Aimee Wagstaff, SBN 278480
aimee.wagstaff@andruswagstaff.com
Andrus Wagstaff, PC
7171 West Alaska Drive
Lakewood, CO 80226
Telephone: (303) 376-6360
Facsimile: (303) 376-6361

Robin Greenwald
rgreenwald@weitzlux.com
Weitz & Luxenberg
700 Broadway
New York, NY 10003
Telephone: (212) 558-5500
Facsimile: (212) 344-5461

Michael Miller
mmiller@millerfirmllc.com
The Miller Firm LLC
108 Railroad Avenue
Orange, VA 22960
Telephone: (540) 672-4224
Facsimile: (540) 672-3055

Attorneys for Plaintiffs

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	Hearing Date: December 11, 2017 Time: 9:00 a.m.

PLAINTIFFS' (1) RESPONSE IN OPPOSITION TO MONSANTO COMPANY'S *DAUBERT* AND SUMMARY JUDGMENT MOTION BASED ON FAILURE OF GENERAL CAUSATION PROOF AND (2) *DAUBERT* MOTION TO STRIKE CERTAIN OPINIONS OF MONSANTO COMPANY'S EXPERT WITNESSES

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Issues to Be Decided

I. Whether Plaintiffs' experts employed reliable methodology in reaching their conclusions.

II. Whether Plaintiffs' expert opinions, considered together, create a triable issue of fact for the jury.

III. Whether Monsanto's experts Drs. Rosol, Goodman, Foster, Rider, and Mucci employ reliable methodology in reaching the challenged conclusions.

I. Introduction

There is only one question before this Court: Is there admissible evidence, when viewed in light most favorable to Plaintiffs, that Roundup causes non-Hodgkin lymphoma ("NHL")? There is overwhelming evidence—whether it be the epidemiology, toxicology, or mechanistic data—that exposure to glyphosate-based formulations ("GBFs") causes NHL. At this point, general causation is a jury issue.

Monsanto's motion illustrates this point. Instead of explaining how Plaintiffs' experts' opinions are inadmissible, Monsanto focuses on why the opinions are wrong. But, that is not the standard under *Daubert* or at summary judgment. Whether Plaintiffs' experts are "wrong" is something Monsanto must argue to the trier of fact. At this stage, there is no dispute that their opinions are based on sound, reliable science and that all of Monsanto's attacks go to weight and credibility, not admissibility.

Monsanto's motion makes three broad challenges. First, Monsanto tries to side-step numerous epidemiologic studies—including multiple meta-analyses (one of which was sponsored and published by Monsanto)—which show a consistent, statistically significant, elevated association between GBF exposure and NHL. Monsanto attempts this feat by asking the Court to ignore all the data and focus, exclusively, on a single study that has been roundly criticized for design flaws and rampant data lapses. This is nothing more than cherry-picking data to support Monsanto's defense. It does not comport with the basic principles of science.

Second, Monsanto argues that toxicology is not methodologically relevant here because

of the existence of epidemiological studies. As Plaintiffs' experts' reports and testimony make clear, animal bioassays are predictive of cancer in humans and are therefore probative of one element of the Bradford Hill Criteria; biological plausibility. The animal bioassays corroborate the epidemiological and mechanistic data, providing further support that the effects seen in exposed humans are caused by Roundup.

Third, Monsanto attempts to discount the results of mechanistic studies which include reliable mechanistic human studies demonstrating genotoxic effects following real world exposure to GBFs. Its argument relies on superficial criticism and an inaccurate assessment of the studies. The results of the human studies validate the other mechanistic data and substantiate the relevance to living human beings.

The evidence, viewed in its entirety, weighs heavily in favor of causation. Monsanto attempts to avoid this fact by asking the Court to atomize the science surrounding GBFs and ignore the overwhelming weight of the evidence. This approach is neither good science, nor do *Daubert* and its progeny support such a process—they require the opposite. *See U.S. v. W.R. Grace*, 504 F.3d 745, 765 (9th Cir. 2007) (emphasis original) ("[T]he expert's opinion testimony must satisfy the requirements of Rule 702—but that requires consideration of the *overall* sufficiency of the underlying facts and data, and the reliability of the methods, as well as the fit of the methods to the facts of the case.").

For these reasons, there is no basis to exclude Plaintiffs' general causation experts' opinions. Their opinions are admissible in full and granting summary judgment in Monsanto's favor is unwarranted.

Expert Qualifications[1]

[1] Plaintiffs' counsel did not represent that their experts were limited to only one specialty, and Monsanto's statement to the contrary lacks candor and necessitates context. In fact, Plaintiffs' counsel stated the opposite. See Monsanto's Ex. 1. The parties had only 25 work days to take 13 expert depositions. Monsanto initially took the position that ***all*** of Plaintiffs' expert had to be deposed before Plaintiffs could begin taking Monsanto's experts' depositions. When it became clear that this arrangement would be impossible to achieve given the short window to take depositions and Plaintiffs' experts' schedules and limited availability, the parties met and conferred to find a solution. As part of that solution, the parties agreed that they would phase

Dr. Beate Ritz M.D., Ph.D. Dr. Ritz is the Chair of the Epidemiology Department at UCLA, which is one of only a few positions specifically assigned to the Center of Occupational and Environmental Health (COEH) mandated by the State of California to conduct research, teaching, and service to communities in California on occupational and environmental health issues. Dr. Ritz has doctoral degrees in Medicine and Epidemiology. She also is the author of numerous publications in toxicology and lectures and gives presentations in the field of toxicology as well. Dr. Ritz engaged in a systematic review of the literature in this case, utilized the Bradford Hill Criteria, and concluded that "to a reasonable degree of scientific certainty, glyphosate causes NHL. Furthermore, to a reasonable degree of scientific certainty, glyphosate based formulations, including Roundup, cause NHL." Ex. 3 – Expert Report of Dr. Beate Ritz at 25.

Alfred I. Neugut, M.D., Ph.D. Dr. Neugut is a practicing medical oncologist, a Professor of Cancer Research and Professor of Medicine and Epidemiology at Columbia University, and Associate Director for Population Sciences for the Herbert Irving Comprehensive Cancer Center. Dr. Neugut was awarded with the Myron M. Studner Professorship in Cancer Research in the Department of Medicine. He is also the Director of Junior Faculty Development for the Department of Epidemiology, overseeing about 30 assistant professors. Dr. Neugut has published over 500 articles in medical journals dealing primarily with carcinogenesis of various agents and compounds. Dr. Neugut engaged in a systematic review of the literature in this case, used the Bradford Hill criteria, and concluded that "epidemiologic and scientific evidence currently available leads to the conclusion to a reasonable degree of scientific certainty for most expert, objective, and reasonable viewers, myself included, that the use of glyphosate in its various combinations can cause non-Hogkin lymphoma." Ex. 4 – Expert Report of Dr. Alfred Neugut at

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expert depositions by discipline. Because Plaintiffs' experts opine about several disciplines, Plaintiffs agreed to provide Monsanto with each expert's principal area of specialty, which is set forth in Monsanto's Ex. 1. Thereafter, Monsanto's counsel sent two emails to Plaintiffs' counsel, the first asking Plaintiffs to withdraw opinions that did not match the specialties set forth in Monsanto Ex. 1, and the second acknowledging that Plaintiffs declined to do so, Ex. 2. At no time did Plaintiffs state that their experts are limited to one area of expertise.

23.

Christopher J. Portier. Dr. Portier received his PhD in Biostatistics (with a minor in Epidemiology) from the University of North Carolina, Chapel Hill, in 1981. For over 32 years, Dr. Portier held prominent leadership positions with the federal government that combined the disciplines of toxicology, statistics, and epidemiology, including: Associate Director of the National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program and thus the nation's chief toxicologist, among other roles at NIEHS; Director of the National Center for Environmental Health, Center for Disease and Prevention; and the Director of the Agency for Toxic Substances and Disease Registry (ATSDR). Dr. Portier is a member of the Society of Toxicology and the American Public Health Association. Dr. Portier has also received many awards for his government and non-government work including the Best Paper Award from the Society of Toxicology, Merit Award from the National Institutes of Health, several "Paper of the Year" awards from the Society of Toxicology, the Outstanding Risk Practitioner Award of the Society for Risk Analysis, and was an elected fellow of the International Statistical Institute. He has published 164 peer-reviewed articles, 35 journal reviews, 33 book chapters, and 46 reports and government agency publications, and he has participated in six IARC working groups, either as Chair or a working group member. His experience encompasses the design, performance, and analyses of studies, including animal bioassays (as well as the supervision thereof), that evaluate the carcinogenic effects of chemicals and pesticides on humans. Dr. Portier engaged in a systematic review of the literature in this case, utilized the Bradford Hill criteria, and concluded that "[i]n my opinion, glyphosate probably causes NHL and, given the human, animal and experimental evidence, I assert that, to a reasonable degree of scientific certainty, the probability that glyphosate causes NHL is high." Ex. 5 – Expert Report of Dr. Christopher Portier at 80.

Dr. Charles W. Jameson Ph.D. Dr. Jameson completed a Ph.D. in Organic Chemistry in 1975 at the University of Maryland. He has worked for National Institutes of Health's National Cancer Institute (NCI) as a senior chemist for the NCI's Rodent Bioassay Program where he served as chief chemist, directing all chemistry activities and participating in the development of all two-year rodent bioassays while also serving as secretary for the NCI's Chemical Selection

Working Group. Dr. Jameson also served as program leader for the National Toxicology Program at the NIH's National Institute of Environmental Health Sciences (NIEHS) for 12 years, during which time he was listed as a contributor to over one hundred chemical peer reviewed bioassay studies. Dr. Jameson worked on the NTP's Report on Carcinogens (RoC) for more than 18 years and is the Senior Author for 69 NTP RoC Background Documents, also serving as the RoC Director for 13 years. Dr. Jameson has participated as an IARC Working Group member, serving as overall Chair or Subgroup Chair, and he is author or co-author in numerous peer-reviewed scientific publication and book chapters, as well as the editor of several editions of the RoC and co-editor of two books on toxicity testing. Dr. Jameson is a member of the American Chemical Society and the Society of Toxicology and he participates in peer reviews for six scientific journals. D. Jameson engaged in a systematic review of the literature in this case, utilized a weight-of-evidence methodology utilized by NTP and IARC, and concluded that to a "reasonable degree of scientific certainty that glyphosate and glyphosate based formulations are probable human carcinogens" and also concluded "to a reasonable degree of scientific certainty that glyphosate and glyphosate-based formulations cause NHL in humans." Ex. 6 – Expert Report of Dr. Charles Jameson at 31-32.

Chadi Nabhan, M.D. Dr. Nabhan is a board-certified clinical medical oncologist and past Assistant Professor of Medicine at the University of Chicago. Currently, Dr. Nabhan serves as Medical Director of Cardinal Health. His clinical practice and academic research for the past 17 years has focused on lymphomas. Dr. Nabhan also has a sub-specialty in the treatment of lymphomas. Until last year, he treated approximately 30 lymphoma patients per week. Dr. Nabhan regularly relies on both epidemiology and toxicology studies in his clinical practice and is well versed in the etiology, background, and treatment of NHL. Dr. Nabhan engaged in a systematic review of the literature in this case, utilized the Bradford Hill criteria, and concluded that "[t]he weight of the scientific evidence supports causality between Roundup/glyphosate exposure and NHL." Ex. 7 - Nabhan Report at 21-22.

Dennis D. Weisenburger M.D. Dr. Weisenburger is Chair of the Pathology Department of the City of Hope Medical Center. He specializes in the studies of the hematopoietic and

immune systems, with a special interest in NHL that has spanned nearly 40 years. His study of the pathological mechanisms by which NHL develops began in the 1980s when he was directing large epidemiologic studies related to NHL. Dr. Weisenburger has published over 300 papers on NHL in peer-reviewed journals, and over 50 papers on the epidemiology of NHL, including studies on glyphosate and NHL. Dr. Weisenburger engaged in a systematic review of the literature in this case, utilized the Bradford Hill criteria, and concluded that to "a reasonable degree of medical certainty that glyphosate and GBFs (including Roundup) can cause NHL in humans exposed to these chemicals in the workplace or environment." Ex. 8 - Weisenburger Report at 13.

The Ninth Circuit addressed Dr. Weisenburger's qualifications and methodology, finding that "[w]here, as here, . . . doctors who stand at or near the top of their field and have extensive clinical experience with the rare disease or class of disease at issue, are prepared to give expert opinions supporting causation, we conclude that Daubert poses no bar based on their principles and methodology." *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1237 (9th Cir. 2017).

IARC Working Group Members Dr. Matthew Ross and Dr. Aaron Blair[2]

Dr. Aaron Blair, is a Scientist Emeritus at the National Cancer Institute Division of Cancer Epidemiology & Genetics, Occupational and Environmental Epidemiology Branch.[3] He is a lead investigator of the Agricultural Health Study and the Overall Chair of the IARC 112 working group. Dr. Blair explains at his deposition how he weighed the totality of the epidemiology studies to support his opinion that glyphosate is a probable human carcinogen. Dr. Matthew Ross is an Associate Professor at the College of Veterinary Medicine, at Mississippi State University. He has a Ph.D in Molecular Biology and expertise on the impact of

[2] Both parties designated Dr. Blair and Dr. Ross as experts after they were deposed. Monsanto designated Ross and Blair to provide expert opinions about "the IARC Working Group 112 deliberations and analysis and the resulting IARC Monograph 112 and the relevant scientific evidence with respect to glyphosate." Curiously, despite its own designation of Drs. Blair and Ross as experts, Monsanto seeks to have them excluded from Plaintiffs' case.

[3] https://dceg.cancer.gov/about/staff-directory/biographies/A-J/blair-aaron.

environmental toxins on signal transduction pathways in cells.[4] He was a part of the mechanism section of the IARC 112 working group. Dr. Ross explains why the strong evidence that glyphosate is genotoxic and causes oxidative stress are relevant to carcinogenicity in human. [5]

II. Legal Standards

Under *Daubert*, the Court's gatekeeping obligation is straightforward—to ensure that the proffered expert testimony is relevant and based on reliable methods. *See Daubert v. Merrell Dow Pharm., Inc*., 509 U.S. 579, 589 (1993). Courts should not weigh evidence or draw conclusions about the strength of any particular piece of evidence; in the Ninth Circuit, the Court's focus "'must be ***solely*** on principles and methodology, not on the conclusions that they generate.'" *Wendell v. GlaxoSmithKline LLC*, 858 F.3d 1227, 1232 (9th Cir. 2017) (emphasis added) (quoting *Daubert*, 509 U.S. at 595). In other words, although the mere *ipse dixit* of an expert is inadmissible, *see Gen. Elec. Co. v. Joiner,* 522 U.S. 136, 146 (1997*)*, it is not the Court's task to decide whether an expert's conclusions are correct. *See Daubert v. Merrell Dow Pharm., Inc*., 43 F.3d 1311, 1318 (9th Cir. 1995) (*Daubert II*) ("[T]he *Daubert* test "is not the correctness of the expert's conclusions but the soundness of his methodology"). Nor is the Court empowered "to determine which of several competing scientific theories has the best provenance." *Milward v. Acuity Specialty Products Group, Inc*., 639 F.3d 11, 15 (1st Cir. 2011)

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[4] http://www.cvm.msstate.edu/academics/departments-centers/basic-sciences/27-faculty-bio/faculty-basic-sciences/164-ross-matthew

[5] Monsanto's reliance on *Arias v. DynCorp,* 928 F. Supp. 2d 10 (D.D.C. 2013), is misplaced. *Arias* involved an expert who did not utilize a proper methodology nor conduct a thorough review of the evidence. *Id*. at 24-25. The Court appropriately found that the expert's opinion was unreliable for failing to follow any methodology in relying on the epidemiology studies. *Id.* ("Dr. Wolfson does not explain why he decided to credit Eriksson's results and dismiss De Roos's results regarding non-Hodgkin lymphoma."). A review of the expert's report illustrates why the *Arias* judge felt compelled to exclude his opinion. His report contains just two conclusory statements that glyphosate was linked to NHL. Ex. 9 – Expert Report of Dr. Michael Wolfoson. Here, the experts give a detailed evaluation of the strengths and weaknesses of each study, explain why they give weight to certain studies, and apply the Bradford-Hill criteria. Finally, the *Arias* expert also did not consider the strong mechanistic and animal data, which strongly supports that glyphosate causes NHL. *Arias* has little relevance compared to the rigorous review conducted by Plaintiffs' experts in this case.

(internal quotation marks and citations omitted). Instead, the party submitting expert testimony must demonstrate that "the expert's conclusion has been arrived at in a scientifically sound and methodologically reliable fashion." *Id*. *Daubert* demands that an expert, "whether basing testimony on professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field." *Id.* (quoting *Kumho Tire Co., Ltd. v. Carmichael*, 526 U.S. 137, 152 (1999)).

The Supreme Court has identified several non-exhaustive factors that a court may consider: "whether the theory or technique employed by the expert is generally accepted in the scientific community; whether it's been subjected to peer review and publication; whether it can be and has been tested; and whether the known or potential rate of error is acceptable." *Daubert II,* 43 F.3d at 1318 (citing *Daubert*, 509 U.S. at 593-94). A further consideration is whether experts are testifying "about matters growing naturally" out of their independent research, or whether "they have developed their opinions expressly for purposes of testifying." *Wendell*, 858 F.3d at 1232. The absence of independent research, however, does not render an expert's methodologies unreliable as an expert may "instead present 'other objective, verifiable evidence that the testimony is based on scientifically valid principles.'" *Id*. at 1235 (quoting *Daubert II*, 43 F.3d at 1317-18).

The Ninth Circuit further expounded that "[t]hese factors are illustrative, and they are not all applicable in each case." *Id*. at 1232. Indeed, the inquiry is "flexible," *id*. (quoting *Daubert*, 509 U.S. at 594), and "Rule 702 should be applied with a 'liberal thrust' ***favoring admission***." *Id*. (emphasis added) (quoting *Messick v. Novartis Pharm. Corp*., 747 F.3d 1193, 1196 (9th Cir. 2014)). Exclusion of expert testimony is only appropriate when such testimony qualifies as irrelevant or unreliable "junk science." *Wendell*, 858 F.3d at 1237. Otherwise, the court should cede complex issues to the jury and rely on the traditional safeguards of the adversary system—cross-examination, presentation of contrary evidence, and instruction on the burden of proof—to test and evaluate weak but otherwise admissible evidence. *See Milward*, 639 F.3d at 13 ("So long as an expert's scientific testimony rests upon 'good grounds, based on what is known,' it should be tested by the adversarial process, rather than excluded for fear that jurors will not be able to

handle the scientific complexities.") (quoting *Daubert*, 509 U.S. at 590, 596). "[T]he interests of justice favor leaving difficult issues in the hands of the jury and relying on the safeguards of the adversary system." *Wendell*, 858 F.3d at 1237 (internal citations omitted).

Further, applying *Daubert* in a phased litigation focused on general causation, Plaintiffs' experts are only required to proffer testimony on the issue of whether a substance such as Roundup can cause the alleged injuries—not whether Roundup caused any particular individual's injury. *See In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1133 (9th Cir. 2002) (general causation addresses "whether the substance at issue had the capacity to cause the harm alleged, while "individual causation" refers to whether a particular individual suffers from a particular ailment as a result of exposure to a substance.).[6]

III. Relevant Regulatory History

A. Recent Glyphosate Assessments

IARC is one "of the most well-respected and prestigious scientific bodies," whose assessments of carcinogenicity of chemicals "are generally recognized as authoritative[.]" Ref. Manual at 20, 565. And, for good reason. Unlike regulatory bodies that often have ties to industry and are shackled with earlier regulatory decisions, IARC is independent. Scientists from around the world, who are renowned and respected experts in their field, systematically reviewed the published and peer-reviewed data and concluded, based on sound, reliable evidence, that glyphosate is a probable human carcinogen.[7] The State of California reviewed the IARC

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[6] Lasker & Hollingsworth. Physicians at the gates of Daubert quoting Note, Navigating uncertainty: gatekeeping in the absence of Hard Science, 113 Harv. L. Rv. 1467, 1474 (2000) (("General causation is 'a showing that the toxic exposure at issue *could have* caused the plaintiff's injury.'") (emphasis added); *Milward*, 639 F.3d at 13 ("'General causation' exists when a substance is capable of causing a disease.") (quoting Restatement (Third) of Torts: Liability for Physical and Emotional Harm § 28 cmt. c(3) (2010) ("Restatement ")). *See also infra* at Section VI.

[7] *See* Reference Manual at 91 ("It appears that many of the most well-respected and prestigious scientific bodies (such as the International Agency for Research on Cancer (IARC), the Institute of Medicine, the National Research Council, and the National Institute for Environmental Health Sciences) consider all the relevant available scientific evidence, taken as a whole, to determine which conclusion or hypothesis regarding a causal claim is best supported by the body of evidence.").

classification and similarly concluded that glyphosate is a substance known to the State of California to cause cancer as of July 7, 2017.[8] Echoing decisions by IARC and the State of California, on October 19, 2017, European Parliament's Environment Committee ("EPEC") voted in favor of an immediate and complete ban on household use of glyphosate-based formulations (GBFs) and a full ban on GBFs by December 2020.[9] And on October 24, 2017, European Parliament representatives overwhelmingly voted in favor of a non-binding resolution banning glyphosate in the 28 European Union member states by 2022, again with an immediate ban on household use.[10] The EPEC is not alone; several governmental bodies outside of United States have instituted similar glyphosate bans.[11]

The EPA's conclusions, by contrast, are not reliable. First, the EPA has never properly analyzed the data. For example, the December 2016 Scientific Advisory Panel ("SAP") meeting, convened to discuss the methodology used by EPA's Office of Pesticide Programs (OPP) in assessing glyphosate, unanimously concluded "that the EPA evaluation does not appear to follow the EPA (2005) Cancer Guidelines." Ex. 10[12] at 19. Numerous panel members concluded that "the weight-of-evidence conclusion based on EPA's 2005 Guidelines naturally leads to suggestive evidence of potential carcinogenic effects." *Id*. at 90. Second, recent documents raise serious concerns about Monsanto's relationship with EPA officials. For example, in an email between the former Director of the OPP Jack Housenger and Daniel Jenkins from Monsanto, Mr. Housenger assures Monsanto that he has spoken to individuals at the Agency for Toxic Substances and Disease Registry (ATSDR) about putting ATSDR's review of glyphosate "on hold." Ex. 11.[13] There were also undocumented meetings between Monsanto's CEO and former

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[8] https://oehha.ca.gov/proposition-65/crnr/glyphosate-listed-effective-july-7-2017-known-state-california-cause-cancer.

[9] http://www.europarl.europa.eu/news/en/press-room/20171019IPR86411/meps-propose-glyphosate-phase-out-with-full-ban-by-end-2020

[10] http://www.europarl.europa.eu/news/en/press-room/20171020IPR86572/meps-demand-glyphosate-phase-out-with-full-ban-by-end-2022 .

[11] http://claregalway.info/wp-content/uploads/2016/09/535_Glyphosate-and-pesticide-bans-around-the-world-as-of-July-20161.pdf

[12] FIFRA Scientific Advisory Panel Meeting Minutes and Final Report at 45 (March 16, 2017).

[13] 6/24/2015 Email between Jack Housenger and Dan Jenkins. MONGLY02060344 at 2.

EPA administrator Gina McCarthy discussing the makeup of the SAP panelists and the "[i]mpacts of IARC classification... on personal injury litigation" involving glyphosate. Ex. 12.[14] Monsanto also used its resources to "[influence positions of [EcHA members] on classification proposal" by exposing them to Monsanto's messaging through "key influential people" and targeted media campaigns. Ex. 13.[15]

B. The "Science" Underlying the Registration of Glyphosate

In 1964, glyphosate was patented as a descaling agent for industrial boilers, due to glyphosate's ability to combine with, and thus strip, metallic minerals. Ex. 14. Monsanto introduced it as an herbicide in the 1970s, and EPA approved its sale, based mainly on toxicology studies by Industrial Bio-Test ("IBT") laboratory that the "FDA/EPA found to generate fraudulent data..." Ex. 15.[16] IBT conducted 30 of the tests used to support glyphosate approval, including a mouse carcinogenicity study deemed invalid.[17] Ex. 16,[18] at 37.

In 1982, an EPA review of a glyphosate rat study found a statistically significant increase in lymphocytic hyperplasia and interstitial testicular tumors.[19] Then, in 1985, an EPA review of another glyphosate mouse study concluded that "glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor..."[20] In reaching this conclusion, an EPA statistician rejected Monsanto's assessment that the tumors were unrelated to glyphosate, stating "a prudent person would reject the Monsanto assumption that Glyphosate dosing has no effect on kidney tumor production..."[21] During a February 1985 consensus review of the available glyphosate data, a

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[14] EPA talking points for Hugh Grant, MONGLY03550799, MONGLY03550800.
[15] Action Plan ECHA, MONGLY03914265
[16] 3/17/2015 email from William Heydens re: CE Collaboration Project MONGLY00990361,
[17] Monsanto was forced to redo carcinogenicity tests on glyphosate (to date, Monsanto has never conducted a carcinogenicity test on Roundup®).
[18] EPA, Summary of the IBT Review Program, July 1983.
[19] February 18, 1982 EPA memo re: Lifetime feeding study in rats with glyphosate, *available at* http://www.centerforfoodsafety.org/files/epa-1983_41310.pdf
[20] April 3, 1985 EPA memo re: mouse oncogenicity study, *available at:* https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/103601-183.pdf
[21] Feb. 24, 1985 EPA memo re: use of historical data, *available at* : https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/103601-

group of eight EPA scientists "classified glyphosate as a category C oncogene," i.e. a possible human carcinogen.[22]

Monsanto, aware that a finding of "one tumor in the control group" would destroy statistical significance, hired a pathologist to review the tumor pathology.[23] However, before the pathologist received the slides, Monsanto seemed to understand that the review would find a tumor in the control group. *Id.* Based upon this review—which predictably found a control group tumor—the EPA required Monsanto to re-cut the mouse kidney slides to obtain further information on the presence or absence of tumors. Ex. 17[24] However, at least two independent pathologists concluded the presence of a tumor could not be definitively established. Ex. 18[25] Similarly, the California Department of Food and Agriculture also did "not consider the [tumor] finding in the control male as real." Ex. 19[26] California therefore also concluded that "[t]here is a possible adverse (oncogenic) effect" with glyphosate. Ex. 20.[27]

After Monsanto failed to deter the EPA scientists, a FIFRA Scientific Advisory Panel (SAP) was formed in 1986 to consider the EPA's classification. Ex. 21[28] Monsanto's strategy was to hire several consultants, including a pathology working group, because "[t]here is a tendency to 'count the votes' at SAP meetings. We can make a difference by lining up a large number of experts on our side." *Id*. The SAP panel did indeed count the votes, and downgraded glyphosate to Class D based on the number of expert reports submitted by Monsanto. [29]

170.pdf

[22] March 4, 1985 memo re: glyphosate consensus review. *Available at:* https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/103601-171.pdf

[23] *See* Plaintiffs' Br. Regarding their Motion to Compel the Original Pathology Slides in Study BDN-77-420 ("Knezevich & Hogan), ECF No. 257, ECF No. 283.

[24] March 13, 1985 letter from Monsanto to EPA, MONGLY00233278.

[25] December 4, 1985 Memo from EPA pathologist, Louis Kazsa

[26] April 3, 1987 letter from Monsanto. MONGLY04278109

[27] Nov. 17, 1986, CDFA evaluation of Mouse study. MONGLY04278139

[28] Aug. 20, 1985, Monsanto Memo re: Roundup SAP Meeting, MONGLY04268982

[29] Feb. 24, 1986, SAP Panel Report, *available at:* https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_24-Feb-86_209.pdf

Nevertheless, it concluded that "the occurrence of three neoplasms in high dose male mice is unusual and using historical controls is statistically highly significant." *Id.* The SAP, therefore, recommended that both the rat and mouse studies be repeated. *Id.*

In June 1991, an EPA reviewer noted that "due to the high incidences of pancreatic islet cell tumors in each of the treated male groups...the Toxicology Branch I has recommended that the carcinogenic potential of glyphosate be addressed by the Peer Review Committee."[30] A divided committee—the majority concluding that the studies did not show carcinogenicity, with three members dissenting—nevertheless cautioned "that designation of an agent in Group E is based on the available evidence at the time of evaluation and should not be interpreted as a definitive conclusion that the agent will not be a carcinogen under any circumstances."[31]

During the 1990s, independent scientists published new studies concluding that GBFs were genotoxic and induced oxidative stress. To combat these studies, Monsanto hired Dr. James Parry who "was at the forefront of studies in genetic toxicology and the founding father of much of this discipline within the UK." Ex. 22[32] Based on published literature and Monsanto's unpublished in-house genotoxicity studies, Dr. Parry provided Monsanto a draft report that concluded "glyphosate is a potential clastogenic[33] in vitro" and the "clastogenic activity may be reproduced in vivo in somatic cells."[34] Ex. 23, p. 12. Dr. Parry recommended that Monsanto conduct several tests to determine glyphosate's saftey, which Monsanto never conducted. Martens Dep. at 116:8-119:24. Ex. 24. Further, Monsanto did not provide the Parry report to EPA, as it was required to do under 40 CFR 159.158. *See Am. Crop Prot. Ass'n v. U.S. E.P.A.*,

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[30] June 3, 1991 Memo from EPA employee William Dykstra, *Available at :* https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-103601_3-Jun-91_263.pdf

[31] Oct. 30, 1991 memo re: Second Peer Review, *available at:* https://archive.epa.gov/pesticides/chemicalsearch/chemical/foia/web/pdf/103601/417300-1991-10-30a.pdf

[32] Waters, et al. James M. Parry (1940–2010) Mutagenesis (2011) 26 (1): 1-2.

[33] A clastogen is a mutagenic agent giving rise to or inducing disruption or breakages of chromosomes, leading to sections of the chromosome being deleted, added, or rearranged.

[34] Parry Report p. 12. Moreover, Dr. Parry's conclusions demonstrate that Plaintiffs' mechanistic opinions enjoy general acceptance. MONGLY01314233

182 F. Supp. 2d 89 (D.D.C. 2002). Recognizing that Dr. Parry's report would not aid Monsanto's messaging, it elected to publish a ghostwritten article austensibly by Gary Williams, concluding that "Roundup herbicide does not pose a health risk to humans," Ex. 25,[35] despite its own scientists admitting internally, "[t]he terms glyphosate and Roundup cannot be used interchangeably ....For example you cannot say that Roundup is not a carcinogen...we have not done the necessary testing on the formulation to make that statement." Ex. 27.[36] Dr. William Heydens, current Regulatory Product Safety Asssessment Lead at Monsanto, admitted he ghostwrote and made final edits to the article. Ex. 28.[37] Monsanto noted in December 2010 that Williams (2000) was "an invaluable asset" for its "responses to agencies; Scientific Affairs rebuttals; and Regulator reviews;" and while Williams "has served us well in toxicology over the last decade...we need a stronger arsenal of robust scientific papers to support the safe use of our products as we face the next set of chemistry registration reviews across the globe." Ex. 30. [38]

The next EPA registration prompted another round of ghostwritten articles, including the Kier and Kirkland study[39] originally written by Monsanto's David Saltmiras. Ex. 32.[40] In requesting funding for the manuscript, Saltmiras stated that it "will be a valuable resource in future product defense against claims that glyphosate is mutagenic or genotoxic." Ex. 33.[41] However, after drafting the manuscript, Monsanto concluded that "the manuscript turned into such **a large mess of studies reporting genetoxic effects,** that the story as written stretched the

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[35] Williams, et al., Safety Evaluation and Risk Assessment of the Herbicide Roundup and Its Active Ingredient, Glyphosate, for Humans. Regulatory Toxicology and Pharmacology, 31, 117-165 (2000); *See* Ex. 26, MONGLY00977264 (we ghost-write the Exposure Tox & Genetox sections...we would be keeping the cost down by us doing the writing and they would just edit & sign their names so to speak. Recall that is how we handled Williams Kroes & Munro, 2000.").

[36] 11/24/2003 email from Donna Farmer. MONGLY00922458.

[37] 6/21/1999 email from Bill Heydens stating "And Dougie [Cantox] thinks I would actually leave the final editing to him unsupervised..."; MONGLY03751016; *See also* Ex. 29. MONGLY02598454, Glyphosate Publications Recommendations for Process.

[38] 12/8/2010, email from Heydens and attachment. MONGLY02067858, pp 12, 16.

[39] Ex. 31 - Kier & Kirkland, "Review of genotoxicity studies of glyphosate and glyphosate-based formulations" Crit Rev Toxicol. 2013 Apr;43(4):283-315.

[40] Kier & Saltmiras Draft Manuscript. MONGLY01691608.

[41] 2/29/2012, manuscript clearance form. MONGLY02117800.

limits of credibility among less sophisticated audiences." Ex. 34.[42] (emphasis added). Monsanto decided it needed to "enhance credibility" of the manuscript by giving the impression that the study was independent and thus replaced Saltmiras as an author with Dr. David Kirkland, a renowned genotoxicity specialist. *Id.*; Ex. 35.[43] Essentially, Monsanto could not let the data speak for itself, because the data shows, as our experts explain, that glyphosate is genotoxic.

Immediately after IARC deemed glyphosate a probable carcinogen, Monsanto devised a response plan due to the "[s]evere stigma attached to Group 2A Classification." Ex. 36.[44] That plan included convening an expert panel, privately selected by Monsanto, to "[p]ublish comprehensive evaluation of carcinogenic potential by credible scientists." *Id.* Monsanto noted that the "Genetox / MOA" section would be important for "future litigation support," *Id.* and the panel would be "[a]ppealing; best if use big names; better if sponsored by some group." *Id.*

It is significant that Monsanto's experts rely on these three ghostwritten papers. *See* Ex. 37 – Expert Report of Dr. Warren Foster at 46; Ex. 38 – Expert Report of Dr. Jay Goodman at 32-33. Ex. 39.[45] It is also important that the EPA OPP relied on these papers:"[t]he CARC evaluated a total of 54 mutagenicity/genotoxicity studies which included studies submitted to the agency, as well as studies reported in the two review articles (Williams et al., 2000, and Kier and Kirkland, 2013)."[46]

It is not surprising then that when IARC—an independent agency—decided to evaluate glyphosate, Monsanto's chief toxicologist Donna Farmer wrote, "what we have long been concerned about has happened. Glyphosate is on for an IARC review in March of 2015." Ex.

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[42] 7/19/2012 Email re: Genotox Review: your approval requested! MONGLY02145917.

[43] Saltmiras noted that Kier & Kirkland was "the fifth such Glyphosate related manuscript I have been involved with over the past few years without co--authorship." MONGLY04086537.

[44] May 11, 2015, Proposal for Post-IARC Meeting Scientific Projects, MONGLY01228577,

[45] Monsanto seems to have underestimated the pervasiveness of its ghostwritten papers, as counsel was unaware that its experts relied on them. "THE COURT: . . . In any of those filings, did you rely on any of these reports that we now know were ghostwritten by Monsanto? MR. HOLLINGSWORTH: No. You're referring to – you're referring to the 2000 article by Williams and others. . . . It's a review article. It's a review of all of the literature. . . . Tr. of Proceedings at 46:18-48:19 (Aug. 24, 2017). Ex. 39.

[46] 10/1/2015 GLYPHOSATE: Report of the Cancer Assessment Review Committee, p. 9, file:///D:/Users/jtravers/Downloads/EPA-HQ-OPP-2016-0385-0014.pdf

40.[47] Dr. Heydens expressed concern also: "we have vulnerability in the area of epidemiology, we also have potential vulnerabilities in the other areas that IARC will consider, namely, exposure, genetox, and mode of action..." Ex. 41.[48] Prior to IARC's evaluation, Monsanto recognized that "a 2A rating (probably human carcinogen) is possible" and developed a plan to "Orchestrate Outcry with IARC Decision" through "robust media / social media outreach." Ex. 42.[49] Although Monsanto publicly attacks IARC, its consultant hired to monitor the IARC evaluation stated, "[i]n my opinion the meeting followed the IARC guidelines," Ex. 43,[50] and its litigation consultant John Acquavella, an epidemiologist, admits that "[t]here is not really much to quarrel about with respect to [IARC's] epidemiology classification." Ex. 44.[51] Under oath, Acquavella admitted that IARC got it right. Ex. 45, Acquavella Dep. at 472:1-10. And, prior to this litigation, an article outlining IARC's methodology was published by over 100 scientists. Ex. 46.[52] Including five scientists from the Harvard School of Public Health and two of Plaintiffs' experts, Drs. Ritz and Weisenburger.[53]

IV. The Bradford-Hill Criteria is the Most Widely Accepted Method for Assessing Causation

The Bradford-Hill criteria, the generally accepted method for assessing causation, consist

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[47] 9/29/2014 email from Donna Farmer to John Acquavella. MONGLY01207342.
[48] 10/15/2014 email from Bill Heydens , MONGLY00989918.
[49] IARC, Carcinogen Rating Of Glyphosate Preparedness And Engagement Plan. MONGLY01021845.
[50] 3/14/2015 email from Thomas Sorahan, MONGLY00977035.
[51], 4/9/2015 email from John Acquavella. ACQUAVELLAPROD00010215.
[52] These independent scientists wrote that IARC "[e]valuations involve consideration of all of the known relevant evidence from epidemiologic, animal, pharmacokinetic/mechanistic, and exposure studies to assess cancer hazard in humans... each discipline provides important evidence toward the overall evaluation of causality according to the Bradford Hill considerations (Hill 1965)." Pearce, et al. "IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans" Environmental Health Perspectives, Vol. 123, no. 6, June 2015.
[53] The fact that these two experts advocated for the IARC methodology prior to being retained as experts makes their opinions particularly admissible because this opinion on the credibility of IARC "w[as] not developed for purposes of this litigation." *Murray v. S. Route Mar. SA*, 870 F.3d 915, 923 (9th Cir. 2017).

of nine factors to consider in determining causality.[54] "There is no formula or algorithm that can be used to assess whether a causal inference is appropriate based on these guidelines. One or more factors may be absent even when a true causal relationship exists." Federal Judicial Center's Reference Manual on Scientific Evidence (3rd. Ed.) (Reference Manual) at 599-600.

Plaintiffs' experts carefully considered and applied the relevant Bradford-Hill criteria in reaching their conclusion that glyphosate can cause NHL. Neugut Rep. at 20-22; Ritz Rep. 23-24; Portier Rep. at 76; Weisenburger Ret. at 11-13; Nabhan Rep. at 19-21. Dr. Jameson used a similar weight-of-the-evidence methodology, also used by IARC and the National Toxicology Program ("NTP"), Jameson Rep. at 9; Reference Manual at 655, which also utilizes the Bradford-Hill methodology.[55] Ex. 48 – Deposition Transcript and Exhibits of Dr. Aaron Blair at 32:24-33:4. Each of these experts came to an independent conclusion as reflected by their similar take on the criteria.[56] Each expert thoroughly considered possible bias and confounding and determined those possibilities do not explain the positive association between glyphosate and NHL.

Monsanto disregards the very authority it relies upon by arguing that the principles espoused in the Reference Manual preclude application of the Bradford-Hill criteria in this case. Monsanto claims, for example, that case-control studies cannot establish temporality. MSJ at 38. However, Monsanto quotes from an irrelevant Reference Manual section dealing with a different

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[54] The nine factors to consider include: 1. Strength of Association, 2. Consistency, 3. Specificity, 4. Temporality, 5. Biological Gradient (Dose-Duration Response), 6. Biological Plausibility, 7. Coherence (coherence with existing knowledge), 8. Experiment, and 9. Analogy. *See* Ex. 47 - Austin Bradford Hill, The Environment and Disease: Association or Causation? 58 Proc. Royal Soc'y Med. 295 (1965).

[55] http://monographs.iarc.fr/ENG/Preamble/currentb2studieshumans0706.php

[56] Generally, Plaintiffs' experts note that: 1. there is sufficient strength of association in the epidemiology; 2. there is specificity in that glyphosate is associated only with NHL; 3. there is strong consistency of an association over multiple studies among multiple populations; 4. the studies establish temporality; 5. dose –response analyses in Eriksson (2008) and McDuffie (2001) show an even stronger association; 6. there is strong biological plausibility based on animal and mechanistic studies; 7. coherence is established because multiple lines of evidence support causality; 8. studies have been replicated and show consistent results; and 9. analogy is not applicable. Neugut Rpt. at 20-22; Ritz Rpt. 23-24; Portier Rpt. at 76; Weisenburger Rpt. at 11-13; Nabhan Rpt. at 19-21.

type of epidemiological study called a cross-sectional study that does not exist in this litigation. Reference Manual at 560-561. Case-control studies specifically look at whether a person was exposed to the chemical before disease diagnosis. Reference Manual at 569 ("The researcher then compares the groups in terms of past exposures.").

Monsanto also claims, but cites no relevant authority, that Plaintiffs' experts must eliminate confounding factors before applying Bradford-Hill.[57] In fact, the Reference Manual includes consideration of bias and confounding as part of the Bradford-Hill analysis. Reference Manual at 605. As Dr. Neugut explains, causality can never be established with "100% surety;" hypothetical associations which eliminate bias and confounding "don't exist" for any chemical; and if such a hypothetical association did exist then you "wouldn't have to have the Bradford Hill criteria to discuss it further." Ex. 49 – Deposition Transcript and Exhibits of Dr. Alfred Neugut at 311:2-314:6.

Monsanto mistakenly claims that "point estimates for associations below a RR of 2.0 would not satisfy the strength criterion." MSJ at 38. While several studies of glyphosate and NHL show RRs greater than 2.0, this is far from a requirement, and Monsanto cites only a law review article, rather than Ninth Circuit precedent, for its position. This argument is "based on a misunderstanding of relative risk, a mis-reading of Ninth Circuit precedent and a lapse in basic logical reasoning." *In re Silicone Gel Breast Implants Prod. Liab. Litig.,* 318 F. Supp. 2d 879, 893 (C.D. Cal. 2004); *In re Hanford Nuclear Reservation Litig*., 292 F.3d 1124, 1137 (9th Cir. 2002) ("the district court erred in requiring epidemiological evidence which would, like the standard rejected by the Third Circuit in *In re TMI Litig*., require a plaintiff to prove exposure to a specific threshold level of radiation that created a relative risk of greater than 2.0."); *In re Bextra & Celebrex Mktg. Sales Practices & Prod. Liab. Litig.*, 524 F. Supp. 2d 1166, 1173 (N.D. Cal. 2007) (J. Breyer) (holding that 2.0 issue is not relevant to general causation). Furthermore,

[57] *Daubert II* makes no reference to Bradford-Hill or to confounding variables. 43 F.3d at 1321. *Hollander v. Sandoz Pharm. Corp.* likewise does not reference Bradford-Hill either and addresses "anecdotal case reports," holding that they are not sufficient for causation precisely because they are not epidemiological studies. 95 F. Supp. 2d 1230, 1237 (W.D. Okla. 2000).

both Plaintiffs' and Monsanto's epidemiologists find relative risks under 2.0 to be sufficient evidence of an association. Ex. 50 – Deposition Transcript and Exhibits of Dr. Lorelei Mucci at 140:3-143:2; Ex. 51 – Expert Report of Dr. Lorelei Mucci at 29; Ex. 52 – Deposition Transcript and Exhibits of Dr. Jennifer Rider at 259:4-260:24 (relative risks between 1.19 and 1.26 are evidence of an association.); Neugut Dep. at 91:2-7 ("Many risk factors that we take very seriously in public health are really at that level of 1.3 and 1.4, and even 1.2, and we consider them significant carcinogens..."); Neugut Dep. at 333:17.

Monsanto's reference to Dr. Neugut for the proposition that the epidemiological evidence is not consistent is false. Dr. Neugut clearly states in his report, and testified at deposition, that the evidence is consistent.[58] And, while the epidemiological studies at issue in this case provide statistically significant risks, statistical significance is *not* required for Bradford-Hill. As Sir Austin Hill states, "[n]o formal tests of significance can answer those questions." Ex. 47. "A causal connection may exist despite the lack of significant findings, due to issues such as random misclassification or insufficient power." *In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 858 F.3d 787, 793-794 (3d Cir. 2017) (Bradford-Hill does not require statistical significance). Monsanto's attempt to disregard the Bradford-Hill criteria is misplaced.

V. Plaintiffs' Experts' Opinions Regarding the Epidemiological Association between GBFs and NHL Are Admissible; Epidemiological Data Supports General Causation

The epidemiology at the heart of the general causation question overwhelmingly shows that there is a real risk of NHL from GBF exposure. Numerous independent studies find statistically significant elevated risks, and those that do not still consistently observe an elevated risk.

Monsanto asks the Court to ignore dozens of positive findings of causality, in favor of one study that was flawed from its inception. In so doing, it invites the Court to weigh the

[58] Neugut Rep. at 22. ("But what is telling in the Forest plots is the consistency – they are primarily positive and to the right of 1. This consistency is amplified by the finding that when the data are meta-analyzed, they do indeed come out to be statistically significant.); *see also* Neugut Dep. at 323:4-7.

persuasiveness of the evidence and, in essence, to consider above all else, one study. Weighing the evidence, of course, is the province of the jury. Monsanto ignores this fact, and fails to explain how reliance on the full body of scientific literature is improper under *Daubert.* As explained below, the epidemiology in this case is so strong and consistently points in a direction of real risk that it would be improper for this Court to stop this case from proceeding to a jury on the issue of general causation.

C. The Court's Role in Considering Epidemiological Data under *Daubert*

Epidemiological studies are probative of general causation. *See In re Bextra*, 524 F. Supp. 2d at 1172; *see, e.g.*, *Brasher v. Sandoz Pharm. Corp.*, 160 F. Supp. 2d 1291, 1296 (N.D. Ala. 2001) ("Unquestionably, epidemiological studies provide the best proof of the general association of a particular substance with particular effects, but it is not the only scientific basis on which those effects can be predicted.").

1. Types of Epidemiological Data

Epidemiological studies include "(1) randomized controlled clinical trials, (2) observational studies [Case-control and cohort], and (3) meta-analyses." *In re Bextra*, 524 F. Supp. 2d at 1173. However, "it may not always be possible to conduct certain types of studies." *Wendell*, 858 F.3d at 1236. For example, a randomized controlled trial for glyphosate or GBF exposure "would certainly be unethical." Rider Dep. at 199:20-200:10; *see also* Nabhan Dep. at 52:14-53:20. Hence, there are no randomized controlled trials for glyphosate.

A case-control study compares people with a disease (cases) to people without a disease (controls) and examines the number of exposed people to determine an odds-ratio, *i.e.,* the increased odds that someone with a disease was exposed to the chemical of interest. Reference Manual at 568. Cohort studies, another type of observational study, compare people who are exposed to a chemical to those who are not exposed and follow them for a certain time period to monitor which individuals develop the disease of interest. *Id.* at 566. "An advantage of the case-control study is that it usually can be completed in less time and with less expense than a cohort

study." *Id.* at 560. In addition, case control studies are useful when dealing with a rare cancer like NHL, "because if a cohort study were conducted, an extremely large group would have to be studied in order to observe the development of a sufficient number of cases for analysis." *Id.*; *see also* Ritz Rep. at 12-13 ("[T]he rarer a disease, the harder it is for a scientist to create a large enough study with enough cancer cases enrolled to have adequate statistical power . . . This is why it is so hard to study NHL with a cohort study design."). Finally, meta-analyses, "pool[] the results of various studies to arrive at a single figure to represent the totality of the studies reviewed. . . Meta-analysis has the advantage of pooling more data so that the results are less likely to be misleading solely due to chance." *In re Bextra*, 524 F. Supp. 2d at 1174.

"There is no universal ideal study design." Ex. 53.[59] Study limitations occur due to technology, resource and human constraints. Reference Manual at 553. That said, in weighing the strength of evidence from strongest to weakest, "systematic review of randomized trials (meta-analysis) is at the top, followed by single randomized trials, systematic reviews of observational studies, single observational studies, physiological studies, and unsystematic clinical observations." *Id.* at 723.

2. Interpreting Epidemiological Estimates

The difference in the percentage of exposed versus unexposed people who develop a disease is called the relative risk ("RR") or odds ratio ("OR"). *Id.* at 568. "[T]he odds ratio from a case-control study is quite similar to a risk ratio from a cohort study." *Id.*at 625. "A relative risk [or odd ratio] greater than 1.0 means the product has the capacity to cause the disease." *In re Bextra*, 524 F. Supp. 2d at 1172. There is no threshold OR risk that is necessary to establish general causation.[60] Neugut Dep. 91:2-7

In evaluating a RR or OR, epidemiologists attempt to control for random error, i.e.,

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[59] Exponent "Design of Epidemiologic Studies for Human Health Risk Assessment of Pesticide Exposures" Prepared for CropLifeAmerica, 1/24/2016, at 29, MONGLY02314040.

[60] Monsanto's claims that to establish general causation, Plaintiffs are required to show a RR or OR of at least 2.0, *see* MSJ at 12, 38, is wrong. *See supra* at 18-19.

determining whether the RR or OR was the result of chance. A confidence interval is the best way to evaluate random error.[61] Reference Manual at 579 ("[A] confidence interval permits a more refined assessment . . . in an epidemiologic study."). It provides the RR or OR "found in the study and a range (interval) within which the risk likely would fall if the study were repeated numerous times." *Id*. at 573.[62] When a confidence interval includes 1, the result is not considered "statistically significant," but, as Dr. Ritz explains: "Statistical significance testing has been . . . often misused in the medical literature, and its use has thus been widely criticized."[63] Thus, while statistical significance is relevant and considered by Plaintiffs' experts, it should not be used as a device to ignore data or otherwise elevate ORs.

D. The Epidemiological Data, when Viewed in its Entirety, Strongly Supports a Causal Association between GBFs and NHL

Numerous epidemiological studies examine the association of GBF exposure and NHL. Many of those studies, *by themselves*, show a statistically significant elevated risk of NHL for individuals exposed to GBFs, even when controlling for other pesticides. Others show an elevated risk, but the confidence interval for the OR encompasses 1 and, thus, is not "statistically significant." However, when these studies are compiled, the causal association between GBFs and NHL is readily apparent. As Dr. Portier explains, "[c]onsistency of the associations across several epidemiology studies is not simply a matter of seeing how many were statistically significant and how many were not but must also address the consistency of ***the direction of the***

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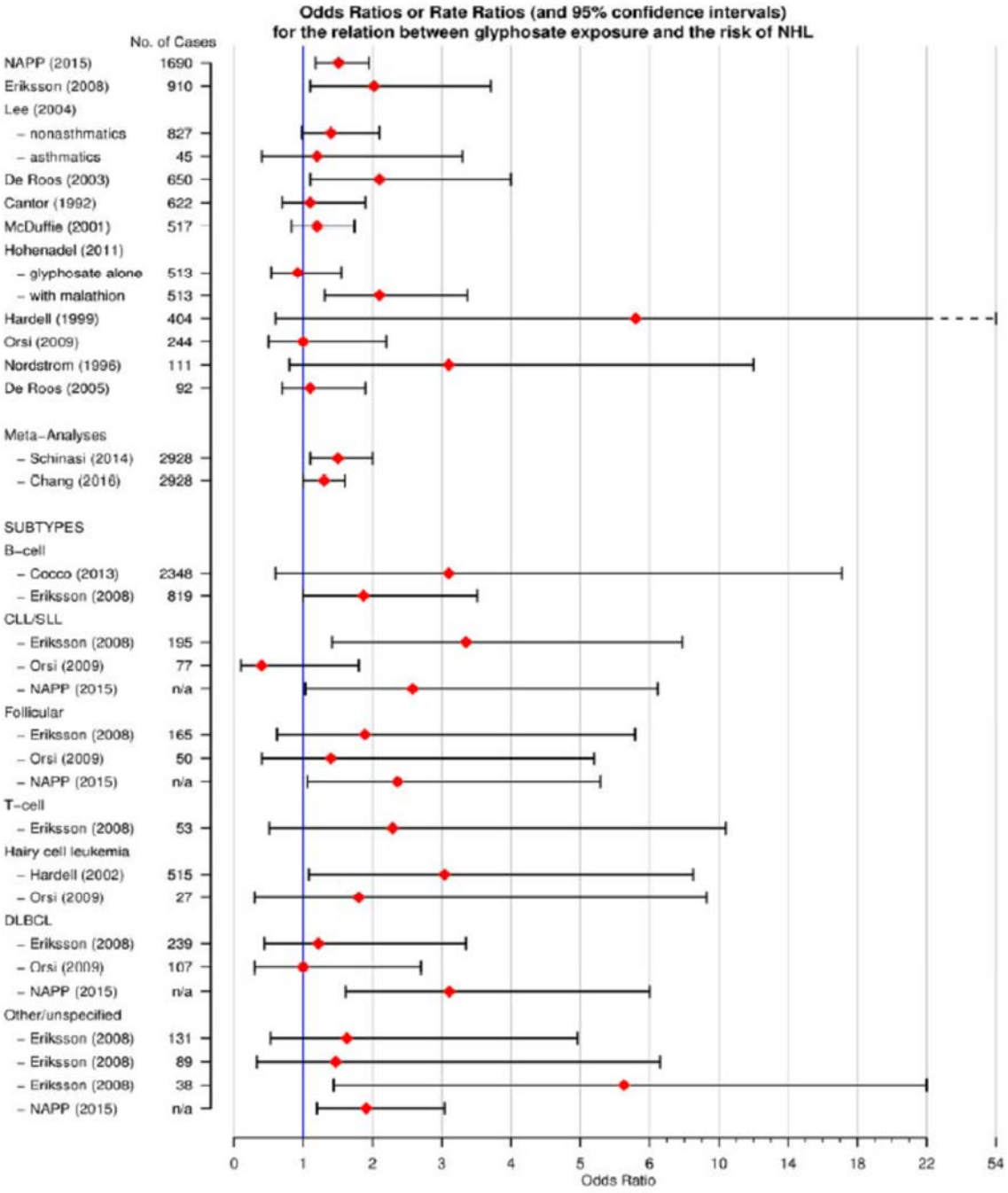
[61] Plaintiffs discuss the other common method, the p-value, in more detail below.

[62] The width of the interval around the estimate is determined by the level of confidence used. For example, a 95% confidence interval will be wider than a 90% confidence interval. *Id.* at 580. "In practice, most published estimates are 95% confidence intervals, which means that in 95 out of 100 times when sampling your study subjects, you will find the true result (effect estimate) within the given confidence interval." Ritz Rep. at 5.

[63] UCLA teaches students "to focus on the point estimate [OR or RR] as a measure of the size of the association between exposure and disease and the confidence interval to gage the precision of this estimate and the informativeness of the data/study." Ritz Rep. at 12;

responses." Portier Rep. at 15 (emphasis added). Dr. Ritz conducted a comprehensive literature search and generated the chart below. Ritz Rep. at 14; *see also* Neugut Rep. at 43 (similar chart); Portier Rep. at 16 (similar chart).



The blue line represents the null, i.e., an OR of 1, the red dots represent the estimated OR from

the study, and the black brackets reflect each OR's 95% confidence interval. Notably, of the 32 ORs, 28 are to the right of 1, indicating a consistently elevated risk associated glyphosate exposure. Assuming, for a moment, that there was no risk of GBH causing NHL, i.e., that the true OR is 1, one would expect to see an equal distribution of ORs above and below 1. Portier Rep. at 15 ("[I]f the true underlying risk ratio was 1 (no effect), you would expect about half of the findings to be below 1 and half to be equal to 1 or greater."); Neugut Rep. at 22 ("[I]f the two phenomena were truly random, then the measured associations in the studies should have randomly distributed themselves around 1."). Here, we see the *opposite*. Overall "the studies are pointing in the same direction toward a positive effect." Neugut Rep. at 22 ("[W]hat is telling in the Forest plots is the consistency – they are primarily positive and to the right of 1."). If the risk were really 1, the probability of observing this number of positive ORs (akin to observing 28 heads of 32 flips of a coin) is1:119,437.[64] Remarkably, Monsanto ignores this fact, electing instead to focus on a single (flawed) cohort study, to the exclusion of all others. That is not valid science—it is cherry picking data.

1. Numerous Well-Controlled, Peer-Reviewed, and Independent Studies Support the Causal Association between GBF Exposure and NHL

There are ample epidemiological studies finding statistically significant elevated risks of NHL following exposure to GBF. A summary of those studies follows:

Erickson (2008). Eriksson[65] is a peer-reviewed, population-based case-control study published in the well-respected International Journal of Cancer. Rider Dep. at 93:10-19.[66] Overall, the study reported a statistically increase in NHL risk with glyphosate exposure (OR

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[64] $\binom{28+4}{28} 2^{-(28+4)} = \frac{(28+4)!}{28! \times 4! \times 2^{28+4}} = \frac{4495}{536\,870\,912} \approx 8.373 \times 10^{-6} \approx \frac{1}{119\,437}$ (assuming a fair coin)

[65] Ex. 54. M. Eriksson et al, *Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis*, 123 INT'L J CANCER 7, 1657-63 (July 2008).

[66] The examined cases were diagnosed between 1999-2002 and, therefore, allowed for a reasonable period of time between exposure and disease development (latency). Ritz Rep. at 17. While a short latency period does not exclude the possibility of exposure-disease relationships in cancer, a longer latency period increases confidence in the results. *Id.*

2.02). Ritz Rep. at 17; Neugut Rep. at 15. The study results demonstrate a dose-response effect. Ritz Rep. at 17; Neugut Rep. at 22. For those with greater than 10 days use, the risk was higher (OR=2.36, CI 1.04-5.37), while the risk was reduced for those with ≤ 10 days use (OR=1.69, CI 0.70-4.07). The authors note that "[g]lyphosate was associated with a statistically significant increased OR for lymphoma in our study, and the result was strengthened by a tendency to dose-response effect... our earlier indication of an association between glyphosate and NHL has been considerably strengthened." Ex. 54 at 6.

DeRoos (2003). De Roos[67] pooled data from three case-control studies on NHL conducted in the 1980s in Nebraska, Kansas, Iowa, and Minnesota designed to examine pesticide exposure in farming. Neugut Rep. at 14.[68] The study revealed a statistically significant elevated risk between glyphosate use and NHL (OR 2.1) using the standard logistical regression approach.[69] *Id.* The authors specifically adjusted for exposure to more than forty other pesticides in arriving at the OR of 2.1. De Roos at 5, Table III ("Each estimate is adjusted for use of all other pesticides listed in Table 3, age and study site."); Ex. 57 – Deposition Transcript and Exhibits of Dr. Dennis Weisenburger at 114:19-115:2 (noting, as an author on the publication, that it adjusted for pesticide exposure); *see also* Ex. 58 – Deposition Transcript and Exhibits of Dr. Beate Ritz at 153:12-14; Neugut Rep. at 14.[70] Further, "the OR for glyphosate was among the

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[67] Ex. 55, De Roos. *Integrative Assessment of Multiple Pesticides as Risk Factors for Non-Hodgkin's Lymphoma Among Men*, 60 OCCUP. ENVIRON MED. e11, 1-9 (2003). Plaintiff's expert Dr. Wiesenburger is an author of this study.

[68] The study, authored by seven independent scientists, was published in the peer-reviewed journal Occupational and Environmental Medicine, owned by the "highly respected ... British Medical Journal." *Routhier v. Keenan* (2008) 25 Mass. L. Rep. 50. The pooled sample population included 870 cases and 2,569 controls. *Id.*

[69] In the study, the authors also conducted an analysis using hierarchal regression, which yielded an elevated risk of 1.6 that was not statistically significant (CI 0.9-2.8). However, as Plaintiffs' experts explain, use of hierarchal regression in this situation is inappropriate. Ritz Rpt. at 19 ("the model assumes that all pesticides included have a similarly strong effect on the outcome; thus we would expect the largest effect estimate to be pulled towards the null of 1 which is what happened."); Neugut Rep. at 14-15E. Chang et al., Meta-Analysis of Glyphosate Use and Risk of Non-Hodgkin Lymphoma, Exponent 1, 5 (2017) at 5. Ex. 56.

[70] Dr. Neugut misspoke when he agreed to a misleading question by Monsanto about whether the logistic regression adjusted for other pesticides. His report states that it did adjust for other

highest of 47 pesticides tested, which suggests that glyphosate may indeed be the pesticide most strongly related to NHL[.]" Ritz Rep. at 19.[71]

De Roos also conducted an analysis of the combined effect of using multiple potentially carcinogenic pesticides which resulted in a doubling of the risk for NHL. *Id.* at 5. However, when glyphosate was removed from the analysis the OR dropped to 1.1 which suggests that glyphosate was responsible for the increase and not other pesticides. *Id.*; Portier Rep. at 11.

Hardell (2002). Hardell[72] involved a pooled analysis of two Swedish case-control studies. The pooled population included 515 cases and 1141 controls. The peer-reviewed study, published in the journal Lymphoma & Leukemia, revealed a statistically significant (CI 1.08-8.52) OR of 3.04, controlling for age, study, county and vital status. Portier Rep. at 10; *see* Ritz Rep. at 17-18. Although the OR was attenuated when exposure to other pesticides was controlled for in the multivariate analysis, exposure to glyphosate still posed the greatest risk factor for NHL when compared to the other pesticides. Hardell at 1047, Table VII.

McDuffie (2001). McDuffie[73] was a multicenter, population-based study performed in six Canadian provinces. Neugut Rep. at 14. It was authored by seven independent scientists and published in a peer-reviewed journal on which Dr. Rider serves as a peer-reviewer. Rider Dep. at 64:18-65:8. The study included 517 male cases and 1506 controls. *Id.* The authors reported a weak increased risk of NHL with never/ever glyphosate exposure, OR=1.26 (CI 0.87-1.81). Ritz Rep. at 18; McDuffie (2001) at 1158, Table 2. But when the authors assessed men with greater

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pesticides. Neugut Rep. at 14-15; *see e.g. Diamondback Firearms, LLC. v. Saeilo, Inc.,* No. 6:10-CV-1664-ORL, 2014 WL 496920, at *10 (M.D. Fla. Feb. 6, 2014).

[71] Monsanto falsely claims that Plaintiffs' experts did not rely on any statistically significant studies that adjusted for pesticides. De Roos (2003) is discussed by *all* of Plaintiffs' epidemiological experts, with reasons provided for why they chose to rely on this study. Ritz Rep. at 15, 19; Weisenburger Rep. at 4-6; Neugut Rep. at 14-15; Naban Rep. at 12; Jameson Rep. at 17; Portier Rep. at 10.

[72] Ex. 59. Hardell L., et al. *Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies*, 43 LEUK LYMPHOMA 5, 1043-49 (2002).

[73] Ex. 60. McDuffie, H.H., et al., *Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health*, CANCER EPI., BIOMARKERS & PREVENTION, Vol. 10, 1155–1163 (November 2001).

than 2 days of GBF exposure per year, it revealed a statistically significant (CI 1.20-3.73) doubling of NHL (OR=2.12). The authors concluded that "we demonstrated a dose-response relationship" with glyphosate and NHL. *Id*. at 1160-1161.

The North American Pooled Project (NAPP) (2015). The NAPP is an ongoing analysis that has pooled data previously analyzed in De Roos (2003) and McDuffie (2001) to examine glyphosate and NHL.[74] With 1690 cases and 5131 controls, "NAPP reported an elevated risk of all NHL with any glyphosate use (OR=1.51, 95% CI 1.18-1.95), and a dose-response effect was seen with greater use (>2 days/year, OR=2.66, 1.61-4.40)."[75] It also showed statistically significant increases among NHL subtypes. Ritz Rep. at 14-15. The odds ratios presented at the three conferences have varied slightly, but always show an increased risk. Ritz Dep. at 278:20-283:4.[76] A draft manuscript cited by defense experts concludes:

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[74] http://www.occupationalcancer.ca/2013/north-american-pooled-project/.

[75] Monsanto incorrectly states that the NAPP reported a relative risk of 1.13 at ISEE 2015. Monsanto and its experts are relying on a draft slide deck produced from Dr. Blair's file. The native file shows that slide 26 was deleted from the power point and not presented at the conference. Ex. 61. Dr. Ritz reviewed it at her deposition and noted: "This is not a valid model in my mind because you have to show me that 2,4-D, dicamba, and Malathion are actually related to glyphosate use and also are independent risk factor for NHL ... . Also I would not accept this model because we would not want to adjust for the use of proxy respondents or personal protective equipment because ...You cannot adjust a model for exposure mismeasurement. These are confounded and shouldn't be in the models." Ritz Dep. at 285:17-286:9, 293:15-21. Dr. Ritz also noted that by excluding proxy respondents "[y]ou are pretty much reducing sample size, and when you reduce sample size, you automatically lose statistical power to show a statistically significant effect." *Id.* 427:20-23.

[76] While a manuscript has not been published, Dr. Ritz reviewed the study's primary results. Ritz Dep. at 400:2-16; Ritz Rep. at 15-16; Ex. 62 – Expert Rebuttal Report of Dr. Beate Ritz at 8 (in order to be presented at meetings like the ISEE's 2015 meeting in Brazil, studies in poster and published-abstract form need to be peer-reviewed). *See also* Ex. 63, Pahwa M., et al. A Detailed Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma in the North American Pooled Project. Canadian Association for Research on Work and Health; October 16-18 2016; Toronto ("CARWH 2016"); Ex. 64, Pahwa M., et al. An evaluation of glyphosate use and the risks of NHL major histological subtypes in the North American Pooled Project. International Society for Environmental Epidemiology; August 31, 2015; Sao Paulo, Brazil ("ISEE 2015"); and Ex. 65, Pahwa M., et al. A Detailed Assessment of Glyphosate Use and the Risks of Non-Hodgkin Lymphoma Overall and by Major Histological Sub-types: Findings from the North American Pooled Project. International Agency for Research on Cancer; June 10, 2016 ("IARC 2016").

> Our results are also aligned with findings from epidemiological studies of other populations that found an elevated risk of NHL for glyphosate exposure and with a greater number of days/year of glyphosate use, as well as a meta-analysis of glyphosate use and NHL risk. From an epidemiological perspective, our results were supportive of the IARC evaluation of glyphosate as a probable (group 2A) carcinogen for NHL.

Ex. 66 (footnotes omitted).[77] The authors specifically considered recall bias, and, similar to Plaintiffs' experts, rejected that recall bias is a concern in the study. *Id.* at 13.

Even with the above data, Monsanto argues that Plaintiffs cannot establish general causation because there is an absence of "statistically significant associations proven through epidemiology." MSJ at 11. Monsanto is wrong.

2. Peer-Reviewed Meta-Analysis of Epidemiological Data Support Causality

The numerous individual, peer-reviewed studies, showing a statistically significant elevated risk, are confirmed in peer-reviewed meta-analyses. Neugut Rep. at 22 ("This consistency is amplified by the finding that when the data are meta-analyzed, they do indeed come out to be statistically significant."); *see also Mullins v. Premier Nutrition Corp.*, 178 F. Supp. 3d 867, 884 (N.D. Cal. 2016) (meta-analysis is considered the strongest of medical evidence types). The first meta-analysis[78] included 2,928 cases from 6 studies[79] and reported a statistically significant (CI 1.1-2.0) increase (OR 1.5) in NHL risk with ***any*** glyphosate exposure. Ritz Rep. at 16; Neugut Rep. at 17.[80] The study also showed a statistically significant (CI 1.1-3.6) doubling in risk for B-

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[77] *See* Pahwa M., et al., An Evaluation of Glyphosate Use and the Risks of Non-Hodgkin Lymphoma Major Histological Subtypes in the North American Pooled Project (NAPP). Occupational Cancer Research Center, 2015 at 2-3 ("NAPP 2015").

[78] Ex. 67. Schinasi & Leon, *Non-Hodgkin Lymphoma and Occupational Exposure to Agricultural Pesticide Chemical Groups and Active Ingredients: A Systematic Review and Meta-Analysis*, 11 INT. J. ENVIRON. RES. PUBLIC HEALTH 4, 4449-4527 (2014).

[79] The studies included De Roos (2003), De Roos (2005), Eriksson (2008), Hardell (2002), McDuffie (2001) and Orsi (2009).

[80] Dividing data between a case control study in people who have ever/never used GBF is, itself, a conservative approach because it groups people with minimal exposure together with people with significant exposure, effectively diluting the risk. *See* Ritz Dep. at 424:20-425:7. Thus, in studies that attempt to better classify exposure, one sees more dramatic odd ratios. For example, in one study, researchers found a statistically significant (CI 1.61-4.40) increased risk of 2.66 in

cell lymphoma (OR 2.0), a common NHL type. Ritz Rep. at 16. IARC conducted the second meta-analysis and examined the same six studies but adjusted the data from Hardell (2002) and Eriksson (2008). Ritz Rep. at 16; Neugut Rep. at 17. IARC's meta-analysis also showed a statistically significant (CI 1.03-1.65) increased risk of GBF exposure (OR 1.3). *Id.*

The third meta-analysis was sponsored by Monsanto and conducted by Exponent, Inc., a for-profit commercial research organization.[81] Like the previous meta-analysis, Exponent used the same six core epidemiological studies but evaluated the data using four unique models. The models yielded the following results: OR 1.27 (CI 1.01[82]-1.59), OR 1.3 (CI 1.03-1.64), OR 1.32 (1.00-1.73), and OR 1.37 (CI 1.04-1.82).[83] Portier Rep. at 15-16. These results were consistent with the first two meta-analyses, showing a "statistically significant positive effect." *Id.* at 16; *accord* Ritz Rep. at 23; Neugut Rep. at 17.[84] For both the IARC and Monsanto meta-analyses, four of the six studies adjusted for other pesticides. Portier Rep. at 21. But because the odds ratios from the two studies that did not adjust for pesticides were lower than 1.3 (Orsi and McDuffie), limiting the analysis to ORs adjusting for pesticides would actually *increase* the strength of the association between glyphosate and NHL.

E. Monsanto's Focus on the AHS Study, to the Exclusion of Others, Is Misplaced

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people who use GBFs more than 2 days per year, versus a smaller, albeit still statistically significant (CI 1.18-1.95) OR of 1.51 for ever/never exposure. Ritz Rep. at 15-16.

[81] Ex. 68. Chang & Delzell, *Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers*, 51 J. ENVIRON. SCI. HEALTH B 6, 402-434 (2016).

[82] In the published report, Exponent did not disclose the confidence intervals beyond a single decimal point, suggesting the confidence intervals included 1. Dr. Portier, however, obtained the complete results, revealing that only one of the estimates included 1. *See* Portier Rep. at 15 n.5.

[83] Ex. 10, FIFRA Scientific Advisory Panel Meeting Minutes and Final Report at 45 (March 16, 2017)

[84] Monsanto's motion cites an unpublished, non-peer-reviewed meta-analysis by Exponent, released three weeks after Plaintiffs served expert reports. Ex. 56. Chang & Delzell, Exponent, Inc., *Meta-Analysis of Glyphosate Use and Risk of Non-Hodgkin Lymphoma*, 1-12 (May 24, 2017). The "new" meta-analysis is based on two documents Monsanto's counsel Eric Lasker gave to Exponent, purportedly containing data from an unpublished AHS manuscript and data from a slide presentation relating to the NAPP study. *Id.* at 1, n.1-2. These documents are "non-peer-reviewed" and the authors admitted they "cannot verify the accuracy of these results[.]" *Id.* at 6. This litigation-driven report, not surprisingly, concludes there is no elevated risk.

Monsanto asks the Court to ignore multiple peer-review studies demonstrating that glyphosate causes NHL and to limit its review to the Agricultural Health Study ("AHS"). At the *Daubert* phase, the only relevant issue is whether Plaintiffs' experts properly considered the AHS in rendering their opinions. Where experts have considered the relevant studies, "Rule 702 [does] not require, or even permit, the district court to choose between the studies at the gatekeeping stage." *Schultz v. Akzo Nobel Paints, LLC*, 721 F.3d 426, 433 (7th Cir. 2013).

Here, there is no dispute that each expert has, in detail, considered the AHS, concluding that its value to the question of causation is limited due to numerous design flaws.[85] In fact, Dr. Ritz, the chairperson of the AHS advisory board, has lectured her students on the limitations of the AHS cohort since 2012, four years before she was retained as an expert. Ritz Dep. at 20:15-24:13 431:1-432. The broad scientific community consensus is that the AHS has serious flaws, limiting its value in assessing the risk of NHL.

1. There Is Broad Consensus that the AHS Is Not Reliable or Informative.

The AHS was a cohort study initiated in 1993 by the National Institute of Health to study the health of licensed restricted use pesticide applicators (RUPAs) and their spouses from North Carolina and Iowa.[86] Its design has been controversial from its inception, and Monsanto has alternatively disparaged or praised the study, depending on how it affects the viability of its products. In November 1999, Dr. Acquavella noted that the AHS could cause "significant concern for industry" and warned of severe "economic consequences of adverse, unopposed epidemiologic findings[.]" Ex. 69.[87] In June 1999, Dr. Farmer stated that "[m]any groups have

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[85] Ritz Rep. at 20-23; Ritz Reb. Rep. at 2-7; Neugut Rep. at 11-13; Portier Rep. at 13-14; Weisenburger Rep. at 5; Nabhan Rep. at 12-13; Jameson Rep. at 17-19; Ritz Dep. at 318:25-334:6, 354:24-395:16, Neugut Dep. at 135:13-148:115, 163:2-172:11.

[86] Exhibit 53, Exponent "Design of Epidemiologic Studies for Human Health Risk Assessment of Pesticide Exposures" Prepared for CropLifeAmerica, 1/24/2016, MONGLY02314040 at pp. 19-23; Ritz Rep. at 22; Neugut Rep. at 12. The data collection entailed an enrollment asks about respondents' pesticide usage from 1993-1997, with health outcome data to be collected through questionnaires or state cancer registries at undetermined points in the future. *Id.* Follow-up questionnaires were planned to update investigators on changes in pesticide use among the cohort. *Id.* Over 250 publications have been generated by the AHS reporting on a wide range of pesticides and endpoints. See https://aghealth.nih.gov/news/publications.html.

[87] November 3, 1999, internal Monsanto memo. MONGLY00894004

been highly critical of the study as being a flawed study, in fact some have gone so far as to call it ***junk science***. It is small in scope and the retrospective questionnaire on pesticide usage and self reported [sic] diagnoses also from the questioneer [sic] is thought to be ***unreliable***." Ex. 70 (emphasis added).[88]

Concerned about how the AHS could adversely affect Monsanto's various products, in 2000, CropLifeAmerica ("CLA"), the pesticide industry group, commissioned scientists from the Harvard School of Public Health and other universities[89] to review the AHS's design study ("The Harvard Study"),[90] Ex. 71. Those scientists identified several serious study flaws, the most notable being that "the low and variable response rates to the supplemental questionnaires could create increased bias potential" and "[n]ondifferential exposure misclassification will produce bias toward the null"[91] Yet Monsanto did not provide this study to its litigation experts, each of whom based opinions on the AHS results. *See* Mucci Dep. 13:12-16:16. Prior to her deposition, Dr. Mucci had not considered the AHS flaws that the Harvard Study identified, raising serious questions about the rigor with which she arrived at her opinions based on the AHS. *Id.* at 17:25-51:9.[92]

Over time, the concerns the Harvard Study raised became a reality. According to a 2016 Exponent report, again commissioned by Monsanto and CLA: "only 44% of enrolled pesticide applicators completed the detailed take-home questionnaire shortly after enrollment, and

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[88] 5/31/1999 email from Donna Farmer. MONGLY00877463

[89] Several of these scientists now consult for Monsanto through Exponent.

[90] Gray, et al. The Federal Government's Agricultural Health Study: A Critical Review with Suggested Improvements Human and Ecological Risk Assessment : Vol. 6, No. 1, pp. 47-71 (2000)

[91] Other flaws identified were: included (1) farmers that apply pesticides frequently and over many years might employ particular experience and care during application that reduces their absorption over farmers who apply them less frequently or have less farming experience; (2) misclassification would reduce the study's ability to detect actual cause-effect relationships and will thus reduce the findng's validity; and (3) the chemicals, formulations and applications used on farms have changed significantly over time, which is important "because if pesticides cause chronic diseases, such as cancer and neurological disease, the biologically meaningful measure of exposure may be a cumulative dose figure that accounts for farming practices years or even decades ago." The Harvard Study at 52, 57-58, 61.

[92] Plaintiffs can find no evidence that this document was provided to the EPA either, which was actively analyzing the AHS study with respect to glyphosate at the time.

participation in follow-up questionnaires was also highly incomplete."[93] Exponent noted even more biases and flaws with the AHS cohort, including:

> [1] ***Crude summary measures of exposure*** . . . [which] substantially limits the potential for results from this study to be used in dose-response assessment . . .
>
> [2] [A]n analysis of bias due to missing data—another form of selection bias . . .
>
> [3] The Agricultural Health Study was restricted to licensed private and commercial pesticide applicators and spouses of private pesticide applicators residing in Iowa and North Carolina at study . . .
>
> [4] In epidemiology, there is no universal 'ideal study design.' . . . [P]rospective study design is often preferred, ***but not for rare outcomes, especially those with a long latency period during which study attrition might be high.***

Id. at 15, 19, 20, 29; *see also* Rider Dep. at 113:10-16; Ritz Rep. at 12-13; Neugut Rep. at. 4-5 (agreeing that NHL is rare with a potentially long latency period).

2. De Roos (2005) is not the most reliable study on Glyphosate and NHL

Only one publication from the AHS addresses the risk of NHL and glyphosate. De Roos (2005) reported a 20% increase in NHL among glyphosate users in its primary analysis. Ex. 72.[94] A 20% increased risk *supports* evidence of causation, even though the OR was not statistically significant—especially in light of so many other significant OR showing the risk. *See* Mucci Dep. at 140:3-143:2 (a non-significant OR of 1.23 can "provide further evidence to support the previously reported association[.]"); Mucci Rep. at 29 ("[S]pecific types of farming were positively associated with NHL risk" with increased risks of 19% and 26%): Rider Dep. at 259:4-260:24 (characterizing an increased non-significant risk of 19% as evidence of "a modest increased incidence of lethal prostate cancer[.]"). Even when an analysis adjusted for other pesticides, the AHS still showed a 10% increase in the risk of NHL. Ex. 72. This elevated risk was apparent despite the analysis being marred by incomplete information, resulting in the

[93]For dates of questionnaires, see https://aghealth.nih.gov/collaboration/questionnaires.html.
[94] De Roos, et al. "Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study" Environ Health Perspect. 2005 Jan; 113(1): 49–54; *see also* Rider Dep. 208:7-10; Ritz Rep. at 22; Neugut Rep. at 12.

exclusion of 13,000 members[95] of the cohort, and effectively reducing the sample to something, as Dr. Farmer called it, "small in scope."

Plaintiffs' experts raise the very issues the Harvard Study and Exponent identified about the AHS, as did EPA's September 2016 Scientific Advisory Panel review of glyphosate:

> The single cohort of the AHS by De Roos et al. (2005), is given a higher weight than case-control studies, without regard to other extremely relevant aspects of the realized study designs... ***for multiple reasons, including the young ages of participants, low cancer incidence rate to date, and selection issues, there are important concerns about the AHS, particularly with the published report*** (De Roos, et al., 2005), that should be taken into account. ***The usual higher ranking of cohort studies vis-à-vis case-control studies is not applicable in this particular review.***

Ex. 10.[96] Drs. Ritz and Neugut agree that the young ages of participants and low cancer incidence rate are problems because of lack of information when following a group of young workers for only 4-8 years. Neugut Rep. at 12; Ritz Rep. at 21.

Another major bias in the AHS study occurs through non-differential misclassification of exposure, as the Harvard Study highlights. In fact, every expert here agrees that non-differential misclassification of exposure in cohort studies will bias results towards the null. Mucci Dep. at 44:11-21; Rider Dep. at 220:17-22; Ritz Rep. at 8; Neugut Rep. at 13. Dr. Blair published a paper in 2011, describing this AHS bias and concluding that "pesticide misclassification may diminish risks estimates to such an extent that no association is obvious, which indicates false negative findings might be common." Ex. 73[97]; Neugut Dep. at 334:25-337:6.

Indeed, the exposure misclassification for glyphosate is exacerbated by changing farming practices as foretold by the Harvard Study. In De Roos (2005), exposure estimates were based solely on the first questionnaires between 1993-1997, yet NHL cases were counted through December 2001. Dr. Mucci agrees that if a cohort member filled out a questionnaire in 1993, but

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[95] *See* Mucci Rpt. at p. 33

[96] FIFRA Scientific Advisory Panel Meeting Minutes and Final Report at 28 (March 16, 2017).

[97] Blair, et al. "Impact of pesticide exposure misclassification on estimates of relative risks in the Agricultural Health Study" Occup Environ Med published online January 21, 2011.

started using glyphosate in 1994, then s/he would be counted as unexposed to glyphosate and is a "valid concern." Mucci Dep. at 278:24-279:20. The SAP affirmed this problem, Ex. 10 at 32; *see* Ritz Rep. at 22; Neugut Rep. at 13,[98] noting another significant bias occurs because the first enrollees were providing data in 1993, two years before the 1995 explosion in Roundup use, while later enrollees provided data two years after the increased use. Ritz Rep. at 22. This time-varying exposure creates different baseline conditions for the cohort members, making any exposure calculations unreliable. *Id.* Based on the above, Monsanto's attempt to rely on the AHS, as published in De Roos (2005), to the exclusion of all other studies, is misplaced. Indeed, Dr. De Roos, the primary author of the only published AHS paper related to glyphosate and NHL, was one of dozens of independent scientists who co-authored a paper supporting IARC's evaluation of the epidemiology relating to glyphosate, agreeing with Dr. Portier and concluding that "[t]he most appropriate and scientifically based evaluation of the cancers reported in humans and laboratory animals as well as supportive mechanistic data is that glyphosate is a probable human carcinogen." Ex. 74.[99]

3. Monsanto's Reliance on an Unpublished AHS Draft Manuscript to Overcome Problems with the Original AHS Study Is Unavailing.

Through discovery of Dr. Blair, Monsanto obtained an incomplete, unpublished, preliminary 96-page draft analysis of the AHS cohort assessing over fifty pesticides (including glyphosate) and their relationship to NHL. This version is not published because "it became clear that it would be impossible to do a thorough evaluation of all major pesticide groupings due to the sheer volume of information that was important to include."[100] The investigators, therefore, decided not to pursue the analysis of the twenty herbicides. *Id.*

In the incomplete manuscript, the AHS researchers attempted to address the problems in

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[98] Before 1996 when genetically modified seeds entered the marketplace, glyphosate accounted for 3.8% of the herbicide's total volume; by 2009, glyphosate accounted for 53.5% of total agricultural herbicide use. Ritz Reb. Rep. at 3.

[99] Portier, et al. 2015 "Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)". Notably, Dr. Alavanja, another author of De Roos (2005), joined the statement.

[100] https://www.reuters.com/investigates/special-report/glyphosate-cancer-data/

the original AHS analysis. They conducted follow-up questionnaires to get more up-to-date exposure assessments from the cohort. Even so, nearly 40% of the cohort did not respond; thus, only about 60% of the exposure data was updated. To fix this problem, the researchers then imputed data from the people who did respond to the non-responders. This is improper:

> While under some, limited circumstances it is an acceptable epidemiological approach to impute or 'guestimate' certain unavailable data, one must be extremely careful when imputing/guestimating a critical piece of data, such as exposure . . . The validity of the results of such an imputation/guestimation become extremely questionable because when applied, the study authors need to assume glyphosate/GBF use was based on historical use, and do not apply the increased use for any person who did not report their pesticide use, i.e. the non-responders.

Ritz Reb. Rep. at 4.[101] Indeed, the increased Roundup use also diminishes power in the AHS study because it further decreases the control group. As of 1998, 76% of the cohort used glyphosate. De Roos (2005). As glyphosate use has increased exponentially, there will likewise be an increase in the percent of the cohort using glyphosate. Ritz Reb. Rep. at 6. These significant errors in the draft manuscript highlight the pitfalls of relying on unpublished material. The AHS investigators did eventually publish the insecticide and fungicide portion of the manuscript, Alavanja (2014). Ex. 76.[102] However, on February 27, 2014, the International Journal of Cancer rejected the article. Ex. 77[103] The disappointed authors noted that "[i]t has been a very long struggle to get the manuscript into its current form." *Id.* The article was then submitted to PlosOne, where it was reviewed by only one peer–reviewer. On June 11, 2014, the journal stated that the manuscript was "not suitable for publication as it currently stands" and required major revisions. Ex. 75.[104] These rejections came after a year of revising and

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[101] When the authors were asked to clarify the number of individuals for which data was imputed, the authors responded that: "Imputation was performed on ***all*** 20,968 applicators..." (emphasis added). See Ex. 75 at 10. 6/21/2014 email re: Plos one decision: revise.

[102] Alavanja, "Non-Hodgkin Lymphoma Risk and Insecticide, Fungicide and Fumigant Use in the Agricultural Health Study". PLoS ONE 9(10): e109332 (2014)

[103] Ex. 77, 2/27/2014 email amongst AHS investigators

[104] 6/21/2014 email re: Plos one decision: revise.

reformulating the data, the draft manuscript relied upon by Monsanto was nowhere near to being ready for publication. The discrepancies, including different counts for NHL, between the published and draft study are highlighted by Dr. Ritz. Ritz Reb. Rep. at 5-6.

Two key questions for the Court under *Daubert* include "whether a theory or technique ... can be (and has been) tested" and "whether the theory or technique has been subjected to peer review and publication." *Daubert*, 509 U.S. at 593-594 (1993). While not dispositive, "submission to the scrutiny of the scientific community is a component of 'good science,' in part because it increases the likelihood that substantive flaws in methodology will be detected." *Id.* Furthermore, draft studies considered solely for the expediency of litigation are particularly unreliable and demand exclusion. *In re Rezulin* F. Supp. 2d at 562 (excluding a preliminary draft report where "reliance on the unpublished [] report was not based on scientific method but on the expediencies of this particular litigation."). While flaws can be exposed on cross-examination, cross-examination "does not act as a substitute for peer review." *Wagner v. Hesston Corp.*, No. CIV.03-4244(JNE/JGL), 2005 WL 1540135, at *5 (D. Minn. June 30, 2005 *aff'd*, 450 F.3d 756 (8th Cir. 2006).

The unpublished draft manuscript also fails the testability factor. The Harvard study predicted AHS's unreliability if there was too much missing data on follow-up questionnaires, and Exponent confirmed in 2016 that the follow-up questionnaires were "highly incomplete." *See supra.*[105] The AHS investigators attempts to fill in these gaps by guessing glyphosate usage based on an admittedly ***"untestable assumption***." Ex. 78.[106] (emphasis added)

In addition to the draft not being peer-reviewed, Dr. Blair, one of the authors, warned Monsanto that it should not use the data from the manuscript: "Now you [Erik Lasker] present it as if the analyses were completed. Analyses were done, manuscripts were in description, but the work wasn't finished, which means it's incomplete, and that you don't want to be reporting on.

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[106] Heltshe, et al. "Using multiple imputation to assign pesticide use for nonresponders in the follow-up questionnaire in the Agricultural Health Study." J Expo Sci Environ Epidemiol. 2012 July ; 22(4): 409–416.

And we didn't." Blair Dep. at 206:25-207:4.[107] Dr. Blair further explained it would be irresponsible "to rush something out that's not fully analyzed or thought out...That's irresponsible."[108] *Id.*. at 204:15-20. Relying on this data against the express wish of the authors also violates scientific norms. For example, the ICJME guidelines state: "Information from manuscripts submitted but not accepted should be cited in the text as 'unpublished observations' with written permission from the source." And, Dr. Weisenburger notes that publicizing draft manuscripts is not "ethical or correct or academically correct… [I]t's not academic practice to make preliminary publications available for public use." Weisenburger Dep. at 259:7-17. Even Dr. Rider acknowledged "the polite thing to do in the scientific community would be to ask the author if they're okay with you citing their work in their paper, given that it's unpublished." Rider Dep. 245:23-246:8. The Court should exclude it from evidence and reject Monsanto's attempt to create science.

It is particularly notable that Dr. Blair, a lead investigator of the AHS study and an author on both AHS manuscripts agrees with Plaintiffs that glyphosate is a probable human carcinogen. Dr. Blair testified that the AHS is not the most powerful study and there is a problem with lack of follow-up in the AHS study. Blair Dep. at 69:21-70:4, 271:14-272:19, 286:1-9. Dr. Blair agreed that the case-control studies showed statistically significant risks. *Id.* at 53:4-66:8. In assessing glyphosate, Dr. Blair weighed the totality of evidence from the numerous positive case-control studies and the negative AHS study and concluded that there was an association between

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[107] Although Drs. Mucci and Rider had access to Dr. Blair's deposition, they were unaware of Dr. Blair's warning that the data was incomplete—a remarkable concession considering their heavy reliance on the document. Rider Dep. at 135:8-12; Mucci Dep. at 170:1-10. The litigation-driven nature of Dr. Mucci and Dr. Rider's use of this draft manuscript is highlighted by their complete denial of its flaws. Dr. Mucci found that the "[o]ne minor weakness is that the updated analysis on glyphosate and other herbicides has not been published to date." Mucci Rep. at 35. Dr. Rider does not acknowledge any weaknesses to the draft manuscript. Ex. 116 – Expert Report of Dr. Jennifer Rider, at 28-29. Their lack of critical analysis of the draft manuscript is fatal to their opinions considering its many flaws. Like the expert in *In re Rezulin Prod. Liab. Litig.*, Drs. Rider and Mucci failed to investigate whether the draft manuscript was a preliminary versus final analysis, relied upon it despite conflicting data in peer-reviewed literature, and used it solely for litigation purposes. 309 F. Supp. 2d 531, 562–63 (S.D.N.Y. 2004). Reliance on the AHS draft manuscript should be excluded.

[108] *Allgood v. Gen. Motors Corp.*, No. 102CV1077DFHTAB, 2006 WL 2669337, at *8 (S.D. Ind. Sept. 18, 2006) (excluding opinion based on draft EPA document); *In re Trasylol Prod. Liab. Litig.*-MDL-1928, No. 1:08-MD-01928, 2010 WL 4053756, at *4 (S.D. Fla. May 17, 2010) (excluding opinion based on unpublished draft obtained in litigation).

glyphosate and NHL. *Id*. at 70:10-15, 365:7-25. After three hours and forty minutes of cross-examination, including questions about the unpublished manuscript, Monsanto was unable to change Dr. Blair's opinion that glyphosate is a probable human carcinogen. *Id*. at 293:6-15.

F. Case-Controlled Studies Were Properly Considered by Plaintiffs' Experts: the Data Shows Risk

1. The Methodologically Sound Approach for Using Statistics To Understand Epidemiological Point Estimates

It is methodologically sound to consider non-statistically-significant data, and arguably ignoring such results would, itself, be improper. It is well-settled that "[a] lack of statistically significant data does not mean that medical experts have no reliable basis for inferring a causal link between a drug and adverse events. . . . courts frequently permit expert testimony on causation based on evidence other than statistical significance[.]" *Matrixx Initiatives, Inc. v. Siracusano*, 563 U.S. 27, 40, 41 (2011). And here, where there are numerous instances of statistically significant elevated ORs, and considering that nearly every other study shows an elevated risk, even if not statistically significant, it is appropriate: "For research studies that aim to measure associations, and infer whether they reflect ***causal connections***, focusing on the ***magnitude*** of these associations ought to be the primary goal: ***estimation of effects*** is decidedly preferable to statistical testing." Ex. 79.[109] Yet Monsanto criticizes Plaintiffs' experts for relying on case control studies that show an elevated OR for GBF exposure but fail to achieve statistical significance. MSJ at18. The notion that "statistical significance…[is] key to any epidemiological analysis", MSJ at 10, ignores a key dictate of epidemiology and general causation: that the

[109] Rothman, K.J., *Six Persistent Research Conceptions*, 29 J. Gen. Intern. Med 7, 1060-64, 1063(2014) (emphasis added). "Significance testing has led to far more misunderstanding and misinterpretation than clarity in interpreting study results." *Id.; see* Ritz Dep. at 87:22-89:13. Defendant takes Dr. Neugut's testimony out of context; he stated in his deposition and report that statistical significance is not required. Neugut Dep. at 42:5-8, 323:7-9, 310:23-311:1 ("in modern epidemiology, statistical significance isn't considered essential."). Monsanto experts Drs. Rider and Mucci also agree that statistical significance is not necessary. Rider Dep. 262:2-15; Mucci Dep. at 143:3-23.

accuracy of point estimates as parameters of association must be evaluated with the overall data in the context of the study design, the biases, the size of the study, the effect we are trying to estimate, [and] the effect size." Ritz Dep. at 88:22-25; *see Milward*, 639 F.3d at 11 (an expert may rely upon a method according to which "each body of evidence [is] treated as grounds for the subsidiary conclusion that it would, if combined with other evidence, support a causal inference."). Plaintiffs' experts weighed the non-statistically significant data according to standard practices in epidemiology.

Finally, NHL is not just a number, it is a disease that affects real people. Even though an risk might not reach the arbitrary statistical significance level, the study still matters to clinicians treating patients and making decisions affecting their health. Ex. 80 – Deposition Transcript and Exhibits of Dr. Chadi Nabhan, at 55:10-24.

2. Monsanto's Concerns Regarding Confounding Are Not Supported by the Data, Are Methodologically Unsound, and Are Precluded by Estoppel

As a threshold matter, Monsanto has either waived or should be estopped from asserting that confounders are relevant at this stage. Plaintiffs sought discovery about the chemicals that Monsanto considers confounders for NHL through Requests to Admit. Monsanto objected to the requests as irrelevant to general causation. *See* Ex. 81 at 14 (responses to requests 34-102). Now, after opposing discovery into the carcinogenicity of other herbicides, Monsanto argues the carcinogenicity of other herbicides is not only relevant but is rather critical to the causation analysis. Monsanto should be estopped from raising this defense.[110]

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[110] *See, e.g., Hamilton v. State Farm Fire & Cas. Co.*, 270 F.3d 778, 783 (9th Cir. 2001) (judicial estoppel is a flexible inquiry that precludes a party from gaining an advantage by asserting one position and then later, when expedient, a clearly inconsistent position); *Wagner v. Prof. Engineers in California Govt.*, 354 F.3d 1036, 1044 (9th Cir. 2004) (estoppel applies "to a party's stated position whether it is an expression of intention, a statement of fact, or a legal assertion"), or, alternatively, it should be deemed to have waived the argument for general causation. Monsanto's strategy highlighting confounders to obfuscate inquiry has been used before. The tobacco companies, for example, used "confounders" to deny a cancer risk. As the Reference Manual notes "[o]ften the mere ***possibility*** of uncontrolled confounding is used to call into question the results of a study. This was certainly the strategy of those ***seeking, or unwittingly helping***, to undermine the implications of the studies ***persuasively*** linking cigarette smoking to lung cancer." Reference Manual at 593 (emphasis added).

Further, Monsanto's analysis glosses over the distinction between an *actual* and a *potential* confounder. For any adjustment to be meaningful, one has to demonstrate that "[the other pesticides] are actually related to glyphosate use and also are independent risk factor for NHL…[c]onfounding is an independent risk factor for the outcome that also has an association with the exposure and is not an intermediate in the pathway to disease." Ritz Dep. at 285:10-22, 143:3-7; Reference Manual (2nd E.D.) at 389 ("confounding factor…a factor that is both a risk factor for the disease and a factor associated with the exposure of interest."). Monsanto is adamant that exposure to ***every*** pesticide is an automatic confounder without providing evidence of how any specific pesticide causes or potentiates NHL. *See, e.g.*, *Deutsch v. Novartis Pharm. Corp*., 768 F. Supp. 2d 420, 432 (E.D.N.Y. 2011) ("[F]ailure to control for an unknown confounding factor does not necessarily render the results unreliable. . . .) "Often the mere ***possibility*** of uncontrolled confounding is used to call into question the results of a study. This was certainly the strategy of those ***seeking, or unwittingly helping***, to undermine the implications of the studies ***persuasively*** linking cigarette smoking to lung cancer." Reference Manual at 593 (emphasis added). The Court should reject Monsanto's effort to use the tobacco company strategy here to divert attention from methodologically sound epidemiological studies.

Finally, it is worth mentioning that the McDuffie, Hardell, De Roos (2003), and Eriksson studies considered multiple pesticides; however, the only consistent positive association with NHL occurred with exposure to glyphosate. In addition, the De Roos (2003) authors, after adjusting for a large number of other pesticides, concluded that "[a]djustment for multiple pesticides suggested that there were few instances of substantial confounding of pesticide effects by other pesticides." De Roos, at 7; *see also* Rider Dep. at 89:18-21 (agreeing that the authors did not find much confounding by other pesticides); Blair Dep. 88:20-22 (agreeing that confounding is a problem that rarely occurs.). The meta-analyses include four out of six studies that adjust for pesticides and it still shows a significant increased risk.

3. Plaintiffs' Experts Considered Bias

Monsanto accuses Plaintiffs' experts of "fail[ing] to account for recall bias, which artificially increases the odds ratios in case-control studies where, as would be expected, people who have cancer recall more exposures than people who do not have cancer and have not been thinking about their prior exposures." MSJ at 18. Initially, it is not always the case that recall bias inflates odds ratios. "If the subject has no way to know which pesticide might have caused a cancer . . . and is asked to report all chemicals they have ever used occupationally, it is unlikely that they would only recall one and not another chemical differentially." Ritz Rep. at 7.[111] The direction of an odds ratio potentially affected by bias—either towards or away from the null—depends upon whether a case recalls more or less exposure than what actually occurred compared to a control subject. Blair Dep. at 95:14-22.[112] Moreover, the data speaks for itself. De Roos (2003), which adjusted for exposure to more than forty (40) pesticides and still found a statistically significant elevated risk, noted the "fact that there were few associations suggests that the ***positive results*** we observed are ***not likely to be due to a systematic recall bias*** for pesticide exposures, or selection bias for the subgroup included in the analyses of multiple pesticides." Ex. 55 at 8 (emphasis added).

In fact, Plaintiffs' experts accounted for bias in reaching their opinions but Monsanto misinterprets the data. For example, Monsanto argues that Eriksson (2008) suffers from systematic bias because, *according to Monsanto*, the study reported elevated odds ratios for all evaluated pesticides. MSJ at 16.[113] However, such an interpretation of bias, as Dr. Ritz indicated,

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[111] Moreover, "[e]ven the best designed and conducted studies have biases, which may be subtle…" Reference Manual at 573.

[112] *See also* Ex. 82. Vrijheid, M., et al., *The Effects of Recall Errors and of Selection Bias in Epidemiologic Studies of Mobile Phone Use and Cancer Risk*, 16 J. of Exposure Sci. & Environ. Epid. 4, 371-384, 372 (2006) ("Differential recall errors in cases and controls may also lead to bias, the direction of which depends on the direction of the differences between cases and controls.").

[113] Monsanto selectively uses Dr. Neugut's testimony on systemic bias. Dr. Neugut testified that the increased risk of NHL with glyphosate in Eriksson (2008) is a "pretty high risk" and higher than "I might expect purely from biases alone." Neugut Dep. at 288:11-22. Dr. Neugut also states that "it is expected that any residual confounding [in Eriksson] would result in an underestimation of the effect of a single pesticide. Given that the results demonstrated increased risk suggests there being a causal relationship despite confounding." Neugut Rep. at 16.

is simplistic and an inaccurate way of analyzing the data.[114] More importantly, the potential presence of bias does not outweigh the significance of the positive associations across studies for the purposes of general causation. *See In re Actos (Pioglitazone) Prod. Liab. Litig.*, No. 12-CV-00064, 2014 WL 60324, at *18 (W.D. La. Jan. 7, 2014) (rejecting the defendants' motion to exclude plaintiffs' expert for relying on an IARC classification that did not rule out bias and confounding and holding that IARC's "limited" language in the context of a 2A determination nevertheless contained "statements, opinions, conclusions, and caveats that are ***definite***."). In sum, Plaintiffs' experts accounted for bias and remain confident in the causal association between GBF and NHL when considering the totality of the available data.[115]

VI. Monsanto's Attempt to Inject Issues Related to Dose and Absorption Is Based on a Misunderstanding and Misrepresentation of the Data

As a preliminary matter, dose is not a proper inquiry at the general causation stage for chemicals, including pesticides. *See In re Hanford Nuclear Reservation Litig.*, 292 F.3d 1124, 1139 (9th Cir. 2002). The limited circumstance in which dose might apply a role in a general causation inquiry is in the context of a pharmaceutical product in which plaintiff alleges injuries at a particular dose for which clinical trials and meta-analysis of clinical trials, which of course do not exist for chemicals, show ***no*** association between product at that dose and alleged disease. *See, e.g., In re Bextra*, 524 F. Supp. 2d at 1175-76, 1180-81 (at general causation stage, court excluded expert testimony of causation for plaintiffs who alleged that taking 200 milligrams a day of Celebrex caused their disease because none of plaintiffs' experts challenged clinical trial findings of no association at that dosage). Nevertheless, Monsanto argues that Plaintiffs' experts

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[114] [I]n this study… a lot of odds ratios… around or even below 1 [are] reported, and many of the odds ratios are duplicate analyses in terms of a dose response….and in many cases you can see that the specificity increases." Ritz Dep. at 311:9-23. Contrary to Monsanto's contention that all of the odds ratios in Eriksson (2008) were above 1, the confidence intervals for exposure to other pesticides included 1 for "very small subgroups with very low exposures. So essentially ***a lot of these estimates are non-informative***." Ritz Dep. at 312:13-19 (emphasis added).

[115] *See, e.g.*, Weisenburger Dep. at 69:25-70:6, 72:2 ("I think that the epidemiologic studies are well-constructed, they're well-done and they took every precaution to, as best they can, eliminate bias… no one would just look at one piece of the information to come to a conclusion.").

should be struck because they fail to consider human exposure. Its argument "ignores the fact that cancer epidemiology, [is] based on real world exposures associated with cancer risks in humans." Ex. 83.[116] Moreover, Monsanto's own scientists do not understand GBFs' bio-availability including its absorption by the human system and subsequent excretion. Ex. 84.[117] Monsanto's ignorance is compounded by its refusal to study the issue, electing instead to ignore significant results and terminate absorption studies that do not comport with product objectives. For example, two Monsanto-sponsored in-vivo dermal absorption studies in the 1980s observed that significant amounts of dermally-applied glyphosate were not recovered in excretions or otherwise accounted for. Ex. 85[118] Such results disprove Monsanto's assertion that "very little of the chemical is absorbed and circulated in the system." MSJ at 5. When Monsanto employee, Richard Garnett, and his colleagues urged others at Monsanto to further explore the issues arising from dermal absorption of glyphosate, their suggestions were rejected due to fears that further research "would be too risky (potential for finding another mammalian metabolite)." Ex. 87.[119]

Monsanto also relies on the EPA OPP's conclusion that "'glyphosate's oral, inhalation, and dermal exposure profile 'suggests that there is low potential for a sustainable biological dose following glyphosate exposure.'" MSJ at 8 (quoting EPA OPP). However, this analysis ignores

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[116] Briefing for Governing Council Members on IARC evaluation of glyphosate.

[117] The science of human exposure is referred to as Absorption, Distribution, Metabolism and Excretion ("ADME"). Monsanto's own Richard Garnett explained that "***ADME has always been the weak link*** in our argument... we have not got rid of the problem.", Sept. 23, 2009 email between Richard Garnett, Gustin Christophe, and David Saltmiras, at *1 (MONGLY06385823).

[118] H.I. Maibach, Study No. MA-81-349, at *3, 11 (MONGLY02142251). ("Swabbing the application site with water and acetone after 24 hours removed 14.2% of the applied dose." The authors did not examine feces to determine the fate of ***the unaccounted 84% of the applied dose***, but instead conjectured that "[a]lthough a definitive explanation can not be offered for the low recovery, previous experience suggests that much of the test material may in some way bind to or in the skin and can not be removed by washing."); *see also* Ex. 86, R.C. Wester et al., *Glyphosate Skin Binding Absorption, Residual Tissue Distribution and Skin Decontamination*, 16 Fundamental and Application Toxicology 725, at 728-730 (MONGLY02431080) (only 2.2% of the more concentrated – undiluted – dose was recovered in urine, , and ***approximately 23% of the dose was unaccounted for***).

[119] Nov. 12, 2008 email from Christophe Gustin regarding Wester study (MONGLY02155826).

that everyday users of Roundup are never exposed to just glyphosate but the cocktail of other ingredients in the formulated product, such as surfactants.[120] Indeed, Monsanto's internal studies have observed that "[s]urfactants are able to increase glyphosate absorption through the skin," but Monsanto has failed to report the results to the EPA. Ex. 88[121]; Ex. 90.[122] This is a vital distinction because, in the real world, *i.e.,* in the context of epidemiological studies, people apply Roundup, not just glyphosate; thus, absorption is, at least according to the unreported Monsanto study, nearly 10 times greater. *Id.*

Additionally, the "Family Farm Exposure" study Monsanto relies on involved the use of "doctored" data, as noted by Monsanto's consultant Dr. Acquavella, an on-site investigator for the study, rendering the results unreliable. Ex. 91.[123] Compounding the data's unreliability, glyphosate is not primarily excreted through urine. Richard Garnett, in a 2008 email, states that for pesticide applicators, "[t]he little data we have suggests that the excretion is significantly more through the faeces than the urine." Ex. 87.[124]

Further, Monsanto's assertion that "[p]laintiffs' allegations are based only on dermal exposure" is untrue and predicated upon comments taken out of context. MSJ at 5. In fact, during

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[120] The Roundup formulation includes adjuvants and surfactants, such as Polyethoxylated tallow amine (POEA), which was banned in the European Union in 2016. *See* Sarantis Michalopoulos, *EU agrees ban on glyphosate co-formulant*, EURACTIV, July 11, 2016, https://www.euractiv.com/section/agriculture-food/news/eu-agrees-ban-on-glyphosate-co-formulant/.

[121] Ex. 88, MONGLY00888353, TNO Report 4478; Ex. 89, July 2001 memo re: Clustering glyphosate formulations with regard to the testing for dermal uptake. MONGLY01839476.

[122] Apr. 5, 2002 email from Richard Garnett re TNO Dermal Penetration Studies at *1-3 (MONGLY03737014) ("in vitro dermal penetration of glyphosate [with surfactant] through rat skin is between 5 and 10%," but was lower than 1.5% "in the absence of surfactants."); TNO Nutrition and Food Research Study Report for results of increased penetration with the addition of surfactants. Ex. 88. Monsanto subsequently stopped the program testing formulations given the increased rate of absorption associated with surfactants and because the results did not aid Monsanto's "regulatory angle." Ex. 90

[123] July 5 2000 Memo re Site Visit to Minnesota field site, at *7-8 (MONGLY07080361). Dr. Acquavella recorded other issues with the study: "Many of the urines were very spotty and we found one day's urine that was obviously ***doctored***…the field team is not reviewing the urines carefully and there is little, if any, coaching of the farm families . . . . There were some obvious errors or missing entries in the questionnaires."). *Id*. (emphasis added).

[124] Nov. 10, 2008 email from Richard Garnett (MONGLY02155826).

the February 24, 2017 court hearing, in response to the Court's inquiry about Plaintiffs' justification for taking the deposition of Richard Garnett, Plaintiffs' counsel explained that the request, in part, was based on statements Garnett had made in emails regarding dermal exposure to glyphosate,[125] which is only *one* of several exposure pathways alleged by Plaintiffs. Ex. 92 at 9-12.[126] At *no time* did Plaintiffs represent an intention to limit their theory of the case to dermal exposure. Monsanto's attempt to take this quote out of context is disingenuous.

Additionally, the EPA reference dose of 2 mg/kg/day has nothing to do with carcinogenicity but rather is based on a developmental endpoint in a rabbit study. As Monsanto noted, "For 12 years, US EPA has based its 2 mg/kg/day US ADI on a conclusion that the 175 mg/kg/day represents both a maternal and developmental NOAEL in this study." Ex. 93.[127] The 2 mg/kg/day number is wrong. As Monsanto's Steven Wratten acknowledged, an ADI of 2 mg/kg/day is too high but Monsanto must support it because "[t]he US is the biggest glyphosate market in the world, and all 3 companies involved enjoy sales that are supported by this position." *Id.* In any event, Defendant's expert, Dr. Foster, concedes that pesticide applicators can be exposed to a systematic dose greater than 2 mg/kg/day. *See* Foster Rep. at 3.

VII. The Toxicology Data is Reliable and Relevant.

Toxicology supports Plaintiffs' experts' opinions that glyphosate and GBFs cause cancer in humans. "[E]pidemiological findings of an adverse effect in humans represent a failure of toxicology as a preventive science or of regulatory authorities or other responsible parties in controlling exposure to a hazardous chemical or physical agent. ... The two disciplines complement each other, particularly when the approaches are iterative." Reference Manual at

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[125] Mr. Garnett's comments regarding dermal exposure made his testimony pertinent to Monsanto's defense that "exposure…will not reach a high enough level to cause cancer…" Ex. 92. Hearing Transcript, February 24, 2017, at 11.

[126] Hearing Transcript, February 24, 2017, at 9-12. In addition, at least three complaints allege exposure pathways "as air (especially during spraying), water, and food. Community exposure to glyphosate is widespread and found in soil, air, surface water, and groundwater, as well as in food." *See McCall v.* Monsanto, 2:16-cv-01609 (C.D. Cal.) ¶ 50; *Means v. Monsanto*, 5:16-cv-112 (W.D. Ky.) ¶ 64; *Morris v. Monsanto*, 16-cv-61992 (S.D. Fla) ¶ 64.

[127] June 13, 2003 email from Stephen J. Wratten, at 3 (MONGLY00896493).

660. Here, the animal studies show an increased risk of multiple tumors in multiple species, including replicated findings of malignant lymphomas in mice**.** These findings strongly support causation in conjunction with the findings of NHL in human epidemiological studies and the findings of genotoxicity in human lymphocytes.

Monsanto argues that, because of the existence of human epidemiology, Plaintiffs' experts' review of animal carcinogenicity data in reaching their causation opinion is improper. Its position contradicts established law and common sense. *See U.S. v. W.R. Grace*, 504 F.3d 745, 765 (9th Cir. 2007) ("[T]he expert's opinion testimony must satisfy the requirements of Rule 702—but that requires consideration of the *overall* sufficiency of the underlying facts and data, and the reliability of the methods, as well as the fit of the methods to the facts of the case.") (emphasis original); *Metabolife Int'l, Inc. v. Wornick*, 264 F.3d 832, 842 (9th Cir. 2001) ("The district court erred in rejecting the animal studies proffered by Metabolife merely because of the species gap.").[128]

A. Highly Qualified Experts Reviewed the Animal Data

Plaintiffs asked two highly qualified experts, Dr. Christopher Portier and Dr. Charles Jameson, to further evaluate glyphosate data, including the chronic toxicity animal bioassays.[129] Both of these experts opinions on GBFs were formed and peer reviewed prior to this litigation. Dr. Portier's resume includes 30-plus years leading federal agencies overseeing various fields of toxicology, of developing, conducting, and analyzing long-term rodent bioassays designed to screen for toxicity and carcinogenicity, as well as developing and applying statistical models

[128] Monsanto "quotes" to *Chapman v. Proctor & Gamble Distrib*., LLC, 766 F.3d 1296, 1308 (11th Cir. 2014), as support for its argument that Drs. Portier's and Jameson's expert opinions are improper is not only a misleading selection from a much longer sentence, but the issue presented in *Chapman* included the fact that the plaintiffs there, on the whole, failed to submit requisite epidemiological or clinical reports. That is not the case for either Drs. Portier or Jameson. *See* Ex. 94 – Revised Expert Report of Dr. Christopher Portier at 6-17; Jameson Rep. 12-19.

[129] Dr. Portier served as an invited specialist of Monograph 112, which reviewed glyphosate. Ex. 95 – Deposition Transcript and Exhibits of Dr. Christopher Portier, at 36:4-11. Dr. Jameson also participated in Monograph 112, and was the chair of the animal carcinogenicity subgroup.

known to withstand peer review that are used by toxicologists globally. Dr. Jameson's expertise is derived from nearly 30 years with the NTP and NIEHS, where he offered scientific and technical expertise in the gathering and evaluating and carcinogenicity data. As Judge Kozinski stated in *Daubert II*, "[t]hat an expert testifies based on research he has conducted independent of the litigation provides important, objective proof that the research comports with the dictates of good science." 43 F.3d at 1317. Dr. Portier's expert opinion and testimony are the product of his independent review of the literature, technical reports, study data, and regulatory documents. Prior to his retention in this litigation, Dr. Jameson served on the IARC 112 working group as the subgroup chair that evaluated the publicly available animal carcinogenicity data for glyphosate, finding sufficient evidence of carcinogenicity in animals. That neither Dr. Jameson nor Dr. Portier's opinion was developed for this litigation, "provides important, objective proof that the research comports with the dictates of good science." *Murray v. S. Route Mar.*, 870 F.3d 915, 923 (9th Cir. 2017).

After the review of even more data subsequent to their work at IARC, both experts came to the conclusions that glyphosate was carcinogenic in rodents. Dr. Portier states:

> Glyphosate has been demonstrated to cause cancer in two strains of rats and one strain of mice. Glyphosate causes hepatocellular adenomas in male Wistar rats and male Sprague-Dawley rats, mammary gland adenomas and adenocarcinomas in female Wistar rats and kidney adenomas in male Sprague-Dawley rats. Glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice and hemangiosarcomas in female CD-1 mice and possibly causes malignant lymphomas in male Swiss albino mice. Thus, glyphosate causes cancer in mammals.

Portier Rep. at 51. And he confirms in his rebuttal to Defendants' expert reports, that

> It is still my opinion that glyphosate probably causes NHL based on the human, animal and experimental evidence and that, to a reasonable decree of scientific certainty, the probability that glyphosate causes NHL is high.

Ex. 96 – Rebuttal Expert Report of Dr. Christopher Portier at 24. Dr. Jameson states:

> I determined that in CD-1 mice, glyphosate exposure causes kidney tumors in males ***in two separate studies***, hemangiosarcomas in males ***in two separate studies***, malignant lymphoma in males ***in two separate studies***, adenocarcinomas of the lung in males in one study, and hemangiosarcomas in females in one study. In one study in Swiss albino mice, exposure to glyphosate causes malignant lymphoma ***in males and females*** and kidney tumors in males [and] that in Sprage-Dawley rats, glyphosate exposure causes pancreatic

> cell tumors in males in one study, interstitial cell tumors in the testes in males in one study, hepatocellular adenomas in males in two studies and thyroid follicular cell tumors in females in one study.

Jameson Rep. at 29. (emphasis added).

These opinions are consistent with the opinions of some members of the SAP panel who found that "there are sufficient data to conclude glyphosate is a rodent carcinogen using the approaches recommended to interpret the biological significance of tumor responses in EPA's 2005 Guidelines for Carcinogen Risk Assessment." SAP Final Report at 18. Accordingly, Plaintiffs' expert opinions enjoy acceptance within the relevant scientific field.

B. The Animal Bioassays Demonstrate that it is Biologically Plausible that Roundup Causes Cancer in Humans

Drs. Portier and Jameson also explain why cancer findings in animals are relevant to humans. The appropriate first step in answering whether a chemical can cause cancer is to test the chemical on rodents; [130] as it is unethical to perform human experimentation for chemicals. Rodent studies are the only available method to *test* the carcinogenicity of a chemical in a clinically controlled manner. Thus, data from animal studies are an important piece of the overall weight of the evidence to be considered in understanding carcinogenicity in humans.[131] This clinically controlled model adds strength to the conclusion that the increased risk of NHL in epidemiological studies is not the result of confounding. *See* Reference Manual at 640.

Dr. Portier states that "animal carcinogenicity studies . . . play a role in establishing biological plausibility" as part of the Bradford-Hill criteria. Portier Rep. at 5. "[T]he toxic responses in laboratory animals are useful predictors of toxic responses in humans."[132]

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[130] *See generally* US EPA Guidelines for Carcinogenicity Risk Assessment (2005). http://epa.gov/iris/cancero32505.pdf.

[131] Monsanto tries to re-frame the central question by isolating the animal studies and asking the court to determine whether the animal bioassays, standing alone, can support reliable expert testimony that GBF exposure causes NHL in humans. However, the Court need not answer that question because, here, the animal studies are not standing alone and Plaintiffs are not offering them to prove stand-alone causation.

[132] REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (THIRD) 636-37 (2011).

Monsanto's expert agrees that animal tumors are predictive of human carcinogenicity, highlighting the general acceptance of using animal bioassays as a predictive tool for human carcinogenicity. Ex. 97 – Deposition Transcript and Exhibits of Dr. Thomas Rosol, at 170:17-22 ("compound-mediated effects constitute 'one step' towards inferring causation").

Animal carcinogenicity studies are performed at multiple doses, including high doses. This design is borne out of necessity: the number of animals in each treatment group in a rodent carcinogenicity study is limited; regulatory agencies typically set it at 50. *Id*. "Doses generally above human experience are used in animal carcinogenicity studies because only relatively small numbers of animals are being used to evaluate risk for a large human population [and] [b]y exposing animals to the highest dose possible, you increase the ability of the study to identify a risk if one is present." Portier Rev. Rep. at 20. [133] Thus, doses used in animal carcinogenicity studies are set sufficiently high to observe likely effects caused by the chemical.

Moreover, with animal carcinogenicity studies, "it matters little what the eventual cancer target site may be; the important observation is whether a chemical *does or does not* cause cancer."[134] Ex. 99. As Dr. Jameson explained, glyphosate animal studies were, "designed to see if glyphosate would cause cancer in the experimental animals." Jameson Dep. 291:23-24; *see also id*., 28:10-115 ("[an animal bioassay is] not -- not looking to investigate does it form a specific kind of tumor that is the same as found in humans."). Thus, the ultimate significance of these bioassays is that they reveal that, "glyphosate *causes cancer* in mammals," and thus support the conclusion that glyphosate *can cause* cancer in humans.[135] Portier Rep. at 52

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[133] *See also* Ex. 98 – Deposition Transcript and Exhibits of Dr. Charles Jameson, at 216:9-217:15; REFERENCE MANUAL ON SCIENTIFIC EVIDENCE (THIRD) 645 (2011) ("proffered toxicological expert opinion on potentially cancer-causing chemicals almost always is based on a review of research studies that extrapolate from animal experiments *involving doses significantly higher than that to which humans are exposed*. Such extrapolation is accepted in the regulatory arena.") (emphasis added).

[134] R. Maronpot, et al. *Relevance of animal carcinogenesis findings to human cancer predictions and prevention* 32 TOXICOL PATHOL 40-8 at 41-2 (2004) (emphasis added).

[135] Monsanto mischaracterizes Dr. Portier's testimony that "rodent models 'are not developed for the purpose of identifying tumors that arise in humans from exposure to chemicals,'" MSJ at 22-23 (quoting Portier Dep. 163:7-23), yet fails to inform the Court that Dr. Portier's statement was in response to a question by Monsanto's counsel relating to a transgenic mouse model developed

(emphasis added).

Monsanto's challenge to Plaintiffs' experts' reliance on animal carcinogenicity bioassays, merely because they show animal tumors other than lymphoma, is not only meritless, but also factually wrong: Drs. Portier and Jameson report that a significant increase in malignant lymphoma was seen in three mouse studies. Portier Rev. Rep. at 40-44; Jameson Rep. at 23-24. Peer-reviewed, scientific literature consistently accepts that B-cell lymphomas found in mice exhibit similar pathological features to those in humans, such that they "exhibit enough parallels to suggest they represent the same disease but in a different species."[136] The publications support the coherence criteria of Bradford-Hill because of "the increased risk of malignant lymphomas in CD-1 mice, the marginal increase in these tumors in Swiss mice and the strong similarity between malignant lymphomas in mice and NHL in humans.[137]" Portier Rep. at 74, 97.

Drs. Portier's and Jameson's opinions meet *Daubert's* "fit" requirement. The fit requirement addresses the relevance of expert testimony:[138] To satisfy the *Daubert*'s "fit" requirement, a court must determine that the testimony is, "'relevant to the task at hand,' [and] that it *logically advances a material aspect* of the proposing party's case." *Daubert II*, 43 F.3d at 1315 (quoting *Daubert*, 509 U.S. at 591) (emphasis added). Here, the cancers (including lymphoma) seen in the animal bioassays make enhances causation.[139] The animal carcinogenicity data is relevant, admissible evidence considered by Plaintiffs' experts in

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for testing potential NHL therapies.

[136] Ex. 100. D. Begley, et al., *Finding mouse models of Human Lymphomas and Leukemia's using the Jackson Laboratory Mouse Tumor Biology Database*, 99 EXPERIMENTAL AND TOXICOLOGIC PATHOLOGY 533-536, 534 (2015); Ex. 101. J. Ward, *Lymphomas and Leukemias in Mice*, 57 EXPERIMENTAL AND TOXICOLOGIC PATHOLOGY 377-381 (2006).

[137] Dr. Portier further found that there was an increase in splenic lymphosarcomas in female mice in Knezevich and Hogan which is also highly relevant to human causation because lymphosarcomas are a type of lymphoma. Portier Reb. Rep. at 7.

[138] In adopting the fit requirement in *Daubert*, the Supreme Court explained that, "[e]xpert testimony which does not relate to any issue in the case is not relevant and, ergo, non-helpful. . . . The consideration has been aptly described . . . as one of 'fit.'" 509 U.S. at 591 (internal quotations and citations omitted).

[139] In contrast, Monsanto's reliance on *Joiner*, MSJ at 24 is unavailing. In *Joiner*, the district court rejected plaintiffs' experts' reliance on animal bioassays because "[n]o study demonstrated that adult mice developed cancer after being exposed to PCB's." 522 U.S. at 144.

determining biological plausibility; it adds to the "accumulation of multiple scientifically acceptable inferences from different bodies of evidence." *Milward,* 639 F.3d at 25.

C. Dr. Portier's Methodology Materially Advances Relevant Science and Is Admissible.

Dr. Portier follows sound, well accepted statistical methodology in reaching his opinions. In addition to conducting a review of each of the individual studies, Dr. Portier further conducted a pooling of the data to compare studies. In fact, members of the SAP's peer review of the OPP's position paper on glyphosate approved of Dr. Portier's pooling methodology, noting that it provided "compelling statistical evidence" of animal carcinogenicity.[140] These members went further and recommended that the EPA adopt Dr. Portier's "pooled analysis approach for combining multiple studies." Ex. 10 at 59.

Dr. Portier's past involvement with glyphosate informs his approach to analyzing glyphosate's carcinogenicity.[141] As part of an EPA submission, Dr. Portier conducted a standard statistical analysis using glyphosate animal carcinogenicity data in late 2016 using the Cochran-Armitage trend test and poly3 trend test.[142] EPA recommends the Cochran-Armitage trend test in its 2005 Carcinogen Risk Assessment Guidelines, and a significant finding using this test is

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[140] Ex. 10 at 3, 59 (The Panel serves as the primary scientific peer review mechanism of the Environmental Protection Agency (EPA), Office of Pesticide Programs (OPP)).

[141] Monsanto tries to exclude Dr. Portier's based on alleged improper motives and biases. Not only are those arguments factually wrong, but they are inappropriate for a *Daubert* analysis and should be left to cross examination at trial. *United States v. Abonce-Barrera*, 257 F3d 959, 956 (9th Cir. 2001) ("Generally, evidence of bias goes toward the credibility of a witness, not his competency to testify, and credibility is an issue for the jury."). One of the bases for this alleged bias is Dr. Portier's part-time work with the Environmental Defense Fund (EDF). Yet Monsanto is currently partnering with the EDF which in its brief it coins as "an environmental activist group opposed to the use of pesticides." MSJ at 3. *See A Coalition of uncommon bedfellow is bringing sustainable agriculture to scale* (partnership between, inter alia, EDF and Monsanto Company), *available at* http://blogs.edf.org/growingreturns/2016/08/31/a-coalition-of-uncommon-bedfellows-is-bringing-sustainable-agriculture-to-scale/; Portier Dep. Ex. 15-44.

[142] *See* footnote [ ] supra. *See also* Portier Rep. at Appendix, Document Two; *see also* Document Three (Tables 1-9). Further, Document 3 is the same set of data tables submitted by Dr. Portier to German Regulators in response to the CLH Report for Glyphosate.

"sufficient to reject the hypothesis that chance accounts for the result."[143] Following that EPA submission, Dr. Robert Tarone, an undisclosed consultant for Monsanto,[144] called for evaluation of the animal carcinogenicity data using the exact trend test.[145] In response, Dr. Portier defended the use of the two previous tests, but acknowledged that evaluation could also be conducted using the exact trend test, which he subsequently performed.[146] However, as Dr. Portier explains, analysis of rare cancers such as renal tumors using the exact test alone would yield inaccurate results if relying solely on p-value:

> For renal tumors, all of the individual studies for which the p-value was less than 0.05 for the *approximate* test have p-values greater than 0.05 and less than 0.065 for the *exact* test. Thus, we go from 3 significant studies to 3 marginal studies. However, there are a few important issues to consider on these numbers. The study by Sugimoto (1997) is the most extreme outcome possible and it is not possible with only 2 tumors to get a p-value smaller than the 0.059 value with the exact test. Similar statements hold true for the 1983 study and the 2001 study. *The point is that for rare tumors, the exact test has a limited ability to identify a positive finding even though it uses the exact p-value. Thus, doing a direct evaluation against the historical controls is warranted.* The historical control test shows statistical significance identical for all of the tests to those in my previous comments. Especially clear is the findings from analyzing all of the data simultaneously.[147]

This is not "p-hacking" or data dredging, *see* MSJ at 25-26. Dr. Portier followed EPA guidelines which also support the use of historical controls for rare tumors to show that "the result is in fact unlikely to be due to chance" even in the absence of statistical significance.[148]

Monsanto nevertheless seeks to strike Dr. Portier's opinions because he does not use the same statistical approach as its experts. Ironically, Monsanto's own experts do not employ the identical statistical approaches when analyzing the same data set: Dr. Corcoran, Monsanto's

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[143] *Available at:* https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf, at 2-19.
[144] https://governance.iarc.fr/ENG/Docs/IARC_responds_to_Reuters_15_June_2017.pdf.
[145] Portier Rep. at Appendix, Document Six.
[146] Portier Rep. at Appendix, Document Seven (emphasis added).
[147] Portier Rep. at Appendix, Document Seven at 2.
[148] Available at: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf, at 2-20, 2-21.

statistician, recommended use of the logistic regression approach,[149] while Dr. Foster, Monsanto's toxicologist, referenced pairwise comparisons via Fisher's exact test.[150] Because are multiple statistical approaches to analyzing data,[151] the appropriate inquiry is *not* whether there is *one* correct method but rather whether Dr. Portier's methodology is reliable. *See Daubert II*, 43 F.3d at 1318. The answer is yes.[152]

Dr. Portier's opinions strengthened after acquiring new data. In spring 2017, Plaintiffs formally asked Dr. Portier to author an expert report in this litigation. As part of that work, Dr. Portier, for the first time, gained access to Monsanto's internal confidential documents, such as unpublished animal data from some of the long-term rodent bioassays and internal memorandum discussing study results. The analysis and revised results were not "made-for-litigation supposition," MSJ at 26. Rather, Dr. Portier's opinions are the predictable outcome of having a more complete data set. Dr. Portier cannot be criticized for failing to consider data he could not have accessed before this litigation.

Dr. Portier's approach is not without precedent. In addition to the endorsement by the SAP, Dr. Portier's ***methodology*** in pooling the data was subjected to the peer review process and published in the scientific literature. An approach similar to Dr. Portier's was used to evaluate the carcinogenicity of 1,4-dioxane.[153, 154] In response to ongoing debate about 1,4-dioxane's carcinogenicity, Dr. Michael Dourson, performed a pooled analysis of the data and concluded

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[149] *See generally*, Ex. 102 – Expert Report of Dr. Christopher Corcoran.

[150] *See generally*, Foster Report

[151] For example, EPA uses both trend tests and pairwise comparisons to determine whether a treatment-related effect is present. In Monograph 112, IARC used both the Cochran-Armitage trend test and the Fisher exact test to evaluate the animal carcinogenicity data on glyphosate. EFSA uses the pairwise comparison and trend tests.

[152] The EPA recognizes both the trend and pairwise tests as appropriate statistical measures. Available at: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf, at 2-19.

[153] 1,4-dioxane is also a contaminant present in Roundup formulations. Ex. 103, *see* MONGLY01041300.

[154] US EPA, 2013 *Toxicological Review of 1,4-Dioxane (with Inhalation Update)*, Washington D.C. EPA/635/R-11/003F, available at https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0326tr.pdf

that 1,4-dioxane promoted the rodent liver tumors observed in the chronic animal bioassays.[155] The results of this pooled analysis were subjected to the rigors of peer-review and subsequently published.[156] Thus, the pooled analysis approach conducted by Dr. Portier is, in fact, *a peer-reviewed and accepted* methodology.[157] Dr. Portier's approach is further backed by his 30-plus years of conducting such analyses in some of the most prestigious health related positions of government. Even were this approach to be considered innovative, it would be admissible. *Kennedy v. Collagen Corp.,* 161 F.3d 1226, 1228 (9th Cir. 1998) ("well-grounded but innovative theories" admissible even if they have not been subjected to peer review).

Dr. Portier's statistical approach for analyzing p-values in rodent carcinogenicity data enjoys general acceptance.[158] Ex. 106. Monsanto claims the Wasserstein article calls for the elimination of the use of p-values in interpreting data and incorrectly claims that the American Statistical Association ("ASA") rejected Dr. Portier's pooling method. MSJ at 28 (citing to the same article). Monsanto is wrong. The ASA statement merely proffers that p-values guide decision making but should not be the only value that guides the decision, which is exactly the manner in which Dr. Portier utilized p-values.

Dr. Portier's analysis focuses on observed tumor incidences in same-species and same-

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[155] Ex. 104. Dourson, et al., *Update: Mode of action (MOA) for liver tumors induced by oral exposure to 1,4-dioxane.* 88 REG. TOXICOLOGY AND PHARMACOLOGY 45-55 (2017). [156] Ex. 105. Dourson, et al., *Mode of Action Analysis for Liver Tumors from oral 1,4-dioxane exposures and evidence-based dose response assessment*, 68 REG. TOXICOLOGY AND PHARMACOLOGY 397-401 (2014). "'Submission to the scrutiny of the scientific community' can be a strong indicator of reliability 'because it increases the likelihood that substantive flaws in methodology will be detected.'" *Murray*, 870 F.3d at 923 (quoting *Daubert*, 509 U.S. at 593). Monsanto makes the nonsensical argument that these articles cannot be considered because Dr. Portier did not include them on his reference list. As Dr. Portier explained, he found these articles *after* Plaintiffs submitted his report. Dr. Portier's application of pooled analyses was the result of his own expertise, but certainly not without precedent.

[157] It is noteworthy that, similar to Dr. Portier, Dr. Dourson's pooled analysis considered studies across time and from different labs; yet, unlike Dr. Portier, Dr. Dourson chose to pool different species and sexes in conducting his analysis. Dourson, et al., (2017), Figures 2-6; Dourson, et al., (2014), Figure 3.

[158] R. Wasserstein et al., *Statement on p-values: Context, Process, and Purpose*, 70 AMER. STATISTICIAN 129 (2016) ("Wasserstein article").

sex from which he runs a trend test to arrive at a p-value, which is first compared against the concurrent controls. In instances of rare tumors, he considers historical control data, and again runs a trend test to arrive at a p-value for those tumors. Dr. Portier's evaluation of the data thus uses p-values only as a *guide* to arrive at a statistical endpoint, followed by a sensitivity analysis to determine the appropriateness of comparison across studies, and, finally, pools results across studies deemed sufficiently similar to compare.[159]

Dr. Portier's opinion is further supported by his false-positive error rate analysis in Table 15.[160] *See e.g. Daubert,* 509 U.S. at 594 (appropriate to consider error rates). Monsanto misinterprets Table 15. MSJ at 28-29.[161] Dr. Portier's report explains that Table 15 and Modified Table 15 illustrate the expected (assumption based on p-values) incidence of three or more tumors appearing in a given site versus the observed (actual results in the data) incidence of three or more tumors in a given animal. Portier Rep. at 50. The p-values in the text describe the probability, for example, that all of the tumors in male mice arose by chance. Table 15 shows that this is extremely unlikely; hence the data shows positive findings in the figures.[162]

In sum, Dr. Portier's opinion is not the product of an "opinion first, data later" approach. MSJ at 26. It is the product of a scientist carefully analyzing each of the endpoints of datasets to arrive at a conclusion for each observed endpoint and to ultimately compare that data across

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[159] *See* Portier Reb. Rep. at 5 ("In pooling across multiple studies, I examined the individual experiments and only pooled data when it was clear the studies were close to identical."). *See also,* Ex. 107. Greenland, S., et al., *Statistical test, P values, confidence intervals, and power: a guide to misinterpretations*, 31 EUR J EPIDEMIOL 337-350 (2016) (specifically noting that significant and insignificant p values are not the final step in the scientific analysis of data).

[160] Portier Rep. at 50; Portier Rebuttal Rep. at 37 (Modified Table 15).

[161] At Dr. Portier's deposition, Monsanto's counsel likewise misinterpreted Table 15, and Dr. Portier corrected that misinterpretation. 296:11-318:18. Further, Monsanto's brief suggests that Dr. Portier used the data of another statistician and failed to verify the information in Table 15. *See* MSJ at 28-29. That is false. *See* Portier Dep. 299:17-301:5.

[162] Monsanto further argues that Dr. Portier's inclusion of historical controls in Table 15 is improper, (*see* MSJ at 29; Corcoran Rep. at 17-18), again, Monsanto misinterprets the table. Dr. Portier only uses historical controls in Table 15 in instances of rare tumors. The use of historical controls in instances of rare tumors is entirely proper, and in fact, favored. *See* Ex. 108 - OECD Guidance Document 116, Section 4.22; Keenan, et al., *Best Practices for Use of Historical Control Data of Proliferative Rodent Lesions,* TOXICOLOGIC PATHOLOGY 679 (2009).

studies. Dr. Portier's approach is typical in meta-analysis seen in epidemiology studies and contributes further to a weight of the evidence analysis. His methodology is sound and accepted.

Monsanto's blanket assertion that review of animal data by global regulatory agencies should be conclusive is misplaced. MSJ at 22. In fact, in 2016, 93 independent scientists joined Dr. Portier in concluding that EFSA fails to follow established guidelines in evaluating rodent studies and supporting the IARC conclusions. Portier Dep. Ex. 15-19. As noted above, the OPP similarly disregarded its own guidelines.[163] Like the OPP, EFSA *a priori* decided to "disagree with IARC" before it even read the IARC monograph.[164]

As a practical matter, regulators receive data from the registrants; this data does not consistently report tumor incidences. Only since the Greim (2015) publication have independent scientists been able to look at each of the tumor incidences reported by the study authors in appendices.[165] EPA, EFSA, and EChA did not analyze the supplemental Greim data; their decisions are based on the summary of tumors reported by the industry, not the study authors. Dr. Portier, in contrast, reviewed the actual data.

D. Dr. Jameson Applies the Correct Scientific Assessment to the Whole of the Evidence

Dr. Jameson has extensive experience evaluating carcinogens at the NTP, an agency congressionally mandated to evaluate whether chemicals cause cancer in humans. Reference Manual at 655-656. The weight of evidence methodology used by the NTP, IARC and Dr. Jameson, an approach akin to preponderance of evidence, is a scientifically sound methodology

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[164] EPAHQ_005644, May 22, 2015 email from Michael Goodis to Jess Rowland. Ex. 123.

[165] Dr. Portier painstakingly reviewed every data point in the Greim appendix because sound statistical analyses starts with all available data. Portier Rep. at 50 (Table 15); Portier Reb. Rep. at 37 (Modified Table 15). And when he did so he considered primary and secondary tumors in his analysis. Yet while fundamental to biostatistics, Monsanto's expert statistician Dr. Corcoran does not even know the difference between primary and secondary tumors, Corcoran Dep. Ex. 124, 150:12-156:19, presumably because *all* of his research has related to dementia and other age-related disease and none has involved statistical analyses of animal bioassays, Corcoran Rep., Curriculum Vitae at 5-16. Accordingly, Dr. Corcoran is not qualified to render an opinion in this case and must be excluded in total.

that passes *Daubert* scrutiny. *Id.* Dr. Jameson explains that "the hazard assessment I am making is to determine whether or not glyphosate and/or glyphosate-based formulations can cause NHL." *Id*. at 9. In answering that question, Dr. Jameson uses a *strength of evidence* approach, rigorously assessing "the toxicological, mechanistic, and epidemiological data to form a judgment" regarding the carcinogenicity of glyphosate. *Id*. at 8. [166]

Dr. Jameson testified that "the purpose of the hazard assessment is to evaluate the material ***to see if it can cause cancer in animals***." Jameson Dep. 248:12-14. And, because "[i]n qualitative extrapolation, one can usually rely on the fact that a compound causing an effect in one mammalian species will cause it in another species," Dr. Jameson's opinions are directly relevant to the question of biological plausibility. Accordingly, and in combination with the epidemiological data, the methodology used by Dr. Jameson is designed to answer the exact question at the heart of this phase of the litigation: Can glyphosate cause NHL in humans?

Dr. Jameson's pre-litigation methodology—the methodology he employed during his work in the IARC working group and years at the NTP—is virtually identical to the methodology he employs in reaching his expert opinions here. Monsanto even acknowledges as much by accusing Dr. Jameson of "bootstrapping IARC's methodology." MSJ at 3. Nevertheless, Monsanto asserts that Dr. Jameson abandoned his pre-litigation methodology on the basis of a nearly 30-year-old publication[167], which lists Dr. Jameson as a contributing author.[168] *Cf.* MSJ at 30. However, Dr. Jameson's opinions are consistent with this methodology. For example, he explains that replication can occur between tumor type and site as well as across

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[166] Monsanto's criticism of Dr. Jameson for not doing a risk assessment is misplaced. As Dr. Jameson described, hazard assessment, while often used interchangeably with risk assessment, is different in that "[r]isk is defined as the probability that exposure to a hazard will lead to a negative consequence, or more simply, risk = hazard x dose (exposure)." In the absence of a known exposure level, risk cannot be meaningfully determined. Moreover, as set forth *supra* and explained by Dr. Jameson, the question of cancer causation in animals is *always* answered by using high doses, including the MTD. Jameson Dep. 216:8-217:2.

[167] Notably, Monsanto did not offer the article of issue as an exhibit at Dr. Jameson's deposition. In fact, despite repeated requests to see the document, Monsanto refused to provide Dr. Jameson an opportunity to review the publication it now cites as evidence of a change in his methodology. Jameson Dep. 33:8-34:20.

species strain and sex. Jameson Dep. 64:7-25. Here, Dr. Jameson observed tumors across studies, *see infra,* thereby establishing his stated criteria for replication. Jameson Rep. at 29. ("This statement is based on my stated criteria of a causal relationship between exposure to glyphosate and an increased incidence of malignant and/or a combination of malignant and benign tumors, in multiple species, at multiple tissue sites, from multiple studies, and to an unusual degree with regard to incidence, site, or type of tumor."). Not only is his methodology consistent, so is his opinion: glyphosate causes cancer in animals and humans.

VIII. Opinions Based on Mechanistic Data Are Reliable and Satisfy the Fit Requirement

The mechanistic evidence, and opinions predicated thereon, satisfy *Daubert*'s fit requirement. Mechanistic data provide evidence of how a chemical causes cellular changes that progress to cancer. The mechanistic evidence here is especially strong because it includes evidence of genotoxicity in human lymphocytes and blood samples following real-world GBF exposure. Moreover, mechanistic data are probative and relevant in considering biological plausibility and coherence as important parts of the Bradford-Hill criteria, particularly where the epidemiology corroborates the carcinogenic effects of GBFs in exposed humans. As explained by Monsanto's expert, evidence of genotoxicity "should be viewed within a context that can include rodent cancer bioassay and epidemiology data." Goodman Rep. at 9.

The results of peer reviewed *in vivo* studies (Paz-y-Mino 2007 and Bolognesi 2009)[169] demonstrate genotoxicity in blood and lymphocyte cells ***in living humans*** following exposure. In light of the human mechanistic data, opinions extrapolating the results of other genotoxicity experiments to humans are substantiated. Bolognesi 2009 and Paz-y-Mino 2007[170] are

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[169] Ex. 109. Paz-y-Miño et al., *Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate*, 30 GENETICS AND MOLECULAR BIOLOGY, 2, 456–60 (2007); Ex. 110. Bolognesi, *Biomonitoring of Genotoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate*, 72 J TOXICOL ENVIRON HEALTH A, 15-16, 986–97 (2009).

[170] A follow-up study, conducted two years after the aerial spraying of GBFs was banned, showed the health of the population improved and that the GBF-induced DNA damage healed. The authors re-affirmed their 2007 findings stating that "the results suggest that the individuals exposed to the broad spectrum herbicide suffered a genotoxic effect." Ex. 111 - Paz-y-Mino et al., *Baseline determination in social, health, and genetic areas in communities affected by*

methodologically sound studies that examined the genotoxic effect of aerially sprayed GBFs on the blood and lymphocyte cells of humans living in the sprayed areas. Monsanto's expert, Dr. Goodman, conceded that most of his criticisms regarding the Paz-y-Mino study, at least, are speculative. *See infra* at 63; Goodman Dep. 223:15-228:24.

Dr. Portier included both studies in his overall evaluation of the genotoxicity data and attached strong weight to them. Portier Rev. Rep. at 55-56. Dr. Matthew Ross, named as a non-retained expert by both parties, confirmed the importance of the Bolognesi study, stating "looking at exposed populations to an agent and seeing evidence of DNA damage is strong evidence that it is occurring, that it can occur." Ex. 112 – Deposition Transcript and Exhibits of Dr. Matthew Ross, 202:15-18.

Responding to Monsanto's question "What strong evidence was presented in the IARC monograph working group 112 that carcinogenesis observed in experimental animals is mediated by a mechanism that also operates in humans?" Dr. Ross explained:

> The mechanistic evidence that was deemed strong was the genotoxicity and the oxidative stress classification. . . .
>
> . . . the data, were obtained in exposed humans in cultured cells – in vitro human cells -- cultured in vitro, exposed to glyphosate. And in some animal models, in vivo there was evidence of . . . genotoxicity. The important thing, in terms of operable in humans, is the fact that exposed humans showed evidence of genotoxicity, and cultured cells of human origin showed evidence of genotoxicity. Those were -- those then showed that this mechanism may operate in humans.

Ross Dep., 104:7-105:10.

Monsanto relies on statements by one of the Bolognesi co-authors, Dr. Keith Solomon. Monsanto does not mention that Dr. Solomon is a paid consultant. *See* Ex. 113, Ex. 114.[171] Monsanto omits the fact that the primary author, Dr. Claudia Bolognesi, has twice affirmed the opinion of Plaintiffs' experts that the results show a statistically significant increase in

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glyphosate aerial spraying on the northeastern Ecuadorian border, 26 REV ENVTL. HEALTH 45 (2011) .

[171] Ex. 113: Apr. 9, 2001 email from Donna Farmer (MONGLY00885224) ; Ex. 114: June 5, 2013 emails between Joy Honegger, Erin Ahlers, and others (MONGLY04234807) demonstrating Keith Solomon is a paid consultant for Monsanto) .

micronuclei frequency.[172] Moreover, the disagreement between Dr. Solomon and Dr. Bolognesi is evidence of valid scientific debate, go to the weight, not the admissibility, of the evidence. *See Milward*, 639 F.3d at 22 (district court erred in choosing sides on an issue "which reasonable scientists can clearly disagree").[173]

Dr. Portier's opinions based on the mechanistic data are reliable. Dr. Portier engaged in a systematic analysis of each of the available mechanistic studies, which he prioritized based on biological impact and biological source data. Portier Rev. Rep. at 52-74.[174] Consistent with Monsanto's expert's approach, Dr. Portier's methodology placed more importance on the observation of genotoxicity in humans than genotoxicity in other mammals. *Id.* at 54; Portier Dep. 357:16-21. Still, Dr. Portier carefully evaluated the available mechanistic evidence on glyphosate, assessed the quality and observed results for the studies individually, and appropriately factored in weaknesses and strengths of the studies in arriving at a conclusion based upon the weight of the evidence. *See, e.g,* Portier Rev. Rep. at 52-74. Accordingly, Dr. Portier did not simply "add up" the positive studies.

Monsanto asks the Court to exclude Dr. Portier's demonstrative Table 17 because he merely counted studies as positive or negative but did no analysis. MSJ at 35. In fact, Dr. Portier

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[172] *See* Ex. 115, C. Bolognesi, et al. *Micronuclei and Pesticide Exposure* 26 Mutagenesis 1, 19-26 (2011): "Results showed significant increases in MN frequency after glyphosate exposure…". *See also*, C. Bolognesi, et al. *The use of the lymphocyte cytokinesis-block Micronucleus assay for monitoring pesticide-exposed populations* 770 Mutation Research 183-203 (2016): "[A] significant increase in the MN frequency associated with [glyphosate] exposure was detected…" and "[A]n indication of a genotoxic risk can be plausibly derived for…singly compounds such as glyphosate…due to consistent positive findings in exposed subjects."

[173] IARC likewise rejected Dr. Solomon's arguments stating it "found the comparisons of the frequencies of micronucleated cells before and after spraying to be particularly informative, while your [Solomon's] interpretation emphasized other results" and "that the foregoing differences are ones of interpretation, rather than of fact." Ex. 117, June 17, 2015 email from Kurt Straif to Keith Solomon re: Genotoxicity of glyphosate in humans.

[174] Dr. Portier considered "(1) data from exposed humans, (2) data from exposed human cells in a laboratory setting, (3) data from exposed mammals (non-human), (4) data from exposed cells of mammals (nonhuman) in the laboratory, (5) data from non-mammalian animals and others, and (5) [sic] data from cells from non-mammalian animals and others." Portier Rev. Rep. at 53-54.

included Table 17 to summarize data; he explains "Table 16 [sic]summarizes these studies in a simple framework that allows all of the experimental data to be seen in one glance. This table ***does not address the subtlety needed to interpret any one study***, but simply demonstrates when a study produced positive versus negative results." Portier Rev. Rep. at 65 (emphasis added).

Adding further confidence to the fact that a carcinogenic mechanism operates in humans is the fact that glyphosate causes lymphoma in mice. Peer-reviewed, scientific literature consistently accepts that B-cell lymphomas found in mice exhibit similar pathological features to those in humans, such that they "exhibit enough parallels to suggest they represent the same disease but in a different species."[175] The publications support the coherence criteria of Bradford-Hill because of "the increased risk of malignant lymphomas in CD-1 mice, the marginal increase in these tumors in Swiss mice and the strong similarity between malignant lymphomas in mice and NHL in humans."[176] Portier Rep. at 76, 97.

IX. SUMMARY JUDGMENT IS INAPPROPRIATE AND MUST BE DENIED

Monsanto moves for summary judgment solely on the basis of its motion to exclude Plaintiffs' general causation experts. On a motion for summary judgment, the Court must consider all facts in the light most favorable to the non-movant. *See Messick v. Novartis Pharm. Corp*., 747 F.3d 1193, 1199 (9th Cir. 2014) (reversing summary judgment because plaintiff's admissible expert testimony created issues of fact). As set forth above, Plaintiffs have submitted relevant and reliable general causation expert testimony, which raises genuine issues of material fact as to whether glyphosate and GBFs can cause NHL. *See id; see also* Fed. R. Civ. P. 56(a). Accordingly, Monsanto is not entitled to summary judgment and the Court should deny the instant motion in its entirety.

X. Monsanto's Experts Do Not Apply Reliable Methodologies in Reaching Their

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[175] Ex. 100. Begley, D., et al., *Finding mouse models of Human Lymphomas and Leukemia's using the Jackson Laboratory Mouse Tumor Biology Database*, 99 EXPERIMENTAL AND TOXICOLOGIC PATHOLOGY 533-536, p. 534 (2015); , Ward, J. Lymphomas and Leukemias in Mice, 57 EXPERIMENTAL AND TOXICOLOGIC PATHOLOGY 377-381 (2006).

[176] Dr. Portier further found that there was an increase in splenic lymphosarcomas in female mice in Knezevich and Hogan which is also highly relevant to human causation because lymphosarcomas are a type of lymphoma. Portier Reb. Rep. at 7.

Opinions.

A. The opinions of Dr. Rosol must be excluded because they are based upon documents withheld from Plaintiffs.

Dr. Rosol's opinions are predicated upon information he reviewed in the "glyphosate reading room" in Brussels, Belgium.[177] The glyphosate reading room was open from August 2016 until October 2016. In-fact, the room closed just days after Dr. Rosol conducted his review. It is now closed to the public and Plaintiffs have no access to the underlying pathology reports Dr. Rosol reviewed. Dr. Rosol acknowledged the "underlying study reports" used in the preparation of his report are available only in the reading room. Rosol Dep. at194:16-25.[178] And, as a veterinary pathologist, the underlying pathology reports were essential to Dr. Rosol's opinions. *Id*. at 51:10-14 ("[the incidence data] would be very helpful. It's very useful data. For many people it might be adequate. ***For me, I really wanted to read the pathology reports***."). In PTO 16, this Court made clear that "neither the plaintiffs nor Monsanto will be permitted to rely in these proceedings on documents they have withheld from the other side." Accordingly, and because all of Dr. Rosol's opinions are predicated upon information to which Monsanto had access but that were withheld from Plaintiffs, he must be excluded in total.

B. Dr. Goodman's Opinions Discounting Two Human In Vivo Studies Are Inadmissible

Dr. Goodman offers several opinions for discounting two human in vivo studies, Bolognesi 2009 and Paz-y-Mino 2007. These opinions, whether individually or collectively are an assortment of speculation, guesswork, and willful blindness. When questioned about one of his reasons for disregarding the Paz-y-Mino study, he testified "***Absolutely, yes it's speculative.***"

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[177] The glyphosate reading room was operated by the Glyphosate Task Force ("GTF"). The GTF is a consortium of companies, including Monsanto, joining resources and efforts in order to renew the European glyphosate registration. *See* http://www.glyphosate.eu/gtf-statements/glyphosate-task-force-opens-reading-room-public-access-studies.

[178] Plaintiffs requested this discovery from Monsanto on December 12, 2016. See Ex.118. Monsanto asserted that it did not have copies of the Pathology reports, even though by that point Monsanto knew that Dr. Rosol had reviewed and likely relied upon the reports. See Ex. 119.

Goodman Dep. 225:3-6 (emphasis added); *see also id*. at 228:6. And, where Dr. Goodman is not speculating, he is wrong or, at best, willfully ignorant of critical information. "[S]peculative testimony is inherently unreliable." *Dept. of Toxic Substances Control v. Technichem, Inc.,* 12-CV-05845-VC, 2016 WL 1029463, at *1 (N.D. Cal. Mar. 15, 2016) (Chhabria, V. quoting *Ollier v. Sweetwater Union High Sch. Dist*., 768 F.3d 843, 860 (9th Cir. 2014)).

Dr. Goodman discounts the Paz-y-Mino results due to what he perceives as a lack of investigation into the "wide-range of reactions" within the exposed population. Goodman Rep. at 12. The "wide-ranging of reactions" he references are actually a list of the consistently reported symptoms of acute GBF toxicity.[179] When asked whether he believed the symptoms reported by the study to be consistent with GBF exposure—the key inquiry in ruling out GBF exposure as the cause—Dr. Goodman admitted that he is neither qualified to opine on nor is even aware of GBF toxicity symptomology at all: "I am a Ph.D., not a medical doctor, ***and I do not know all of the symptoms of glyphosate poisoning*** and I do not know the particular concentrations, exposures necessary to cause this particular plethora of – ailments." Goodman Dep. 220:7-12.[180] If Dr. Goodman is unqualified to rule in GBF exposure as the cause of the symptomology, it is axiomatic that he is likewise unqualified to rule out GBF exposure as the cause—especially in the face of reliable evidence. Accordingly, Dr. Goodman is not qualified to offer the speculative belief that something other than GBF exposure may have caused the reported symptoms. And, without any evidence supportive of his hypothesis, his opinion must be excluded.[181]

Dr. Goodman readily admits that his second criticism of Paz-y-Mino 2007—that during

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[179] In-fact, two studies Dr. Goodman has found "methodologically sound," detail the most common symptoms of GBF toxicity and corroborate *every* symptom listed in the Paz-y-Mino study. *See* Zouaui, K. et al., *Determination of glyphosate and AMPA in blood and urine from humans: About 13 cases of acute intoxication*, 226 Forensic Science International e20 (2013), and Roberts, Darren M et al. "A Prospective Observational Study of the Clinical Toxicology of Glyphosate-Containing Herbicides in Adults with Acute Self-Poisoning." *Clinical toxicology (Philadelphia, Pa.)* 48.2 (2010): 129–136. *PMC*. Web. 15 Oct. 2017 at 5, describing the symptoms of acute glyphosate toxicity. *Cf*. Goodman Rep. at 34-35; *Id.* at 40-42.

[180] Dr. Goodman repeatedly referred to his perspective as that of a "layman," Goodman Dep. 215:16-218:2, an admission that Dr. Goodman is not qualified to offer the opinion.

[181] Moreover, Goodman could not provide any alternative hypothesis for what *could* have caused the reported symptoms, if not GBF exposure. Goodman Dep. 217:5-13.

the time between blood sampling, the exposed population "might have been exposed to numerous chemicals, other than GBFs, which could have influenced the results," —is speculation.[182] Goodman Rep. at 12. In fact, when questioned directly about his hypothesis, Dr. Goodman testified: "***Yes, it is speculative***." *Id.* at 228:6. This lack of intellectual rigor fails the *Daubert* reliability prong. *See* 509 U.S. at 590.

Dr. Goodman's criticisms of the study's methodology are similarly unfounded.[183] For example, he assumes that more than one individual "might have participated" in performing the analysis; however, when questioned, Dr. Goodman admitted his assertion was speculative. Goodman Dep. 225:16 ("Is this speculative, the answer is yes").[184] And, Dr. Goodman's final methodological critique—that the authors' lack of discussion of heterogeneity renders their findings unreliable—is absurd. His criticism relates exclusively to *discussion* of the study results, not the validity or reliability of the results themselves—findings he admitted are indicative of genotoxic effects. *Id.* at 228:20-21.

Dr. Goodman's opinion discounting the Bolognesi 2009 study is premised on two key errors. In his report and testimony, Dr. Goodman discounted the higher rates of binucleated cells with micronuclei (BNMN), an admitted marker of genotoxicity,[185] in exposed populations on the basis that "the highest reported frequency of BNMN" occurred in one of the control regions (Boyaca) "where no aerial spraying of glyphosate was conducted." Goodman Rep. at 15; Goodman Dep. 202:18-203:1; 204:1-11. However, Boyaca reported the highest *baseline*

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[182] The study authors took efforts to ensure that the test population was not exposed to other confounding chemicals, a finding Dr. Goodman admitted he has no reason to dispute. Paz-y-Mino 2007 at 485; Goodman Dep. 216:10-217:4.

[183] Dr. Goodman's criticism of the authors' use of a "Rank Numbers" is similarly speculative. When pressed as to whether this issue lead him to question the results of the study, Dr. Goodman could only opine that authors' use of rank numbers lead him "to wonder about the analysis" before deflecting to his criticism regarding multiple reviewers. Goodman Dep. 223:10-12

[184] Moreover, Dr. Goodman admitted that even if his speculation were correct, his belief would not render the Paz-y-Mino study unreliable. *Id*. 226:24-227:3 ("multiple reviewers or multiple observers, however we want to categorize this, in and of itself**,** in my opinion, would not be problematic..."). Thus, Dr. Goodman's criticism, even if based in evidence and established as fact, does not support the opinion he offers.

[185]Goodman Dep. 202:6-17

frequency of BNMN *before any other regions were exposed to GBFs*. However, following spraying with GBFs, the observed rates of BNMN in the GBF-exposed regions were higher.[186] Second, Dr. Goodman incorrectly believed that the Boyaca population had no glyphosate exposure. *Id*. 204:12-21. In-fact, the population of this area was exposed to a number of pesticides and chemicals *including glyphosate,* only not aerially.[187] Therefore, and at a minimum, Dr. Goodman's opinions related to the Bolognesi and Paz-y-Mino studies must be excluded.

C. Dr. Goodman's Opinions Are Based Upon A Result Driven Methodology

Dr. Goodman's review of the data is not a rigorous one. Dr. Goodman accepts ***all*** negative findings at face value—even when these findings are the product of methods he deems unreliable in positive studies and despite purporting to apply the same criteria to all studies reviewed. *Id*. at 230:12-22. [188] On the other hand, he discounts the results of nearly every positive study demonstrating that glyphosate or GBFs cause genotoxicity or oxidative stress. Such a biased approach to data is inconsistent with *Daubert* and its progeny.[189] *See In re Zoloft (Sertraline Hydrochloride) Products Liab. Litig*., 858 F.3d 787, 797 (3d Cir. 2017)

Dr. Goodman discounts evidence of genotoxicity in a comet assay on the basis that it did not account for cytotoxicity and/or demonstrate dose response, even though the study evaluated for cytotoxicity[190] ***and*** demonstrated dose response. *See* Ex. 120 - Alvarez-Mayo, 2014 p. 106, 107-108, Figs. 1, 2, 3. Goodman Rep. 30-31; *Cf.* Goodman Dep 72:18-22, 86:4-16.[191] And,

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[186] Bolognesi at 991. Dr. Goodman acknowledged this fact—which contradicts his reported opinion—upon being presented with the results of the study. Goodman Dep. 206:14-20.

[187] Bolognesi at 994. Dr. Goodman conceded that he had no reason to disagree with the authors' statement that the population of Boyaca was exposed to glyphosate. *Id*. 207:11-19.

[188] Dr. Goodman was unable to point to a ***single negative study*** within any data set that he did not find credible. Conversely, Dr. Goodman discounted nearly every positive study.

[189] Such a facially absurd result is indicative of a conclusion-oriented process. *See Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 607 (D.N.J. 2002), aff'd, 68 Fed. Appx. 356 (3d Cir. 2003)(unpublished) (To establish that an expert's methodology "is truly a methodology, rather than a mere conclusion-oriented selection process that weighs more heavily those studies that supported an outcome, ***there must be a scientific method of weighting that is used and explained***.") (emphasis added).

[190] Dr. Goodman testified that the Trypan Blue method used to evaluate cytotoxicity is adequate. Goodman Dep.150:19-151:2

[191] Several other opinions contain similar, fundamental errors related to cytotoxicity testing.

although failure to account for cytotoxicity is fatal for positive studies, it is irrelevant for negative ones under Dr. Goodman's methodology.[192] In-fact, many of the negative studies Dr. Goodman relies upon contain methodological flaws identical to, or worse than, the positive studies he disregards.[193] This degree of misapplication requires exclusion. *See* Fed. R. Evid. 702(d).

In yet another example of clear error, Dr. Goodman reports to have relied upon 38 Ames tests "conducted with GBFs" in support of his opinions. Goodman Rep. at 18-19. However, at least five of these tests do not involve glyphosate at all. [194] This mistake underscores the lack of reliability and rigor in Dr. Goodman's methodology. Dr. Goodman is either unable to discern the chemical tested, or is so careless that he did not realize 13% of the data set had nothing to do

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Goodman discounts the results of Mañas et al., 2009 for not performing cytotoxicity tests, however, this study *did account* for cytotoxicity using the Trypan Blue method. Goodman Rep. at 30; Manas, F. et al., *Genotoxicity of glyphosate assessed by the comet assay and cytogenetic tests*, 28 Envtl. Toxicology & Pharmacology 37 (2009). In another example Goodman opines that the elevated frequency of micronuclei following exposure to glyphosate in the Koller et al 2012 in vitro microneuclei induction test in mammalian cells should be discounted because the micronuclei induction observed was secondary to cytotoxicity. *Id*. at 27; Goodman Dep. 84:9-17. However, Koller *did* evaluate for cytotoxicity and demonstrated that cytotoxicity *was not observed* with glyphosate. Thus, Goodman discounts the positive genotoxic findings for glyphosate in that study *even though cytotoxicity was ruled out. See* Koller, V. et al., Cytotoxic and DNA-damaging properties of glyphosate and Roundup in human-derived buccal epithelial cells, 86 Archives Toxicology 805 (2012).

[192] In Dimitrov et al, a study Goodman explicitly relies upon as "negative," cytotoxicity was not determined. Goodman testified that could not recall whether cytotoxicity tests were performed. *Id*. 115: 6-9. Dimitrov, B. et al., Comparative genotoxicity of the herbicides Roundup, Stomp and Reglone in plant and mammalian test systems, 21 Mutagenesis 373 (2006).

[193] For instance, Dr. Goodman accepts at face value the results of Holeckova (2006), showing no chromosomal aberration with glyphosate *in vitro*. However, this study did not use a metabolic activation system, rendering the results unreliable and in non-compliance with OECD guidelines. Dr. Gooman's consistently discounts positive findings for the noncompliance with OECD guidelines. However, notwithstanding these glaring shortcomings, Dr. Goodman saw no reason for scrutiny or concern. *See* Holeckova, B., *Evaluation of the In Vitro Effect of Glyphosate-based Herbicide on Bovine Lymphocytes Using Chromosome Painting*, 50 Bull. Veterinary Inst. Pulawy 533 (2006).

[194] Monsanto's counsel identified the 19 additional tests not accounted for in Appendix 1 of Dr. Goodman's report. See Ex.121 (email from H. Pigman to D. Wool). Notable, references 132, 213, 271, 353, were conducted with neither GBFs nor glyphosate, a fact acknowledged by Monsanto's counsel.

with glyphosate or GBFs at all. Either way, his methodology does not pass *Daubert* muster and his resultant opinions must be excluded.

D. Dr. Foster Applies Inconsistent and Erroneous Methodologies and Must be Excluded in Total

Dr. Foster's opinions are not based on scientifically solid methodology, and his report and testimony are replete with less than rigorous analyses geared towards a pre-determined conclusion. In part, Dr. Foster's methodology is to compare tumor incidences across studies in an effort to identify repeatability or replication of the tumors. Ex. 122 – Deposition Transcript and Exhibits of Dr. Warren Foster, 86:10-17, 176:9-12, 209:3; Foster Rep. at 23, 26. Scrutiny of his method reveals a glaring absence of scientific rigor. For instance, he concludes that the interstitial testicular tumors observed in the Lankas (1981) study were not glyphosate related because there was no replication of the testicular tumors in other studies in rats at the same or higher doses. Foster Rep. at 15.[195] He explained that he arrived at this opinion in part by comparing the Lankas study with the Atkinson and Suresh studies, based on similar dose regiments. Foster Dep., 203:25-205:18. Dr. Foster stated that the only comparable dose groups were the *high dose* male group in the Lankas study and the *low dose* male groups in the Atkinson and Suresh studies.[196]

However, at the time of Atkinson and Suresh, chronic toxicity and carcinogenicity study guidelines did not require full histopathological examinations of the testes in low- or mid-dose group animals unless there was an observed dose response seen between the control group and the high dose group animals.[197] Atkinson reported three testicular tumors in the control group

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[195] When questioned, Dr. Foster responded that rats receiving similar doses showed no incidence of testicular tumors. Foster Dep. at 205:6-9 (referring to Atkinson, 1993); 207:19-208:1 (referring to Suresh 1996).

[196] Foster Dep. 203:14-205:18.

[197] Instead, pursuant to the standards of the time, the study authors would only conduct full histopathology on those animals from the low and mid dose groups that either died prior to study termination or that showed macroscopic tumors. This approach would potentially miss tumor production in the low- and mid-dose animals; accordingly, the 2006 revisions altered the guidelines to require full histopathology of the animals in the study, which is the present standard. *See*, NTP, Standard Protocols, 2-Year Study, Histopathology List,

and two testicular tumors in the high dose group. Greim (2015)(Study 3). Suresh did not observe any testicular tumors in the control or high dose males. Greim (2015)(Study 4). Therefore, full animal examination of the entirety of the low dose groups in Atkinson and Suresh were not performed because neither study noted a clear dose response between the control animals and the high dose animals. *Id.* Because in Atkinson only 25 of the 50 low dose males were evaluated,[198] and in Suresh only 30 of the 50 low dose males were evaluated,[199] (those animals that died before the study ended or exhibited macroscopic tumors), neither conducted full animal histopathology analysis on the entirety of the low dose animals. As a result, it is factually implausible and thus methodologically unsound to make a comparison between these two studies and Lankas.[200] Data obtained from the examination of only a portion of the treated animals cannot be reliably used as a basis of the comparison Dr. Foster purports to have performed.

Dr. Foster's inadequate scientific rigor is further reflected in the cavalier way he dismisses any potential relationship between glyphosate and the tumors observed in animals treated with it. Dr. Foster dismisses certain observed tumor incidences due to lack of histopathological evidence of progression from adenoma to carcinoma and/or hyperplasia in some studies, and concludes that the detected tumors are not compound-related.[201] These conclusions are scientifically unsupported and premised on a clear misunderstanding of carcinogenic processes.

For example, Dr. Foster assumes that all carcinomas develop from adenomas. See e.g., Foster Rep. at 14, 18, 19, 23. He further states that a lack of observed hyperplasia is evidence that the observed tumors were not compound-related. Foster Dep. at 200:23-201:2. Both those

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https://ntp.niehs.nih.gov (last accessed Oct. 26, 2017).

[198] Greim (2015)(Study 3)(Data Supplement). Still, Atkinson reported one interstitial testicular cell tumor in the low dose group males. *Id.*

[199] Greim (2015) (Study 4)(Data Supplement).

[200] Dr. Foster believes Suresh is a "thorough study," that conducted full histopathology on all animals. Foster Dep. 207:19-298:1. Dr. Foster is mistaken. Further, three testicular tumors (two Leydig cell tumors, and one Seminoma) were observed in the 30 mid-dose animals fully examined in Suresh. (Greim Data Supplement, Study 4, Table 48 at 4).

[201] *See* Foster Rep. at 15, 16, 17, 20, 22, 24 (dismissing numerous different tumors for lack of evidence of tumor progression).

assertions are wrong. In fact, carcinogens have the capability to produce carcinomas without adenomas and some tumors have no precursor lesions.[202] Further, in the absence of a concurrent toxicology study, as was the case here, histological examination is performed after the animals have been euthanized. Thus, hyperplasia and/or tumor progression is not often noted (if ever) because the animals are only reviewed for the presence of adenomas/carcinomas once—at death. Dr. Foster offers no support for his conclusion to the contrary other than his alleged experience. Therefore, Dr. Foster asks this Court to admit his opinions based solely on an *ipse dixit* basis. "If admissibility could be established merely by the *ipse dixit* of an admittedly qualified expert, the reliability prong would be, for all practical purposes, subsumed by the qualification prong." *United States v. Frazier*, 387 F.3d 1244, 1261 (11th Cir. 2004). Dr. Foster's methodology fails the reliability prong.

Dr. Foster dismisses certain tumors based solely on speculation. For example, Dr. Foster discounts the kidney tumors observed by Knezevich and Hogan based on a speculative confounder—the weight loss observed in the high dose group. Foster Rep. at 21-22. Dr. Foster dismissed the renal tubule adenomas in that study because he believed the uncited 11 percent weight loss confounded the data. Foster Dep. at 69:4-11. However, he does not provide any information about the source of this purportedly important information. Foster Dep. at 65:21-66:1 ("No, I cannot tell you exactly where I found that…."). In addition, he offers no support for the claim that the weight loss somehow contributed to the observed tumors. In this instance, Dr. Foster failed to apply any methodology—he dismisses rare tumors based on the notion that he came across the data "somewhere," he therefore discounts the kidney tumors seen at the higher dose, and accordingly concludes that the study did not show a dose-response relationship.

Dr. Foster has years of expertise in reproductive toxicology, but no expertise in animal carcinogenicity screening assays. Likely, Dr. Foster's flawed methodologies are the result of this inexperience. His report and deposition testimony do not satisfy the requisite level of intellectual

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[202] D. Dixon, et al., *Summary of chemically induced pulmonary lesions in the National Toxicology Program* (NTP) toxicology and carcinogenesis studies, 36 TOXICOL PATHOL 3 at 428-39 (2008).

rigor that *Daubert* requires from an expert and precludes its admission.

E. Drs. Rider and Mucci's Opinions Predicated Upon the Unpublished AHS Study Must be Excluded

Neither Dr. Mucci nor Dr. Rider engaged in a serious review of the epidemiology in this case. Their uncritical acceptance of the unpublished unfinished AHS manuscript—despite the author's warnings that the analysis was "incomplete" and that it would be "irresponsible" to report the results—reflects litigation-driven opinions. *See Supra, AHS Section.* Blair Dep. at 204:15-20, 206:25-207:4. Further, despite commissioning two articles heavily critiquing the methodology of the AHS study, Monsanto failed to provide those articles for consideration by these experts. As explained above, both the incomplete and methodologically flawed draft AHS study manuscript and any opinions based on it should be excluded, including Chang (2017).

CONCLUSION ON OFFENSIVE DAUBERTS

As explicated above, because Monsanto's experts Drs. Rosol, Goodman, Foster, Rider, and Mucci apply methodologies that do not satisfy the *Daubert* standard, the Court should exclude their opinions.

Dated: October 27, 2017

Respectfully Submitted,

/s Robin Greenwald, Michael Miller and Aimee Wagstaff

Robin Greenwald
rgreenwald@weitzlux.com
Weitz & Luxenberg
700 Broadway
New York NY 10003
Ph 212-558-5500
F 212-344-5461

Michael Miller
mmiller@millerfirmllc.com
The Miller Firm LLC
108 Railroad Ave
Orange VA 22960
Ph 540 672 4224

F 540 672 3055

Aimee Wagstaff
Aimee.wagstaff@andruswagstaff.com
Andrus Wagstaff, P.C.
7171 West Alaska Drive
Lakewood CO 80226
Ph 303-376-6360
F 303-376-6361

ECF CERTIFICATION

Pursuant to Civil Local Rule 5-1(i)(3), the filing attorney attests that she has obtained concurrence regarding the filing of this document from the signatories to the document.

DATED: October 27, 2017

/s/ Aimee Wagstaff

ANDRUS WAGSTAFF, PC
Aimee H. Wagstaff, SBN 278480
aimee.wagstaff@andruswagstaff.com
7171 West Alaska Drive
Lakewood, CO 80226
Telephone: (303) 376-6360
Facsimile: (303) 376-6361

CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of the foregoing document was filed with the Court and electronically served through the CM-ECF system which will send a notification of such filing to all counsel of record. .

DATED: October 27, 2017

/s/ Aimee Wagstaff

ANDRUS WAGSTAFF, PC
Aimee H. Wagstaff, SBN 278480
aimee.wagstaff@andruswagstaff.com
7171 West Alaska Drive
Lakewood, CO 80226
Telephone: (303) 376-6360
Facsimile: (303) 376-6361