	Participant, Developmental Planning for Office of Dietary Supplements (ODS), National Institutes of Health.
1997	Member, Working Group on Short/Medium Term Carcinogenicity Tests and Genetic and Related Effects. International Agency for Research on Cancer.
1998	Member, Working Group - Re-evaluation of Some Industrial Chemicals. International Agency for Research on Cancer.
1999-2003	Member, Subcommittee on Upper Safe Reference Levels of Nutrients, Committee on Reference Levels of Nutrients, National Academy of Sciences, Institute of Medicine.
1999-present	Member Accreditation Committee, International Academy of Toxicologic Pathology; Chairman, 2007.
1999	Member, Working Group on Predictive Value of Gastric Neuroendocrine Tumours and Forestomach Tumours in Rodents for Carcinogenic Hazard Identification. Co-Chairperson, Forestomach Tumors. International Agency for Research on Cancer.

2000	Member and Report Coordinator, Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Scientific Advisory Panel. U.S. Environmental Protection Agency.
2000-2006	Reviewer, Office of Dietary Supplements, National Institutes of Health. Annual Bibliography of Significant Advances in Dietary Supplement Research.
2002	Peer Review Member, U.S. Environmental Protection Agency "Perchlorate Environmental Contamination: Toxicological Review and Risk Assessment."
2002	Temporary Advisor, World Health Organization, 59th Meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO.
2002	Participant, Joint FAO/WHO Project to Update the Principles and Methods or the Risk Assessment of Chemicals in Food. Workshop 1: Introduction, Toxicological Tests & Evaluation, Human Data, Margins of Safety.
2003	Panelist, Dietary Supplement Use in the Elderly Conference. Office of Dietary Supplements. National Institutes of Health.
2003	Temporary Member, Metabolic Pathology Study Section, National Institutes of Health.
2003-2005	Member, Workgroup on Mechanism of Action in Assessing Human Relevance of Animal Tumors, Risk Science Institute, International Life Science Institute.
2003	Temporary Advisor, World Health Organization, 61st Meeting of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA).
2004	Temporary Advisor, World Health Organization, 63rd Meeting of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA).
2004 -05	Member WHO Task Group on Environmental Health Criteria for Modelling Dose-Response for the Risk Assessment of Chemicals, World Health Organization.

2004	Temporary Advisor, World Health Organization International Programme on Chemical Safety Author's Workshop on Dose-Response Modeling, World Health Organization.
2004-06	Member, Committee on EPA's Exposure and Human Health Reassessment of TCDD and Related Compounds. National Research Council, National Academies of Science.
2005-2008	Member, International PPAR Task Force, International Atherosclerosis Society.
2005	Temporary Advisor, World Health Organization, 65th Meeting of the Joint Food and Agriculture Organization / World Health Organization Expert Committee on Food Additives (JECFA).
2005-2006	Member, Project Committee on Biological Significance of DNA Adducts, International Life Sciences Institute, Health and Environmental Sciences Institute.
2006-2007	Scientific Advisor, Emerging Issues Steering Committee, International Life Sciences Institute, Health and Environmental Sciences Institute.
2006-2007	Member, Expert Group on the Application of the Margin of Exposure (MOE) Approach to Genotoxic Carcinogens in Food. International Life Sciences Institute, European Branch.
2006	Temporary Advisor, World Health Organization, 67th Meeting of the Joint Food and Agriculture Organization / World Health Organization Expert Committee on Food Additives (JECFA).
2007	Temporary Advisor, World Health Organization, 68th Meeting of the Joint Food and Agriculture Organization / World Health Organization Expert Committee on Food Additives (JECFA).
2008	Temporary Advisor, World Health Organization, 69th Meeting of the Joint Food and Agriculture Organization / World Health Organization Expert Committee on Food Additives (JECFA). Rome, Italy.

2009 –2010	Corresponding Member, Expert Group of the Risk Assessment of Genotoxic Carcinogens in Food Task Force. Data selection for BMD modeling of genotoxic and carcinogenic substances. International Life Sciences Institute – European Branch.
2009	Peer Reviewer, External Peer Review of the Environmental Protection Agency/Integrated Risk Information System, Draft Report Toxicological Review of Pentachlorophenol, US Environmental Protection Agency/Office of Research and Development/National Center for Environmental Assessment.
2009	Member, Task Group on Environmental Health Criteria on Principles and Methods for the Risk Assessment of Chemicals in Food, Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO)
2010	Temporary Advisor, World Health Organization, 72nd Meeting of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA). Rome, Italy.
2010	Temporary Advisor, World Health Organization, 73rd Meeting of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA). Geneva, Switzerland.
2012	Expert, World Health Organization, 76th Meeting of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA). Geneva, Switzerland.
2014	Expert, World Health Organization, 79th Meeting of the joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA). Geneva, Switzerland.
2015	Member, World Health Organization, 80th Meeting of the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives (JECFA). Rome, Italy.

BIBLIOGRAPHY 1969-2015

537 publications

(16) All communications and documents related to the three corrigenda and "expression of concern" published in Critical Reviews in Toxicology on September 26, 2018 regarding the five manuscripts by the Intertek Expert panel.

Response:

As noted in the response to Item 16 "Expression of Concern" and five Corrigenda have now been published on-line in the Taylor and Francis web site for Critical Reviews in Toxicology. All of the communications and documents in my possession related to this matter have been provided in the Response to Item 15.

(17) Communications and documents related to any medical literature, studies, journal articles, tests, and/or scientific analyses related to the potential adverse human health effects of GBFs, AMPA, and/or surfactants for GBFs for which You were involved with the peer-review process. This request includes drafts

Response:

I do not recall my involvement in the peer-review process related to potential adverse human health effects of GBFs, AMPA, and/or surfactants for GBFs that relate to any medical literature, studies, journal articles, tests, and/or scientific analyses other than those discussed above related to manuscripts published in Critical Reviews in Toxicology which I serve as Editor-in-Chief.

(18) All communications related to the de-classified internal Monsanto documents dubbed the "Monsanto Papers."

Response:

Reference has been made to the "Monsanto Papers" during the investigation described above in to the manner in which the five papers published in the Special Supplement to Volume 46 (2016) of Critical Reviews in Toxicology. I am not aware of any other communications to me or from me involving the "Monsanto Papers."

(19) Documents relied on or reviewed to prepare for this Deposition.

Response:

I have not relied on any documents, other than those referenced above, responding to this Subpoena and preparing for my deposition.