EXHIBIT 124

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	)	MDL No. 2741
THIS DOCUMENT RELATES TO ALL CASES	)	Case No. 16-md-02741-VC

WEDNESDAY, SEPTEMBER 20, 2017

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

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Videotaped deposition of Christopher Corcoran, Sc.D., held at the Hampton Inn, 1665 North Main Street, Logan, Utah, commencing at 9:13 a.m., on the above date, before Carrie A. Campbell, Registered Diplomate Reporter, Certified Realtime Reporter, Illinois, California & Texas Certified Shorthand Reporter, Missouri & Kansas Certified Court Reporter.

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VIDEOGRAPHER:
LANCE HARRISON,
Golkow Litigation Services

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INDEX

VIDEOGRAPHER: We are on the record.

My name is Lance Harrison. I'm the videographer. The court reporter is Carrie Campbell. We represent Golkow Litigation Services.

The time and date indicated on the video screen is September 20, 2017, 9:13 a.m.

This is in regards of the Roundup Products Liability Litigation, MDL Number 2741, Case Number 16-MD-02741 in the United States District Court, Northern District of California.

Counsel will now introduce themselves, and the court reporter will swear in the witness.

MS. GREENWALD: Robin Greenwald for the plaintiffs.

MS. ROBERTSON: Pearl Robertson for the plaintiffs.

MR. GRIFFIS: Kirby Griffis, Hollingsworth, LLP, for Monsanto.

MR. KALAS: John Kalas for

Monsanto.
MR. WISNER: Appearing by phone, Brent Wisner for the plaintiffs.

CHRISTOPHER CORCORAN, Sc.D., of lawful age, having been first duly sworn to tell the truth, the whole truth and nothing but the truth, deposes and says on behalf of the Plaintiffs, as follows:

DIRECT EXAMINATION
QUESTIONS BY MS. GREENWALD:
Q. Dr. Corcoran, I know we just introduced ourselves, but I'll do it again.
My name is Robin Greenwald, and I represent the plaintiffs in this lawsuit.
Just a couple of preliminary issues before we get into the substance.
I talk fast, first of all. I live in New York, so if I go too fast, just tell me to slow down.
Okay?
A. Okay.
Q. So I'm going to be asking you

several questions today, and if you don't understand a question I ask, please ask me to rephrase it.
Okay?
A. Okay.
Q. One of the things you have to do for the court reporter is you have to audibly answer. You can't shake your head because she can't take a shake of the head, so we have to give audible answers.
A. Okay.
Q. All right?
And the other thing we have to be careful about is I have to finish my question before you start to answer, and vice versa, I can't start a question until you finish your answer. So we have to try to do that for the court reporter also.
A. Okay.
Q. Have you ever been deposed before?
A. I have not.
Q. Okay. So I'm sure you've learned all about what the deposition is, but I'm glad I went through those preliminary

issues with you.
The videographer has to take a certain break at a certain time because of the tape, how long a tape will go, but if you need a break before then, just let me know and we can take a break. The only rule is you can't take a break when a question is pending. But other than that, if you need a break, this is your deposition, and you should just tell me you want to take a break and we'll take one.
Okay?
A. Okay. Thank you very much.
Q. All right. Terrific.
So the first thing I want to do is mark as -- so we're going to be marking exhibits also through the course of the day, so there's just some legal stuff that goes on.
A. Right.
(Corcoran Exhibit 21-1 marked for identification.)
QUESTIONS BY MS. GREENWALD:
Q. I'm going to mark as Exhibit 21-1 a copy of the expert report of

Dr. Christopher D. Corcoran in this litigation and give you a copy of that.
Dr. Corcoran, is Exhibit 21-1 the expert report that you prepared in connection with this litigation?
A. Yes.
Q. Okay. So I'm going to be asking you a lot of questions about that today, so we'll just leave it here and we'll mark this, and so this way it will just be handy for you.
A. Okay.
(Corcoran Exhibit 21-2 marked for identification.)
QUESTIONS BY MS. GREENWALD:
Q. Okay. The second document I want to mark is Exhibit 21-2, which is a copy of the notice for your deposition today.
Have you seen that before?
A. Yes.
Q. So if you could turn to the last two pages of Exhibit 21-2, which is a series of requests for production.
Do you see that?
A. Yes.

Q. Okay. When did you receive this, approximately, from -- well, let me strike that.

Did you receive this from the Hollingsworth firm?

A. I did.

Q. Okay. Approximately when did you receive this?

A. It's been within the last two weeks, I think.

Q. Okay. And how did you go about searching for documents that are responsive to the documents that are requested in the request for production?

A. I just read through the list and just, I guess, checked that those things were available.

Q. Okay. Do you keep paper files in your office?

A. Some.

Q. And did you check paper files in connection with responding to the request for production?

A. Let's see. Do you mind if I just read through again this one more time --

Q. No. Not at all.

A. -- just to make sure?

Q. That's fine.

A. I would say most everything on this list I keep as electronic files. There were a couple of items that are -- that I have hard copies of.

Q. Okay. So you searched your electronic files for documents that would be responsive to the request for production contained in 21-2?

A. Yes.

Q. Okay. And did you produce to your attorneys everything that you had in your files that were responsive to your request for production?

A. Yes. Everything that they -- that they -- that they told me was required, I provided for them.

Q. Okay. And do you have an assistant in your job at the university?

A. No.

Q. Okay. So in other words, if it's not in your electronic file, it doesn't exist for purposes of this work; is that

correct?

A. That's right, yeah.

Q. Okay. Great. Thank you.

Can you turn to page 9 of your expert report, please?

And I'm going to be referring to the lines on the left, which are actually very useful for this deposition, so I can actually tell you where on the page we're looking.

A. Sure.

Q. If you look at lines 33 and 34 --

A. Uh-huh.

Q. -- you state as follows: "As shown in Tables 1 and 2, of the hundreds of individual tumor types evaluated across all 12 experiments, 1,016 were observed in at least one mouse or rat."

Do you see that?

A. Yes.

Q. Did I read that accurately?

A. Yes.

Q. What sources did you use to come up with that number?

A. The data that I used all came from the supplement that was produced by Greim that I cited in the expert report.

Q. And what did you actually do from the Greim -- or what did you actually use from the Greim paper to calculate the 1,016?

A. The supplement that Greim provided that had all of the data tables, I -- I guess I just transcribed all of those. I made -- I made my own data files, basically, using the tables from Greim, and those were the tables I used to produce that number.

Q. So when you refer to the Greim -- so the Greim -- there's the Greim paper and then there are multiple supplements to the Greim paper, correct?

A. That's right.

Q. And about how many are there?

A. I actually don't know.

The supplement that I used, I guess I'm looking at the overall body of data tables that were provided by Greim as a supplement to his paper.

Q. So did you actually look at all the supplements to the Greim paper, the multiple hundreds of pages or thousands of pages of supplemental material to the Greim paper, or are you talking about something else?
A. Are you talking about the --
MR. GRIFFIS: Excuse me. Objection.
THE WITNESS: Okay. Are you talking about the supplements that actually had the data printed?
QUESTIONS BY MS. GREENWALD:
Q. Yeah.
A. Yes, I did. I actually went through every page.
Q. About how many pages is that; can you approximate?
A. I can't recall. I mean, it's at least hundreds.
Q. Okay. But not a thousand?
A. I don't know. I can't recall.
Q. Do you know about how many supplements there are?
A. By supplements, are you talking

about individual data tables from the other 12 studies?
Q. Right.
So within -- within the 12 studies, there's data tables, correct?
A. Uh-huh.
Q. And did you review all of the data tables for all of the studies that were available in the supplements to Greim?
A. I did.
Q. Okay. And can you approximate how many pages of data that was that you reviewed?
A. I can't. It was just an enormous number, but I can't recall exactly how many pages there were.
Q. But -- well, let me ask it this way then. You said a couple hundred before, but it could be more.
It's less than a couple of thousands, would you say?
I'm just trying to cabin it and get some sense of what you recall having looked at.
A. I really don't know. I just

know that it was a big task going through all those data tables, and that's -- if I -- I mean, obviously if I had the supplement in front of me, I could tell you exactly, but I can't remember off the top of my head.
Q. I didn't want to kill all those trees. Way too many trees to put all this in front of you.
I have the Greim paper, but let's wait on that for right now.
A. Okay.
Q. So you came up with the number of 1,016, and you're saying that number is from a review by you of the supplemental material to the Greim paper; is that correct?
A. Yes.
Q. Okay. And so what did you actually do to calculate the 1016?
A. Well, I took the data from the Greim supplement. I hand-entered it myself into -- into a format that I could use to analyze and, you know, checked it, double-checked it. And then when I actually did the analysis, I filtered out all of the -- all of the tumor types, all of the

sites for which at least one lesion was observed among the rats or mice. And so that's where that 1,016 came from.
Q. Prior to working on this case in connection with your expert report, had you done any research about glyphosate?
A. No.
Q. Did you even know about glyphosate before you were retained in this case?
A. No, not really.
Q. So in other words, you hadn't read the IARC Monograph 112 before being retained in this case?
A. That's right.
Q. Okay. Had you ever done any consulting work for Monsanto before this case?
A. No, I haven't.
Q. Did you ever do any consulting work for any other company before this case that manufactures pesticides?
A. No.
Q. Is this your first consulting work for industry?

A. I do do some consulting work for Cytel Software Corporation in Boston, but other than that, no. That's mostly to develop software.
Q. Okay. Right. I won't have a lot of questions to ask you about that.
A. All right.
Q. So approximately when were you contacted by -- let me -- is it the Hollingsworth firm that contacted you --
A. Yes.
Q. -- in connection with representation in this case?
A. Yes.
Q. And when was that first contact?
A. It was August, I think, last year was the first time I heard from Hollingsworth.
Q. Okay. And that was August of 2016?
A. I think so. August -- at the latest it was September. I know for sure it was no later than September.
Q. I just want to get the year

right.
It was 2016?
A. Yeah, about a year ago.
Q. Okay. And how long ago before you actually agreed to act as a consulting and expert witness in this case did you have contact from the Hollingsworth firm?
A. I'm not sure exactly how long, but I know that it was within two months.
Q. Okay. And who contacted you from Hollingsworth?
A. It was John Kalas.
Q. And what were you asked to do?
A. He asked me to review some data from the IARC monograph because I had some expertise in computing the trend test which was used for the animal toxicology studies, and so I reviewed their analysis.
(Corcoran Exhibit 21-3 marked for identification.)
QUESTIONS BY MS. GREENWALD:
Q. Okay. Let me mark -- so I'm first going to mark as 21-3 a letter dated August 31, 2016, from the Hollingsworth firm to you. Hand that to you.

A. Thanks.
Q. Is this the retention agreement between you and the Hollingsworth firm in connection with this case?
A. Yes.
Q. Okay. So if August 31st is the date you entered into this agreement, presumably if it was two weeks before that you first talked to them, you would have been in contact with them sometime in mid-August probably; is that right?
A. Yeah. I think that's right.
Q. Of 2016, right?
A. Yeah.
Q. Okay. And is there anything that the Hollingsworth firm asked you to do that's not reflected in Exhibit 21-3?
MR. GRIFFIS: Objection to the extent this calls for confidential communications between us and Dr. Corcoran as to things we asked him to do.
You can ask him about his expert report and his work in creating that.

THE WITNESS: As far as this letter goes, no --
MR. GRIFFIS: You don't need to answer.
MS. GREENWALD: Yeah, I think he's telling -- I think he's saying it's invading the attorney-client privilege, so I'll move on to something else.
THE WITNESS: Okay. Thanks.
MS. GREENWALD: Sorry.
(Corcoran Exhibits 21-4, 21-5 and 21-6 marked for identification.)
QUESTIONS BY MS. GREENWALD:
Q. Okay. So now I'm going to mark as 21-4 an invoice from you dated January 20, 2017, which covers the period August 16, 2016, through January 1, 2017.
A. Thanks.
Q. Sure.
And just for ease, I'm going to mark them all right now. I'm going to mark the next one as 23-4 {sic}, the invoice from you dated May 20, 2017, that covers -- wait, that must be 21-5. Yeah, I'm sorry, 21-5.

Page 22

That's my fault -- 21-5, the period of February 10, 2017, through May 20th of 2017, and I think I mentioned the invoice is dated May 20, 2017.

Okay. And then last I'm going to mark as 21-6 your invoice dated May 20th -- wait a minute. Is this one also dated -- just give me one second. I'm sorry. I'm just noticing something.

Yeah, it's also dated May 20, 2017. That threw me off. This covers the period May 21, 2017, through July 20, 2017, and again, I'm marking that as 21-6.

A. Thanks.

Q. And let me get you yours.

A. Oh, sorry, I think I put the wrong date on here. It was supposed to be July 20th.

Q. Okay. So I can -- I assume you've been continuing working on this case since July 20, 2017, obviously, right?

A. Yes. Yeah.

Q. This is just the last bill that you've given so far?

A. Right.

Page 23

Q. Okay. Approximately how much time -- so I notice on your -- on your invoices that you don't actually describe what specifically you're analyzing or reporting on; is that right?

A. No.

Q. So all of your entries are actually one of three types, basically.

A. Uh-huh.

Q. They're either data, analysis and report, or they reference a meeting or a teleconference, which I'll bundle as one type, or they're specifically mentioning that you are looking at a plaintiff expert report and again doing research and data analysis; is that right?

A. Yes.

MR. GRIFFIS: Objection to form.

QUESTIONS BY MS. GREENWALD:

Q. Okay. So you don't have any -- you don't have past experience, right, in doing consulting work in any kind of litigation; is that right?

A. That's right.

Page 24

Q. Were you asked to give general descriptions like this when you were retained?

MR. GRIFFIS: Objection. Don't answer that question.

THE WITNESS: Right.

QUESTIONS BY MS. GREENWALD:

Q. All right. Is this the type of -- so can you look at this -- these exhibits I just gave you, 21-4, -5 and -6, and tell me approximately how much time you spent reviewing the Greim papers and the supplemental materials?

A. Yes, I think I can. I can tell you that I would say that the -- if you look at -- from, I'd say, about January to -- January through the end of May, that would be the time that my effort was concentrated on the Greim supplement.

Because of the enormous amount of data that I had to -- that I had to enter based on the Greim supplements and the volume of work, the number of analyses that were performed, I'd say that, you know, during that period a good proportion of the time

Page 25

that was spent on the data analysis and report had to do with transcribing the data from the Greim supplement and analyzing it.

Q. Okay. And you said January through what month? Did you say May, through May?

A. I'd say the end of May.

Of course, you know, a lot of that had to do with the actual writing as well, but the volume of work involving the Greim supplement was concentrated during that time.

Q. When did you start working on your expert report, the writing of it?

A. I'm actually not sure exactly when I actually, you know, put pen to paper, as it were, but I would say probably in December-ish, around there, November, December, is when I actually started, you know, doing a bulk of the writing.

Q. So if you look at Exhibit 21-6 --

A. Uh-huh.

Q. -- and you have three entries: a May 6th, May 8th, and May 12th, plaintiff

Page 26

expert report, research and data analysis.
A. 21-6. Do you mean 21-5?
Q. I must have written the wrong number on here. I'm sorry.
A. The one I have with May 5th, 6th -- and 6th is on 21-5.
Q. I think I messed up because the date's the same on the invoice. It's my fault.
A. Yeah, sorry, that's --
Q. No, no, no, that's my fault. I could have gotten it right. I didn't.
Okay. All right. So let me ask the question again.
So if you look at 21-5, there's three entries from May 6th, May 8th, and May 12th of this year --
A. Uh-huh.
Q. -- and it says, "plaintiff expert report - research and data analysis."
Do you see those?
A. Yes.
Q. And those are the only entries that reference plaintiff expert report, correct?

Page 27

A. Well, there's the one on the 4th.
Q. On 21-5.
A. There's also the one on the 4th.
Q. Oh, I'm sorry, you're absolutely right. Thank you for catching that. So on May 4th also.
So those are the only four; is that correct?
A. Those are the only four listed on this invoice, yeah.
Q. Okay. Does that mean those are the four times that you were reviewing and -- or researching and analyzing the data of the plaintiff expert reports in this case?
A. I wouldn't say that those are the only times I actually referred to the plaintiff expert report, but I think that that reflects the fact that during that time I had just received the plaintiff expert report. And so the bulk of the time that I spent reviewing it was -- was on those four days.
But, you know, I've referred to

Page 28

it since, on and off, not in as significant a way -- in a way that I did during that time, but -- but that was where I spent the bulk of my time, initially studying his expert report.
Q. Okay. And if you look at all three invoices that you have produced in this case, which is 21-4, -5 and -6, am I right that those are the only four entries that you have in any of these invoices that reflect research -- I'm sorry, plaintiff expert report - research and data analysis?
MR. GRIFFIS: Objection to form. Misstates what he just said.
THE WITNESS: Those are the only four entries I have in my invoices, that's true, but I've referred to the plaintiff expert report many times on and off since.
That kind of is a natural part of, you know, data analysis is iterating. But certainly at that time I spent, you know, some focused time actually reading it and looking at his results.

Page 29

QUESTIONS BY MS. GREENWALD:
Q. Okay. When you say "data analysis and report" in these invoices, what does that mean?
A. It means analyzing the data that produced the results of my expert report and actually writing the expert report.
Q. Okay. And when you mention research/reading -- so, for example, on 21-4 there's several entries at the top that say "research/reading."
What does that mean?
A. Well, initially when -- when I was first given the IARC report and was first assessing it, I spent some time looking at the IARC report and also referring to, you know, some of my references that had to do with my analysis of that report, particularly that -- at the time, again, like I told you before, I was kind of tasked with looking at what they had to say about the animal toxicology results, and that was mostly focused on the study that in my expert report I list as the Knezevich study.
So that's what I was looking at

Page 30

at the time, the IARC report and just related materials, to kind of understand what they were doing.

Q. So your recollection is back then research/reading meant the IARC report and the Knezevich study?

A. And other material related to the issues that I was assessing with their computation of P value and the trend test and so on.

Q. And so how did you go about deciding what you were going to look at besides the IARC Monograph 112, I assume we're talking about, right, and the Knezevich?

A. Yeah, well, that's kind of a good question is, you know, how does any academic decide what they're going read, you know, when they're actually assessing, you know, the results from somebody else.

You know, my expertise happens to be in categorical data analysis, or that's part of my expertise, and so, you know, I was kind of relying on the typical sources that I use in that research area.

Page 31

Q. So what else would you have researched other than -- your expertise is in categorical data analysis, so -- so did you -- I'm just trying to understand, what would you have researched at the time -- again, I'm going back to September of 2016 -- besides IARC and, I believe you said, the Knezevich study?

What else did you research in those -- the first, appears to be, month, month and a half?

A. Well, what I was reading and what I was looking at is what was contained in the IARC report, mainly.

Q. Okay.

A. As far as, you know, how -- my expertise in terms of, you know, the trend test and so on, I mean, that arises from just kind of the bulk of my training over 20, 25 years.

Q. Okay. So when you were reviewing the material that was contained in the IARC report, did you look at any of the underlying materials that were cited in the IARC report, or was it just reviewing the

Page 32

IARC 112 itself?

A. I can't really recall exactly what I looked at at the time. I just read the report. I read about their analysis.

You know, I have a lot of years of experience doing the same kinds of analyses working in, you know, statistical software, and so that just more or less had to do with my evaluation of their analysis using, again, my -- my own history, my own training.

Q. So Exhibit 21-1, which is your expert report --

A. Right.

Q. -- did you write that report in its entirety?

A. Yes.

Q. Did you have help from anybody else in writing that report?

A. No.

Q. Is there any language in the report that someone else provided to you?

A. No.

Q. Do you recall how much time you spent analyzing Dr. Portier's expert report?

Page 33

A. No. I mean, I guess if I pore through my invoices for a while, I can, you know, try to give you an estimate of that again. But like I said, I think that's just largely reflected in my billing record.

Q. But how would you do that? Let's -- I mean, I'm not going to have you do that because I'm not going to spend the day having you pore through them.

But how would you go about, based on these three invoices that we marked here 21-4 through 21-6, how would you go evaluating, based on these entries, how much time you spent evaluating Dr. Portier's original report?

A. Well, part of it is my memory. I mean, I've been working on this for a year now. I've spent a lot of hours on it. And so I think were I to just kind of go through these invoices and, you know, recreate the, you know, the -- I don't know, I guess my sort of internal dialog in looking at his expert report and so on, I think I could probably give you a pretty good estimate if I were to, you know, sit down and kind of go

Page 34

through this month by month.
I mean, I worked on it very hard, personally, over the past several months, and so -- and so I have a pretty bright recollection of what I've done, more or less at a high level, from month to month.
So if you wanted me to actually kind of go through the invoices and reproduce that, I could.
Q. I don't want to you do that.
But you're saying reproduce it from memory. You don't have any handwritten notes that would more reflect what these entries mean, correct?
A. I wouldn't say I have a lot of handwritten notes. I just have -- I just have my expert report that basically reflects, you know, what it is that I've looked at, what I've prioritized.
Q. No, I understand that.
I guess I'm asking a slightly different question, and maybe I'm not asking it artfully.
I wanted to know whether you have any notes that underlie the entries in

Page 35

21-4 through 21-6 that would reflect time spent on, for example, looking at Greim and the supplemental material or Dr. Portier's original report. Or when it comes about, the next invoice, I assume, will show review of Dr. Portier's rebuttal report.
I wanted to know whether you keep any notes from which you then generate these invoices or whether -- or whether you just keep time, like, okay, today I worked one hour; tomorrow I worked -- I mean, yesterday I worked two hours, and that's -- and you don't have anything else but that?
MR. GRIFFIS: Objection. The discovery of notes is something that we have addressed in the MDL agreements in this case are privileged and not subject to discovery.
Dr. Corcoran, you can -- you may answer whether you have taken any notes and not as to the content of such notes.
THE WITNESS: You know, the truth of it is that I haven't taken many notes about what I did

Page 36

specifically. I kept these invoices as a record of work, and so the invoices reflect the effort from day to day. But I never took any notes that actually, you know, specified what I was doing from minute to minute.
QUESTIONS BY MS. GREENWALD:
Q. Okay. How about day to day? I'm not asking for minute to minute.
A. No, outside of these invoices, I have not.
Q. So your entry would generally be in a calendar or wherever you kept it --
A. Actually in the --
Q. -- data analysis.
A. Right.
And any invoice, as I was working, I would just kind of fill in hours on the certain days.
But the record of my work is in the expert report. I mean, that's where the -- that's where the summation of my work is, and so the expert report reflects actually what it is that I worked on.

Page 37

Q. And you've been paid up till now $107,250; is that correct?
A. That's what I've invoiced.
Q. I'm sorry, I should have asked it that way.
And you have continued to work since then?
A. Yes.
Q. Okay. Have you performed any additional analyses since -- sorry.
Have you performed any additional analyses since reviewing Dr. Portier's rebuttal report?
A. No.
Q. Have you done any research since receiving Dr. Portier's rebuttal report?
MR. GRIFFIS: Objection. Vague.
THE WITNESS: I haven't outside of just reviewing, you know, what's already been available.
QUESTIONS BY MS. GREENWALD:
Q. Did you review each of the 12 studies on glyphosate that you mentioned in

Page 38

the summary of your report?
And if you'd like to refer to it, it is line 7 through 9.
MR. GRIFFIS: Objection. Vague as to "studies."
THE WITNESS: Which page?
QUESTIONS BY MS. GREENWALD:
Q. Page -- I'm sorry, page 1 of your report. It says, "This report examines the rodent studies of glyphosate and cancer risk, particularly the seven feeding experiments using rats and five using mice that were reviewed in the expert report prepared by Dr. Chris Portier."
Do you see that?
A. Yes.
Q. Okay. Did you review each of the 12 studies that you refer to in line 7 through 9?
MR. GRIFFIS: Objection. Vague as to the word "studies."
THE WITNESS: Well, I guess I'm wondering what you mean by "review" and what you mean by "study."
Do you mean the published

Page 39

results as cited in the Portier report?
QUESTIONS BY MS. GREENWALD:
Q. No. I'd want to know if you reviewed any of the underlying data or manuscripts or documents relating to the 12 -- the seven feeding experiments using rats and the five using mice that you reference in line 7 through 9, other than the summaries in Greim and other than what is referenced in Dr. Portier's report and IARC.
A. I am not sure. I mean, I think the bulk of my knowledge about these 12 studies comes from, you know, the collective work that's been cited both by me and Dr. Portier.
So, yes, the Greim -- the Greim study or the Greim publication, actually, was a comprehensive review that both myself and Dr. Portier relied on for expert reports, so I reviewed that.
I've, you know, reviewed every page of data in the Greim supplement because I, you know, basically hand-entered it since that was the only means possible to actually

Page 40

analyze the data from that report.
And I looked at the IARC report.
I've read a lot of the background material that was -- that's been provided, I think -- well, for example, the EPA report, Portier's report.
I guess in that sense, yes, I've reviewed the studies through the various sources that were available to me.
Q. Okay. You're working on behalf of Monsanto Corporation in this case, right?
A. No. I'm working for Hollingsworth --
Q. Sorry.
A. -- as far as I know.
Q. But it's on behalf of Monsanto, correct?
A. Well, I'm invoicing Hollingsworth, and so...
Q. Let's go back to Exhibit 21-3, which is your retention letter.
A. Right.
Q. This first sentence reads: "This letter confirms that Hollingsworth,

Page 41

LLP, on behalf of Monsanto Company, has retained you to provide expert consulting services to HLLP for the purposes of assisting HLLP in representing Monsanto in connection with potential and/or actual litigation against Monsanto involving injuries allegedly caused by Roundup and/or glyphosate, paren, the litigation, close paren," close quote.
Do you see that?
A. Yes.
Q. Okay. So is it your understanding that your work is on behalf of Monsanto in connection with litigation brought against Monsanto by various plaintiffs?
A. Well, it's my understanding that I'm working for Hollingsworth and that they're representing Monsanto, yes.
Q. So as you sit here today, you don't believe you're doing work for the benefit of Monsanto?
MR. GRIFFIS: Objection. Argumentative. Asked and answered.
THE WITNESS: I've just been

asked by Hollingsworth to help them perform an independent data analysis, and that's my understanding, that it's on Monsanto's behalf for the sake of this litigation. But I'm doing this for Hollingsworth -- or I guess in the employment of Hollingsworth.

QUESTIONS BY MS. GREENWALD:

Q. Have you been paid on any of your invoices yet?

A. Yes.

Q. Do you get your check from Hollingsworth?

A. Yes.

Q. But just to be clear, you do understand this work is being done on behalf of Monsanto, correct?

MR. GRIFFIS: Objection to form. Argumentative. Asked and answered multiple times.

THE WITNESS: Well, you're right, you read the -- you read the letter of retainer, and that's my understanding.

QUESTIONS BY MS. GREENWALD:

Q. Okay. Did you receive the underlying data for any of the studies that are -- any of the 12 studies that were sponsored by Monsanto?

A. Well, through the Greim supplement? Yes.

Q. No, the actually studies.

Do you know whether any of those 12 studies that are referenced in the Greim paper were Monsanto-sponsored studies?

A. My understanding is the -- like the initial study I looked at, the Knezevich study, that was a Monsanto-sponsored study, but I haven't actually been in communication with any of the original, you know, scientists who conducted those studies, no.

Q. Do you know whether any of the other studies -- any of the other 12 besides Knezevich were Monsanto-sponsored studies?

A. I can't recall off the top of my head which ones were sponsored by Monsanto and which ones weren't.

Q. Well, if I told you that the Lankas study and the Stout and Ruecker study

were Monsanto studies, would that help refresh your recollection?

A. I guess that would be interesting. I mean, I'd like to see the source to verify that, but it wouldn't really change any of my conclusions. I mean, they're the -- they're the studies that were analyzed by --

Q. Okay. So --

MR. GRIFFIS: Excuse me, I don't believe Dr. Corcoran was done with his answer.

MS. GREENWALD: Oh, I'm sorry, forgive me.

THE WITNESS: Oh, I'm sorry. I just didn't know if you were listening to the rest of my answer.

I just know that they were the 12 studies that were analyzed by Dr. Portier, and so I used the same 12 studies that were presented in Greim.

(Corcoran Exhibit 21-7 marked for identification.)

QUESTIONS BY MS. GREENWALD:

Q. Okay. I'm going to mark now --

we have to staple this together. I apologize. The stapling came apart, but we'll use a paperclip or something.

I'm going to mark Exhibit 21-7, which is an article from Critical Reviews in Toxicology, and the first author's name is Helmut Greim, and ask you to take a look at that.

A. Thanks.

Q. Sure.

If you can go to the -- so is this the Greim paper that we've been talking about so far this morning?

A. Yes.

Q. Okay. If you look under table the contents --

A. Uh-huh.

Q. -- on the left-hand column --

A. Yes.

Q. -- you'll see that it says, "Rat carcinogenicity."

Do you see that?

A. Yes.

Q. And it says, "Study 1, Monsanto, 1981"?

Page 46

A. Uh-huh.
Q. And it says, "Study 2, Monsanto, 1990"?
A. Uh-huh.
Q. Do you know which studies those are?
A. Do you mind if I look?
Q. Not at all.
A. So it looks like that was the Lankas study, using my own table in my expert report in the Stout study.
Q. Okay. And then to the right of that, the remainder of the table of contents mentions under "mouse" -- do you see that?
A. Uh-huh.
Q. -- study number 10 --
A. Right.
Q. -- and it says "Monsanto," correct, "1983"?
A. Right.
Q. And that's Knezevich?
A. That's the Knezevich study, yes.
Q. Okay. So -- and those are the only three in the table of contents that

Page 47

reference Monsanto as the sponsor of the study, correct?
A. It looks like it, yeah.
Q. Okay. So you read the Greim paper, right?
A. Yes.
Q. In fact, you said you spent a lot of time studying it, right?
A. Yes.
Q. Okay. Did you ever ask Monsanto for the underlying data for those three studies?
A. Well, no. I mean, since they were available in the supplement of this paper, I didn't think it was necessary to go and look for the data elsewhere.
I mean, it appeared that, you know, based on the number of citations that this paper has received, that most everybody agrees that data in the Greim supplement are acceptable.
Q. But, I mean, is that -- as you sit here today, do you believe that all of the data in the Greim paper are accurate?
A. Well, I can only make my

Page 48

judgment based on what everybody else has found acceptable. And I know that those were the same data used in the Portier report and in some other sources, and so I have to assume that they're credible.
Q. Well, of course, Dr. Portier doesn't work on behalf of Monsanto Corporation, does he?
A. No.
Q. And so he wouldn't have had the same access to these papers as you might have had, for example, as a person who is working with the Hollingsworth firm on behalf of Monsanto; isn't that right?
MR. GRIFFIS: Objection. Argumentative. Misstates testimony.
THE WITNESS: Well, I don't really know. I don't know what kind of access Hollingsworth has to Monsanto data. But, you know, if they've been made freely available through the Greim paper and other people have used them besides Dr. Portier and myself, I have to assume that they're -- that the data

Page 49

are sound.
QUESTIONS BY MS. GREENWALD:
Q. So if you have a choice, just generally speaking -- take it out of the context of this litigation and this case, even your report.
If you have a choice between reading a paper that summarizes someone else's data or actually getting the data itself, the actual study itself, which would you choose as you do research?
A. Have you seen the Greim supplement?
Q. I have.
A. Because the data tables are the original tables from the scientists who actually produced the data. So as far as I -- as far as I know, they look like the original, you know, documents that were produced by these scientists who actually carried out the study.
So I don't know that there was a more original source than what was -- what seemed to be available through the Greim supplement. Unless somebody actually used

Page 50

Wite-Out on those sheets, I think those were the original data tables.
Q. Do you know as you sit here today that the supplements to the Greim paper are the actual results from the 12 studies?
A. Well, if they aren't, I guess I'm not sure why we're sitting here.
Q. I'm just asking -- I'm -- I don't want to -- I'm just asking a simple question, and if you want me to rephrase it, I can.
I just want to know, as you sit here today, whether you know that the data that's attached as supplements to the Greim paper are in fact the data from each of those 12 studies.
A. Well, I assume that based on their use by multiple other scientists, including myself, Dr. Portier and others.
Q. Okay. But you don't know; you assumed it. Is that right? Is that fair?
I just want to make sure I understand your testimony, that's all.
A. All I can say is just I have to assume that because everybody else is

Page 51

treating these data as credible, and so it makes sense for me to do the same.
Q. Well, okay. I don't know that -- let's move on from that for a minute, but let me go back to the question I originally asked.
As a -- if you're working on a subject, whatever that subject is, and you have a choice of looking at an article or a study or a paper that summarizes the works -- of the work of others or getting the actual work that's the underlying work that's summarized in that study, which would you choose?
A. Well --
MR. GRIFFIS: Objection. Asked and answered.
MS. GREENWALD: No, he never asked that question, actually.
THE WITNESS: I'm actually happy to answer it because this paper that you gave me is the summary. The supplement that I used to actually, you know, hand -- hand-enter the data, those supplements are the data tables

Page 52

that, you know, everybody has relied on who has looked at glyphosate across the 12 studies.
And so you're kind of asking two different things. One is, am I relying on the summary?
Well, I'm not relying on this summary for the data. I'm relying on the supplements which contain the original data tables.
QUESTIONS BY MS. GREENWALD:
Q. Which you assume contain the original data tables, correct?
A. Of course, yeah. I assume that because, you know, Dr. Portier and other scientists have used the same tables.
Q. Okay. So your -- I'm going to go back to my question for a minute.
If you're not looking at Greim -- and we're not talking about glyphosate --
A. Uh-huh.
Q. -- and you don't know if other people have relied on it, okay, you don't know what other people have done, and you

Page 53

have a paper that's a summary paper, and you have a choice of reviewing the summary paper that reviews data of another or actually getting the paper that has the -- of the actual person who conducted the study, which would you choose?
A. Well, you know, that's an interesting hypothetical, but that's not what happened here.
Q. I understand that's not what happened here. I want to know what you would pick.
A. Well, what happened here is I got the original data that was used and cited by, you know, several other scientists, including Dr. Portier, and so that helps to reassure me that these data are credible. That's what happened here.
You know, what I would do in another case, I can't say. I mean, you'd have to put me in that position and show me the data, and I'd have to make an independent judgment in that case.
In this case, all I can say is everybody's used these data. If they're not

Page 54

credible, then I guess there's no reason for us to really be here.
Q. So hypothetically speaking, and it doesn't have to be in the context of a litigation, I just want to know if you would choose a summary paper of another person's data over the actual data of this study --
MR. GRIFFIS: Objection.
QUESTIONS BY MS. GREENWALD:
Q. -- if you had access to both.
MR. GRIFFIS: Objection. Asked and answered multiple times.
MS. GREENWALD: I have not gotten an answer to that question.
QUESTIONS BY MS. GREENWALD:
Q. I just want to know which one you would choose.
Outside of the context of this litigation, in any research you're doing, would you not want to get the underlying study over a summary paper that is reviewing that data and other data together?
A. Again, as a statistician who has been practicing for over 20 years and looking at people's data, the supplement that

Page 55

was provided in Greim is nearly -- you know, it tabulates data in as nearly raw a form as I could imagine. So I have no question that the data in the Greim supplement are credible based on their use by Portier and other scientists.
So there's no hypothetical necessary because I'm not using a summary paper. I'm not using this paper for the data. I'm using the supplement to this paper which actually contains the original data tables.
Q. Does Greim include the individual animal pathology for each study in its supplements?
A. No.
Q. Are pathology reports typically part of underlying data of a study?
A. Yeah, absolutely. That's why I said there -- that's why I actually said they're nearly as original as -- the tables that are presented are the original tables based on their tabulation of the original animal data.
Q. It doesn't contain the

Page 56

pathology report, correct?
A. No.
Q. Now, if you've answered this before, I'm sorry, but I don't recall that you did.
Did you ever ask Monsanto or Hollingsworth for the underlying data for the Lankas study, the Stout and Ruecker or the Knezevich and Hogan?
MR. GRIFFIS: Objection. Asked and answered.
THE WITNESS: I didn't ask --
QUESTIONS BY MS. GREENWALD:
Q. Other than Greim, did you ever ask --
A. I didn't ask for any additional data because the Greim data are the ones that everybody seems to rely on, are the data that everybody seems to rely on.
Q. So if you can look at exhibit -- I'm sorry, yeah, Exhibit 21-1.
A. Sure.
Q. And if you could go to page -- so you have -- first, get past your expert report. So get past page 47.

Page 57

Because of the numbering here, I don't know else how to do it. So go past the expert report and get to the materials considered, which is five pages. It's 1 of 5.
And if you go to --
A. 1 of 5? Okay. Got it.
Q. If you can go to page 3 of 5?
A. Right.
Q. And if you can go to entry 39, please?
A. Uh-huh.
Q. So you reference the Knezevich and Hogan paper here, right?
A. Uh-huh, yes.
Q. Does that mean you considered the actual underlying study of Knezevich and Hogan, or are you referring to Greim here in 39?
A. I'm not sure I understand what you're asking.
Q. Well, did you have the Knezevich and Hogan paper?
A. Yeah, that was available to me.
Q. And did you have the underlying data for Knezevich and Hogan?

Page 58

A. Yeah, through that source, the individual-level data are available, yes.
Q. Okay. So why did you want it for Knezevich and Hogan if you had Greim?
MR. GRIFFIS: Objection. Form.
THE WITNESS: I'm not -- again, I'm not quite sure what you're asking, but Greim contains the same totals that you could obtain from Knezevich.
QUESTIONS BY MS. GREENWALD:
Q. Okay. So then let me ask that question again.
If Greim, if I understand your answer correctly, contains all of the data that you needed to do your work, why would you have consulted the Knezevich and Hogan study but not any of the other studies that you -- that were Monsanto studies?
A. Those -- if you're -- are you asking about individual-level data? Is that what you're asking me?
Q. I'm just -- so, okay, let me make it in smaller pieces.
For number 39, did you actually get the Knezevich and Hogan underlying data?

Page 59

A. Those were available, yes.
Q. And available from Monsanto, correct, or did you get them somewhere else?
A. No, I did not get them from Monsanto.
Q. Did you get them from Hollingsworth?
A. I actually don't know. I think most of -- most of the material I received was through Hollingsworth, so...
Q. Okay. Did you ask to get the Knezevich and Hogan study in particular? Did you ask for that study?
A. No.
MR. GRIFFIS: Objection to "communications."
Please don't answer questions about what you asked for and were sent specifically by us.
THE WITNESS: Oh, okay.
QUESTIONS BY MS. GREENWALD:
Q. Can you estimate about how many hours you spent reviewing the Greim paper and the associated supplemental materials?
A. I think you asked that earlier,

Page 60

and I -- like I said, I think that based on my invoices, the bulk of that analysis was -- that examination of the Greim supplement was probably the first four or five months of this year, through May.
Q. Did you do any calculations of the animal bioassay data in Greim using false data -- I'm sorry, false discovery rate?
A. Did I use --
Q. Did you do any calculations of the animal bioassay data in Greim using false discovery rate?
A. I'm sorry, what -- what -- what calculations are you talking about?
That's kind of a confusing question.
Q. Well, did you apply the false discovery rate to any of the animal bioassay data in Greim?
A. Are you talking about the animal bioassay data that I analyzed in my expert report? Is this what we're talking about?
Q. From -- I'm asking about the data of Greim, which you said you've

Page 61

reviewed.
A. Right. So my expert report, like I said, those are the data that I used. I obtained those data from the Greim supplement.
Q. Uh-huh.
A. Uh-huh.
Q. And did you apply the false discovery rate to that data?
A. I used false discovery rate -- false discovery rate approach to, you know, adjust for multiple testing, as I outlined in my expert report.
Q. So where are those calculations in your report?
A. There's -- there's a section -- first of all, going to page 6, I guess pages 5 and 6, I talk about why some sort of adjustment for multiple testing is necessary when you're -- when you're looking at hundreds, in this case, of tumor types simultaneously.
Q. So let's just stay on that page for a minute --
A. Okay.

Page 62

Q. -- okay, because otherwise we'll have to double back.
A. All right.
Q. Did you do any -- did you do any calculations using the false discovery rate on pages 5 or 6?
A. I applied the false discovery rate correction that's mentioned on page 6. I applied that to the data as I describe in Section 4.
Q. Okay. Where on page 6? Which lines?
A. Page 6 -- I'm sorry, page 6 is where I say I talk about -- I give some context for multiple testing then talk about why it's necessary, but the calculations are not on page 6.
Q. Okay. I'm sorry. So let's move on from 6 then.
So where else?
I'm sorry, you were going to show me where in the report --
A. Oh, I'm sorry.
Q. No, it's my fault. I should have gone back to that.

Page 63

So where in the report do you show any calculations of the data using the false discovery rate?
A. Let's see. On page 9, and this is where I mentioned that these calculations -- I performed these calculations.
Q. Can you tell me which line?
A. Uh-huh. Starting in the paragraph that starts at line 15.
Q. Okay.
A. And then I report -- starting on the next paragraph, on line 28, I report kind of the results of that analysis. And then as I -- I adjusted for the false discovery rate for every -- every P value, but to not bulk up the appendix, I focused on those that had -- that had P values less than .05. So those are reported in the appendix, in Appendix C.
Q. So Appendix C --
A. It's on page 47. Or I'm sorry, appendix -- yeah, Appendix C and Appendix D. Pages 46 and 47.
Q. So make sure -- I just want to

Page 64

make sure I understand this correctly.
Appendix C and Appendix D on pages 46 and 47 are the places where you applied --
A. The calculations are not contained here. The results are contained here. The results are summarized in Appendices C and D.
Q. All right. So just make sure I understand. Page 5 and 6 where you talk about the content -- or the context of the false discovery rate, right?
A. Yes.
Q. And then the next page you referred me to was page 9, the paragraph starting at line 15, correct?
A. Yeah. So pages 9 and 10, I think that's where the results for the P value analysis are reported.
Q. Anywhere else in the report?
And I understand -- I understand Appendix C and D --
A. Appendix C and D, right.
MR. GRIFFIS: Excuse me. Objection. If this isn't just a test

Page 65

of his current memory and you want him to find every single spot, he's going to have to look because there are other pages.
THE WITNESS: I guess I'd add that, you know, the multiple testing is also discussed on pages 11 and 12 and 13, starting with the beginning of Section 5 and extending through Section 5A.
If you're interested in other incidents where I mentioned -- or other occasions where I mention multiple testing, I mention that also in Section 5B with respect to his analysis, Dr. Portier's analysis, of historical controls.
And I also mentioned the issue of multiple testing within Section 5C with respect to his pooled analysis.
QUESTIONS BY MS. GREENWALD:
Q. Those two sections you just talked about, though, don't have any calculation of yours, correct?
A. It talks about -- you were

Page 66

saying earlier -- you said there were multiple testing issues, and so I'm just pointing out that those are other places where I mentioned that as well.
Q. Okay. Now, number 66 in your consideration material --
A. Uh-huh.
Q. -- mentions Weber.
A. Uh-huh.
Q. Klaus Weber.
MR. GRIFFIS: We've been going about an hour, so when you find a good spot, I'd like to take a break.
MS. GREENWALD: After this question, we can do that.
THE WITNESS: Right, I got it.
QUESTIONS BY MS. GREENWALD:
Q. So you also reviewed the evaluation done by Klaus Weber; is that right?
A. Yes.
MS. GREENWALD: Okay. So you want to take a break now?
MR. GRIFFIS: Sure, yeah.
THE WITNESS: I'm fine if you

Page 67

want to continue with the Weber line of questioning.
MS. GREENWALD: It's up to you guys. I'll let you discuss it.
THE WITNESS: And we can take a break after we discuss Weber.
MS. GREENWALD: The post-Weber break.
QUESTIONS BY MS. GREENWALD:
Q. How did you get the Weber paper?
A. I got it through the attorneys at Hollingsworth.
Q. Who is Klaus Weber?
A. I am not sure exactly where he is from. I mean, I've -- I actually looked at the paper, but I can't remember where he's from or what his affiliation is.
Q. Okay. Have you ever heard of the Glyphosate Task Force?
A. Affiliated with whom?
Q. I just want to know if you've ever heard of the Glyphosate Task Force.
A. It's talked about in the information that I've --

Page 68

Q. It's not in your report, I promise you.
A. I don't recall off the top of my head --
Q. Okay.
A. -- knowing much about that.
Q. Okay. Do you know whether Klaus Weber is a consultant for Monsanto?
A. I actually don't.
Q. Okay. What did you understand to be the purpose underlying the Weber paper?
A. My evaluation of it was just that it was -- there was -- you know, there was an additional pathology report, and so some -- as I said in my expert report, it appeared that some of the counts changed for a couple of the tumor types, and so I reevaluated and included a table in my report to address that.
Q. Part of the reason for the Weber report was to look at the Kumar study to see if there was a virus in the mice?
A. I don't know what the purpose was of the Weber paper. I just know that I, you know, analyzed the data that were kind of

Page 69

re-reviewed in that paper.
Q. Okay. Did the Weber paper factor into your opinions in your expert report?
A. Well, I included it in the expert report.
Do you mind if I just turn to it so I can --
Q. No, no, no, your expert report is yours to review and look at any time during this deposition today.
A. I think that -- I think on page -- it's page 11, starting at line 3, that kind of summarizes my, you know, use of my opinions based on the Weber analysis.
So I -- like I said, some of the reported tumor counts differed slightly from the data in Greim, so I, you know -- I included an additional table.
I had -- I had the Kumar mouse table based on what I got from Greim, and then I had an additional table that I included in my appendix based on this Weber reevaluation. But as I said, it didn't really change my overall conclusion.

Page 70

Q. So you accepted the numbers in the Weber paper over those contained in Greim; is that correct?
A. Well --
Q. In reaching -- I'm sorry, in reaching your opinions in this case?
A. Well, I don't know if I, you know, give one more credence than the other. I think that because that paper was made available, and it was kind of made available late in this process, that I became aware that these data were available.
I just included that table for the sake of completeness, but I wouldn't say I have an opinion about, you know, which data are the more airtight.
Q. When you have two different data sets for the same study, how do you decide which one you're going to use?
A. Well, that's a good question, but the issue with this whole analysis is that we have hundreds and hundreds of tumors that we're looking at.
Now, in the case of Weber, you know, there were some counts that changed for

Page 71

some of the reported tumors, but we still have the overarching issue that there are hundreds and hundreds of tumors that we're evaluating at the same time. So in other words, there was nothing that changed about the overall analysis accounting for all of these tumors when I actually, just for the sake of, you know -- just for the sake of completeness analyzed those changed tumor counts as well.
Q. So in reaching your opinion in this case, are you saying it doesn't matter whether you use the numbers from Greim or Weber?
A. Oh, it matters.
Q. I just want to make sure -- I want to make sure I understand your testimony.
A. That's why I included both. That's why I included both, because it does matter which numbers you're using.
What I am saying is that because of the number of analyses that we're doing, that's the thing that really impacts the bottom line here. How many tumors are

Page 72

we, you know, investigating here. I mean, we're investigating hundreds.
And so the question is, well, okay, if the Weber reanalysis, if that's the one that's accurate, then, you know, let's analyze the data using -- using the Weber data, and let's see what happens.
And there was no change in the substantive conclusions based on that analysis.
So whether we used the Weber or whether we used kind of the original Kumar data from Greim, it really didn't make any difference.
Q. But the Weber study, am I not correct, realized that the study authors in Greim had conflicting numbers; isn't that right?
A. Again, I would have to go back and read the entire Weber paper to know exactly what motivated the paper. All I know is that I got the data from the Weber reanalysis that I included for the sake of completeness. And either way, using the Kumar data from Greim, using the Weber data,

Page 73

it didn't make any difference.
Q. Do you recall sitting here today whether Weber reanalyzed the original -- the original histopathological -- histopathological data?
A. Histopathological.
Q. Histopathological.
Wow, I can't get it out today.
A. No, I don't recall that off the top of my head.
Q. You don't recall?
A. But if I -- again, if I had a chance to read the entire paper, I could tell you.
Q. Well, at the time you wrote your expert report, would it have made a difference to you if you knew that Weber had reanalyzed the original histopathological --
A. Histopathological.
Q. -- histopathological data? Would that have made a difference?
A. I don't know how a court reporter keeps up with a word like that.
Q. Histopathological. Sorry about that.

Page 74

Would that have made a difference to you?
MR. GRIFFIS: Objection. Asked and answered.
THE WITNESS: Oh. Well, like I said, I went over the reanalysis of time in my expert report. You know, I analyzed the data, I included the table, and it didn't change my overall opinion.
QUESTIONS BY MS. GREENWALD:
Q. Did you count the tumors reported by Weber in the Kumar study when you came to your 1,016 that's on page 9 of your expert report?
A. You know what, I don't know. I mean, I -- I don't think that given that we're talking about a handful of tumors that it would have changed the discussion.
I think on page 9 -- is that what we're talking about?
Q. Yeah, of your 1,016 that we talked about earlier, I wanted to know whether you counted the tumors reported by Weber.

Page 75

A. I think that the 1,016 is based on my analyses of the data from Greim.
What I'm basically saying on page 11 is, yes, you know, I didn't change the numbers in the previous paragraphs to reflect the Weber data because the Weber data came to me so late.
What I did do is I looked at the Weber data and I did -- I did take that into consideration with regard to the overall numbers of tumors, the 1,016, as well as the 345 tumor types that had at least three incidence of tumors.
So I weighed that, but that didn't change substantively.
MS. GREENWALD: Okay. Break time.
THE WITNESS: All right. Thanks.
VIDEOGRAPHER: We're going off the record. The time is 10:24.
(Off the record at 10:24 a.m.)
VIDEOGRAPHER: Okay. Back on the record. The time is 10:43.

Page 76

QUESTIONS BY MS. GREENWALD:
Q. Dr. Corcoran, do you recall about how many pages the full Knezevich and Hogan study was that you reviewed?
A. No.
Q. Do you remember if it was like hundreds of pages? A thousand pages?
A. I don't at all.
Q. And do you recall how many pages the supplement is to the Greim paper relating to the Knezevich and Hogan?
A. Like I told you before, I know it was a ton because I went through them by hand, but I can't remember exactly what the number is.
Q. So do you recall sitting here today whether the data set was much larger in the actual Knezevich and Hogan study that you received versus the supplemental material that was attached to Greim?
A. So what do you mean by "larger" exactly?
Q. Just many more pages, many more pages of data and information when you had the actual Knezevich and Hogan study.

Page 77

A. Like I said, I don't know how many pages the Knezevich study occupied.
Q. I'm asking a different question. So I realize you don't know the number of pages.
I'm just asking if you recall as you sit here today whether the -- did the actual materials that were associated with the actual Knezevich and Hogan study that you received, which is in your consideration material, was a much larger set of materials than what's attached as a supplement to the Greim paper.
A. Yeah, I don't remember what the relative size was.
Q. Okay. So do you recall the Suresh study?
A. Yes.
Q. Okay. Isn't it true that there was a 48 percent tumor response rate in the controls in the Suresh study?
A. You know, if we're going to look at actual data, I think I'd have to have, you know, kind of something in front of me to recall things like that.

Page 78

Q. Okay. So what would you --
A. I mean, there are like, you know, over a thousand tumors that I entered. I can't remember exactly what the response rates were in every treatment group for every study --
Q. Okay. So -- sorry.
A. -- every tumor type.
That's all right.
Q. What could I give you that would help you?
So you have Greim, and you have your report. I also have a copy of Dr. Portier's expert report, and I have a copy of his rebuttal report.
A. Well, I would need to have something that actually shows me the data from the Suresh study that you're talking about for that particular tumor type. So wherever that is.
Q. So I'm going to go back to that --
A. Okay.
Q. -- so we don't waste time here.
Okay. So I'd like to talk a

Page 79

little bit about your background.
A. Okay.
Q. And your CV is contained in your expert report right after your consideration materials.
A. I've got it.
Q. So it's in Exhibit 21-1, and it's 1 of 28 pages, correct?
A. Right.
Q. And it says a report generated on July 29, 2017, correct?
A. Yes.
Q. So is this your most updated CV?
A. As of July 29th, yeah.
Q. Okay. Nothing substantial has happened in the last two months that would require updating in your CV?
A. I'm not -- I mean, in terms of papers published, I'm not totally sure, but, no, nothing in terms of my professional positions or anything.
Q. Okay. On pages 4 and 5, you have a section of book chapters that have been published.

Page 80

A. Uh-huh.
Q. Do any of these publications involve methodology to be employed for evaluating animal bioassays for cancer outcomes?
A. Yes. I mean, there are chapters here that could be applied to the analysis of the data that we're talking about here.
You know, I suppose that you could say that any one of them, you know, in some sense relates to the analysis of animal toxicology data if these methods are useful for analyzing data from a given experiment.
Q. Do they actually contain information about application of these methods to animal toxicology?
A. You know, often in my area of research where we're developing or describing methodologies, we'll use examples that illustrate the utility of the methods, and I actually don't know off the top of my head if we used any --
(Telephone interruption.)
MS. GREENWALD: I apologize. I

Page 81

turned it on at the break and I forgot to turn it off.
THE WITNESS: No problem.
I don't really know if I used any examples from animal toxicology studies, but it's possible.
QUESTIONS BY MS. GREENWALD:
Q. Okay. So on the top of page 5, you reference analysis of correlated data StatXact, that's S-t-a-t, capital X-a-c-t, version 8.0 user manual, paren, PP 895 to 935.
A. Per version 8, yeah.
Q. Okay. So can you explain what your work has been with StatXact and preparing a user manual?
A. Sure. I -- my advisor, Cyrus Mehta, when I was in graduate school, was the founder of Cytel Software Corporation, and so I've worked on research projects with him and other colleagues at Cytel since I was a graduate student in the late '90s. And some of the research that I've conducted in statistical methods has actually been implemented in their software package

Page 82

StatXact. And so because my work was used, I helped them to write parts of the user manual.

Q. So was part of your -- so you said he was your advisor in your Ph.D. program?

A. That's right, yeah.

Q. Okay. Was part of your work in your Ph.D. program working on StatXact then?

A. My doctoral program?

Q. Right.

A. Not directly.

Q. Okay.

A. It's just that they found that what I developed was useful, and they felt like it should be made available for other people to use and apply.

Q. Do you know what the first version of StatXact was?

This says version 8. I don't know --

A. Version 1.0. I mean, that was before I even met my advisor. That was probably in the late '80s that that was developed.

Page 83

Q. Okay. That's what I was wondering. Late '80s. Okay.

And this version 8 would have been in approximately what year, 2009?

A. Yes, 2009 when the reference -- the date for that reference.

Q. So you didn't actually help develop StatXact, correct?

A. No.

Q. And have you been part of the development of any of its later versions?

A. Indirectly. You know, the way that StatXact works is it's just a suite of software tools that people use in statistics and data analysis, and so, you know, their versions kind of build, they just add compatibilities.

And so, you know, I've served to kind of evaluate later versions. I haven't made, you know, any really huge contributions to -- like new capabilities in that package.

Q. Okay. So when they update StatXact, would it be fair to say that you're consulted or you give advice on the --

Page 84

A. Sometimes, yeah.

Q. -- supplementation or I mean on the new version?

A. At times, yeah.

Q. Okay. Are you under a consulting agreement with -- let me step back for a minute.

StatXact is owned by Cytel, right?

A. Yeah.

Q. Cytel Corporation?

A. Yeah.

Q. Okay. Are you under retainer with Cytel Corporation?

A. Not right now.

Q. Were you ever?

A. No, not under -- I never signed any formal retainer. We had grants from the National Institutes of Health to develop software. That's what led to the implementation of some of the modules in StatXact that I helped to, you know, develop and document. And so I was paid as a consultant out of those NIH funds.

Q. By Cytel?

Page 85

A. By Cytel Software Corporation, yeah.

Q. Okay. So if I understand that right, Cytel had a grant from the NIH; is that right?

A. Yeah, they've had several.

Q. Okay. And one of the grants that Cytel has from the NIH is working on developing and further developing StatXact; is that correct?

A. Yeah. That's correct.

Q. Okay.

A. They're called small business innovation research grants where they try to take innovative technology and make it commercially available.

Q. Okay. And so you -- so your consulting work with -- on StatXact then has been through Cytel?

A. Right.

Q. Okay. Other than your work with Cytel on advising on updated versions of StatXact and preparing the manual, have you done any other work with Cytel relating to StatXact?

Page 86

A. No.
Q. Did you get paid for writing the manual?
A. No. I mean, through the, you know, NIH grant consulting, I guess you could say.
Q. Okay. So the manual update was also part of the NIH grant?
A. I think more or less, yeah.
Well, I'm -- I think -- I wasn't paid directly to write parts of the manual. It's just that I did it because, you know, as an academic statistician, that's what I do, I publish. And so I was participating with the documentation of that manual.
Q. But this analysis of correlated data that's referenced on the top of page 5 of your CV is not -- it's not a peer-reviewed, published manual, is it?
A. No. That's why it's under book chapters.
Q. That's what I thought. Okay.
A. Right. Book chapters are separate from peer-reviewed -- or the referee

Page 87

journals articles below that, those represent peer-reviewed publications.
Q. Right.
A. That's why I'm keeping them separate from book chapters.
Q. That's what I thought.
A. That's --
Q. I was just a little confused by your answer before.
So you answered, "It's just that I did it because, you know, as an academic statistician, that's what I do, I publish. And so I was participating with the documentation of that manual."
But you don't mean that you've done publications for peer-reviewed journals with respect to your work with StatXact, right?
A. No.
Q. Okay.
A. I mean, just to be clear, you know, that's kind of what happens in academic statistics. If you -- you know, if you develop something that is -- that has high utility, then often, you know, software

Page 88

packages such as SAS, StatXact, SPSS or whatever, they implement those tools so they're available to a wider number of users.
So in other words, the things that I've contributed to StatXact are things that I've published that are below, kind of in my list of refereed journal articles that are now available through a widely used software package so that other people can use those tools as well.
Q. About how much money have you been paid from Cytel over the course of your professional career for your work on StatXact?
A. I have no idea.
Q. Can you approximate?
A. No, I can't. I mean, I've worked for them for -- since I was a graduate student. There was would no way for me to approximate that.
Q. Do you know how much you made last year from Cytel?
A. No. I mean, not off the top of my head. I'd have to -- I'd have to go check through my records.

Page 89

Q. Can you give me a range?
Are we talking about $10,000? $50,000?
A. I really don't know. I mean, I'd have to go back and check my records, you know, my invoicing records with them, but I wouldn't want to venture a guess off the top of my head.
Q. I'm not asking you to guess.
So you're saying as you sit here today, you can't even give me a range of how much you made in payments from Cytel in the year 2016?
MR. GRIFFIS: Objection. Asked and answered.
QUESTIONS BY MS. GREENWALD:
Q. I'll make sure I understand your answer.
A. Yeah, that's what I'm saying. I'm saying I'm not sure that I can give you a range without going and checking.
Q. You said you've been paid by them since you were doing your doctoral thesis, right?
A. To varying -- in varying

Page 90

amounts, yeah, depending on, you know, what projects we have going on.
Q. Would you say it's been every year that you've had a project from them that you've been paid by them?
A. No, it hasn't been every year.
Q. In the last ten years, have you been you paid by them every year?
A. No. I'd say no.
Q. In the last --
A. But again, I mean, I -- I wasn't prepared to answer questions about my invoicing history with Cytel, so I'd have to go back and actually recreate that billing history to know for sure.
Q. Have you ever been an employee of Cytel?
A. No.
Q. Have you ever served as a board member?
A. No.
(Corcoran Exhibit 21-8 marked for identification.)
QUESTIONS BY MS. GREENWALD:
Q. Let me mark as Exhibit 21-8 a

Page 91

PowerPoint presentation that says -- that's titled "New StatXact Toolkit for Correlated Data," Chris Corcoran, Utah State University and -- I'm not going to try to pronounce his name, the other person from Cytel Software Corporation.
A. Pralay Senchaudhuri. I'm excited you found this.
Q. I did. The Internet is an amazing thing.
Do you recall any prepared document -- by the way, have you seen this before?
A. Yeah, I prepared it.
Q. Okay. So this looks to be the PowerPoint presentation that you prepared?
A. Yes, I created this.
Q. Okay. Well, I just want to make sure, since I got it off the Internet, that it looks like it's an accurate copy.
A. Yep.
Q. Okay. Do you recall when you prepared this?
A. Yes.
Q. When was that?

Page 92

A. I'm not sure exactly which year I gave this presentation because I've given other presentations related to the same topic.
Q. Last five years?
A. Likely. I'm not sure. Like I said, I've given different presentations about this, so I'm not sure what -- I'd have to go to the site where you found this to know exactly what the context was.
Q. Who did you give this presentation to?
A. This one? I am not sure because I've given similar presentations on a couple of occasions, so I can't remember which group this was for.
Q. Because I noticed there's four organizations mentioned in the four corners of the document. One says Utah State University.
A. Yes.
Q. Do you see that?
A. Yes.
Q. Do you do this work on behalf of Utah State University?

Page 93

A. I do this work as an academic statistician with Utah State. So, you know, the funding comes from the National Institutes of Health, and the funding was to support Cytel and to support me as well.
Q. Okay. And that's why the logo for Utah State University appears here?
A. That's right.
Q. Okay.
A. Because I work for Utah State University.
Q. Okay. And is that sort of your university policy, that when you do work like this you're supposed to put your university logo? I'm curious.
A. I don't know if we have a policy about it. I just know that since I work for Utah State, you know, in academics, when we go and give presentations, that's something that we want to kind of maintain a record of because it -- you know, whatever helps us helps the university, and so the university wants us to keep a record of the presentations that we make. And our own employment in our roles, we get credit for

Page 94

that.
Q. So that would be in part, am I correct -- and correct me if I am wrong -- because you're doing this work indirectly through an NIH grant because Cytel is being paid by an NIH grant? Is that part of the reason why?
A. No, I was -- I was -- I was directly -- I was, you know, listed as key personnel for that grant, so there's nothing indirect about it.
Q. Okay. For this grant here, for doing this PowerPoint?
A. For the grant that supported the work that we are talking about here.
Q. Okay. Maybe you can tell me which grant that is. So it's page 37.
Which grant would that be?
It's page 27 I think your grants are on.
A. I think for some reason it looks like only current grants are listed here, not past. It must have just been, you know, the setting when I generated this report.

Page 95

Q. So you have more grants from NIH than appear on page 27?
A. Yeah, I have a history of grants, but these are -- these were, I guess, in some sense current grants.
Q. Okay. Well, that will help answer some of the questions I had about the distinction between your expert report and some of the grants mentioned here, but we'll wait a minute to get there.
A. Okay. It would just take a few minutes, actually, to look at the NIH database to find, you know, the grant that actually funded this work, if you want to take the time to do it.
Q. Well, I'll -- maybe we can do that later.
A. Okay.
Q. Right now I don't really need to.
Okay. So NIH's logo is on there, again, because this was being done by you in connection with NIH?
A. Because they provided the support for Cytel that led to the work that

Page 96

led to this toolkit, yes.
Q. Okay. And why is SBA on there?
A. It's the Small Business Administration, because they're the ones that sponsor the Small Business Innovation and Research grants. They're called -- they're referred to as SBIR grants.
Q. And you said you've given other presentations besides the one that's reflected in 21-8, correct?
A. I've given, yeah, a lot of presentations about -- about correlated -- exact tests for correlated data.
Q. Okay.
A. So starting when I was a doctoral student and, you know, until relatively recently.
Q. So give me some examples of the audiences to which you give these presentations.
A. Mostly other academic statisticians and students.
Q. So it's usually in a university setting?
A. Usually in a university

Page 97

setting. I think one time I, you know, I presented at the FDA. So in other words, there were other statisticians, analysts, who work for the FDA who were just interested in knowing kind of more about the toolkit.
Q. Is there a different cost structure for having the software for StatXact if you are an educational institution versus a commercial establishment?
A. I actually don't know.
Q. So you don't know anything about the pricing structure for StatXact?
A. Not really. I haven't looked at it for a while, I mean, because I -- you know, because of my close connection to them, I -- so it's not an issue that I've dealt with.
Q. So I know I asked you the question if you know the differential.
Do you know anything about the pricing structure at all for StatXact, regardless of who's using it, who the user is?
A. Not currently.

Page 98

Q. Did you ever know it?
A. I think I've probably seen the prices at some point in my life, but I can't remember what they are off the top of my head or at what time that was.
I -- well, nevermind.
Q. For what use is StatXact marketed?
A. It's marketed to, you know, statisticians and analysts and academics and biopharmaceuticals and federal agencies.
Q. What kind of federal agencies would --
A. Well, like I said, for example, I gave a talk at the FDA, so there are statisticians there at the FDA who apparently use it.
I don't know what the -- what their numbers are, but I think that -- I think -- at least I know that there are some users there.
Q. Do you know that they use it, or were you there to market it?
A. I have no idea who is actually using it from day to day. I was there to --

Page 99

they were interested in having some people connected with Cytel to come and kind of show them, you know, what the capabilities were, what the new tools were for the new version, so that was -- that's what I did was just show them examples how to analyze data and so on.
Q. Right.
So you don't actually know whether FDA uses this. You just know that you presented its capabilities to the FDA?
A. Well, I know that on Cytel's website they -- they present, you know, a list of people who actually use StatXact, so...
Q. Okay. And you've looked at that recently?
A. Not really recently. I've looked at it in the past.
Q. Any other federal agency that you recall as a user of StatXact besides the FDA?
A. Not off the top of my head, but most -- you know, most all statisticians who work for, you know, the government or in

Page 100

academics at least know what StatXact is, but I don't know what the actual numbers are.
Q. Do you know if StatXact also -- I'm sorry, if Cytel also lists corporate users of StatXact?
A. I think that they probably do, but I haven't looked at their website for a while.
Q. Okay. So the last entry of your book chapters mentions Cytel but not StatXact. It says Egret.
What is Egret?
A. Oh, Egret was a package that I think they no longer produce. It was a package that they -- that they -- that they made available, I think, that was -- I can't remember what the acronym stood for.
Q. Okay.
A. But it was a package that was used, I think -- I think it was more focused on epidemiology. But that was kind of in the late '90s when I was a student that I helped out with that a little bit.
Q. Okay. All right. So if you look at pages 5 through 16 of your CV that's

Page 101

attached to your report, which is Exhibit 21-1 --
A. Uh-huh.
Q. -- those appear to be the pages where you list your peer-reviewed journal articles, right?
A. Right.
Q. Okay. So Dr. Corcoran, my review of the titles of these articles suggest that there are about a hundred peer-reviewed journal articles in which you are an author or a coauthor.
Does that sound about right?
A. I don't know. I'd have to go through and count them.
Q. I actually counted them.
Just generally, does that sound about right? I'm not going to hold you to the hundred.
A. It looks like dozens.
Q. Unless I'm a bad counter, I think it's a hundred.
So we'll say roughly a hundred, okay, just for purposes of some of these questions.

Page 102

For the articles here, which, as I say, I counted about a hundred, isn't it true that all but a few relate to issues of dementia, Alzheimer's and cognitive, age-related issues?
A. What do you mean by "a few"?
Q. Five or less.
A. I don't know. I guess I'd have to go through and count that up.
Q. Okay. Well, then I'm actually going to ask you to do something for me.
A. Okay.
Q. Other than if you exclude peer-reviewed articles on dementia, Alzheimer's and other cognitive, age-related health issues, and you exclude articles relating to religion and depression, how many of your peer-reviewed articles -- how many peer-reviewed articles have you published?
A. I haven't the faintest clue. I mean, I'd have to go through this entire list and comment about that.
Q. Well, as you sit here today, can you tell me any peer-reviewed article that you published that does not relate to

Page 103

either dementia, Alzheimer's, cognitive, age, health-related issues or religion and depression?
A. Just off the top of my head, no.
Q. What's the -- is it Cache or Cache -- how do you say the name of this --
A. It's Cache.
Q. What is the Cache study?
A. It's a large study of memory in old age and Alzheimer's disease.
Q. Okay.
A. It represents actually several studies that were kind of coordinated.
Q. Is that being coordinated through Utah State University?
A. Mostly.
Q. Okay. And are you one of the coordinators of that study?
A. I wouldn't call myself a coordinator. I'm kind of a lead statistician on a lot of the efforts that they have initiated.
Q. Is that an epidemiological study?

Page 104

A. Yes, in large part. I mean, it's an observational study of, you know, of aging in this area, in this geographic area.
Q. Have you ever designed a rodent carcinogenicity study to assess the ability of a chemical to cause cancer?
A. No, I haven't.
Q. Have you ever performed or overseen any rodent carcinogenicity study to assess the ability of a chemical to cause cancer?
A. Carcinogenicity study?
Q. Carcinogenicity. Boy, I'm really tripping over my words today.
A. No, I haven't.
Q. Have you ever designed a study that addresses the optimal dosing pattern for rodent carcinogenicity studies -- I'm doing it again -- to assess the ability of a chemical to cause cancer?
A. No, I haven't.
Q. So I think I'm going to know the answer to this because of the grants.
You stated in your expert report that you received over $25 million in

Page 105

NIH grants, correct?
A. That I've helped -- I've assisted as an analyst in studies that total that amount, yeah.
Q. Okay. So the 25 million is not grants that went directly to you; is that correct?
A. That's right.
Q. All right. And am I correct then -- so let me rephrase that.
A. No federal grant, like an NIH grant for a large, complex study, no amount of funding goes to one person. These -- these studies are complex and involve a lot of personnel across different universities. They're very interdisciplinary.
Q. Is the Cache County study an NIH-funded grant?
A. Yes, it was funded by several grants from the NIH.
Q. Okay. And is that part of the $25 million figure you're using -- I can find it. Just give me a second. I'm sorry -- on page 2 of your expert report?
A. Yeah, I'm talking about all

Page 106

grants that I've -- that I served.
Q. Okay. Now, you say -- back to -- back to your CV.
A. Uh-huh.
Q. Sorry. Go back to your grants. Give me a second.
I believe it's page 27. Just give me a second before I take you there.
Yeah, page 27.
I know you said this -- this didn't have the full numbers of grants that you've received. I just want to ask you about one in particular.
A. Sure.
Q. You mentioned the top one, and you're named as, I think, grant recipient. The second person is the supporting.
Does that mean that your name would or would not appear on a grant application?
A. I think it would --
Q. It would. Okay.
A. -- appear.
Q. And that's the one that the NIH funded in the amount of $1,067,869; is that

Page 107

right?
A. That's right.
Q. And that's for epidemiology of Alzheimer's disease, resilience and risk pedigrees?
A. Yes.
Q. And that is from September 1, 2016, through August 31, 2021?
A. Yeah.
Q. Okay.
A. That's what the dates are.
Q. Okay. You signed your retention agreement with the Hollingsworth firm in August of 2016, right?
A. Yes.
Q. August 31st, the day before you received this grant; is that right?
A. I don't know if that's exactly how the grant awards work. I mean, you get a notice of award, but the funding period is something that's determined separate from the notice of the award, so --
Q. Okay. So when you would have gotten notice --
A. So it's not like you get a

Page 108

phone call that says your grant is starting tomorrow. I mean, you're told that months in advance, and then they set -- once they actually have their budget set, then they tell you when the award starts.
Q. So you probably would have gotten the green light on the request for the grant months before September 1, correct?
A. Yes.
Q. Do you know whether NIH has any ongoing requirement or obligation on researchers to update potential conflicts of interest?
A. I don't know.
I know that our university has requirements, and so I try to, you know, adhere to those. They actually have us -- they actually have us update, you know, our own contacts, and so they -- I think that just kind of happens annually. And so I usually update what's going on in terms of my research and consulting work then.
Q. Have you disclosed to your university that you're a consultant to Hollingsworth and Monsanto in this

Page 109

litigation?
MR. GRIFFIS: Objection. Misstates prior testimony with regard to Monsanto.
THE WITNESS: I -- I'm actually just consulting for Hollingsworth, but I --
QUESTIONS BY MS. GREENWALD:
Q. Okay. So I'll ask it that way.
Did you disclose to your university that you are a consultant for the Hollingsworth firm on behalf of Monsanto Corporation?
MR. GRIFFIS: Objection to form.
THE WITNESS: I don't -- I don't know if I've actually -- if they've actually kind of sent through that update recently, so I don't know if I've actually filed that.
QUESTIONS BY MS. GREENWALD:
Q. So you don't have an ongoing obligation at your university to update information as it -- as it occurs?
A. We do, and we -- they actually

Page 110

send us something every year, like a reminder that helps us to kind of make sure that we're updated.

Q. So help me understand how this works.

If you are -- if you get your update, let's say, January 1st, but February 1st you become a consultant for a corporation in connection with some private consultancy work, are you saying that you at that point are supposed to update your information to the university at that time, or do you wait until the following January?

A. I'm not actually certain what their timing requirements are.

Q. Okay. But as you sit here today, you haven't informed your university, is that correct, about your consulting work with Hollingsworth?

A. I'm not sure. Like I said, I -- you know, those things get updated periodically, and I'd have to go back and check.

Q. Well, would anyone update it but you?

Page 111

A. No.

Q. Okay. So do you recall, sitting here today, whether you have updated any information with the university -- with the Utah State -- let finish my question.

A. Oh, I'm sorry.

Q. -- with the Utah State University about your consultancy work for Hollingsworth corporate -- Hollingsworth, LLP, on behalf of Monsanto Corporation?

A. No.

MR. GRIFFIS: Objection to form.

THE WITNESS: Like I said, I -- I -- I'm updating things constantly. I mean, I get dozens of requests per month to file papers, and so I would just have to go back to see if that's something I've done.

QUESTIONS BY MS. GREENWALD:

Q. So I'm almost finished with this part of questioning.

The reference materials that are pages 1 through 6 -- 1 through 5 that are attached right after your -- I'm sorry,

Page 112

materials considered list. I should use the right term -- right after your expert report text, does this accurately list all the materials you have reviewed in preparation as an expert in this case up to the present day?

A. Yes.

Q. Did you perform any analysis that's not set forth in your report?

A. No --

MR. GRIFFIS: Objection to form.

Yeah, to the extent that we've asked him to do things outside the scope of the expert report, such request would be privileged.

Don't answer with regard to other analyses we've asked you to perform or other consultations we've asked you to do.

You may answer with regard to the subject matter of your expert report, whether there were analyses concerning contents therein that aren't disclosed in the expert report, so...

Page 113

THE WITNESS: Well, what I was going to say is no. I mean, I think what's in my expert report is fairly comprehensive.

You know, at the same time I received Dr. Portier's rebuttal report. I haven't done any initial -- or like additional analyses based on that, but I do have -- I do have some concerns about what he -- what he reported in his -- especially in his deposition, but I haven't done any analyses to follow up on that.

QUESTIONS BY MS. GREENWALD:

Q. So are your concerns about what Dr. Portier testified about in his deposition part of what you deem to be part of your opinions in this case?

A. Pending, you know, some further exploration, yes, because he talked in his deposition about -- he gave some details that were not really provided before about how he conducted his dose response analyses for the pooled -- for his pooled procedures.

Q. Okay. So let's do it now. Why

Page 114

don't you tell me everything that you -- let me use your words.

Why don't you tell me all the concerns that you have about what Dr. Portier testified about in his deposition, which in this case was taken on September 5, 2017.

A. Sure.

MR. GRIFFIS: That are beyond what's already stated in the expert report, do you mean?

MS. GREENWALD: Correct. Yes. If it's in the expert report, correct. Thank you for that clarification. Sorry about that.

THE WITNESS: Besides what I've said in my expert report, he -- he talked in his deposition about how he actually did the dose response analyses for the -- for his pooled data procedures, and he, you know, conducted those in a way that I think was flawed.

QUESTIONS BY MS. GREENWALD:

Q. Stay there for a second.

A. Okay.

Page 115

Q. In what way is it flawed?

A. Well, I already expressed my concern in my expert report about him combining data sets from different sources into the same table without accounting for study differences.

On top of that, he's also -- he's also combined them in a way that -- that places studies that have extreme doses, I mean, upper treatment groups, he kind of combines them with studies that actually have relatively lower doses, and they're higher treatment groups.

He does that in a way that I think influences the P values that he's computing when he pools the data sets together. Because it turns out that when you -- when you actually have extreme dose groups and you're conducting a trend test to compute a P value for dose response effects, that those higher doses actually have more influence. So any incidence of tumor that you see in the higher dose groups then has -- places greater influence on the result, undue influence.

Page 116

It's kind of like if -- you know, if Bill Gates walked in here and we computed our average salary with him present, what would -- you know, how that would kind of inflate -- that would inflate all of our salaries on average. That's kind of what is happening with these extreme dose groups. They place more -- they give more prominence, basically, to tumors that are found in higher dose groups.

So I have a concern about that, but I actually haven't done an analysis to -- you know, to really better understand exactly what kind of impact that's having on his P value computation.

Q. What else?

A. That's all I have to add to my expert report.

Q. So everything in your expert report, plus what you just explained -- what you just testified about relating to his testimony at his deposition about dose response for pooled procedures, right --

A. Right.

Q. -- that you just testified

Page 117

about?

A. So in addition to the other flaws in his pooled procedure, that's one that could be fairly significant.

Q. Did Dr. Portier do pooling in his deposition different than he did in his expert report?

A. Well, I think in his deposition he explained how he did it in his expert report, and that's something that was not -- that I didn't pick up from his expert report because he didn't explain it.

So once he explained it in his deposition, it was clear to me, you know, that that was a problem.

Q. What are the study differences you're referring to among these studies?

For example, let's talk about the rat studies first.

A. Uh-huh.

So what are the study differences?

Q. Uh-huh.

A. You mean --

Q. I mean, other than I understand

Page 118

the dose treatment. Let's put dose -- let's talk about rats first, and let's put aside dose.

A. Uh-huh.

Q. What are the study differences that you have knowledge about?

A. Well, do you mind if I just refer to my report?

Q. No, it's there for you all day.

A. Let me just point this out. Kind of starting in the -- starting in the summary.

Q. What page are you on?

Oh, the summary of your report. Okay.

A. Yeah.

Q. Uh-huh.

A. So at the very end, starting in -- on line 28, I point out that his combining or pooling of data from across several sources, that these are the differences I'm talking about: using experiments carried out during different years and in different laboratories, under different conditions, without appropriately

Page 119

accounting for these studies' unique characteristics.

So those are kinds of differences I'm talking about.

Q. Okay. So what are the different conditions, the different laboratory conditions, among the seven rat studies that you looked at in connection with your expert report?

MR. GRIFFIS: Objection to form.

THE WITNESS: They were not carried out in the same lab. Those are the differences.

QUESTIONS BY MS. GREENWALD:

Q. Okay. So is it possible to control environment in different labs so that the -- do you mean just like different buildings?

A. Well, different places, different times, under different conditions.

Q. So do you believe that if you have different buildings or different places but they otherwise control the environment within the research laboratory the same, that

Page 120

those would not be appropriately compared?

A. Yeah, that's -- that's a good question. But it's fairly common statistical knowledge that if you have different experiments -- different experiments that are carried out at different times and different locations under different conditions, that in spite of your best efforts to try to control those, even using in this case, you know, rats or mice from the same strain, that there will be variations in the environment that will lead to different underlying tumor rates.

Q. Okay. But I just want to understand.

My one, I hope, simple question is that if you have same period of time, same mouse strain -- we were talking about rats, but we can go to mice, doesn't matter -- same mouse strain, two different places but the laboratories themselves where the mice are being studied have controlled environments, are you saying that those could not be compared?

A. I think I lost track of what

Page 121

you were saying.

You're saying at the same time in two different labs? Is that what you said?

Q. Well, within a two to three year period that you otherwise control for the environment within the laboratory.

Are you saying that those --

A. What do you mean by "control"?

Q. Well, temperature, light --

A. Oh, so -- you know, in terms of controlling the conditions?

Q. Well, let me -- rather than answering that question, why don't you tell me what do you mean by different conditions?

Let's go through your sentence. Let's parse it out.

"In addition, Dr. Portier violated conventional statistical practice in his use of historical controls and in combining or pooling data from across several sources - using experiments carried out during different years" -- that I understand -- "and in different laboratories" --

Page 122

Do you mean by that like different actual buildings, like different laboratories? Like one might be the --

A. Physical. Yes, different physical --

Q. -- Utah State --

A. Facilities, yeah.

Q. Okay.

-- "and under different conditions."

So what do you mean by "under different conditions"?

A. I mean the conditions that are inherent to the environment.

Q. Like?

A. That laboratory.

Q. Give me some examples, please.

A. I think that, you know, it would be best to, you know, actually cite some of the sources that Dr. Portier used himself. I think they explain this even better than I could off the top of my head.

Q. Okay. I'm not asking you right now for any specific conditions in any particular laboratory with respect to the 12

Page 123

studies that are at issue in this case.

I'm really merely asking you when you use this sentence here, and you use that phrase on line 29 of page 1 of your report, what did you mean when you said "different conditions"?

What do you mean by the words "different conditions"?

A. Well, I'm not in the job, as you pointed out, of actually, you know, conducting animal toxicology experiments. I'm a statistician. So what I'm hired to do is to analyze data that come from the types of studies that, you know, say, a toxicologist would produce.

And what I know is that based on the, you know, the literature, the literature that Chris Portier cited, the, you know, materials that I cite in my own list, what I know is it's accepted across, you know, the toxicology community as well as across the statistical community that in spite of your best efforts to control environmental conditions from lab to lab across different -- you know, at different

Page 124

times and different locations, using different -- you know, even the same strains of mice, that there is variability that can't be entirely controlled.

Now, what those things are are a matter of conjecture. We don't know them. If we did know them, then the people who designed the experiments could control those things. But you can't control everything.

So what you do as a statistician is that you control for those things as a part of the analysis, and that -- again, that's very well-understood, as I've outlined in my expert report, and that's what Dr. Portier didn't do.

So whether or not you're actually controlling every little thing and what those things are is kind of immaterial. The point is, as a statistician, my job is to control those things as a part of my analysis.

Q. So when you use the word "different conditions" in line 29, you're not thinking of any particular concrete conditions?

Page 125

A. No. What I'm saying is the data demonstrate from, you know, thousands and countless studies in toxicology and in all other fields of science that when you -- that when you try to combine data from different experiments that were carried at different times, different locations, there are things that make those studies different that are not measurable, in spite of everything that they do to try to control that. And so what you do is you control it as part of the statistical analysis.

So that's what Dr. Portier is not doing in his expert report. What he's doing is he's just combining data into tables as though they came from the same experiment and the same study, and that is an absolute violation of statistical practice. That's where, as a statistician, I control those things since I'm not involved in the design of the experiments themselves.

(Corcoran Exhibit 21-9 marked for identification.)

QUESTIONS BY MS. GREENWALD:

Q. I'm going to mark as

Page 126

Exhibit 21-9 the expert report of Dr. Christopher J. Portier.
A. Thanks.
Q. Sure.
And you've read that report before, right?
A. Yes.
Q. Can you turn to page 33?
A. (Witness complies.)
Q. For example, the paragraph that starts out with "Brammer 2001" sort of in the top part of the page?
A. Yes.
Q. Can you -- you want to take a look at that for a minute, that paragraph?
A. Okay. I've read it.
Q. Okay. Is it still your testimony that Dr. Portier didn't describe and explain in his expert report how he was comparing the data among the rat -- the rat studies?
A. Yes, that is my testimony.
Q. Do you also want to go to page 19 and 20 of the same report?
A. Before we turn to pages 19 and

Page 127

20, can I -- I point out here that Dr. Portier says -- he says, "Given different doses and different sample sizes" -- this is on page 33 in the middle of the paragraph you just had me read.
Q. Uh-huh.
A. "Given different doses and different sample sizes, we need to formally test for consistency in these studies."
Q. Correct.
A. There is no formal test in this paragraph. So he has not formally tested for any differences. He's eyeballed it, and he's decided that he -- you know, he's decided that they're different just based on his -- these eyeballed proportions. And on top of that, there's no reason for him to...
Q. Oh, I'm sorry.
A. I'm sorry, I was answering your question. I just ----
Q. No. No. I'm listening. I'm listening. No, I'm listening. I'm sorry, we multi-task.
A. Okay. What I'm saying here is that he, first of all, didn't formally test

Page 128

it.
Secondly, there's no reason to simply exclude a study even if he had formally tested it. So if his test was formal and he decided that Suresh had a larger -- a larger response rate, then there would be no statistical reason for him to just simply exclude it from his pool analysis. That's what I'm pointing out in my expert report.
So notice how he says further on, "All three studies use different diets and were conducted in different facilities; thus, there is no obvious explanation for the dramatically different rates."
So in other words, that -- you were asking me before is it possible to do studies in different laboratories under different -- you know, even trying to control environmental conditions and still -- and still observe studies that are markedly different.
And the answer is yes. This paragraph explains, you know, how -- for things that he has no explanation for that

Page 129

can't be controlled in the laboratory.
Q. Dr. Corcoran, did you read the sentence that says, "Suresh saw 48 percent response" --
A. Uh-huh.
Q. -- "of hepatocellular adenomas in controls, whereas the other two studies saw no tumors in the control animals"?
A. Yes.
Q. Okay. Do you think that's one of the reasons why the Suresh study was not included in this combining of data?
A. But what I point out in my expert report is that there's no reason to exclude studies for having these different baseline rates.
The thing that you're studying is not what the -- not what the kind of spontaneous rate of tumors is in mice and rats. That's not what you're trying to study.
What you're studying is whether or not there's, you know, some sort of compound-related effect. That's what you're studying.

Page 130

So in other words, had he used kind of one of the standard methods for analyzing data that come from different studies that allow you to look at dose response, even if they do come from different places and have different rates, then there was no reason for him to exclude that study.

That's a very arbitrary decision, and there was no -- you know, even though, yes, you eyeball that and you say, well, a 48 response rate compared to zero, that appears to be, you know, significantly different, but there was no formal test done. He never actually carried out a statistical procedure that told him that.

Q. What's the purpose of having a control animal in a bioassay?

A. What's the purpose of having a control animal in a bioassay?

Q. Uh-huh.

A. So you can compare treatment to animals that were not exposed.

Q. Okay. If you go to page 19 and 20, the bottom of 19, top of 20, starting with -- well, he doesn't have lines.

Page 131

So if you go to the last full sentence on 19 and the carryover on 20?

A. Okay.

Q. Starts with "these studies are conducted."

A. Yeah, you know, he's -- do you want me to read that out loud, first of all?

Q. No.

I mean, do you have any reason to believe that the animals were not -- sorry, let me strike that. I'm going to start over.

Do you have any reason as you sit here today to believe that the studies were not conducted in a way that controlled for the animals' food type, water quality and how often the animals are handled?

A. This is the whole problem with Dr. Portier's pool analysis, because he's right. He's saying that you're trying to control everything in the environment that you can control, so he's absolutely right about that.

But the key word is "trying." And the truth is that even based on his own

Page 132

sources that he cited and the materials I use in my material list, the truth is, in spite of your best efforts to control everything, you cannot control everything in terms of the animals' environment. That's why they end up with these, you know, different -- these different tumor rates amongst controls. That's one of the main reasons. That cannot be completely controlled for.

And so on page 33, you know, the page that, you know, you just pointed out to me, he's illustrating exactly why that happens. I mean, even though the studies try to use the same environmental conditions, you still have a tumor response rate in one group that's nearly 50 percent and the other group zero percent.

Q. So are you saying this Suresh study saw a 48 percent tumor rate in the controls because of the difference in the animals' food type, water and how often the animals were handled?

A. I have no concrete explanation for that, but what I'm saying is as a statistician that is an easy thing to control

Page 133

for, and it's something that Dr. Portier didn't.

Q. So that's easy to control for, but it's not easy to control for food type, water quality and how often an animal is handled; is that you're saying?

A. It's the beauty of a statistical model is that you can control for -- you can control for conditions like that even though they weren't --

Q. So as you sit --

A. Sorry, I just want to finish my answer.

That's the beauty of using a statistical analysis that does control for things like that. I mean, using the right statistical analysis, you can control for those factors.

Q. Okay. So I want to ask my one question again because I still don't think I've gotten an answer for it.

As you sit here today, do you know whether the food type, water quality and how often the animals were handled in these rat studies were different?

Page 134

Do you know -- do you know factually whether there was a difference --
A. What I'm telling you --
Q. -- among those studies?
A. -- is that as a statistician, it doesn't really matter because -- because what I do as a statistician is I say, well, here are data from different studies. How do I account for those potential differences through my statistical analysis?
And that's using the approach that I talk about in my expert report that Dr. Portier doesn't use at all.
Q. So how do you account for those factors in your methodology?
A. Do you want to refer to my expert report? Because I think I explain it in there.
So if you go to page 15 of my expert report in Section 5C.
Q. Uh-huh.
A. First go to line 15.
So my point is, "First and most critically, Dr. Portier's pool procedures flout statistical standards by making no such

Page 135

adjustments at all for differences between experiments or for the similarities among mice within each study. Dr. Portier simply aggregates data across various subsets of rat and mouse studies treating rodents born and raised in different environments, fed from different sources, measured using different tools by different researchers over a 30-year span as though they were all included within a single experiment at the same time."
So -- and then below that -- I mean, I won't read the entire thing, but below that paragraph I outline exactly how one would conduct that kind of analysis, and it's a very common approach when you're actually looking at data that arise from different studies.
The first step is to determine formally whether or not the studies do have those kind of differences.
Now, he said that he did that on page 33 with, you know, those -- those rat studies, but he actually carried out no formal test. He just eyeballed it. So that's one checkmark.

Page 136

Second, you have to actually account for those differences within the model, which his own sources tell us to do, because, again, that's fairly conventional statistical practice.
So instead of actually accounting for those differences, what he did was he just put all the data together in the same table, which is really grievously wrong in statistical practice.
And then the third thing is that you have to make sure not only that you're accounting for those differences but that the different dose response effects across the studies are accounted for as well, and that he didn't do either.
Q. But what did you do?
I'm still trying to understand. Tell me what you did with this data.
What analysis -- what are you doing different or what are you proposing or what -- yeah, help me under -- I'm still trying to understand what you did.
I understand your criticism of Dr. Portier.

Page 137

A. Are we talking about the pooled analyses?
MR. GRIFFIS: Objection. Compound.
QUESTIONS BY MS. GREENWALD:
Q. I'm trying to understand what your approach is -- well, let me ask it this way.
Are you testifying that none of these studies should be compared?
A. I'm testifying that they should be -- if they're going to be compared, there are steps that you have to take to make sure that it's done properly. And I'm testifying that he took none of them when he was actually pooling data.
Q. What steps did you take to determine whether they should be compared?
A. Well, you know, the steps I took in analyzing the data were to first look at, you know, the 12 studies in total, in other words, you know, to actually look at the evidence across all tumor types, across all studies, and to actually account for the fact that we're doing many, many tests as

Page 138

opposed to just cherry-picking P values.
So my task was to kind of evaluate, well, is there any evidence of, you know, a compound-related effect.
And after having assessed all of the -- all of these trend tests over many hundreds of tumor types across all 12 studies, seven rat and five mice, my decision was that there was no compound-related effect.
My evaluation -- my evaluation of the pool analyses had more to do with what Dr. Portier was trying to do to assess the evidence on his own.
Q. Okay. Can you tell me where in your report you explain the steps you took to compare the data? Give me a page number.
A. To -- the steps that should be taken if you're going to combine data?
Q. No, what steps you took to decide that there was no compound effect.
What steps did you take with respect to the rat studies, for example, on whether they could or could not be compared?
A. Well, the --

Page 139

MR. GRIFFIS: Objection. Compound.
THE WITNESS: Well, this is the -- kind of the bulk of, you know, my first four sections. I step through, starting with my summary, you know, my own background, you know, talking about -- talking kind of more generally about -- about the background of the problem, what happens when you actually conduct a study that has hundreds and hundreds of P values. So I gave some context for that. I carried out my own analysis based on those P values.
My -- you know, the material that you're referring to in Section 4 is then my assessment of -- I'm sorry, in Section 5 is my assessment of what Dr. Portier did to, you know, demonstrate what he thought was evidence of a compound-related effect.
So in other words, if you're asking, you know, what it requires to do a proper combined analysis across

Page 140

many data sets, that's in Section 5B. That's what's required.
QUESTIONS BY MS. GREENWALD:
Q. You didn't do that analysis, though, with this data set, did you?
A. What I did was I looked at what he did, and I pointed out how it was flawed. And I also, as an example -- you know, since you brought up page 33 in his report, as an example, I addressed -- I addressed that very example, page 14 -- on page 14.
Q. But you didn't -- did you or did you not do an analysis --
A. Oh, I'm sorry, not on page 14. It's page 18, sorry.
Q. 18 of whose report? Yours?
A. Yes.
Q. That's where you did an analysis of the data?
A. That's where I addressed the example that you just showed me from page 33 of his report.
So I outlined the steps before that, and then I actually applied it to illustrate why what he was doing was so

Page 141

deeply flawed.
Q. And you're saying that's on 18, lines 3 through 29 -- 28?
A. That's where I look at the example that you just cited on page 33 in this report.
Q. And how in your analysis here do you account for the 48 percent tumor rates in the control in Suresh?
A. So looking down -- looking down in the paragraph below, starting on line 31, my own --
MR. GRIFFIS: Let's pause one moment. We just had a knock on the door.
MS. GREENWALD: Right.
VIDEOGRAPHER: We're going off the record. The time is 11:51.
(Off the record at 11:51 a.m.)
VIDEOGRAPHER: We're back on the record. The time is 11:51.
THE WITNESS: Yeah, I can finish that answer.
QUESTIONS BY MS. GREENWALD:
Q. Were you in the middle of an

Page 142

answer? Yeah, sorry.
A. So that's okay.
Starting on line 31, "My own analysis of the liver adenoma data first demonstrated definitively that there is higher -- highly significant correlation among rats within each study."
So I actually did conduct a formal test of differences between the groups, which he didn't.
And then -- and then I looked at the dose response effects across the three studies that he was discussing, and what I found was that the Brammer study, you know, had a 21 percent increase in odds for every -- you know, every unit of dose, hundred milligrams per kilogram of body weight per day, whereas the other two studies, the Suresh and Wood studies, had only 1 percent increase each.
And so in other words, that would be -- the first step is actually adjusting for those differences.
The second step is looking for differences in dose response effect.

Page 143

Q. Okay. I'm still trying to understand, like, where did you account for the 48 percent tumor rate?
I understand your writing.
Where did you account for that in your methodology?
A. Yeah, when -- when -- in statistics, when you actually fit a model, like in this case logistic regression, which actually not just -- it doesn't just compute a P value. It allows you to actually estimate what the dose response effect is.
It's an easy thing -- as Dr. Portier pointed out in his rebuttal report, it's a fairly easy thing to use logistic regression and then add in an effect in the model that actually accounts for these study differences. There are two or three different ways to do it, but they're all fairly well-accepted.
And so what I did was I included that kind of effect in my logistic regression model, and that accounts for the fact that you have this variability between the tumor rates across these three studies.

Page 144

Q. How do you do that with the controls when you have two studies that have no tumors in the controls and one that has 48 percent?
MR. GRIFFIS: Objection. Asked and answered.
THE WITNESS: The way that you do that is pretty easy.
QUESTIONS BY MS. GREENWALD:
Q. Not for me.
A. Well, yeah, I mean, I'm talking about for a statistician, but it's not -- it's not that complicated in a statistical model because, you know, you fit the model that fits a line that helps you to model dose response.
And then, you know, essentially what you're doing is you're adding another term in the model that accounts for study type. So in other words, it's allowing -- you know, it's allowing that dose response to vary -- that tumor rate to vary across different studies.
Q. What's the name of this model you applied?

Page 145

A. This is logistic regression.
Q. You did not do an analysis of the seven rat studies, correct?
A. I did analyze the seven rat studies.
Q. Together?
A. Well, yeah, those are the tables in my appendices. I analyzed them all together.
Q. That's C and D that we talked about earlier?
A. Yeah. I mean, I analyze them in the aggregate and actually, you know, looking at the distribution of P values across the trend tests.
Q. Am I right, we're talking about C and D, correct, pages 46 and 47?
A. We're talking about A, B, C and D.
Q. All four. Okay.
A. So those are the results of -- those are, you know, the bulk of my results for the analysis across all of these studies.
Q. Where in your study do you explain the steps you took to get your

Page 146

results?
A. Results for what?
Q. That are in Appendix A, B, C and D.
A. So go into my expert report, starting on page 9, line 28. Trend test results for the seven rat studies are summarized by the tables in Appendix A, and results for the five mouse studies are summarized in Appendix B. And my, you know, summary of where those results come from are in the paragraphs preceding that.
Q. Preceding what?
So I understand, you tell us where those numbers are.
Where do you explain how you got those numbers?
A. The trend test P values?
Q. The numbers that you just talked about that you said they're in Tables A, B, C and D.
How do you -- where do you explain the methodology that you used to derive those numbers?
MR. GRIFFIS: Objection. Asked

Page 147

and answered.
THE WITNESS: Well, so let's start on page 8, line 8.
QUESTIONS BY MS. GREENWALD:
Q. Okay.
A. Actually, look at the first two questions preceding that in the preceding paragraph.
First, how do we evaluate the dose response effect of glyphosate on a single tumor type?
Second, how do we account for many dose response analyses across multiple tumor types?
And then the following paragraphs explain where that comes from.
And then like I say on page 9, starting on line 28, I sum that up by saying -- so there's where the results come from in these appendices.
Q. Do you know Dr. Foster?
A. No.
Q. Do you know that Dr. Foster submitted an expert report in this case on behalf of Monsanto?

Page 148

A. I've heard his name but I've never met him, and I don't know what his role is, really, in this case.
Q. Have you read his expert report?
A. No.
MR. GRIFFIS: It's almost noon and lunch is here. Should we break?
MS. GREENWALD: Sure.
VIDEOGRAPHER: We're going off the record. The time is 11:58.
(Off the record at 11:58 a.m.)
VIDEOGRAPHER: Okay. We are back on the record. The time is 12:37.
QUESTIONS BY MS. GREENWALD:
Q. Okay. So a quick question from before the lunch, and then we're going to move on to something different.
A. All right.
Q. What's the basis for your assumption that the data from the various studies, both the rat studies and the mice studies, cannot be tabulated together?
A. Just the weight of the

Page 149

literature about, you know, about combining data from different sources and including, you know, again, some of the sources that were cited by Portier and the sources that I included in my materials list.
Q. Okay. So if I understand you right, the only authority that you are relying on would be either documents or articles cited by Dr. Portier in either his report or rebuttal report or that's cited in your expert report; is that fair?
A. I'm saying that, you know, with the couple of decades of training I have, that it's pretty well-accepted that when you actually try to analyze data by combining them across different studies that, you know, data that arise from different sources like that, that it's fairly common, in fact, I would say it's conventional, to handle those analyses in the way that I describe in my expert report.
Now, having said that, the specific citations in Dr. Portier's report and mine explain why, but there are, you know, textbooks written about those.

Page 150

Q. Okay. So other than potential textbooks and your years of experience and the citations in both your consideration lists and Dr. Portier's consideration lists, that would be the totality of the evidence, so to speak, that would be the basis of your opinion that these studies cannot be combined?

A. Yeah, that's a big totality, but, yes, that's the basis for it.

Q. I believe that.

Would you agree that there's a difference between primary and secondary tumors?

A. I am not really kind of familiar with the differences between primary and secondary tumors.

Q. So you don't know what a primary tumor is?

A. Well, I do. I mean, I wouldn't say that I'm an expert in tumor pathology, no.

Q. Okay. What's your understanding of what a primary tumor is?

A. I don't know if I want to

Page 151

answer as a statistician. I mean, that's not really my training is in pathology. I just know that, you know, that they -- you know, they're kind of diagnosed or assessed separately.

Q. So when you were calculating tumors identified in the Greim paper, did you distinguish between primary and secondary tumors?

A. The tumors I analyzed from the Greim paper were just as reported in the tables within the supplement.

Q. Okay. So the answer to my question is you did not distinguish in your calculations between primary and secondary tumors; is that correct?

MR. GRIFFIS: Objection. Misstates testimony.

THE WITNESS: Well, that's not what I'm saying at all. I'm saying that what I reported in my own expert report in Appendices A through D, that's the way those tumors were reported in the Greim supplement.

And so if they reported

Page 152

separately in the Greim supplement by the original scientists who produced the data, if they were reported as primary or secondary tumors, if those were distinguished in that way, then, you know, they're listed separately in my appendices. They're listed as-is.

QUESTIONS BY MS. GREENWALD:

Q. I have to mark one more document. I thought I was finished with marking documents, but I'm incorrect.

(Corcoran Exhibit 21-10 marked for identification.)

QUESTIONS BY MS. GREENWALD:

Q. Okay. I'm going to mark as 21-10 the rebuttal report of Dr. Christopher J. Portier in support of general causation on behalf of plaintiffs.

A. Great. Thanks.

Q. Sure.

You've seen that before, right, Dr. Corcoran?

A. Yes.

Q. Give me one second, I'm sorry.

As you sit here today, do you

Page 153

have reason to disagree -- if you can go to page 2, I'm sorry.

A. Okay.

Q. Do you have reason to disagree with the sentence on page 2 of Dr. Portier's rebuttal report that reads, "81 of the tumor sites appearing in Dr. Corcoran's tables A.1-7 and B.1-5 in his appendix are metastatic secondary tumors and should not be included in the P value count for this analysis"?

A. Well, I'd say that that's his -- that's his own expert opinion, but I -- as I said, when I analyze the data, I analyze the tumors as they were reported by the original scientists who contributed to the tables in Greim.

Q. Okay. Do you understand that some tumors in animal bioassays are organ-specific?

Do you understand what that means?

A. Yeah, I have come to understand that.

Q. Okay. And an organ-specific

Page 154

tumor is one that develops in a specific organ in the body; is that right?
A. Uh-huh, yes.
Q. And there are also systematic tumors; is that correct?
A. Yes.
Q. And an example of a systematic tumor is a malignant lymphoma; is that right?
A. I think that would be an example, yes.
Q. Okay. And the analysis in your expert report, which is marked 21-1, does not combine systematic tumors, right?
A. Not unless they were reported in any kind of combined way in the Greim supplement.
Q. Okay. But you yourself didn't combine any systematic tumors; isn't that right?
Unless it was combined in Greim, you're saying?
A. No, that's right.
Q. Why not?
A. Because I -- I wouldn't -- I don't think the -- I don't think that that

Page 155

was -- I didn't think that that was appropriate, I mean, based on my examination of the Greim tables.
I mean, my job was to look at the weight of evidence across the -- you know, the tumors that are reported in the Greim supplement. Some of them were reported as combined; some of them were not.
In this kind of complex analysis, what you would do -- and I think that, you know, Dr. Portier even mentioned this in his own deposition.
Ideally what you would do is that you would -- if you were going to decide on those kinds of combinations, what you would do is you would sit down with pathologists or toxicologists and find out whether or not there was some sort of consensus.
I mean, what I do know is that, you know, Dr. Portier reported in his original expert report that there were -- I can't remember the exact number, 450-plus tumors that he analyzed or that he considered that had three or more -- three or more

Page 156

incidence of tumor within the study, and then that number dropped down to 419 in his rebuttal report.
In other words, it's clear that, you know, the -- you know, even in his case, he couldn't really decide on what the final list was. So the point was not necessarily in just deciding on, you know, which number that you were going to use, what total. The point is that we actually account for the number of tests that we're doing through some sort of multiplicity adjustment -- for accounting for the multiple tests that we're doing.
So in other words, you know, if given a chance, you could sit down with a pathologist and you could -- or multiple pathologists and you could come to some sort of consensus about that.
Q. So I still don't understand why you don't think it's appropriate or methodologically sound to combine systematic tumors in your analyses.
MR. GRIFFIS: Objection. Argumentative.

Page 157

THE WITNESS: Oh, I'm sorry.
I wouldn't say that it's not -- that it's not methodologically sound at all. I mean, I've worked for over 20 years on interdisciplinary projects involving scientists from all kinds of backgrounds, you know, medical doctors, psychiatrists, psychologists, tomographers, statisticians, geneticists, biologists.
I mean, what you do in a setting like this is you don't just make an executive decision about what you're going to combine based on your role as a statistician. You consult with pathologists who help you to make that determination.
What I did was I tried to apply kind of a consistent methodology. In other words, a priori, I decided that I was going to look at the Greim supplement, then I was going to analyze those tumors as reported in the Greim supplement, some of which were reported as combined, some of

Page 158

which were not, and then make my analysis based on that.

Like I said, I mean, my -- my own take on Dr. Portier's analysis is that his number of tumors change from his, you know, initial analyses prior to his expert report, to his expert report, to his rebuttal report. So that kind of illustrates why it would be important to actually sit down and consult with a pathologist if you're going to decide how to do those.

However, the overarching concern is that regardless of which list, you know, Dr. Portier ends up with or me or some -- in some consultation with pathologists, whether you're talking about 450 tumors or 419 or whichever number you're going to use, you have to account for the hundreds of tests that you're doing in order to, you know, make an evaluation of the evidence.

That's kind of the overarching concern.

Page 159

QUESTIONS BY MS. GREENWALD:

Q. Would you also want to sit down and talk to a toxicologist as well in this collaboration?

A. You know, if we were going to talk specifically about this issue, you know, what to combine, I think that it's clear from, you know, Dr. Portier's own reports and other, you know, material that I've read related to this case that that would be a natural part of the process.

Q. Isn't it true that logistic regression analysis is more commonly applied in epidemiology?

A. No, I wouldn't say that at all. Logistic regression is used countless times, I think, every day around the planet for all kinds of different applications across genetics, biology, business, sociology. It probably is, you know, I'd say, easily one of the most commonly {sic} statistical tools that's applied across all different sciences, settings.

Q. Okay. Can you give me any example in the 12 studies at issue in this

Page 160

case where logistic regression analysis was applied to the data?

A. I'm sorry, can you clarify that?

Q. Sure.

There are 12 studies that are reported in Greim, right?

A. Right.

Q. And those are the 12 studies that have been the subject of your report and all the reports in this deposition today, right?

A. That's right.

What I'm asking is are you -- are you asking whether or not the original investigators used logistic regression?

Q. Correct. Correct.

Do you know?

A. I'm not sure if they did, but for the individual studies it wouldn't be entirely necessary for somebody who just actually conducted one study.

The trend test, in most cases, would often be a sufficient way of assessing -- assessing any kind of, you know,

Page 161

dose response, compound-related effect.

What we're talking about here is something different. In other words, none of the other scientists who, you know, originally conducted these studies actually considered combining, you know, information at the time with -- with other studies that have been done.

So in other words, that's kind of the issue in this case is that we're talking about combining data from across different studies. And that's specifically what requires logistic regression to take care of the problems that I talked about, that Dr. Portier didn't.

Q. Did Greim use logistic regression analysis in his paper?

A. I don't recall.

Q. You don't recall whether Greim used logistic regression analysis in his paper?

A. No, I don't.

Q. When's the last time you read Greim?

A. I think some weeks ago, I

Page 162

think, when I read it through completely, but that's not -- not -- I'm not sure that that was something that he needed, because at the time, you know, I think when -- when they published that paper, they weren't actually trying to combine results to get kind of an overall -- evidence of an overall effect.

Q. The article's entitled "Evaluation of carcinogenic potential of the herbicide glyphosate drawing on tumor incidence data from 14 chronic/carcinogenicity rodent studies," right?

A. Yes.

Q. That's the name of it?

And your testimony is, if I understand it correctly, that you're not sure that was something that needed because at the time when they published the paper, they weren't actually trying to combine results to get an overall evidence of an overall effect; is that right?

A. So they weren't -- they weren't pooling data sets in the way that -- that Dr. Portier was.

Q. What do you understand Greim

Page 163

was doing in this paper?

A. I think he was just presenting a summary of all the findings having to do with glyphosate.

Q. But you don't know if he applied logistic regression analysis, right?

A. Do you want me to take a look at the paper and I can tell you?

Q. Sure.

A. Is that a paper you gave me already?

Q. I did. It is exhibit --

MR. GRIFFIS: 7.

MS. GREENWALD: -- 21 -- thank you.

THE WITNESS: So looking at page 190 of the Greim paper, the summary paper, if you look at the paragraph on the top right column, it says, "Statistical methods are noted in the manuscript tables where statistical significance was attained. Statistical differences in neoplasm incidence summary tables are reported in online data supplements."

Page 164

So in other words, the statistical methods -- the statistical methods, he says, are contained in the tables, but in the tables themselves I've not seen anything that says logistic regression.

What I meant by combining is that he, you know -- this article contains information about each study, but he's not actually trying to combine the data from the studies together to, you know, compute one effect or P value in the way that -- the way that Dr. Portier was.

QUESTIONS BY MS. GREENWALD:

Q. Isn't it true that the false discovery rate is expected in circumstances where one is only rejecting positive findings and not rejecting negative findings?

A. I'm sorry, I don't understand that question.

Could you repeat that, please?

Q. Sure.

Isn't it true that the false discovery rate --

Page 165

A. Uh-huh.

Q. -- is expected in circumstances where one is only rejecting a positive finding --

A. Can I just stop you for just one second?

Q. Sure.

A. Because the first part of your question, I think, is the part that's confusing.

Q. Okay.

A. The false discovery rate is expected in certain circumstances.

The false discovery rate exists for any -- in any setting where you're talking about computing hundreds or thousands or more P values. The false discovery rate, it's -- it's something that just kind of is. It's a quantity that exists.

Q. So how do you define it? Maybe you should just define "false discovery rate."

A. Sure. Yeah. The false discovery rate is the -- I guess you'd say the expected ratio of -- of, I guess, of true

Page 166

findings among those that are actually -- you know, I guess in the case of a -- just to make it more concrete for P values, you know, you have -- you're doing hundreds of analyses or thousands of analyses. The false discovery rate has to do with the proportion of instances where you have P values less than .05 that actually are false positives.

Q. So it's the same as a false positive rate; is that fair?

A. No, it's not.

Q. No.

How is it different than a false positive rate?

A. A false positive rate in terms of P -- are we talking about P values?

So if you set a P value threshold at .05 and you say that if I observe a P value less than .05, then that's statistically significant, in that case the false positive rate would be the rate at which you observed findings of P values less than .05 when, in fact, there's no effect.

Q. Okay. Got it. Okay. That was my error for sure.

Page 167

Okay. So I just want to make sure, I'm going to your last sentence of your answer before my poor question.

"The false discovery rate has to do with the proportion of instances where you have P value -- P values less" -- and the answer is cut off.

I'm sorry.

Okay, "less than .05."

Would that be a fair short answer to what the false discovery rate is?

A. So suppose that you're using P values. So suppose that that's what we're doing. And suppose that you say that -- that you're actually looking for P values less than .05, that if you see that, you're going to -- you're going to decide that, you know, that's no worth.

So what the false discovery rate measures is it says, okay, well, if you're going to carry out hundreds of tests like we are here, we have hundreds of P values that we're computing across all these different tumor types, we're going to expect that a certain proportion of those are going

Page 168

to result in P values less than .05.

Now, what the false discovery rate attempts to at least characterize is, okay, well, what proportion of those are -- are results for experiments where there's no evidence of an effect, in other words.

So that's what the false discovery rate is -- is trying to measure.

Q. Is the false discovery rate more appropriately used in a study for proving or disproving a hypothesis versus screening?

A. I don't really know how to answer that question. All I know is that, you know, the false discovery rate is something that's been -- that's been recommended, even within our own profession, in situations where you have hundreds or thousands or even millions of P values and you want to make sure that you are not being too strict about, you know, throwing out potentially interesting findings, basically.

Q. Do you know if EPA uses the false discovery rate --

A. I don't.

Page 169

Q. -- in cancer bioassays?

A. No. Like I said, what I do know is that it's something that's been recommended within our profession, the American Statistical Association.

Q. But you don't know if EPA uses it?

A. No, I don't.

Q. Do you know what EFSA is?

A. No.

Q. The European Food Safety Administration?

A. Yeah. No, I don't.

Q. Okay. Then you won't know if it uses it.

Do you know what ECCA is?

A. I don't.

Q. Okay. Then I'm not going to ask you those questions.

A. Okay.

Q. Can you cite to a single peer-reviewed article that applies false discovery rate to animal bioassays?

A. I don't think so. Not off the top of my head.

Page 170

Q. You know, you've mentioned Dr. Portier quite a few times in the deposition today and obviously in your expert report.

Prior to being hired as an expert in this case, had you ever heard of Dr. Portier?

A. Yes.

Q. And had you ever met him?

A. No.

Q. How did you hear about him?

A. I think I cited a paper of his when I published my dissertation.

Q. Other than that time that you cited one of his papers, have you had any other interaction with his writings or his work?

A. No, not that I know of.

Q. Until this case?

A. That's right.

Q. In preparation for your expert report, did you ask the Hollingsworth firm for any particular documents to help you prepare your expert report?

MR. GRIFFIS: Objection.

Page 171

THE WITNESS: No.

MR. GRIFFIS: Don't answer that question.

MS. GREENWALD: I just wanted to know if he had any documents that he wanted that he asked you for.

I'm not asking you for communications that you guys had about a document.

MR. GRIFFIS: Yeah, our communications and our exchange of documents is privileged.

QUESTIONS BY MS. GREENWALD:

Q. In preparation for your report, were there any documents -- is there any documents that you felt you needed to prepare your report that you did not have access to?

A. No.

Q. Okay. You can go to page 3 of your report.

Just one second. I'm sorry. I'm sorry. I have a miscite here. Forgive me. I'm so sorry.

A. That's okay.

Q. I'm going to -- I have to look for that cite, sorry.

Okay. So on page 4 now.

A. Okay.

Q. Line 32.

A. Great.

Q. Well, it starts, though, at line 31. "The tendency of researchers, along with scientific journals and other media venues, is a bias towards, quote, positive, close quote, findings."

Do you see that?

A. Yes.

Q. Can you identify any publications in the peer-reviewed literature that report a positive finding for any of the 12 rodent studies that you've discussed in your report?

A. Not off the top of my head, no.

Q. Okay. So I found the other one. If you go to the -- sorry, I took you to the wrong page before. If you can go to the bottom of page 2 --

A. Okay.

Q. -- and then we're going to flip over to 3.

Page 173

A. Okay.

Q. I'm sorry about that.

A. That's okay.

Q. "This is largely because" -- so if you want to look -- it's in the statistical background section.

A. Right. I'm there.

Q. "This is largely because, one, data are generally full of uncertainty and variation, particularly when we study complex diseases or other phenomenon in humans or animals; two, many questions in health and medicine have strong statistical overtones" -- and then there's a parenthetical -- "and three, the comparison of different treatments or potential risks relies heavily on statistical concepts - especially probability - in both designing and analyzing experiments."

Do you see that?

A. Yes.

Q. Okay. Is this also the case for animal chronic toxicity studies?

MR. GRIFFIS: Objection to form.

Page 174

THE WITNESS: I think under number one, particularly where we study complex diseases or other phenomena in humans and animals.
QUESTIONS BY MS. GREENWALD:
Q. But -- sorry, so let me focus on number 3.
A. Uh-huh.
Q. "The comparison of different treatments or potential risk relies heavily on statistical concepts - especially probability in both designing and analyzing experiments."
Is that also the case for animal chronic toxicity studies?
A. Well, since, you know, both Dr. Portier and I are using the Cochran-Armitage trend test which is based on, you know, a probability model, then, yes, it applies, you know, when we use a method like that.
Q. Isn't it true that general screening studies are not hypothesis-driven in toxicology?
A. I'm not sure what you mean by

Page 175

"general screening studies" because that's kind of a -- that's a broad term, I guess, in statistical practice.
Q. So I'm not a statistician. I'm going to try to put it in a framework of -- the only way I can do it.
So you are looking at a chemical to find out its outcome. You have no preconceived notion one way or the other of what that outcome's going to be versus a hypothesis where you say, "I see an uptick in cancer in this community, and I wonder if it's because of the fact that it's -- this community is being exposed to X," the second one being a hypothesis, the first one being screening.
A. Uh-huh.
Q. Does that -- is that a fair -- I mean, is that a sort of ex -- an explanation we can live with for that question, or is that not satisfactory?
MR. GRIFFIS: Objection to form.
QUESTIONS BY MS. GREENWALD:
Q. I mean, obviously it's spoken

Page 176

not by a statistician, so I realize --
A. Yeah, and I'm -- you know, I'm sorry if this sounds technical, but any test that you do, you know, statistically speaking, should start with a hypothesis, whether you're -- you know, whether you're looking at, you know, hundreds of things or one.
So there has never been an analysis that I've done in my life, you know, over thousands of different analyses and different settings where -- you know, where we actually apply a statistical test there isn't a hypothesis.
So that's -- that's why you'll have to forgive me if that question -- I'm not really sure what you're asking, because every statistical test requires a hypothesis.
Q. So you would consider a hypothesis just the general question: Is this chemical capable of causing any health outcome; that would be a hypothesis?
A. Well, I think my hypothesis is stated, you know, in the expert report.
Q. No. No. I'm asking a

Page 177

different question. I understand that. I'm not asking you what your hypothesis is in your expert report. I'm asking would you consider it -- I just want to have the same nomenclature.
A. Uh-huh.
Q. In your nomenclature would you deem it a hypothesis to -- for just the pure statement is this chemical capable of having a health outcome?
Would that be a hypothesis in your nomenclature?
A. Not in a statistical sense, no.
Q. Okay.
A. Because, you know, I -- you know, again, you know, I know that, you know, if you say I'm a statistician, you're an attorney, but I'll -- you know, I can only tell you what it is that I'm -- you know, that I do from day to day.
And what I'm doing here is I'm assessing, you know, tumor incidence across these studies for, you know, dozens of different tumor types, and so the hypotheses here are very specific for the trend test.

Page 178

Q. Okay. Isn't it true, though, that the 12 rodent studies that have been discussed today and are in your expert report are general screening tests?

A. I don't know if -- if I would say that at all because I -- that's not my real purview.

I mean, you know, what the reasons were for designing those experiments are known to the scientists who design them originally. I'm just looking at the data that was generated by those experiments.

Q. This is all good. I just want you to know that when I scratch things out, that's all good for you.

A. Okay. Because when I scratch things out at the university, that's not good for the students.

Q. Scratching out, yeah, I know. When the deposition's over, I'll tell you why I didn't like statistics. I'm not going to tell you until the deposition's over.

Let me just get my -- I'm winding down here. Okay. I'm really nearing the end here.

Page 179

Have you reached any additional opinions in this litigation or in connection with your work with the Hollingsworth firm that are not expressed in your report?

A. Only the opinion that I shared earlier about the nature of this pooled analysis that I already kind of stepped through.

Q. Right.

A. But other than that, no.

Q. Okay. Right.

So are there any opinions that you intend to offer in the general causation phase of this case that are not contained in your expert report or that you testified about today?

A. No, I don't think so. I mean, I -- I guess the one thing I would say is the -- well, scratch that. I'm just repeating myself.

I mean, the only thing I'd have to add would be the issue about the pool analysis, but other than that, no.

Q. Which you talked about today, though, earlier in your --

Page 180

A. Right, we already talked about it.

MS. GREENWALD: Right. Okay. I'm going to pass the witness.

CROSS-EXAMINATION

QUESTIONS BY MR. GRIFFIS:

Q. All right, sir. You have criticisms and responses to the critiques that Dr. Portier offered in his rebuttal report of your own analysis, correct?

A. Right.

Q. Including, for example, criticisms of his modified Table 15 and all of -- each of the specific critiques that he made of your methodology and his defenses of his methodology; is that right?

A. Yes.

MR. GRIFFIS: I have no further questions.

REDIRECT EXAMINATION

QUESTIONS BY MS. GREENWALD:

Q. Okay. Whenever he does that, I have a few more then.

So tell me what criticism you have of his modified Table 15 that's not

Page 181

already contained in your testimony today or that is -- well, it wouldn't have been in your expert report.

A. Well, I guess I -- I guess I'm kind of starting with his -- that Table 15 that was in his original report.

I think that some of my original comments obviously stand on page 12 of my own expert report.

Q. Page 12 of yours, okay.

A. Yeah.

Q. Right.

So I -- I don't -- you're welcome to go to 12. I just wanted to know if there's anything -- I'm really responding to the question you just answered --

A. Uh-huh.

Q. -- in that I want to make sure there's no additional testimony, evidence or information that you would have, other than what's already in your expert report and what you testified about today when you talked about the pooling.

A. Yes.

Q. Is there anything else that you

Page 182

would have to testify about at the general causation hearing relating to modified Table 15 that is not contained either in the report that you already wrote and/or what you talked about today during your deposition?

A. Do I have a copy of his rebuttal report? I can't remember --

MR. GRIFFIS: It's Exhibit 10.

MS. GREENWALD: Yes.

THE WITNESS: Oh, I see it.

It's right here.

QUESTIONS BY MS. GREENWALD:

Q. It's the last page of the report, if that helps. Page 37.

A. Right. 37.

You know, my criticisms are an extension of what I put in my expert report.

But the problem with this Table 15, he modified Table 15. He has an observed number of tumor sites that have -- he says there's significant trends. They're not significant. They're P values that are less than .05, but they're not statistically significant.

But anyway, he's got this

Page 183

expected number of P values less than .05 versus the observed. This is kind -- you know, kind of a foundational point of his argument that if you look down -- and he tallies everything up at the bottom. He has 30 observed P values less than .05. He has 20.9 that he would expect using his counting.

But the problem is that this table is very deeply flawed because his expected -- or his total sites, in other words, is much smaller than it should be in his -- in his modified table.

In other words, he's -- you know, he's -- he has a total site -- his number of total sites is equal to 418, but yet he's also -- he's also reporting trend tests that he -- that were less than .05 when he incorporated historical controls.

So in other words, what he's doing is he's including the 418, but he's -- he's kind of -- he's kind of double-counting, in other words. He's computing P values using a different -- a couple of different approaches, and if either one of them is less than .05, then he's including them in that

Page 184

total.

So in other words, I feel like he's kind of misrepresented in his modified Table 15 what his -- what his observed versus expected should be.

If he's going to actually do analyses -- if he's going to actually do analyses that involve historical controls, then the number of tests that he is performing is larger than the 418. It's larger than what he's reporting.

So he's looking at -- he's computing P values, you know, several different ways. He's not doing it consistently.

You know, in my case what I did is I took the tumors that were reported in Greim as-is, and I applied, you know, the same consistent methodology in computing these -- computing these P values and assessing whether or not there was statistical significance.

What he did was he took all the tumors, he -- for some of them he used historical controls; for some of them he

Page 185

didn't; for some of them he combined, you know, with different studies and so on.

So in other words, he's computing P values kind of inconsistently using several different methods as opposed to just one method. And so in that sense, this 418 and the 20.9 is completely incorrect.

Q. So let me just ask you to look at page 50 of Dr. Portier's original report --

A. Okay.

Q. -- which is the old Table 15, or the original Table 15, before modified Table 15.

A. I'm there.

Q. Okay. And on all the -- other than the numbers, all of the axes are the same, right? The left and the top --

A. It looks like it.

Q. -- columns are the same?

Okay. And you already critiqued Table 15 in your expert report, right?

A. But now he's actually changed it, and it's become even more problematic

Page 186

because that number down at the bottom of 30, as opposed to the 19 on page 50 in his original report, that is a big difference between the two. And it kind of -- it again demonstrates his -- as I describe in my expert report, it demonstrates his tendency to just look for P values in all kinds of different ways, in other words, to do the P hacking that I described in my expert report, to look for P values using many, many different methods that are not reflected in the 418 or the 20.9 next to it.

And so the problem has become even more -- you know, has become even greater in his modified Table 15 as opposed to his original.

Q. So am I correct that your -- the new critique is the new calculations, essentially, that he has in modified Table 15?

A. Yeah, but I think -- I think it's really important to note that because in addition to that, his new table also includes -- I don't know if you look down at footnote 2 --

Page 187

Q. Yes.

A. -- do you see where he has -- toward the very end of that footnote it says "SL, skin lymphoma."

Q. Uh-huh.

A. So, you know, in other words, a big critique I have of his rebuttal report is that he, you know, spends some time in his report pointing out that I was not, you know, combining certain tumor types -- and, you know, you asked me about that earlier as well -- when, in fact, here, you know, he's kind of including skin lymphoma based on my own finding. He's including that in his table without reconciling why it was -- why it was he didn't combine that.

So in other words, again, pointing to this 30 at the bottom of the observed, this is really a crucial point with respect to this rebuttal report. He's -- he's counted these up in ways that are not reflected in the 20.9 you would expect or the 418 that he's counting. He's computing P values in all different ways and coming up with an even larger total than he had at the

Page 188

beginning, which, again, is just kind of the -- what I would deem as consummate P hacking.

Q. Okay. Did you read -- I think you testified, did you not, that you read Dr. Portier's deposition, right?

A. Yes.

Q. And he explained this recalculation and why he has these different numbers in his -- in his deposition, didn't he?

A. And that was a great explanation about why it is that one person would not make an executive decision about where those are combined, that instead you would -- you know, you would consult as a part of an interdisciplinary team to make that determination.

Q. Right.

But he actually explained that the skin lymphoma didn't mean skin lymphoma. It actually meant spleen lymphoma. It was just a typo in his footnote.

A. Well, my understanding is that --

Page 189

Q. And people make typos, right?

A. Yeah, but in his -- in his rebuttal report what he pointed out was that I didn't understand what the meaning of a systemic tumor was, that, you know, lymphoma should be combined somehow, and he's not doing it here.

And so what that tells me is that, you know, that really the bigger concern is are these numbers, 418, 20.9, and what they represent, that he didn't use kind of a consistent approach.

What he did was he just kind of mined P values in four or five different ways, and then he totaled them up here misrepresenting how that compares to what you would expect.

Q. Did you not understand that Dr. Portier was doing a modified Table 15 in large measure in response to your criticism of him and it's resulting from your approach of only using Greim data?

A. Well, yeah, he used Greim data in his first report as well --

Q. Not exclusively.

A. -- just as I did.
Well, I think the bulk of it in the same way that I did.
So, yes, I understand that he modified Table 15 in response to me, but what I'm saying is that he actually -- he actually magnified the problem from his original Table 15.
Q. So just so I'm clear, other than what you just explained about table -- modified Table 15 and what you talked about earlier on pooling and what's in your expert report, that's the totality of the evidence that you intend to present -- of your opinions, I'm sorry, that you -- let me start over again. Wow.
Just want to make sure I'm correct that other than what you just explained, what you explained earlier on pooling and what's in your expert report, that's the totality of the opinions and the reliance of those opinions that you intend to testify about in the general causation phase of this case; is that right?
A. As of right now, yeah, that's

all I can say about it.
MS. GREENWALD: Okay. I don't have anything else.
MR. GRIFFIS: I have no further questions.
MS. GREENWALD: Thank you.
THE WITNESS: Thanks.
VIDEOGRAPHER: Going off record. The time is 1:24.
(Deposition concluded at 1:24 p.m.)

CERTIFICATE

I, CARRIE A. CAMPBELL, Registered Diplomate Reporter, Certified Realtime Reporter and Certified Shorthand Reporter, do hereby certify that prior to the commencement of the examination, Christopher Corcoran, Sc.D. was duly sworn by me to testify to the truth, the whole truth and nothing but the truth.

I DO FURTHER CERTIFY that the foregoing is a verbatim transcript of the testimony as taken stenographically by and before me at the time, place and on the date hereinbefore set forth, to the best of my ability.

I DO FURTHER CERTIFY that I am neither a relative nor employee nor attorney nor counsel of any of the parties to this action, and that I am neither a relative nor employee of such attorney or counsel, and that I am not financially interested in the action.

_____
CARRIE A. CAMPBELL,
NCRA Registered Diplomate Reporter
Certified Realtime Reporter
California Certified Shorthand Reporter #13921
Missouri Certified Court Reporter #859
Illinois Certified Shorthand Reporter #084-004229
Texas Certified Shorthand Reporter #9328
Kansas Certified Court Reporter #1715
Notary Public

Dated: September 20, 2017

INSTRUCTIONS TO WITNESS

Please read your deposition over carefully and make any necessary corrections. You should state the reason in the appropriate space on the errata sheet for any corrections that are made.
After doing so, please sign the errata sheet and date it. You are signing same subject to the changes you have noted on the errata sheet, which will be attached to your deposition.
It is imperative that you return the original errata sheet to the deposing attorney within thirty (30) days of receipt of the deposition transcript by you. If you fail to do so, the deposition transcript may be deemed to be accurate and may be used in court.

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ACKNOWLEDGMENT OF DEPONENT

I,_____, do hereby certify that I have read the foregoing pages, and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

_____
CHRISTOPHER CORCORAN, Sc.D. DATE

Subscribed and sworn
to before me this
_____ day of _____, 20____.
My commission expires:_____

_____
Notary Public

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	Case No. 16-md-02741-VC MDL No. 2741
This document relates to: ALL ACTIONS	

EXPERT REPORT OF DR. CHRISTOPHER D. CORCORAN, Sc.D.

EVALUATION OF GLYPHOSATE EXPOSURE AND CANCER RISK IN RATS AND MICE

Dr. Chris Corcoran
Department of Mathematics and Statistics
Utah State University, Logan, UT

I. SUMMARY

This report examines the rodent studies of glyphosate and cancer risk, particularly the seven feeding experiments using rats and five using mice that were reviewed in the expert report prepared by Dr. Chris Portier. The overarching question is whether these animal experiments provide a scientific basis to opine that glyphosate causes cancer in rats and mice. A few critical characteristics of these studies require careful consideration in addressing this question. Most crucially, the hundreds of individual tumor types evaluated within each experiment across both male and female rodents make it virtually certain that apparent "statistically significant" results will be observed for individual tumors that are in fact due to nothing more than chance. This necessitates the use of common statistical methods that account for multiple tests applied repeatedly to the same data. In addition, most of the tumor types are relatively uncommon, which warrants additional prudence in choosing appropriate statistical methods. In this report, I outline these issues, discussing in Section III how they are managed in everyday statistical practice. In Section IV, I apply the appropriate methods to the glyphosate rodent data and find no evidence whatsoever of a glyphosate effect on the risk any of the tumors evaluated across these studies after accounting for multiple tests. In Section V, I consider the discussion and results in Sections III and IV in the context of Dr. Portier's expert report. Dr. Portier suggests that the glyphosate experiments do provide some evidence of tumor risk among rodents. However, his statistical approaches are deeply flawed, leading him to overstate his findings and seriously misrepresent the data in aggregate. These flaws would prove fatal in any peer review. Most significantly, the results from the animal experiments that were highlighted by Dr. Portier were handpicked because of their "statistical significance", without appropriately accounting for the large number of tests for other tumors that demonstrated no evidence of a glyphosate effect. In addition, Dr. Portier violated conventional statistical practice in his use of historical controls and in combining or "pooling" data from across several sources – using experiments carried out during different years and in different laboratories under different conditions – without appropriately accounting for these studies' unique characteristics. In Section V we illustrate these flaws and their impact on Dr. Portier's conclusions.

II. RESUME AND QUALIFICATIONS

I am a professor of Statistics, and head of the Department of Mathematics and Statistics at Utah State University (USU) in Logan, Utah. I joined the faculty as an Assistant Professor at USU in 1999, after

receiving a B.S. in Statistics from USU in 1995 and a doctorate in Biostatistics from Harvard University in 1999. I was tenured and promoted to the rank of Associate Professor in 2005, and then promoted to the rank of Professor in 2011.

My research interests as a biostatistician focus largely on statistical methods for categorical data analysis, including the analysis of proportions and counts. My dissertation and much of my subsequent work has focused particularly on so-called exact methods for categorical data, developing software tools for researchers that allow them to analyze proportions and counts using exact tests for previously unaddressed study designs, including settings in which data are clustered or correlated (e.g., gestational or developmental toxicology studies using rats or mice), or for large-scale studies of genetics and disease. Much of this work has been funded by the National Institutes of Health, and implemented in the software packages StatXact and LogXact through Cytel Software Corporation (Cambridge, MA). These packages have long been considered the industry standard for exact statistical analysis.

I have also served as a senior biostatistician for a number of large interdisciplinary research projects focused on the epidemiology and genetic causes of complex disease, including Alzheimer's disease, cognitive decline among the elderly, hip fracture, autism, birth defects, and cancer. I have advised collaborators about study design, data management, and data analyses and the appropriate application of statistical methods, and I have either led or assisted with numerous manuscripts and presentations to disseminate research results. This work has likewise largely been funded by the NIH. In all, the collective extramural funding for these efforts has exceeded $25 million.

I have been asked examine data from the rodent glyphosate feeding experiments, and to assess any evidence of potential compound-related effects on the incidence of mouse and rat tumors, and have been compensated for this work at a rate of $250/hour. Unless otherwise stated, all of my opinions are expressed to a reasonable degree of scientific certainty. I reserve the right to amend or supplement my report in response to any rebuttal by plaintiffs' experts or as new information becomes available. I have not testified as an expert witness over the past 4 years. My curriculum vita is included as an attachment to this report.

III. STATISTICAL BACKGROUND

The fields of health and medicine abound with questions that likewise often appear straightforward: What is the best diet for a healthy heart? Are men or women at higher risk for a particular disease? Does a new drug lengthen life for cancer patients? In collaboration with other scientists, a biostatistician's role is to design experiments that address these questions, and to contribute to the analysis of the resulting experimental outcomes or data. Proper statistical methodology has assumed an increasingly important role in health and medicine as research has become more evidence-based. This is largely because (1) data

are generally full of uncertainty and variation, particularly when we study complex diseases or other phenomena in humans or animals; (2) many questions in health and medicine have strong statistical overtones (e.g., How common is a disease? Who is most likely to contract it?); and (3) the comparison of different treatments or potential risks relies heavily on statistical concepts – especially probability – in both designing and analyzing experiments.

As an example, suppose we pose the simple question: Does a flu vaccine work? This could be answered in part by considering a study of people who are randomly assigned to two groups, one receiving the treatment and the other some sort of placebo. At the study's end, the flu rates between the groups would be compared to assess whether the treated subjects experienced less flu than those on placebo. To continue the illustration, suppose such a study was designed with 20 patients in treatment and 20 in control (i.e., given placebo). Suppose further that we subsequently observe 0 flu cases (a 0% flu rate) among those who are treated and 20 cases (a 100% flu rate) among controls. With such a dramatic difference between the respective flu rates, common sense and intuition would strongly suggest that the treatment prevents flu.

On the other hand, suppose that this experiment alternatively results in 5 flu cases within the treatment group versus 10 in control (25% flu rate for treatment versus 50% for control). While the observed flu rate in this scenario is likewise lower within the treatment group, we are clearly *less* certain about declaring that the treatment works more generally. Why? Because it is more difficult to discern whether this result demonstrates an advantage for treatment, or if it could be simply due to chance variation between the people participating in the study. In other words, assuming that the vaccine does not work at all, we would expect that the observed flu rates within the two groups would differ by chance, much as we would expect that the number of heads we observe with 20 flips of a coin would be different than the number we observe if we flipped the same coin an additional 20 times.

How can we quantify the possibility that an experimental result is due simply to chance? The role of probability and statistics is especially critical in providing insight into this question. Common scientific and statistical practice involves designing an experiment with two competing hypotheses in mind. For a study comparing different treatments or groups, the primary hypothesis – generally referred to as the *null hypothesis* – is that there is *no difference* between the groups. The competing or *alternative hypothesis* is that there is a difference between the groups. At the end of the experiment, a probability is computed that measures the evidence against the null hypothesis. This probability, called a *p-value*, represents the likelihood of having observed the experimental result or data given that the null hypothesis is true. A relatively smaller p-value therefore indicates that there is evidence *against* the null hypothesis, since it tells us that the data are unlikely, assuming that the null is correct. On the other hand, a relatively larger p-

value provides no evidence against the null. The process of determining hypotheses and computing and interpreting a p-value based on resulting data is called a *hypothesis test*.

Two generally crucial issues with regard to testing a given hypothesis are (1) how the p-value is computed, and (2) how the p-value is used to make a decision about the null hypothesis. With regard to (1), even for relatively straightforward experiments, such as our hypothetical flu vaccine trial, there may be multiple approaches available for computing a p-value, each of which has certain advantages or disadvantages – these characteristics often depend on a specific study setting, and a biostatistician's role is to evaluate the strengths and weaknesses of competing methods for any given experiment to ensure that the data analysis is as accurate and reliable as possible. With regard to (2), the primary question is: How small does a p-value need to be in order to determine that there is sufficient evidence against a null hypothesis? A decision rule generally provides a cutoff against which the p-value is compared. For a single hypothesis test, the scientific community over time has settled on a threshold of 5%, meaning that a p-value less than 5% indicates sufficient evidence against the null, whereas a p-value greater than 5% provides insufficient evidence. This threshold is called a *significance level*, and p-values below this level are referred to as "statistically significant". Another important role of a biostatistician is to ensure for any given data analysis that the significance level is preserved. Any violation or inflation of the significance level can result in greater likelihood of spurious conclusions, especially in declaring "significant" treatment effects based on experimental results that are only due to chance.

IV.A *Interpreting p-values in the presence of many hypothesis tests*

The "p-value < 0.05" decision rule is relatively straightforward for a single experiment. However, the role of the p-value has become more complicated in today's data-driven world. The fathomless ocean of available data – generated from billions of dollars spent annually on research in health and medicine, and from the sheer volume of electronic transactions and online activity, among other sources – along with the relative ease of computing software for generating statistical analyses, necessitate some additional prudence in interpreting p-values. Nearly every day, online or other media news sources tout claims about an association between an exposure and an outcome, often with some implication of dramatic or broad consequences for the public. Many of these results often do not hold up under additional scrutiny or attempts at replication. How do these kinds of findings so readily find their way into the scientific literature and popular press? Explanations may sometimes include inadequate study design or poor data, but in our "big data" era the culprit is most often the amount of data available from large studies, or from a large number of smaller studies that are examined simultaneously. The tendency of researchers, along with scientific journals and other media venues, is a bias toward "positive" findings. This has led in turn to an overreliance on p-values and statistical significance, at the frequent expense of context, especially in underreporting or ignoring the large number of additional tests performed resulting in "negative" findings.

This issue is relatively straightforward to illustrate, given the application of hypothesis tests and p-values just described. Researchers can easily draw incorrect conclusions from an analysis of a large data set when many associations are examined across a large number of hypothesis tests that each look for a p-value that is less than the conventional 5% significance level. Simply put, when multiple tests are performed, "p-value < 0.05" outcomes will occur quite often even when there are no real effects. Note that the p-value < 0.05 rule was developed relative to a single test. However, this logic breaks down when multiple comparisons or tests are performed within a single analysis. With a 1-in-20 chance of a false positive for a single test, we would expect to see about one false positive for every 20 tests that we compute. In fact, it is straightforward to show using basic probability that there is a 64% chance of at least one false positive among 20 independent tests, and a 99.4% chance of at least one false positive among 100 tests.

This so-called multiple testing issue and the general overreliance on p-values has been discussed and studied extensively within the statistics and epidemiology professions. These issues have likewise been paid some considerable attention over the past several years in the popular media, especially given the many highly publicized findings that create an initial sensation but then fail to hold up under additional study and experimentation. (As just a small sampling of this coverage, within the scientific literature see "Why Most Published Research Findings Are False" by JPA Ioannidis in *PLoS One*, "Statistical Errors: *P* values, the 'gold standard' of statistical validity, are not as reliable as many scientists assume" by R Nuzzo in *Nature*, and "Evolution of Reporting *P* Values in the Biomedical Literature, 1990-2015" by D Chavalarais, JD Wallach, AHT Li, and JPA Ioannidis in *JAMA*. In the popular press see "Trouble at the lab", "How science goes wrong", and "Metaphysicians" in the *Economist*; "Science Isn't Broken: It's just a hell of a lot harder than we give it credit for" at *538.com*; "Striking results, little reliability" in the *Los Angeles Times*; and "New Truths Only One Can See" in the *New York Times*.)

Statisticians have long warned against the practice of computing a multitude of p-values – especially when applying arbitrary criteria to examine the same data in various ways – in order to identify positive associations. More recently, in response to this growing problem and the attention paid to it, our largest and oldest professional organization, the American Statistical Association (ASA), took the unusual step in 2015 of producing "The ASA's Statement on p-Values: Context, Process, and Purpose" (*The American Statistician*), under the direction of a committee comprised of some of our most respected colleagues. Several underlying principles regarding p-values are briefly emphasized in the document. In particular, the committee crystallizes the ongoing issues with multiple testing by noting that

> *P-values and related analyses should not be reported selectively. Conducting multiple analyses of the data and reporting only those with certain p-values (typically those passing a significance threshold) renders the reported p-values essentially uninterpretable. Cherrypicking promising*

> *findings, also known by such terms as data dredging, significance chasing, significance questing, selective inference, and "p-hacking," leads to a spurious excess of statistically significant results in the published literature and should be vigorously avoided. One need not formally carry out multiple statistical tests for this problem to arise: Whenever a researcher chooses what to present based on statistical results, valid interpretation of those results is severely compromised if the reader is not informed of the choice and its basis. Researchers should disclose the number of hypotheses explored during the study, all data collection decisions, all statistical analyses conducted, and all p-values computed. Valid scientific conclusions based on p-values and related statistics cannot be drawn without at least knowing how many and which analyses were conducted, and how those analyses (including p-values) were selected for reporting.*

Of course, none of this means that all science is unreliable, or that we should give up on experimentation altogether. The problem is not with research, generally, but with the overuse and misapplication of p-values. The good news is that the same statisticians and scientists who have identified potential problems with p-values have often also developed or proposed constructive and accessible approaches for increasing the reliability of research results. In addition to the basic suggestions about disclosure quoted above from the ASA report, a couple of the most common among the recurring recommendations include (1) the use of multiple test corrections or what we call "false discovery rates" to adjust for a large number of hypothesis tests; and (2) the reporting of actual effect sizes (in addition to p-values), along with measures of uncertainty about the effect size.

With regard to (1), how does a biostatistician make sure that p-values < 0.05 for an analysis involving many tests are not merely due to chance? This is generally accomplished by first assessing the number of tests that need to be carried out, and then by computing the individual p-values using a method that accounts for the number of tests. This kind of multiple testing method will yield a set of p-values that can then be individually compared to the 0.05 testing level to identify truly significant findings. Such multiple testing methods are readily available in any one of the most widely-used statistical analysis software packages, and are illustrated in the large number of dedicated multiple testing textbooks and manuals. These methods are taught as a matter of course within many university statistics curricula. In particular, so-called stepwise or closed testing procedures can be readily applied to a set of many p-values computed in a given analysis, adjusting the p-values to preserve the false positive rate not only for the individual tests but for any combination or subset of null hypotheses under consideration. While several options are available, the so-called False Discovery Rate (FDR) approach has been increasingly recommended and used in statistical practice.

IV. ASSESSING THE GLYPHOSATE FEEDING EXPERIMENTS

Section III broadly outlined some of the crucial statistical issues that are highly relevant to the rodent glyphosate feeding experiments and to the analysis provided in Dr. Portier's expert report. Most

importantly, given the dozens of tumor types evaluated for both male and female rodents across the twelve studies we are considering, some sort of multiple comparison correction is imperative to avoid a very serious problem with false positives. In this section, we consider these issues in analyzing the rodent data, and summarize the results. In the next section we discuss these results in light of Dr. Portier's conclusions.

The available data come from 12 different experiments (7 using rats and 5 using mice) in which rodents were randomized – males and females, respectively – to increasing doses of glyphosate, then examined after their natural lifespan or at a pre-specified limit and evaluated for the presence of many

			Glyphosate Doses (mg/kg bw/day)		# Types w/ ≥1 observed		# Types w/ ≥3 observed	
Study	Year	Strain	MALE (M)	FEMALE (F)	M	F	M	F
Lankas	1981	SD	0, 3, 10, 32	0, 3, 11, 34	51	68	19	28
Stout	1990	SD	0, 89, 362, 940	0, 113, 457, 1183	45	44	17	14
Atkinson	1993	SD	0, 11, 112, 320, 1147	0, 12, 109, 347, 1134	46	35	15	11
Enemoto	1997	SD	0, 104, 354, 1127	0, 115, 393, 1247	53	37	20	12
Suresh	1996	Wistar	0, 6, 59, 595	0, 9, 89, 886	50	41	15	11
Brammer	2001	Wistar	0, 121, 361, 1214	0, 145, 437, 1498	45	44	14	15
Wood	2009	Wistar	0, 86, 285, 1077	0, 105, 349, 1382	52	40	16	14

Table 1: Summary of 7 rat glyphosate feeding experiments.

			Glyphosate Doses (mg/kg bw/day)		# Types w/ ≥1 observed		# Types w/ ≥3 observed	
Study	Year	Strain	MALE (M)	FEMALE (F)	M	F	M	F
Knezevich	1983	CD-1	0, 157, 814, 4841	0, 190, 955, 5874	57	98	16	32
Atkinson	1993	CD-1	0, 98, 297, 988	0, 102, 298, 1000	25	27	9	13
Sugimoto	1997	CD1	0, 165, 838, 4348	0, 153, 787, 4116	23	31	6	10
Kumar	2001	Swiss	0, 15, 150, 1453	0, 15, 151, 1467	19	30	8	10
Wood	2009	CD-1	0, 71, 234, 810	0, 98, 300, 1081	21	34	9	11

Table 2: Summary of 5 mouse glyphosate feeding experiments.

specific tumor types. These studies are summarized in Tables 1 and 2 (the totals given in these tables exclude cases where proportionally few mice or rats were apparently evaluated for a given tumor type, as the limited number of animals evaluated may reduce the interpretive value of the results to such a degree as no conclusions may be drawn). There are two critical questions to address in evaluating the collective evidence of a possible glyphosate effect on tumors among rodents. First, how do we evaluate the dose-response effect of glyphosate on a single tumor type? Second, how do we account for many dose-response analyses across multiple tumor types?

In answer to question 1, the most commonly used tool for assessing a dose-response effect is the Cochran-Armitage trend test. In the context of the rodent feeding experiments, this approach provides a p-value to test the null hypothesis of *no dose effect on tumor rate* versus the alternative hypothesis that the *tumor rate increases with increasing dose*. This trend test is generally applicable to any experimental data where subjects are randomized to increasing doses of some drug or other intervention, and then observed to experience (on average) an increasing or decreasing percentage of subjects who experience the outcome of interest. As with much of the analysis provided by Dr. Portier, these results are based on a one-sided exact trend test – "one-sided" in that we are testing the trend in only one direction for a given tumor, and "exact" in that we are using the actual probability distribution under the null hypothesis, instead of a normal or bell-curve approximation (also called the "approximate" or "asymptotic" trend test). The exact test is recommended when outcomes of interest are not common, which is often the case across the glyphosate experiments.

What motivates this recommendation, and why does it matter whether we use the exact or approximate p-value? While it may seem like a statistical technicality, the choice turns out to be germane to the glyphosate rodent carcinogenicity question. The International Agency for Research on Cancer (IARC) monograph on glyphosate used the approximate p-value to conclude that results from the Knezevich experiment (included in Table 2) implicated glyphosate as a cause of kidney adenomas among male mice, based on their reported approximate trend test p-value of 0.034 (without adjusting for multiple tests). However, the exact one-sided test – subsequently reported by Dr. Portier in other material and ultimately his expert report – yields a p-value of 0.062 for these same data. The discrepancy between the approximate and exact p-values in this case illustrates why the former should be avoided when tumor incidence is low. It turns out that the approximate p-value is an estimate of the actual or exact p-value, and tends to be more accurate when the overall sample size is relatively larger and when relatively more investigative events (in this case, tumors) are observed. In general, approximate p-values tend to *underestimate* the exact p-values they are supposed to estimate. When sample sizes and numbers of observed outcomes (such as tumors) are relatively large, this underestimation may not be consequential. However, in cases like the glyphosate feeding experiments – where tumors are relatively less common –

the inaccuracy of approximate p-values when they are used can lead to a significant increase in the number of false positives. In other words, because the approximate test tends to underestimate the exact, we will see more "p-value < 0.05" results with the approximate test when there is actually no dose-response effect. This can lead to serious exaggeration of the evidence in favor of trend effects.

Given the large relative error of this normal approximation for the Knezevich data, one might wonder why anyone would ever use it. Normal approximations in applied research had much greater utility before the widespread availability of powerful computing tools. Without some sort of special calculator or software, a normal probability is relatively much easier to compute than an exact probability. Even now, some analyses of counts and proportions rely on more sophisticated statistical models for which the exact distribution is prohibitively difficult to compute, and so some form of normal approximation can still be useful. However, for many experiments – particularly controlled experiments such as the glyphosate mouse studies – exact p-values can be computed instantaneously with a desktop computer, and no approximation is needed, even in cases where the sample sizes and counts are sufficiently large to justify such an approximation.

Given appropriate computation of the trend test p-value, the second necessity is accounting for the many dose-response analyses across multiple tumor types. As discussed earlier in Section III, the False Discovery Rate (FDR) approach recommended by Ioannidis and others is particularly useful for these data. It is a less conservative adjustment that is recommended in settings where there are hundreds or even thousands of p-values under consideration. Of all multiple testing options available in this setting, the FDR approach minimizes the chance that we would fail to detect an actual glyphosate-related effect. It should be noted that an FDR adjustment could and should be used for any set of p-values computed to assess potential glyphosate effects on tumor incidence, including any pairwise comparisons made between the tumor rates of two dose groups. Such two-group comparisons are not reported here as Dr. Portier's conclusions do not appear to rely upon them, but the same multiple testing problem applies, and even more so: in an experiment with four dose groups, respective comparisons of the three treatment groups to control can yield up to three p-values – as opposed to one trend test p-value – for each tumor type.

Trend test results for the 7 rat studies are summarized by the tables shown in Appendix A, and results for the 5 mouse studies are similarly summarized in Appendix B. Each table contains exact one-sided p-values for each study, reported by tumor type and sex, testing specifically for evidence of increasing tumor probability. In addition, for those p-values < 0.05 reported and highlighted in Appendix A and Appendix B, a multiple testing FDR adjustment is applied and reported in the table shown in Appendix C.

As shown in Tables 1 and 2, of the hundreds of individual tumor types evaluated across all 12 experiments, 1,016 were observed in at least one mouse or rat. Among rats, there were 13 trend test p-

values < 0.05 when testing for increasing incidence of each tumor, without accounting for the false discovery rate. Among mice, there were 7 such trend test p-values < 0.05 without accounting for the false discovery rate. All of these are highlighted in blue for easy identification in the tables contained in Appendices A and B. Note that – assuming no effect of glyphosate on tumor incidence – we would conservatively expect about 5% of all individual trend tests to yield p-values < 0.05 only by chance. This would represent about 51 p-values < 0.05 out of the 1,016 individual cancer types for which at least one tumor was observed. However, it makes sense to consider those cancer types for which three tumors were observed. Given the typical study design of four dose groups with approximately 50 animals per dose, about 3 tumors in total are necessary for an exact one-sided p-value no greater than 0.05. Given 345 tumor types across the 12 rodent studies with at least 3 observed tumors (as summarized in Tables 1 and 2), assuming no compound effects we would expect roughly 17.3 p-values < 0.05. In other words, given the 20 observed p-values < 0.05, the overall results are entirely consistent what we should observe given no compound-related effect on tumor incidence. This is analogous to flipping a coin 345 times that has a 5% probability of heads, and observing 20 heads with an expected number of 17.3. This result is highly likely: there is actually about a 62.5% chance of observing this many independent p-values < 0.05 relative to the expected proportion, given no compound-related effects.

In addition, when computing the trend test p-values to account for the false discovery rate, not one of the 1,016 tests is statistically significant. FDR-adjusted p-values for all tumor types with individual trend test p-values < 0.05 are summarized in Appendix C, and not one has a value even marginally close to 0.05. (Note that adjusting for multiple tests always increases the p-value, so that there is no need to report FDR adjustments for any individual trend test results with p-values > 0.05.) There is no statistical evidence whatsoever that glyphosate increases the risk of any of the tumors examined across these 12 studies.

I would emphasize that the results summarized above correspond to a one-sided test that only evaluates the hypothesis that increased glyphosate exposure is associated with an increased rate of tumors – what we would refer to as a *positive* association. However, the data may also be analyzed to evaluate a *negative* association – that is, a decreased tumor rate as glyphosate exposure increases. In fact, it turns out that the one-sided p-values for testing negative effects can simply be computed as 1.0 minus the one-sided p-values reported in Appendices A and B. In other words, any p-value reported in Appendices A and B that is larger than 0.95 represents a p-value < 0.05 for testing for a negative association. There are 13 such outcomes, as summarized in Appendix D (additionally adjusted for the false discovery rate). Again, as with the tests for positive associations, we would expect 5% of all 345 tumor types with at least three observed tumors to likewise yield one-sided p-values < 0.05 when testing for *negative* associations. The 13 such results are again entirely consistent with this expected proportion: there is actually about a 24.5%

chance of observing this many independent p-values < 0.05 relative to the expected proportion, assuming no compound-related effect.

Finally, I have also been made aware of a statistical reanalysis carried out by Dr. Klaus Weber of data from Kumar mouse study. I have evaluated the reported data used by Dr. Weber. Some of the reported tumor counts differ slightly from the data reported in Greim. My own analysis indicates that utilizing the data tables reported by Dr. Weber does not substantively change my conclusions. I have included my results both based on the Kumar data as reported in Greim, et al, and the data reported by Dr. Weber (see Appendix B, Tables B.5 and B.6).

V. RESULTS FROM DR. CHRIS PORTIER'S EXPERT REPORT

Given that the 1,016 p-values computed across all 12 studies yield nothing more than the expected pattern of false positives given no effect from glyphosate exposure, Dr. Portier nevertheless most recently asserts that there is sufficient evidence glyphosate increases the risk for a handful of cancers, including liver adenomas, thyroid C-cell adenomas and carcinomas, skin keratocanthomas, and kidney adenomas in male rats; mammary gland adenomas and adenocarcinomas in female rats; hemangiosarcomas, kidney tumors, and lymphomas among male mice; and hemangiomas among female mice. His analysis unfortunately would certainly not pass the scrutiny of any meaningful peer review, and could actually be used as an excellent case study in any university statistics course to illustrate the misappropriation of p-values. Most critically, virtually any experienced statistician reviewing Dr. Portier's work with the animal data would see immediately that his approach has led to a very serious multiple testing problem. Dr. Portier's analysis is entirely dependent on p-values, arising from three types of computations: those for individual tumor types by gender across each specific study (handpicked from among the more complete results contained in Appendix A and Appendix B of this report), those that incorporate additional "historical control" data, and those that "pool" data from across studies for a given tumor type. Dr. Portier provides a patchwork of p-values from across these three sources, reporting significant findings (for increased risk, only) wherever and in whatever manner they are found in order to manufacture a pattern implicating glyphosate.

While the multiple testing problem overarches all of these p-values, there are additional chronic flaws with his use of historical controls and pooling procedures that need to be illustrated separately. These three issues – multiple testing, historical controls, and pooling of data sets – are correspondingly addressed in Sections V.A–V.C. Section V.D subsequently summarizes how the conclusions in Dr. Portier's report have evolved from his prior work.

(V.A) *The Use and Interpretation of P-Values*

Given the large number of animal tumors under investigation here, any analysis should consider the concerns and recommendations of statisticians and researchers about the use and misuse of p-values, as discussed in Section III. Unfortunately, Dr. Portier does not consider or apply even one of the common or recommended remedies for this problem. In his tables summarizing results for individual rat and mouse studies, he includes only what he terms as "Tumors of Interest", which appear to be selected primarily on the basis of their statistical significance within at least one of the several studies. His report makes no effort to directly adjust p-values for multiple comparisons, for example by using the false discovery rate approach recommended by experts in the profession. This is in spite of Dr. Portier's brief comment on page 40 of his expert report that "an adjustment for multiple comparisons is indeed warranted in evaluating the outcomes of these studies."

The only other mention of the multiplicity problem is the inclusion of Table 15, which Dr. Portier constructed in response to comments submitted last year to the EPA by Dr. Joseph Haseman. Dr. Portier has used Haseman's tally of the expected number of false positives as a basis for demonstrating that there are more significant results among male CD-1 mice than would be expected by chance, given no glyphosate effects. A couple of critical differences in Dr. Portier's approach account for his findings. First, Haseman bases his own expected false positive number on the number of tumors for which there are at least 3 observed cases (roughly the number required for a possibility of a p-value < 0.05). Haseman confined his estimate to sites with three tumors based on the use of an exact one-sided p-value, given that the study designs used for the glyphosate feeding experiments generally cannot yield a p-value < 0.05 unless at least three rodents are observed with a given tumor type. However, Dr. Portier is including his historical control test, which (while not validated, as illustrated in the following section) can yield p-values < 0.05 for *observed* tables that contain only two tumors. For example, the Sugimoto hemangiosarcoma figures in male mice (0/50, 0/50, 0/50, 2/50) generates an exact one-sided trend test p-value of 0.062, which is > 0.05. When reanalyzed by Dr. Portier using historical controls his resulting p-value (what he refers to as "P_{Hist}") is 0.004, which is < 0.05. In other words, when he incorporates historical controls he is able to generate a p-value < 0.05 for smaller numbers of tumors in the observed table. In addition, since he appears to be counting either trend test result with a p-value < 0.05, or a "P_{Hist}" result < 0.05, as "positive," he is at least doubling the number of observed tests among those tumor types for which historical control data are available. These uses of historical controls explain the disparity in Dr. Portier's Table 15 between what is observed and what is expected relative to statistically significant findings among male CD-1 mice.

However, in addition to that, such a comparison of observed and expected – while interesting for exploratory purposes – does not directly address the more pressing question: is there evidence of a compound-related effect with respect to any *specific* cancer type? The answer in part requires multiple

testing adjustments to individual p-values, such as the false discovery rate approach we use for both the rat and mouse studies. As reviewed in Section III, other recommendations for balancing the overuse of p-values include full disclosure of all tests performed, and the estimation of actual effect sizes along with measures of effect size variability (such as confidence intervals). Dr. Portier uses neither of these approaches.

(V.B) ***P-values Using Historical Controls***

The quantitative use of historical controls for the sake of establishing treatment effects within a given statistical analysis is not universally accepted in experimental research. Many researchers view historical controls at best as a means of laboratory quality control (to check consistency of outcome rates) or as a qualitative measure before reaching any determination of causation. However, even if the historical data are judged by study toxicologists to be comparable and potentially useful for inclusion with new experimental data, any statistical analysis needs to be carefully planned and conducted to ensure that p-values are computed appropriately. Dr. Portier's expert report helps to illustrate why. He argues that we can compare prior experimental results for unexposed rats or mice to what we observe among treated rodents in a given experiment. Particularly for rare or uncommon events, such as the cancer types investigated for the glyphosate experiments, it may appear compelling or interesting when the number of tumors observed in a treatment group is markedly higher than what we would expect given the average control rate in prior experiments. However, the approach not only is not helpful for this particular analysis, but is fundamentally inaccurate and is moreover applied inconsistently by Dr. Portier.

Most critically, underlying response rates almost always vary across different experiments, even when those experiments are studying the same outcomes but using different samples at different times and in different settings or laboratories. Even for the best or most consistently controlled studies, there are underlying factors inherent in the sampling, the methods, the environment, and so forth, that can significantly affect the likelihood of response. This is why, for example, statisticians account for study differences or heterogeneity when combining data from different experiments or study sites (as discussed more extensively in the following section – Section V.C – in the context of Dr. Portier's "pooled" analyses).

Dr. Portier illustrates this with an example on page 28 of his report. In this case, he uses historical controls to assess hepatocellular adenoma in the Wistar rats studied by Brammer, and cites results from 16 historical control groups with an underlying range in adenoma rates of 0% to nearly 18%. This relatively wide range in adenoma rates, across studies using the same genetic strain of rat, is a perfect example of how significantly these outcome rates can vary between experiments. However, Dr. Portier's solution is simply to apply the average rate of 4.3% across the 16 studies to the results of the Brammer

experiment, which yielded 0/53, 2/53, 0/52, and 5/52 male rats with liver adenomas across the four respective dose groups. Although Portier appears to dismiss the possibility, it is entirely possible that the Brammer sample actually *did* have an underlying liver adenoma rate nearer to 18% than to 0%. In that case, observing 7 liver adenomas out of 210 mice would not be at all remarkable. Because Dr. Portier failed to formally account for the potential range of historical control tumor rates when generating his test statistic, his resulting p-value is flawed.

Even assuming justification for including historical controls in his analysis (i.e., the historical controls are sufficiently consistent with the given feeding experiment data), Dr. Portier's approach is deeply flawed, and alarmingly inconsistent even with the recommended statistical methods cited within his own sources. He appeals on page 21 of his expert report to four references as "guidelines" (numbers 30, 33, 34, and 66 in his citation list). The first three provide an exceptionally thin foundation for such a key aspect of Dr. Portier's analysis: the first is somewhat of a self-reference (the preamble to the IARC glyphosate monograph, written by a group chaired by Dr. Portier), and the second and third are regulatory references specific to the EPA and the European Chemicals Agency. The fourth is an expository article authored by Dr. Joseph Haseman in an environmental health journal – the only one of the four references that outlines specific statistical methodology for incorporating historical controls. The Haseman paper describes the heterogeneity problem described above – the tendency of different study samples to have significantly different tumor rates – and proposes a sensible modeling method that accounts for these differences. Dr. Portier offers no explanation for why he fails to use this approach, in spite of his citing the paper in which it was suggested. Moreover, there are other references in the statistical literature that specifically address the problem of incorporating historical controls. For example, Fung et al (*Canadian Journal of Statistics*, 1996), Greim et al (*Human & Experimental Toxicology*, 2003), and Peddada et al (*Journal of the American Statistical Association*, 2007), among others, all offer overviews and options for a proper analysis using historical controls – none of them mentioned or utilized by Dr. Portier, in spite of his citing these articles in a recently published commentary (Portier and Clausing, 2017). The common principle underlying all of these methods is the need to account for differences in underlying tumor rates for controls drawn from a variety of experiments. As explained more fully in the following section, the general consequence of not properly adjusting for such differences is underestimation of p-values, which leads to inflation of p-values < 0.05 and "statistically significant" findings due to nothing more than chance. Given the hundreds of tumor types under consideration across the glyphosate rodent experiments, this is a problem that should be meticulously avoided.

Aside from his completely incorrect analysis, the p-values computed by Dr. Portier using historical controls do not change any of the substantive conclusions of the analysis, since Dr. Portier neglected to account for the enormous multiple testing problem. Even when the corresponding trend test p-values in

Tables A1–A7 and B1–B5 of this report were replaced by Dr. Portier's historical control-based results and then adjusted with respect to the false discovery rate, none of them was significant. In addition, Dr. Portier neglects to explain why he selectively highlights tests using historical data – there were apparently many other tumor types for which historical control data were available but not used. It appears that such results were reported by Dr. Portier primarily if they resulted in a p-value < 0.05.

(V.C) ***P-values From "Pooled" Analyses and Interpretation of Results Across Studies***

Given the multiple testing problem and the relative rarity of most all of the cancer types, there would seem to be some impetus to attempt combining data from across studies. Aggregating the sample size and tumor counts could potentially increase the likelihood of observing a compound-related effect, if any such an effect exists. Dr. Portier's attempts to accomplish this through his "pooled" analyses are nevertheless completely unreliable. His analysis and comparative interpretations across the various experiments disregard conventional statistical practice in several fundamental and egregious respects, and his approach is ad hoc and inconsistently applied, without any kind of systematic analysis plan across the available studies or tumor types.

First and most critically, Dr. Portier's "pooled" procedures flout statistical standards by making no adjustments at all for differences between experiments or for the similarities among mice within each study. Dr. Portier simply aggregates data across various subsets of rat and mouse studies, treating rodents born and raised in different environments, fed from different sources, measured using different tools by different researchers over a 30-year span as though they were all included within a single experiment at the same time. This is an astonishing violation of accepted practice that would serve as an example in any relevant college class of how not to combine data from different sources.

Generally speaking, any combining of data across experiments such as those considered here requires that (1) the experiments are comparable enough in terms of their measurements and conditions to justify their inclusion in a combined analysis; and (2) if the studies are sufficiently comparable, some adjustment is made for similarities or correlation of subjects within each study, as well as for differences in treatment effects that are often observed. Addressing (1) is a primarily qualitative first step that usually relies on some consensus among collaborating investigators with complementary expertise, who assess the admissibility of available studies in terms of their comparability (e.g., that they consistently measured outcomes and administered treatment doses). Without such strong justification, any attempt to quantitatively combine the data from the individual studies can be unreliable. Dr. Portier has provided very little information in his report about how he conducted such a review – for example, describing consultations with other collaborators or sources about whether pathologies were examined consistently for the handful of tumors types that he selected for his pooled analyses.

Putting aside the lack of a qualitative review, the "pooling" approach used by Dr. Portier to simply combine data from different studies – as though they arose from the same experiment – is completely inappropriate and incorrect. The underlying principle in any analysis that combines data from independent studies is that the studies themselves – carried out at different times and in different settings – may be distinct in ways that may or may not be measurable. These differences, often referred to in experimental research as sample or study *heterogeneity*, need to be considered within the statistical analysis in order to avoid bias when computing p-values. Why is this so crucial? There are two reasons to account for study differences. First, ignoring them often leads to an increased chance of a false positive result. To illustrate, consider an example where we have access to data for a flu vaccine that was administered to 10 large nuclear families, with 5 family members in each home. For the sake of illustration, suppose that the members within each of these families – for one reason or another – have the exact same response to the vaccine. In other words, if one member of a given family responds to the vaccine, then *all* family members respond. If one does not respond, then neither to any of the other family members. Although there are 50 total individuals enrolled in this study, our *effective* sample size is only 10. In other words, one family member from each home is sufficient. The other 4 give us no additional information about the treatment effect, and are statistically redundant. From a statistical standpoint, naively assuming that all 50 individuals are somehow independent could lead to significant underestimation of the p-value testing the vaccine effect, making a false positive much more likely.

This example is obviously extreme. In practice, we would seldom (if ever) observe that kind of perfect correlation among data from a given study site or experimental source. However, in any analysis of data from multiple sites or experiments, some appreciable correlation within each will exist due to variations in the different sampling populations or experimental conditions. This heterogeneity will result in at least some effective reduction of the sample size, in proportion to the strength of the correlation between subjects within each study. Suppose that we ignore those study differences by simply aggregating the data and analyzing them as though they all came from the same experiment, as Dr. Portier has done. Then p-values computed to test overall treatment effects will be inaccurate. Generally speaking, they will be too small, leading researchers to overstate any evidence of a treatment effect.

The second reason to assess and account for study differences is that the treatment effect often differs between the individual studies, both with respect to the size and even the direction of the effect (e.g., increasing or decreasing trend). Another crucial step in combining datasets is to compare the effects across studies, to understand how they are either alike or different with respect both to their direction and magnitude. This typically involves some estimation of effect sizes, along with additional formal statistical comparisons to ensure that the effects are consistent before any data from across the various studies are pooled. Treatment effects in dose-response experiments are often summarized using an odds ratio or

relative risk, which in the case of the glyphosate experiments would estimate the relative increase or decrease in the odds or risk of tumor for some given increase in glyphosate dose. For example, the so-called logistic regression model that is used extensively by researchers across numerous fields (particularly in biomedicine) allows researchers to estimate such odds ratios in ways that can examine whether the estimated odds ratios are consistent across experiments. A logistic regression can help an investigator to make a reasonable judgment about whether the observed results – expressed as odds ratios relative to glyphosate dose – in two or more different experiments are significantly different. This is a crucial assessment in any combined analysis that statisticians use to decide whether they are justified in estimating a "common" or averaged effect across all of the studies. The important point is that such methods are generally applied as a matter of course in this kind of analysis, although they are not used at all by Dr. Portier.

In short, Dr. Portier has apparently made no reasonable effort to address study heterogeneity, either with respect to the correlation of rodents within study or to differences in dose-response effects across studies. The seriousness of this flaw cannot be overstated. In addition to his failure to account for the way that mice and rats are correlated within the individual studies, Dr. Portier has combined data from different sources without regard for the magnitude or direction of observed effects within groups. At a minimum, by failing to account for within-study correlation, Dr. Portier has underestimated the actual p-values – hence overstating the evidence (and increasing the chance for a false positive result) – for those tumor types that he has selected for "pooled" analyses. Moreover, relying only on p-values for these "pooled" analyses, even if they correctly account for study heterogeneity, masks study differences in ways that can seriously undermine any possible understanding of potential compound-related effects. I know of no available applied statistical text or handbook that touches on this topic that even entertains the possibility that an analyst would simply combine data from various experiments as Dr. Portier has done, without carefully examining and accounting for study differences. His approach can only be described as naïve at best, and deliberately misleading at worst.

Interestingly, Dr. Portier provides two citations (numbers 92 and 93 in his report) that he uses to justify his combined analyses, and that provide some guidance about how he should conduct them. They are expository articles from epidemiological journals, and – while not statistical sources, strictly speaking – both provide general information about how to analyze data from different sources, consistent with the principles summarized above. Both emphasize the importance of evaluating and accounting for study heterogeneity to avoid bias in statistical inference, and both recommend the use of logistic regression models to estimate treatment effects between studies and to assess whether those effects differ significantly. Neither of these sources mention the option of aggregating data in the way that Dr. Portier has done. On the contrary, one of them suggests that study heterogeneity should conservatively be

assumed even if there is statistical evidence that it does not exist. Dr. Portier astonishingly and inexplicably ignores all of this information within his own sources.

How does this enormous oversight specifically compromise Dr. Portier's conclusions? As just one example among his several pooled analyses, consider Dr. Portier's assessment of liver adenomas among rats. Relying only on his personal qualitative judgment, and without any formal statistical justification, Dr. Portier chose to focus only on studies using Wistar rats (including the Brammer, Suresh, and Wood studies in Table 2), and to ignore female rats altogether. (If a logistic regression model was used, the analysis could readily include the other four rat studies as well as all female rats, easily accounting for any possible differences between the genetic strains and genders.) The Brammer study observed counts of 0/53, 2/53, 0/53, 5/52, with a trend test p-value of 0.008 and an FDR-adjusted trend p-value of 0.370. Note that the Suresh study resulted in 24/50, 22/50, 10/48, and 21/50 liver adenomas across the male dose groups, an increasing trend that was not statistically significant (trend p–value = 0.391; FDR-adjusted trend p-value = 0.715). The Wood study resulted in 0/50, 2/51, 1/51, and 1/51 liver adenomas across the male dose groups, a weak increasing trend that was also not statistically significant (trend p–value = 0.418; FDR-adjusted trend p-value = 0.839). Even after excluding the other rat studies, along with any results for females, in an argument spanning pages 32 and 33 of his report, Dr. Portier first suggests pooling the Brammer, Wood, and Suresh liver adenoma data for male rats, and then arbitrarily excludes the Suresh study because of its higher overall rate of liver adenomas (based again only on personal judgment, without any formal statistical analysis). Dr. Portier then combines the data from Brammer and Wood into a single table to produce a single trend test p-value, that he concludes demonstrates evidence that glyphosate increases incidence of liver adenomas. Dr. Portier takes the same approach with mammary tumors, combining only the data from Brammer and Wood, in order to generate a p-value < 0.05. However, he then elects to combine data from all three studies in order to obtain a p-value < 0.05 with respect to skin keratocanthomas. Notably, he reports that using only Brammer and Wood for skin keratocanthoma does not generate a "statistically significant" p-value. This appears to be a straightforward case of the "p-hacking" phenomenon discussed earlier in Section III, as he offers no empirical justification for how he chooses to include or exclude the Suresh study from these additional analyses.

Unfortunately, Dr. Portier's arbitrary and incorrect analysis renders his resulting "pooled" p-value entirely meaningless. Accounting for heterogeneity and estimating study-specific effects, as recommended by Dr. Portier's own sources, my own analysis of the liver adenoma data first demonstrated definitively that there is highly significant correlation among rats within each study (using an exact test for correlation in the StatXact software package). In addition, using a logistic regression model to estimate observed effects, I found that the Brammer study indicates an odds ratio (OR) of 1.21 with

respect to an increased dose of 100 mg/kg (meaning a 21% increase in odds of liver adenoma for every additional 100 mg/kg bw/day). The Wood study resulted in an estimated OR of 1.01 (only a 1% increase in the odds of liver adenoma for an increased dose of 100 mg/kg), and the Suresh study also resulted in an estimated OR of 1.01. Moreover, the logistic regression revealed that there is a highly statistically significant difference in observed effects between the three studies – specifically, the effect observed in Brammer is higher than the effects observed in the Wood and Suresh data. In other words, Dr. Portier included two of the three studies in his "pooled" analysis that actually are demonstrably different with respect to glyphosate. This further invalidates Dr. Portier's "pooled" p-value for evaluating a common potential effect across studies, which he computed using the Brammer and Wood data. Nevertheless, aggregating the two datasets, without accounting for these potentially serious differences between the underlying adenoma findings, Dr. Portier reports a significant "pooled" finding that is entirely driven by the Brammer data. He implies that this somehow makes the result more convincing, which is a logical leap equivalent to combining a gallon of paint with a gallon of paint thinner, and then selling the product as two gallons of paint.

In addition to this conspicuous and fatal problem, Dr. Portier takes a highly inconsistent approach with his "pooled" analyses that appears to focus primarily on achieving statistical significance. He "pools" and "re-pools" rat and mouse data (always ignoring study heterogeneity), using different combinations of studies without any predefined strategy or logical criteria. Dr. Portier's "Joint Analysis" of the mouse studies on pages 45-47 of his expert report is a particularly confusing and ad hoc jumble. To summarize the arbitrary and incongruous nature of his approach:

- Dr. Portier proposes that the only neoplasms that he needs to examine for combined or "pooled" analyses are the five for which at least one of the four CD-1 studies resulted in a statistically significant finding. Why the dozens of others should be ignored is not explained. At the very least, Dr. Portier is compounding the grievous multiple testing problem discussed earlier, since the significance of the "pooled" trend test p-values that he reports are driven entirely by the five individual statistically significant results. A more systematic analysis would combine data from across studies for each tumor type (assuming that the tumor types are consistent, and appropriately accounting for study heterogeneity); estimate a common observed effect for each tumor type, along with measures of statistical significance (including p-values and confidence intervals), assuming that the effect is consistent across studies; and finally account for multiple comparisons (e.g., adjust for the false discovery rate) among the set of resulting p-values. However, conducting such a systematic analysis would still need to be preceded by a sound qualitative toxicological analysis to ensure that the studies are comparable, as discussed at the beginning of Section V.C.

- After confining himself to the CD-1 studies, Dr. Portier alternatively combines the two 18-month studies, the two 24-month studies, and then all four studies together, and then for each tumor type simply bases his conclusions on the one of those three that results in statistical significance. For example, in the summary of his findings, he claims there is evidence that glyphosate "causes" kidney tumors, after pooling all four CD-1 studies. However, he also claims there is evidence that glyphosate "causes" malignant lymphomas, conveniently based on the result from "pooling" only the two 18-month studies, even though there is no statistically significant effect when all four CD-1 studies are used. This is internally inconsistent and another example of "p-hacking."
- Dr. Portier's analysis of hemangiosarcomas in males is especially troubling. After first "pooling" the two 18-month studies (significant result), and then the two 24-month studies (no significant result), *he proposes simply removing the 0/50 count observed in the highest dose group of the Knezevich study*. By excluding the mice in this high dose group – none of whom were observed with any hemangiosarcomas, which would suggest no effect of the test compound – Dr. Portier is then able to manufacture a statistically significant p-value when he pools the 24-month studies, as well as a significant p-value when pooling all four CD-1 studies. This is a breathtaking manipulation that can only be charitably described as statistical malpractice.
- Dr. Portier's summaries of the results for each of the five tumors introduce logical circularities and other redundancies that artificially boost the impact of his findings. For example, consider his discussion of kidney tumors. After alternately pooling the 18-month, 24-month, and all CD-1 studies, Dr. Portier then compares the observed adenoma rates to historical controls. (As an aside, historical controls are not considered by most statisticians or statistical sources as a valid means of establishing causation, as discussed earlier. However, even using Dr. Portier's criterion on page 21 of his report, it is unclear why he uses historical controls in his analysis of the mouse studies that were not "from untreated control groups from studies in the same laboratory within two to three years of the study being evaluated.") His conclusion is that, given historical control rates, the two adenomas observed in each of the highest dose groups of the 24-month studies is highly improbable, and strengthens the evidence of a compound-related effect. However, as discussed earlier in Section III in the context of multiple hypothesis tests, this is self-evident when we are evaluating hundreds of tumor types across 12 studies: while such a result may be improbable for a single analysis, it is nearly certain that we would observe such results for many tumors when we are computing hundreds of p-values. Dr. Portier is merely providing another outstanding explanation for how a false positive arises when we carry out a large number of statistical tests.

- Dr. Portier declares that all five mouse studies, including the four CD-1 studies and the Swiss Albino study, are "useful", but then confines his analysis to the CD-1 studies. No explanation is given for the omission of the Kumar study.

Dr. Portier's joint analysis of the rat studies (under "Summary – Rats" on pages 32-35 in his expert report) is similarly uneven, suffering from inconsistencies similar to his mouse analyses. To highlight:

- As with the mouse studies, for his "pooled" analyses of rats Dr. Portier selects only those tumor types with statistically significant individual p-values (unadjusted for false discovery rates). There is no systematic approach applied to the dozens of other tumor types that were evaluated, and no attempt to make an adjustment for multiple comparisons.
- Dr. Portier carried out "pooled" analyses of both liver adenomas, mammary gland tumors, and skin keratocanthomas among the three studies that used Wistar rats (Brammer, Suresh, and Wood in Table 2). As discussed previously, for his analysis of liver adenomas Dr. Portier eliminated the Suresh study, without any formal statistical justification, based only on his personal judgment that the studies cannot be combined because of differences in underlying tumor rates. He likewise excluded the Suresh study from his "pooled" analysis of mammary gland adenomas, but then included Suresh for testing skin keratocanthomas. For all three tumor types, Dr. Portier's arbitrary exclusion or inclusion resulted in a "pooled" p-value < 0.05. Again, as noted before, an averaged or pooled effect can be estimated even if the underlying average tumor rates differ, provided that the observed effects across the studies are consistent. Dr. Portier made no attempt to evaluate the latter issue, which invalidates his results.

(V.D) Evolution of Dr. Portier's Analyses of Animal Carcinogenicity Studies

In addition to the flaws in Dr. Portier's expert report, there are other serious questions about the consistency of his approach, particularly in light of how his work has evolved. He at times appears to selectively rely on analytic strategies motivated primarily by arbitrarily seeking for "statistical significance" (i.e., computing more p-values < 0.05). A few illustrations:

- The IARC Glyphosate monograph – for which Dr. Portier served as an invited specialist – used approximate trend test p-values to assess potential glyphosate effects for the Knezevich data. As discussed in Section IV, approximate p-values tend to underestimate the corresponding actual p-values, and thus increase the potential for "statistically significant" results that are only due to chance. As outlined in the supplementary material of Dr. Portier's expert report, criticism of the approximate trend test by Dr. Joseph Haseman and others prompted Dr. Portier to rely solely on the exact test in his subsequent work. However, he has resorted again to approximate p-values for some of the p-values he computes using historical controls, arguing that the sample sizes justify their use. Since exact p-values can be computed instantaneously using modern software, there is no good reason to use approximate

tests, particularly when their substantive results disagree with the exact p-values that they are merely estimating.

- It is particularly puzzling that Dr. Portier has previously dismissed the rat feeding studies, declaring that they provide no collective evidence that glyphosate increases cancer risk (for example, on page 11 of Document 9 in the supplementary material of his expert report). He offers no explanation regarding why he has now decided that the statistical evidence supports such an association.
- Dr. Portier reports only results that demonstrate increasing tumor incidence for increasing glyphosate dose, but mentions nothing about tumors that demonstrate decreasing risk of tumor across the treatment groups. When computing one-sided p-values in the absence of any strong prior evidence in favor of either a positive or negative effect, statistical convention dictates that we maintain equipoise about what is observed, even if the result is counterintuitive or in a direction opposite of what we would either hope for or expect.
- Dr. Portier also appears to be inconsistent in his standard for statistical significance. After quoting EPA guidelines on page 20 of his expert report, establishing a significance threshold of 5%, he later (on page 25) fudges somewhat to suggest that we should also consider p-values between 5% and 10%. This is borne out in Tables 8 and 14, where he implies "statistical significance" by highlighting p-values > 0.05 for multiple tumor sites. This further elevates the likelihood of observing false positive results, even assuming his other strategies (i.e., historical controls and "pooled" analyses) were actually valid.

VI. Conclusion

As discussed in Sections III and IV, in the context of the hundreds of tumors evaluated across all 12 rodent glyphosate feeding experiments, it is clear that the individual statistically significant findings closely follow the pattern we would expect given that glyphosate does not increase the risk of cancer. Dr. Portier's own analysis of the rodent feeding studies violates several major foundational principles of statistical practice. His entire approach is based on p-values, which he has selectively reported and used to highlight those findings that are statistically significant, without applying any commonly recommended methods to account for the hundreds of individual tumor types evaluated across the 12 experiments. Dr. Portier has further employed other flawed strategies, including the use of historical controls and the "pooling" of subsets of the data to generate additional p-values, which he has computed using inconsistent and arbitrary standards. Dr. Portier's "pooled" analyses are deeply defective, lacking any accounting for study heterogeneity or differences in observed effects as recommended by Dr. Portier's own cited sources. His simple aggregating of data – as though data from disparate studies arose from the same experiment – is completely inappropriate and unsupported by any credible statistical text or manual

regarding methods for analyzing data from multiple sources. Dr. Portier's analytic strategy seriously violates our own profession's "Statement on p-Values: Context, Process, and Purpose" (*The American Statistician*), referenced in Section III, which notes in part: "*P-values and related analyses should not be reported selectively. Conducting multiple analyses of the data and reporting only those with certain p-values (typically those passing a significance threshold) renders the reported p-values essentially uninterpretable. Cherry-picking promising findings, also known by such terms as data dredging, significance chasing, significance questing, selective inference, and 'p-hacking,' leads to a spurious excess of statistically significant results…and should be vigorously avoided.*"

July 31, 2017

Christopher D. Corcoran — Date

APPENDIX A – RESULTS FOR RAT FEEDING STUDIES

TABLE A.1 – Lankas Rat Results, by Tumor Type and Adjusted for Multiple Tests.

MALES	
TUMOR SITE AND TYPE	p
pituitary adenoma	0.394
pituitary carcinoma	0.785
brain glioma	0.703
heart sarcoma	0.253
lung met undiff sarcoma	0.250
lung cell carcoma	0.514
lung lymphoma	0.750
lung met ost sarcoma	0.750
lung met mixed tumor	0.500
liver cell sarcoma	0.440
liver lymphoma	0.626
liver met undiff sarcoma	0.750
liver neo nodule	0.474
liver hep carcinoma	0.061
mes lymph angioma	0.547
mes lymph lymphoma	0.623
mes lymph cell sarcoma	0.454
pancreas islet cell adenoma	0.509
pancreas islet cell carcinoma	0.251
pancreas acinar cell adenoma	0.251
pancreas lymphoma	0.749
pancreas cell sarcoma	0.644
salivary cell sarcoma	0.250
med lymph fibrosarcoma	0.241
med lymph cell sarcoma	0.593
spleen angiosarcoma	0.750
spleen lymphoma	0.626
spleen cell sarcoma	0.201
stomach cell sarcoma	0.250
jejunum cell sarcoma	0.255
kidney adenoma	0.813
kidney lymphoma	0.750
kidney cell sarcoma	0.735
kidney lipoma	0.735
testis cell tumor	0.009
prostate cell sarcoma	0.251
bladder papilloma	0.494

FEMALES	
TUMOR SITE AND TYPE	p
pituitary adenoma	0.938
pituitary carcinoma	0.084
brain carcinoma	0.189
brain lymphoma	0.251
brain glioma	0.251
spinal cord	0.250
heart lymphoma	0.250
heart sarcoma	0.750
trachea fibrosarcoma	0.751
esophagus fibrosarcoma	0.636
lung cell carcoma	0.282
lung lymphoma	0.317
lung mamm adenocarcinoma	0.253
lung adrenal carcinoma	0.253
lung met fibrosarcoma	0.753
liver cell sarcoma	0.490
liver lymphoma	0.062
liver met fibrosarcoma	0.750
liver hep carcinoma	0.156
liver neo nodule	0.732
mes lymph lymphoma	0.267
mes lymph cell sarcoma	0.070
pancreas islet cell adenoma	0.874
pancreas islet cell carcinoma	0.292
salivary fibrosarcoma	0.250
thymus lymphoma	0.224
thymus thymoma	0.266
med lymph fibrosarcoma	0.744
med lymph cell sarcoma	0.094
med lymph lymphoma	0.058
spleen lymphoma	0.062
spleen sarcoma	0.062
stomach lymphoma	0.250
stomach cell sarcoma	0.750
stomach fibrosarcoma	0.750
jejunum leiomyosarcoma	0.500
ileum cell sarcoma	0.249

thyroid ccell adenoma	0.738
thyroid carcinoma	0.253
thyroid foll adenoma	0.123
parathyroid adenoma	0.743
adrenal cell sarcoma	0.250
adrenal chromocytoma	0.158
adrenal cort adenoma	0.844
adrenal lymphoma	0.750
skin cell tumor	0.251
skin adenoma	0.251
muscle cell sarcoma	0.747
harderian lymphoma	0.759
marrow lymphoma	0.646
marrow sarcoma	0.597

colon cell sarcoma	0.244
kidney lymphoma	0.250
kidney ret cell sarcoma	0.108
kidney trans cell sarcoma	0.250
bladder trans cell carcinoma	0.232
ovary gran cell tumor	0.657
ovary theca cell tumor	0.234
uterus cell carcinoma	0.247
uterus endo sarcoma	0.247
uterus adenoma	0.197
uterus polyp	0.605
uterus ret cell sarcoma	0.809
thyroid ccell adenoma	0.671
thyroid ccell carcinoma	0.003
thyroid foll adenoma	0.964
thyroid fbirosarcoma	0.244
parathyroid adenoma	0.240
adrenal cell sarcoma	0.109
adrenal chromocytoma	0.351
adrenal cortical adenoma	0.850
adrenal cortical carcinoma	0.386
adrenal lymphoma	0.246
mammary adenoma	0.497
mammary fibroadenoma	0.804
mammary adenocarcinoma	0.457
mammary ret cell sarcoma	0.746
eye fibrosarcoma	0.242
harderian lymphoma	0.240
harderian fibrosarcoma	0.240
marrow lymphoma	0.188
marrow sarcoma	0.062

1 **TABLE A.2 – Stout Rat Results, by Tumor Type and Adjusted for Multiple Tests.**

MALES	
TUMOR SITE AND TYPE	p
adrenal adenoma	0.063
adrenal chromocytoma B	0.248
adrenal chromocytoma M	0.585
adrenal ganglione	0.504
brain astrocytoma	0.297
bone sarcoma	0.245
cervical astrocytoma	0.496
cervical glioma	0.747
duodenum carcinoma	0.749
eyes sarcoma	0.250
kidney lipoma	0.938
kidney liposarcoma	0.500
kidney mesenchymal	0.500
kidney adenoma	0.751
liver adenoma	0.016
liver carcinoma	0.610
liver sarcoma	0.313
liver neoplasm	0.500
mammary gland adenoma	0.282
mammary gland carcinoma	0.717
mammary gland canthoma	0.243
lymph node gioma	0.250
nose adenoma	0.245
pancreas adenoma	0.147
pancreas carcinoma	0.752
pituitary distalis	0.665
pituitary intermedia	0.251
prostate carcinoma	0.750
parathyroid adenoma	0.243
skin canthoma	0.077
skin carcinoma	0.546
skin adenocarcinoma	0.752
skin cytoma	0.500
skin zymbal's gland adenoma	0.498
skin basal cell	0.248
skin papilloma	0.735
skin sebaceous gland adenoma	0.312
skin fibroma	0.752
sp cord thoracic cytoma	0.500
testies interstitial	0.297

FEMALES	
TUMOR SITE AND TYPE	p
adrenal adenoma	0.664
adrenal chromocytoma b	0.268
adrenal chromocytoma m	0.250
adrenal carcinoma	0.015
brain cell tumor	0.500
cecum sarcoma	0.507
kidney lipoma	0.500
kidney carcinoma	0.500
kidney hemangioma	0.750
liver adenoma	0.922
liver carcinoma	0.167
liver sarcoma	0.500
liver giosarcoma	0.500
liver cholangioma	0.750
lung adenoma	0.750
mammary gland adenoma	0.252
mammary gland carcinoma	0.770
mammary gland carcinosarcoma	0.438
nose carcinoma	0.500
ovary granulosa	0.684
ovary theca	0.749
pancreas adenoma	0.962
pituitary adenoma	0.996
pituitary carcinoma	0.434
parathyroid adenoma	0.859
skin carcinoma	0.248
skin zymbal's cell adenoma	0.500
skin basal cell	0.748
skin clitoral gland adenoma	0.748
spleen lymphoma	0.250
spleen hemangioma	0.250
spleen sarcoma	0.750
thyroid adenoma	0.050
thyroid carcinoma	0.500
thyroid cystadenoma	0.438
thyroid foll cell carcinoma	0.250
thymus lymphoma	0.937
urinary papilloma	0.500
uterus polyp	0.355
uterus hamartoma	0.498

thyroid adenoma	0.067
thyroid c cell carcinoma	0.441
thyroid cystadenoma	0.407
thyroid follicular cell carcinoma	0.254
thymus lymphoma	0.479

uterus sarcoma	0.498
uterus adenoma	0.749
uterus leiomyoma	0.749
uterus fibroma	0.749

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1 **TABLE A.3(i) – Atkinson Male Rat Results, by Tumor Type and Adjusted for Multiple Tests.**

MALES	
TUMOR SITE AND TYPE	p
adrenals cortical adenoma	0.909
adrenals uni phaeochromocytoma (M)	0.517
adrenals uni phaeochromocytoma (B)	0.134
adrenals bi phaeochromocytoma (B)	0.517
brain granular cell tumor	0.307
brain glioma	0.685
kidneys tubular adenoma	0.800
kidneys urothelial carcinoma	0.400
liver carcinoma	0.681
liver adenoma	0.322
lungs squamous cell carcinoma	0.403
lungs alveolar/bronchiolar adenoma	0.763
mammary glands fibroadenoma	0.303
mammary glands carcinoma	0.548
mesenteric lymph nodes haemangioma	0.819
pancreas exocrine adenoma	0.945
pancreas islet adenoma	0.973
parathyroids adenoma	0.699
pituitary carcinoma	0.750
pituitary adenoma	0.981
prostate carcinoma	0.307
prostate adenoma	0.307
salivary glands parotid fibroma	0.796
skin trichoepithelioma	0.331
skin basal cell tumor	0.697
skin zymbal's carcinoma	0.697
skin squamous-cell carcinoma	0.303
skin sarcoma	0.690
skin schwannoma	0.545
skin papilloma	0.303
skin fibrosarcoma	0.296
skin fibroma	0.489
skin dermal fibroma	0.561
skin lipoma	0.725
skin epithelioma	0.047
testes uni interstitial-cell adenoma	0.976
testes bi interstitial-cell adenoma	0.303
testes interstitial-cell adenoma	0.303
thymus thymoma	0.684
thyroids follicular carcinoma	0.310

FEMALES	
TUMOR SITE AND TYPE	p
adrenals cortical carcinoma	0.269
adrenals uni phaeochromocytoma (B)	0.975
adrenals bi phaeochromocytoma (B)	0.736
brain glioma	0.586
duodenum carcinoma	0.263
kidneys mesenchymal tumor	0.798
liver adenoma	0.235
lungs alveolar/bronchiolar carcinoma	0.400
lungs sarcoma	0.800
mammary glands fibroadenoma	0.334
mammary glands met carcinoma	0.267
mammary glands carcinoma	0.259
mammary glands adenoma	0.450
ovaries granulosa cell tumor	0.425
pancreas exocrine carcinoma	0.732
pancreas islet adenoma	0.733
parathyroids adenoma	0.448
pituitary carcinoma	0.384
pituitary adenoma	0.525
salivary glands mandibular fibroma	0.395
skin basal cell tumor	0.428
skin sebaceous carcinoma	0.733
skin zymbal's carcinoma	0.744
skin squamous-cell carcinoma	0.583
skin sarcoma	0.733
skin fibroma	0.505
skin lipoma	0.070
skin epithelioma	0.733
thyroids uni c-cell adenoma	0.108
thyroids bi c-cell adenoma	0.927
uterus stromal sarcoma	0.265
uterus met endometrial carcinoma	0.584
uterus endometrial carcinoma	0.461
uterus endometrial adenoma	0.735
uterus polyp	0.367

thyroids follicular adenoma	0.067
thyroids uni c-cell carcinoma	0.310
thyroids bi met c-cell carcinoma	0.310
thyroids uni c-cell adenoma	0.400
thyroids bi c-cell adenoma	0.310
thyroids uni adenoma	0.310

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1 **TABLE A.4 – Brammer Rat Results, by Tumor Type and Adjusted for Multiple Tests.**

MALES	
TUMOR SITE AND TYPE	p
adrenal phaeochromoytoma b	0.806
adrenal adenoma	0.313
adrenal phaeochromocytoma m	0.313
brain astrocytoma	0.438
brain meningioma	0.313
brain ependymoma	0.250
epididymis mesothelioma b	0.316
epididymis mesothelioma m	0.502
heart schwannoma	0.750
kidney haemangioma	0.250
kidney mesenchymal tumour	0.250
lacrimal gland neurofibrosarcoma	0.750
liver adenoma	0.008
liver liposarcoma	0.250
lung adenocarcinoma	0.500
lymph node-m haemangioma	0.687
lymph node-m haemangiosarcoma	0.814
nasal cavity fibrosarcoma	0.250
nasal cavity papilloma	0.250
nasal cavity ameloblastoma	0.500
pancreas exocrine adenoma	0.095
pancreas exocrine adenocarcioma	0.500
pancreas islet cell adenoma	0.576
parathyroid gland adenoma	0.500
pharynx carcinoma	0.753
pituitary gland adenoma pars distalis	0.386
pituitary gland adenoma pars intermedia	0.387
salivary gland neurofibrosarcoma	0.254
skin papilloma	0.247
skin basal cell tumour	0.387
skin basal cell carcinoma	0.247
skin pilomatrixoma	0.430
skin xeratoacanthoma	0.387
skin adenoma	0.496
skin trichofolliculoma	0.498
skin sarcoma	0.749
spleen not otherwise specified sarcoma	0.500
spleen not otherwise specified sarcoma	0.500
testis leydig cell tumor	0.791
testis mesothelioma b	0.502

FEMALES	
TUMOR SITE AND TYPE	p
adrenal ganglioneuroma	0.498
adrenal phaeochromocytoma	0.890
brain astrocytoma	0.202
brain meningioma	0.250
brain pineal gland tumour	0.250
cervix stromal cell polyp	0.250
cervix adenocarcinoma	0.438
cervix sarcoma	0.062
cervix haemangiosarcoma	0.250
duodenum adenocarcinoma	0.506
duodenum leiomyoma	0.506
harderian gland anaplastic sarcoma	0.502
ileum leiomyosarcoma	0.519
kidney liposarcoma	0.250
liver adenoma	0.250
lymph node-m haemangioma	0.762
lymph node-m haemangiosarcoma	0.432
mammary gland adenocarcinoma	0.264
mammary gland adenoma	0.894
mammary gland cystadenoma	0.519
mammary gland fibroadenoma	0.377
nasal cavity papilloma	0.187
nasal cavity adenoma	0.500
pancreas adenocarcinoma	0.252
pancreas islet cell adenoma	0.252
pituitary gland adenoma pars distalis	0.280
salivary gland adenoma	0.751
skin squamous carcinoma	0.313
skin basal cell tumour	0.250
skin pilomatrixoma	0.438
spleen haemangiosarcoma	0.502
stomach squamous papilloma	0.251
thymus thymoma b	0.629
thymus thymoma m	0.626
thymus not otherwise specified sarcoma	0.252
thyroid gland follicular cell adenoma	0.833
thyroid gland parafollicular cell adenoma	0.499
thyroid gland parafollicular cell carcinoma	0.252
uterus stromal cell polyp	0.950
uterus adenocarcinoma	0.816

testis mesothelioma m	0.502
thymus benign thymoma	0.112
thyroid gland follicular cell adenoma	0.072
thyroid gland parafollicular cell adenoma b	0.882
thyroid gland parafollicular cell adenoma m	0.502
voluntary muscle haemangioma	0.251

uterus leiomyoma	0.438
uterus carcinoma	0.297
uterus haemangiosarcoma	0.625
uterus haemangioma	0.250

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1 **TABLE A.5 – Suresh Rat Results, by Tumor Type and Adjusted for Multiple Tests.**

MALES	
TUMOR SITE AND TYPE	p
salivary gland duct palpinoma	0.691
stomach adenocarcinoma	0.307
stomach papilloma-forestomach	0.503
pancreas islet cell adenoma	0.742
pancreas carcinoma	0.509
pancreas sarcoma	0.308
pancreas lymphosarcoma	0.698
liver cholangiocarcinoma	0.263
liver hepatocellular adenoma	0.391
liver carcinoma	0.418
liver b.d. adenoma	0.937
liver histiocytic sarcoma	0.624
liver tumour emboli	0.370
liver fibrosarcoma	0.495
liver lymphosarcoma	0.747
liver benign b.d. adenoma	0.253
lungs histiocytic sarcoma	0.433
lungs cholangiocarcinoma	0.503
lungs adenocarcinoma	0.296
lungs hepatocellular carcinoma	0.322
lungs squamous cell carcinoma	0.704
lungs giant cell tumour	0.296
heart histiocytic sarcoma	0.445
spleen cholangiocarcinoma	0.515
mesentric lymph nodes sarcoma	0.695
mediastinal lymph node sarcoma - metastatic	0.634
mediastinal lymph node cholangiocarcinoma	0.494
mediastinal lymph node hepatocellular carcinoma	0.494
mediastinal lymph node giant cell tumour	0.306
mediastinal lymph node sarcoma	0.306
mandibular lymph node lymphoma	0.087
kidneys carcinoma	0.503
kidneys histiosarcoma	0.299
testes leydig cell tumor	0.182
testes seminoma	0.296
epididymes sarcoma	0.250
brain squamous cell carcinoma	0.309
thyroids c cell adenoma	0.595
pituitary adenocarcinoma	0.503
pituitary adenoma	0.376

FEMALES	
TUMOR SITE AND TYPE	p
stomach papilloma-forestomach	0.355
pancreas islet cell adenoma	0.355
pancreas cholangio-carcinoma	0.638
pancreas histiocytic sarcoma	0.638
liver cholangiocarcinoma	0.746
liver adenoma	0.922
liver carcinoma	0.869
liver b.d. adenoma	0.503
liver histiocytic sarcoma	0.711
lungs bronchio alveolar adenoma	0.434
lungs histiocytic sarcoma-metastatic	0.667
lungs adenoma	0.633
lungs fibroma	0.480
lungs round cell sarcoma	0.333
lungs histiocytic sarcoma	0.633
trachea sarcoma	0.472
heart histiocytic sarcoma	0.594
heart round cell sarcoma	0.350
mediastinal lymph node histiocytic sarcoma-m	0.650
mediastinal lymph node cholangiocarcinoma	0.650
mediastinal lymph node histiocytic sarcoma	0.482
kidney lymphosarcoma	0.352
urinary bladder carcinoma	0.350
uterus adenoma	0.289
uterus adenocarcinoma	0.643
uterus carcinoma	0.514
uterus leiomyosarcoma	0.289
uterus adenoma papillary	0.514
uterus hemangioma	0.289
thyroids c cell adenoma	0.537
pituitary adenocarcinoma	0.684
pituitary adenoma	0.967
adrenals cortical cell adenoma	0.400
adrenals pheochromocytoma	0.133
thymus thymoma	0.755
mammary gland adenoma	0.538
mammary gland adenocarcinoma	0.982
tumour/mass histiocytic sarcoma	0.658
tumour/mass cholangiocarcinoma	0.635
tumour/mass fibroma	0.635

adrenals cortical cell adenoma	0.922
adrenals pheochromocytoma	0.066
adrenals m. pheochromocytoma	0.213
tumour/mass squamous cell carcinoma	0.301
tumour/mass histiocytic sarcoma	0.123
tumour/mass cholangiocarcinoma	0.659
tumour/mass giant cell tumour	0.123
tumour/mass fibroma	0.315
bone sarcoma	0.694
sternum sarcoma	0.690

tumour/mass undifferentiated sarcoma	0.635

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1 **TABLE A.6 – Enemoto Rat P-Values, by Tumor Type and Adjusted for Multiple Tests.**

MALES	
TUMOR SITE AND TYPE	p
heart schwannoma	0.297
hematopoietic and lymphatic myelogenic leukemia	0.750
hematopoietic and lymphatic malignant lymphoma	0.813
hematopoietic and lymphatic cell leukemia	0.813
spleen histiocytic sarcoma	0.500
lung adenoma	0.146
lung squamous cell carcinoma	0.250
lung adenocarcinoma	0.250
stomach leiomyosarcoma	0.250
small intestine leiomyoma	0.250
small intestine adenocarcinoma	0.250
small intestine malignant schwannoma	0.500
liver adenoma	0.250
liver carcinoma	0.323
pancreas acinar cell adenoma	0.120
pancreas islet cell adenoma	0.846
pancreas islet cell carcinoma	0.250
kidney adenoma	0.004
kidney lipoma	0.250
testis cell tumor	0.576
coagulating gland adenoma	0.250
pituitary anterior adenoma	0.132
pituitary adenoma (intermediate part)	0.500
pituitary (mass not in section)	0.250
thyroid follicullar adenoma	0.947
thyroid c-cell adenoma	0.623
thyroid follicullar adenocarcinoma	0.750
thyroid c-cell carcinoma	0.514
adrenal cortical adenoma	0.620
adrenal pheochromromocytoma	0.892
adrenal cortical adenocarcinoma	0.250
cerebrum glioma	0.392
cerebrum malignant reticulosis	0.750
cerebellum cell tumor	0.250
bone (femur) osteochondroma	0.250
bone (other) osteosarcoma	0.250
eye shwannoma	0.750
skin papilloma	0.946
skin keratoacanthoma	0.029
skin trichoepithelioma	0.500

FEMALES	
TUMOR SITE AND TYPE	p
heart schwannoma	0.250
hematopoietic/lymphatic lymphoma	0.259
small intestine leiomyoma	0.250
large intestine histioctytoma	0.750
liver hepatocellular adenoma	0.813
pancreas islet cell adenoma	0.812
pancreas islet cell carcinoma	0.500
kidney lipoma	0.500
kidney trans cell carcinoma	0.750
bladder papilloma	0.500
ovary granulosa cell tumor	0.750
ovary luteoma	0.250
uterus stromal polyp	0.656
uterus grnaular cell tumor	0.750
uterus adenocarcinoma	0.750
uterus schwannoma	0.250
uterus (mass not in section)	0.750
vagina polyp	0.750
vagina leiomysarcoma	0.250
pituitary anterior adenoma	0.819
pituitary anterior adenocarcinoma	0.750
thyroid follicular adenoma	0.688
thyroid c-cell adenoma	0.908
adrenal cortical adenoma	0.500
adrenal ganglioneuroma	0.500
adrenal pheochromocytoma	0.500
cerebrum meningioma	0.500
cerebrum reticulosis	0.813
bone (vertebra) chordoma	0.750
skin papilloma	0.500
skin keratoacanthoma	0.250
skin fibroma	0.400
skin lipoma	0.932
skin (mass not in section)	0.580
mammary gland adenoma	0.813
mammary gland fibroadenoma	0.106
mammary gland adenocarcinoma	0.595

skin sabaceous gland adenoma	0.500
skin basal cell adenoma	0.015
skin fibroma	0.262
skin lipoma	0.873
skin squamous cell carcinoma	0.187
skin basal cell carcinoma	0.250
skin fibrosacoma	0.500
skin liposarcoma	0.750
skin hemangiosarcoma	0.250
skin hemangiopericytoma	0.250
skin osteosarcoma	0.313
skin schwannoma	0.250
skin histiocytic sarcoma	0.250

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1 **TABLE A.7 – Wood Rat Results, by Tumor Type and Adjusted for Multiple Tests.**

MALES	
TUMOR SITE AND TYPE	p
adrenal cortical adenoma	0.813
adrenal cortical carcinoma	0.750
adrenal phaeochromocytoma b	0.062
adrenal phaeochromocytoma m	0.805
bone osteoma	0.250
brain/spinal cord astrocytoma	0.250
brain/spinal cord granular cell tumour b	0.813
brain/spinal cord granular cell tumour m	0.250
intestinal tract leiomyoma	0.250
intestinal trace leiomsarcoma	0.250
epididymis mesothelioma b	0.750
epididymis mesothelioma m	0.751
heart schwannoma	0.500
kidney lipoma	0.250
kidney tubular carcinoma	0.750
liver hepatocellular adenoma	0.418
liver hepatocellular carcinoma	0.750
lymph node angioma	0.357
lymph node angiosarcoma	0.945
nasal cavities adenoma	0.938
pancreas islet cell adenoma	0.827
parathyroid adenoma	0.750
pituitary adenoma	0.045
pituitary adenocarcinoma	0.750
skin - subcutaneous fibroma	0.595
skin - subcutaneous fibrosarcoma	0.903
skin - subcutaneous histiocytic sarcoma	0.500
skin - subcutaneous lipoma	0.250
skin - leiomyosarcoma	0.250
skin - cutaneous basal cell tumor	0.750
skin- cutaneous carcinoma	0.675
skin - cutaneous keratoacanthoma	0.030
skin - cutaneous adenoma	0.500
skin - cutaneous adenocarcinoma	0.500
skin - cutaneous trichoepithelioma	0.250
skin - cutaneous papilloma	0.250
skin - cutaneous s.s. carcinoma	0.500
spleen angioma	0.250
spleen angiosarcoma	0.750
stomach papilloma	0.370

FEMALES	
TUMOR SITE AND TYPE	p
adrenal cortical adenoma	0.813
adrenal ganglioneuroma	0.250
brain/spinal cord oligodendroglioma	0.750
brain/spinal cord ependymoma	0.813
heart schwannoma	0.938
kidney clear cell carcinoma	0.250
liver adenoma	0.392
liver carcinoma	0.250
liver cholangioma	0.750
lymph node angioma	0.748
mammary gland fibroadenoma	0.824
mammary gland adenoma	0.062
mammary gland adenocarcinoma	0.042
ovary granulosa cell tumour	0.928
ovary granulosa-theca cell tumour	0.943
ovary sarcoma	0.750
pancreas adenocarcinoma	0.250
pharynx papilloma	0.250
pituitary adenoma	0.014
pituitary adenocarcinoma	0.500
skin - subcutaneous fibroma	0.250
skin - subcutaneous lipoma	0.313
skin - subcutaneous angioma	0.062
skin - cutaneous basal cell tumour	0.750
skin - cutaneous carcinoma	0.250
skin - cutaneous papilloma	0.500
stomach papilloma	0.500
thymus thymoma b	0.765
thymus carcinoma	0.250
thyroid follicular adenoma	0.372
thyroid follicular adenocarcinoma	0.813
thyroid parafollicular adenoma	0.997
thyroid parafollicular adenocarcinoma	0.500
tongue granular cell tumor	0.250
uterus polyp	0.221
uterus adenocarcinoma	0.602
uterus sarcoma	0.438
uterus leiomyoma	0.514
uterus angiosarcoma	0.500
lymhoid/haemopoietic lymphoma	0.830

testis interstitial cell tumour	0.778
thymus thymoma b	0.187
thymus thymoma m	0.313
thyroid adenoma	0.066
thyroid adenocarcinoma	0.250
thyroid parafollicular adenoma	0.823
thyroid parafollicular adenocarcinoma	0.938
thyroid hibernoma	0.250
urinary bladder papilloma	0.500
abdominal adenocarcinoma	0.500
abdominal carcinoma	0.250
lymphoid/haemopoietic lymphoma	0.500

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APPENDIX B – RESULTS FOR MOUSE FEEDING STUDIES

TABLE B.1 –Knezevich Mouse P-Values, by Tumor Type and Adjusted for Multiple Tests.

MALES	
TUMOR SITE AND TYPE	p
brain lymphoblastic lymphosarcoma w/leuk	0.251
heart lymphoblastic lymphosarcoma w/leuk	0.337
lung adenoma	0.294
lung adenocarcinoma	0.906
lung lymphoblastic lymphosarcoma w/leuk	0.772
lung lymphoblastic lymphosarcoma	0.505
liver adenocarcinoma	0.717
liver adenoma	0.251
liver carcinoma	0.062
liver sarcoma	0.503
liver liposarcoma	0.189
liver composite lymphosarcoma	0.754
liver lymphoblastic lymphosarcoma	0.539
mesenteric sarcoma	0.492
mesenteric lymphosarcoma	0.624
mesenteric lymphoblastic lymphosarcoma (S)	0.827
mesenteric lymphoblastic lymphosarcoma (M)	0.061
mesenteric lymphoblastic lymphosarcoma w/leuk	0.492
mediastinal sarcoma	0.489
mediastinal lymphosarcoma	0.631
mediastinal lymphoblastic lymphosarcoma w/leuk (S)	0.373
mediastinal lymphoblastic lymphosarcoma w/leuk (M)	0.463
salivary glands lymphoblastic lymphosarcoma w/leuk	0.628
spleen hemangioendothelioma	0.250
spleen sarcoma	0.505
spleen composite lymphosarcoma	0.631
spleen lymphoblastic lymphosarcoma w/leuk (S)	0.827
spleen lymphoblastic lymphosarcoma w/leuk (M)	0.442
stomach lymphoblastic lymphosarcoma w/leuk	0.746
pancreas sarcoma	0.508
pancreas lymphoblastic lymphosarcoma w/leuk	0.256
ileum composite lymphosarcoma	0.733
ileum lymphoblastic lymphosarcoma w/leuk	0.733
cecum lymphoblastic lymphosarcoma w/leuk	0.753
colon composite lymphosarcoma	0.755
kidney adenoma (using EPA reeval)	0.442
kidney carcinoma (using EPA reeval)	0.063
kidney sarcoma	0.505

FEMALES	
TUMOR SITE AND TYPE	p
brain lymphoblastic lymphosarcoma w/leuk	0.251
heart lymphoblastic lymphosarcoma w/leuk	0.433
lung adenoma	0.999
lung adenocarcinoma	0.183
lung granulosa cell tumor	0.500
lung leiomyosarcoma	0.500
lung liposarcoma	0.753
lung composite lymphosarcoma	0.442
lung lymphoblastic lymphosarcoma w/leuk	0.717
lung lymphoblastic lymphosarcoma	0.253
liver adenocarcinoma	0.828
liver adenoma	0.497
liver hemangioendothelioma (M)	0.249
liver leiomyosarcoma	0.497
liver granulocytic leukemia	0.875
liver hemangioendothelioma (S)	0.437
liver composite lymphosarcoma	0.064
liver lymphoblastic lymphosarcoma w/leuk	0.787
liver lymphoblastic lymphosarcoma	0.061
mesenteric leiomyosarcoma	0.495
mesenteric granulocytic leukemia	0.495
mesenteric adenocarcinoma	0.747
mesenteric composite lymphosarcoma	0.141
mesenteric lymphoblastic lymphosarcoma w/leuk (M)	0.522
mesenteric lymphoblastic lymphosarcoma w/leuk (S)	0.782
mesenteric composite lymphosarcoma	0.141
mesenteric lymphoblastic lymphosarcoma (M)	0.060
mesenteric lymphoblastic lymphosarcoma (S)	0.247
mesenteric hemangioendothelioma	0.247
mediastinal leiomyosarcoma	0.489
mediastinal granulocytic leukemia	0.489
mediastinal liposarcoma	0.761
mediastina composite lymphosarcoma	0.266
mediastinal lymphoblastic lymphosarcoma w/leuk (S)	0.717
mediastinal lymphoblastic lymphosarcoma w/leuk (M)	0.760
mediastinal lymphoblastic lymphosarc (M)	0.489
mediastinal lymphoblastic lymphosarc (S)	0.267
salivary glands leiomyosarcoma	0.239

kidney composite lymphosarcoma	0.753
kidney lymphoblastic lymphosarcoma w/leuk	0.463
testes cell tumor	0.649
testes lymphoblastic lymphosarcoma w/leuk (S)	0.508
testes lymphoblastic lymphosarcoma w/leuk (M)	0.254
epididymides leiomysarcoma	0.317
bladder histiocyticsarcoma	0.500
bladder lymphoblastic lymphosarcoma w/leuk	0.810
renal gland adenoma	0.574
renal gland lymphoblastic lymphosarcoma w/leuk (U)	0.503
renal gland lymphoblastic lymphosarcoma w/leuk (B)	0.246
skin/ears fibrosarcoma	0.245
skin/ears liposarcoma	0.245
skin/ears composite lymphosarcoma	0.745
skin/ears lymphoblastic lymphosarcoma w/leuk	0.245
eyes lymphoblastic lymphosarcoma w/leuk	0.643
harderian gland adenoma	0.750
harderian gland liposarcoma	0.255
marrow lymphoblastic lymphosarcoma w/leuk	0.566

salivary lymphoblastic lymphosarcoma w/leuk	0.485
spleen hemangioendothelioma (M)	0.370
spleen hemangioma	0.250
spleen granulocytic leukemia	0.877
spleen adenocarcinoma	0.745
spleen hemangioendothelioma (S)	0.250
spleen composite lymphosarcoma (S)	0.580
spleen lymphoblastic lymphosarcoma w/leuk (S)	0.824
spleen lymphoblastic lymphosarcoma w/leuk (M)	0.438
spleen composite lymphosarcoma (M)	0.016
spleen lymphoblastic lymphosarcoma (M)	0.250
spleen lymphoblastic lymphosarcoma (S)	0.250
stomach leiomyosarcoma	0.254
stomach adenocarcinoma	0.254
duodenum composite lymphosarcoma	0.770
pancreas granulocytic leukemia	0.508
pancreas composite lymphosarcoma	0.638
pancreas lymphoblastic lymphosarcoma w/leuk	0.746
jejunum composite lymphosarcoma	0.761
ileum composite lymphosarcoma	0.758
cecum composite lymphosarcoma	0.766
colon composite lymphosarcoma	0.743
colon lymphoblastic lymphosarcoma w/leuk	0.743
kidney leiomyosarcoma	0.500
kidney granulocytic leukemia	0.500
kidney composite lymphosarcoma	0.395
kidney lymphoblastic lymphosarcoma w/leuk	0.597
kidney lymphoblastic lymphosarcoma	0.250
bladder granulocytic leukemia	0.519
bladder composite lymphosarcoma	0.822
bladder lymphoblastic lymphosarcoma w/leuk	0.838
ovaries luteoma	0.246
ovaries teratoma	0.508
ovaries cell tumor	0.508
ovaries leiomyosarcoma	0.508
ovaries adenocarcinoma	0.754
ovaries lymphoblastic lymphosarcoma w/leuk (U)	0.508
ovaries lymphoblastic lymphosarcoma w/leuk (B)	0.641
ovaries composite lymphosarcoma	0.246
uterus leiomyoma	0.619
uterus leiomyosarcoma	0.385
uterus sarcoma	0.505
uterus hemangioma	0.505

uterus adenocarcinoma	0.939
uterus hemangioendothelioma	0.255
uterus lymphoblastic lymphosarcoma w/leuk	0.821
thyroid adenoma	0.271
skin/ears fibrosarcoma	0.516
skin/ears liposarcoma	0.759
skin/ears rhabdomyosarcoma	0.759
skin/ears lymphoblastic lymphosarcoma w/leuk	0.592
mammary adenocarcinoma	0.842
mammary lymphoblastic lymphosarcoma w/leuk	0.250
muscle liposarcoma	0.749
muscle lymphoblastic lymphosarcoma w/leuk	0.623
harderian gland adenoma	0.830
harderian lymphoblastic lymphosarcoma w/leuk	0.250
marrow lymphoblastic lymphosarcoma w/leuk	0.385
marrow lymphoblastic lymphosarcoma	0.065
marrow composite lymphosarcoma	0.257

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TABLE B.2 – Atkinson Mice Results, by Tumor Type and Adjusted for Multiple Tests.

MALES	
TUMOR SITE AND TYPE	p
adrenals phaeochromocytoma (M)	0.486
adrenals carcinoma	0.486
adrenals phaeochromocytoma (B)	0.338
adrenals adenoma	0.648
adrenals subcap adenoma	0.716
brain meningioma	0.347
kidneys carcinoma	0.813
kidneys adenoma	0.813
liver carcinoma	0.450
liver adenoma	0.583
liver (assoc) adenoma	0.077
lungs carcinoma	0.456
lungs adenoma	0.339
lungs (assoc) adenoma	0.217
pancreas adenoma	0.340
pituitary intermediate adenoma	0.326
prostate sarcoma	0.350
skin carcinoma	0.655
skin sarcoma	0.641
skin papilloma	0.345
skin lipoma	0.345
spinal cord ganglioneuroma	0.655
stomach carcinoma	0.340
testes adenoma	0.520
vascular haemangiosarcoma (using IARC)	0.004

FEMALES	
TUMOR SITE AND TYPE	p
adrenals carcinoma	0.500
adrenals subcap adenoma	0.750
liver carcinoma	0.750
liver adenoma	0.642
lungs carcinoma	0.105
lungs adenoma	0.358
lungs (assoc) adenoma	0.072
lungs secondary tumor	0.201
lymphoreticular sarcoma	0.575
lymphoreticular lymphoma	0.475
mammary glands carcinoma	0.845
mammary glands adenocarcinoma	0.250
ovaries granulosa cell tumor	0.750
ovaries luteal cell tumor	0.250
ovaries adenoma	0.062
pancreas adenoma	0.500
pituitary anterior adenoma	0.155
pituitary intermediate adenoma	0.250
skin carcinoma	0.187
skin sarcoma	0.392
skin papilloma	0.750
spleen sarcoma	0.250
thyroids adenoma	0.250
uterus sarcoma	0.299
uterus stromal tumor	0.250
uterus polyps	0.433
uterus leiomyoma	0.108

TABLE B.3 – Wood Mice Results, by Tumor Type and Adjusted for Multiple Tests.

MALES	
TUMOR SITE AND TYPE	p
adrenal adenoma	0.172
adrenal carcinoma	0.754
bone marrow lipoma	0.750
brain sarcoma	0.251
brain oligodendroglioma	0.754
harderian adenoma	0.502
kidney haemangiosarcoma	0.250
liver adenoma	0.335
liver carcinoma	0.921
liver haemangiosarcoma	0.615
lung adenoma	0.926
lung adenocarcinoma	0.030
seminal adenoma	0.938
seminal leiomyosarcoma	0.250
skin fibrosarcoma	0.542
spleen haemangioma	0.750
testis cell tumor	0.938
abdominal mesothelioma	0.250
abdominal sarcoma	0.250
lymphoid/haemopoietic myeloid leukaemia	0.500
lymphoid/haemopoietic lymphoma	0.007

FEMALES	
TUMOR SITE AND TYPE	p
bone osteoma	0.750
bone marrow sarcoma	0.250
brain oligodendroglioma	0.750
harderian adenoma	0.155
harderian adenocarcinoma	0.938
intestinal adenoma	0.750
liver carcinoma	0.500
liver haemangioma	0.500
liver haemangiosarcoma	0.250
lung adenoma	0.637
lung adenocarcinoma	0.591
mammary adenocarcinoma	0.391
mammary carcinoma	0.500
mesenteric sarcoma	0.534
ovary luteoma	0.514
ovary haemangioma	0.250
ovary cell tumor	0.250
ovary cystadenoma	0.062
ovary sarcoma	0.500
pancreas adenocarcinoma	0.750
pituitary adenoma	0.108
skin haemangiosarcoma	0.500
spleen haemangiosarcoma	0.438
thymus sarcoma	0.250
uterus polyp	0.170
uterus haemangioma	0.500
uterus leiomyoma	0.250
uterus carcinoma	0.750
uterus sarcoma	0.719
uterus leiomyosarcoma	0.750
abdominal lipoma	0.750
lymphoid/haemopoietic myeloid leukaemia	0.250
lymphoid/haemopoietic lymphoma	0.353
lymphoid/haemopoietic sarcoma	0.482

TABLE B.4 – Sugimoto Mice Results, by Tumor Type and Adjusted for Multiple Tests.

MALES	
TUMOR SITE AND TYPE	p
hematopoietic & lymphatic system lymphoma	0.016
lymph nodes lymphoma	0.500
spleen sarcoma	0.750
lung adenoma	0.512
lung adenocarcinoma	0.148
intestine adenoma	0.500
intestine adenocarcinoma	0.250
liver adenoma	0.984
liver hemangioma	0.750
liver sarcoma	0.750
liver carcinoma	0.391
kidney adenoma	0.062
urinary bladder papilloma	0.751
testis cell tumor	0.500
testis hemangioma	0.750
thyroid adenoma	0.751
adrenal b cell tumor	0.500
cerebrum lipoma	0.500
ilarderian gland adenoma	0.515
skin papilloma	0.813
skin hemangiosarcoma	0.062
skin leiomysarcoma	0.187
skin osteosarcoma	0.250

FEMALES	
TUMOR SITE AND TYPE	p
hematopoietic & lymphatic system leukemia	0.250
hematopoietic & lymphatic system lymphoma	0.307
thymus lymphoma	0.250
spleen hemangioma	0.250
spleen hemangiosarcoma	0.250
spleen sarcoma	0.250
lung adenoma	0.800
lung adenocarcinoma	0.597
small intestine adenoma	0.250
liver adenoma	0.735
liver hemangioma	0.250
urinary bladder leiomyoma	0.187
ovary hemangioma	0.250
uterus polyp	0.751
uterus hemangioma	0.062
uterus leiomyoma	0.370
uterus sarcoma	0.500
uterus leiomyosarcoma	0.624
pituitary adenoma	0.500
thyroid adenoma	0.751
adrenal a cell tumor	0.595
adrenal pheochromocytoma	0.751
bone osteoma	0.250
harderian gland adenoma	0.040
skin papilloma	0.750
skin lipoma	0.626
skin carcinoma	0.500
skin liposarcoma	0.250
skin hemangiosarcoma	0.250
mammary gland adenoma	0.500
mammary gland adenocarcinoma	0.814
thoracic cavity osteosarcoma	0.400
abdominal cavity hemangioma	0.257
abdominal cavity osteosarcoma	0.257

TABLE B.5 – Kumar Mice Results, by Tumor Type and Adjusted for Multiple Tests.

MALES	
TUMOR SITE AND TYPE	p
cecum adenoma	0.648
liver hemangiosarcoma	0.327
liver adenoma	0.846
liver carcinoma	0.249
lungs squamous cell carcinoma	0.500
lungs broncheo-alveolar adenoma	0.463
lungs broncheo-alveolar carcinoma	0.347
mesenteric hemangioma	0.431
mesenteric hemangiosarcoma	0.245
kidneys adenoma	0.090
kidneys hibernoma	0.671
testes tumor	0.345
epididymes leiomyoma	0.503
skin carcinoma	0.791
tumor/mass hemangioma	0.304
bone osteoma	0.582
lymphoreticular sarcoma	0.624
lymphoreticular lymphoma	0.064
lymphoreticular leukemia	0.744

FEMALES	
TUMOR SITE AND TYPE	p
stomach sarcoma	0.515
pancreas sarcoma	0.515
liver sarcoma	0.769
liver adenoma	0.515
lungs endometrial stromal sarcoma	0.365
lungs broncheo-alveolar adenoma	0.165
lungs broncheo-alveolar carcinoma	0.750
mesenteric hemangioma	0.016
mesenteric sarcoma	0.500
kidneys sarcoma	0.511
bladder sarcoma	0.368
ovaries hemangioma	0.304
ovaries sarcoma	0.735
ovaries tumor	0.304
ovaries luteoma	0.304
uterus leiomyosarcoma	0.311
uterus sarcoma	0.793
uterus leiomyoma	0.311
pituitary adenoma	0.372
adrenals sarcoma	0.511
adrenals adenoma	0.363
adrenals pheochromocytoma	0.363
skin carcinoma	0.588
thymus lymphoma	0.629
mammary adenocarcinoma	0.598
tumor/mass hemangiosarcoma	0.562
femur osteoma	0.297
lymph node sarcoma (M)	0.189
lymph node sarcoma (I)	0.189
hemolymphoreticular sarcoma	0.199
hemolymphoreticular lymphoma	0.070
hemolymphoreticular leukemia	0.602

TABLE B.6 – Kumar Mice Results Using Data from Weber Reanalysis, by Tumor Type and Adjusted for Multiple Tests.

MALES		FEMALES	
TUMOR SITE AND TYPE	p	TUMOR SITE AND TYPE	p
cecum adenoma	0.750	stomach sarcoma	0.500
liver adenoma	0.846	pancreas sarcoma	0.500
liver carcinoma	0.155	liver sarcoma	0.688
lungs squamous cell carcinoma	0.500	liver adenoma	0.395
lungs broncheo-alveolar adenoma	0.438	lungs endometrial stromal sarcoma	0.250
lungs broncheo-alveolar carcinoma	0.250	lungs broncheo-alveolar adenoma	0.069
kidneys adenoma	0.250	lungs broncheo-alveolar carcinoma	0.750
kidneys hibernoma	0.750	mesenteric sarcoma	0.500
testes tumor	0.237	kidneys sarcoma	0.500
epididymes leiomyoma	0.500	bladder sarcoma	0.250
skin carcinoma	0.813	ovaries sarcoma	0.495
lymphoreticular sarcoma	0.534	ovaries tumor	0.250
lymphoreticular lymphoma	0.141	uterus leiomyosarcoma	0.250
lymphoreticular leukemia	0.830	uterus sarcoma	0.704
femur osteoma	0.750	uterus leiomyoma	0.830
hemangioma	0.261	pituitary adenoma	0.250
hemangiosarcoma	0.438	adrenals sarcoma	0.500
		adrenals adenoma	0.250
		adrenals pheochromocytoma	0.250
		skin carcinoma	0.500
		mammary adenocarcinoma	0.438
		femur osteoma	0.113
		hemolymphoreticular sarcoma	0.199
		hemolymphoreticular lymphoma	0.085
		hemolymphoreticular leukemia	0.602
		hemangioma	0.014
		hemangiosarcoma	0.750

APPENDIX C – MULTIPLE TESTING ADJUSTMENTS

TABLE C.1 – Summary of findings with individual p-values < 0.05 for exact one-sided trend tests for increasing tumor incidence with increased dose, computed across 1,016 total tumor types, with multiple testing adjustment for the false discovery rate.

Study	Rodent/Strain/Sex	Tumor Type	Exact Trend P-Value	P-Value Adjusted for False Discovery Rate
Lankas	Rat/SD/Male	Testis Cell Tumor	0.009	0.473
	Rat/SD/Female	Thyroid Cell Carcinoma	0.003	0.175
Stout	Rat/SD/Male	Liver Adenoma	0.016	0.703
	Rat/SD/Female	Adrenal Carcinoma	0.015	0.662
Atkinson	Rat/SD/Male	Skin Epithelioma	0.047	0.801
Brammer	Rat/Wistar/Male	Liver Adenoma	0.008	0.370
Enemoto	Rat/SD/Male	Kidney Adenoma	0.004	0.189
	Rat/SD/Male	Skin Keratoacanthoma	0.029	0.510
	Rat/SD/Male	Skin Basal Cell Adenoma	0.015	0.395
Wood	Rat/Wistar/Male	Pituitary Adenoma	0.045	0.684
	Rat/Wistar/Male	Skin Cutaneous Keratoacanthoma	0.030	0.684
	Rat/Wistar/Female	Mammary Gland Adenocarcinoma	0.042	0.616
	Rat/Wistar/Female	Pituitary Adenoma	0.014	0.557
Knezevich	Mouse/CD-1/Female	Spleen Composite Lymphosarcoma (M)	0.016	0.858
Atkinson	Mouse/CD-1/Male	Vascular Haemangiosarcoma	0.004	0.089
Wood	Mouse/CD-1/Male	Lung Adenocarcinoma	0.030	0.312
	Mouse/CD-1/Male	Lymphoid/Haemopoietic Lymphoma	0.007	0.139
Sugimoto	Mouse/CD-1/Male	Hematopoietic & Lymphatic System Lymphoma	0.016	0.373
	Mouse/CD-1/Female	Harderian Gland Adenoma	0.040	0.554
Kumar	Mouse/Swiss/Female	Mesenteric Hemangioma	0.016	0.468

APPENDIX D – MULTIPLE TESTING ADJUSTMENTS

TABLE D.1 – Summary of findings with individual p-values < 0.05 for exact one-sided trend tests for decreasing tumor incidence with increased dose, computed across 1,016 total tumor types, with multiple testing adjustment for the false discovery rate.

Study	Rodent/Strain/Sex	Tumor Type	Exact Trend P-Value	P-Value Adjusted for False Discovery Rate
Lankas	Rat/SD/Female	Thyroid Follicular Adenoma	0.036	0.956
Stout	Rat/SD/Female	Pancreas Adenoma	0.038	0.693
	Rat/SD/Female	Pituitary Adenoma	0.004	0.166
Atkinson	Rat/SD/Male	Pancreas Islet Adenoma	0.027	0.410
	Rat/SD/Male	Pituitary Adenoma	0.019	0.410
	Rat/SD/Male	Testes Uni Interstitial-Cell Adenoma	0.024	0.410
	Rat/SD/Female	Adrenals Uni Phaeochromocytoma (B)	0.025	0.781
Brammer	Rat/Wistar/Female	Uterus Stromal Cell Polyp	0.050	0.805
Suresh	Rat/Wistar	Pituitary Adenoma	0.033	0.671
	Rat/Wistar	Mammary Gland Adenocarcinoma	0.018	0.671
Wood	Rat/Wistar/Female	Thyroid Parafollicular Adenoma	0.003	0.120
Knezevich	Mouse/CD-1/Female	Lung Adenoma	0.001	0.056
Sugimoto	Mouse/CD-1/Male	Liver Adenoma	0.016	0.378

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55. Portier, C., *Carcinogenicity of Glyphosate: A Systematic Review of the Available Evidence*, echa.europa.eu (Nov. 21, 2016).

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57. Portier, C., *Comments of C. Portier on USEPA (EPA-HQ-OPP-2016-0385-0094)*, Regulations.gov (Oct. 4, 2016).

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59. *Problems with scientific research: How science goes wrong*, The Economist (Oct. 21, 2013).

60. Son, W. and C. Gopinath, *Early occurrence of spontaneous tumors in CD-1 mice and Sprague-Dawley rats*, 32 Toxicologic Pathology 371 (2004).

61. Tarone, R., *Comment submitted by R. Tarone (December 07, 2016)*, Regulations.gov (Dec. 7, 2016).

62. Tarone, R., *Comment submitted by R.E. Tarone and Response to comments prepared by Christopher Portier (dated October 4, 2016) for the glyphosate EPA SAP meeting*, Regulations.gov (Oct. 27, 2016).

63. Uno, H., et al., *A versatile test for equality of two survival functions based on weighted differences of Kaplan-Meier curves*, 34 Statistics Med. 3680 (2015).

64. *Unreliable research: Trouble at the lab*, The Economist (Oct. 18, 2013).

65. Wasserstein, R. & N. Lazar, *The ASA's Statement on p-Values: Context, Process, and Purpose*, 70 The American Statistician 129 (2016).

66. Weber, K., *Statistical Evaluation of Pre-Neoplastic and Neoplastic Lesions from Study: Study No. TOXI: 1559.CARCI-M Carcinogenicity Study with Glyphosate Technical in Swiss Albino Mice* (Jan. 23, 2017).

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Education

ScD, Harvard University, 1999.
Major: Biostatistics
Supporting Areas of Emphasis: Genetic Epidemiology

BS, Utah State University, 1995.
Major: Statistics
Supporting Areas of Emphasis: Computer Science

Professional Positions

Professor, Utah State University. (July 2011 - Present).

Associate Professor, Utah State University. (July 2005 - July 2011).

Assistant Professor, Utah State University. (August 1999 - July 2005).

Professional

Department Head, Department of Mathematics and Statistics, Utah State University. (2016 – Present)

Associate Department Head, Department of Mathematics and Statistics, Utah State University. (2014 – 2016)

Director of Graduate Studies, Department of Mathematics and Statistics, Utah State University. (2013 – 2016)

Director, Data Management and Statistics Core, Center for Epidemiologic Studies, Utah State University. (2004 - Present).

Research Fellow, Cytel Software Corporation. (2009 - 2010).

Teaching Assistant, Harvard University, Department of Biostatistics. (1995 - 1999).

Research Assistant, Dana Farber Cancer Institute, Department of Biostatistics. (1996).

Awards and Honors

Researcher of the Year, College of Science, Utah State University. (April 2012).

Researcher of the Year, Department of Mathematics and Statistics, Utah State University. (April 2012).

Teacher of the Year, Department of Mathematics and Statistics, Utah State University. (2006).

Researcher of the Year, Department of Mathematics and Statistics, Utah State University. (2005).

Top Professor, Mortar Board Honor Society, Utah State University Chapter. (2002).

Teaching Fellow, Department of Biostatistics, Harvard School of Public Health. (1996).

Academic Achievement Award, Utah State University. (1995).

NIH Cancer Research Training Grant Recipient. (1995).

Mortar Board, Utah State University. (1994).

Golden Key National Honor Society Peat Marwick Scholarship. (1993).

ACADEMIC INSTRUCTION

Teaching Experience

Utah State University

MATH 2260, Internship and Cooperative Studies, 1 course.
MATH 4910, Directed Reading and Conference, 2 courses.
MATH 5910, Directed Reading and Conference, 4 courses.
MATH 6250, Graduate Internship/Cooperative Studies, 5 courses.
MATH 6910, Directed Reading and Conference, 6 courses.
MATH 7810, Topics in Mathematics (Topic), 2 courses.
MATH 7910, College Teaching Internship, 2 courses.
MATH 7990, Continuing Graduate Advisement, 8 courses.
STAT 3000, Statistics for Scientists, 5 courses.
STAT 4250, Advanced Internship/Co-op, 1 course.
STAT 5100, Linear Regression and Time Series, 3 courses
STAT 5120, Categorical Data Analysis, 6 courses.
STAT 5810, Topics in Statistics, 4 courses.
STAT 5820, Topics in Statistics, 1 course.
STAT 5820, 6910, Topics in Statistics, 1 course.
STAT 5970, Seminar, 3 courses.
STAT 6250, Graduate Internship/Co-op, 1 course.
STAT 6550, Statistical Computing, 1 course.
STAT 6810, Topics in Statistics (Topic), 1 course.
STAT 6820, Topics in Statistics (Topic), 1 course.
STAT 6910, Seminar in Statistics, 14 courses.
STAT 6950, Directed Reading and Conference, 1 course.
STAT 6990, Continuing Graduate Advisement, 2 courses.
STAT 7810, Topics in Statistics (Topic), 1 course.
STAT 7990, Continuing Graduate Advisement, 1 course.

Directed Student Learning

Dissertation Committee Chair, "Network Meta-Analysis," Mathematics & Statistics. (September 1, 2014 - Present).
Advised: Brinley Zabriskie

Master's Committee Chair, "Statistical Strategies for Public Database Access and Analysis," Mathematics & Statistics. (September 1, 2014 - Present).
Advised: Christina Stevens

Dissertation Committee Chair, Mathematics & Statistics. (August 2013 - Present).
Advised: Divya Nair

Dissertation Committee Chair, Mathematics & Statistics. (August 2013 - Present).
Advised: Sarah Schwartz

Master's Committee Chair, Mathematics & Statistics. (August 2013 - Present).
Advised: Michael Steelman

Master's Committee Chair, Mathematics & Statistics. (August 2012 - Present).
Advised: Jenny Clements

Dissertation Committee Member, Nutrition, Dietetics and Food Sciences. (August 2010 - Present).
Advised: Meo La

Dissertation Committee Chair, "Computational methods for family-based association tests." (August 2008 - May 2012).
Advised: William Welbourn

Master's Committee Chair, "Serum cytokine levels and risk of dementia." (2011).
Advised: Austin Bowles

Master's Committee Chair, "TBD." (2011).
Advised: Elizabeth Giles

Master's Committee Chair, "Patterns of stressful life events and Alzheimer's disease risk." (2011).
Advised: Megan Platt

Supervised Research/URF, "Effectiveness of surgical strategies for hysterectomy," Biology. (2010).
Advised: Erica Huelsmann

Master's Committee Chair, "Comparing methods for family-based association tests." (2009).
Advised: Abbie Lundgreen

Master's Committee Chair, "Heritability of cognitive change." (2009).
Advised: Colette Childs

Dissertation Committee Chair, "Small-sample inference for correlated categorical data." (2008).
Advised: Larry Cook

Master's Committee Chair, "Heritability of cognitive traits using complex pedigrees and sibships." (2008).
Advised: Cassidy Allen

Master's Committee Chair, "Multivariate analysis of longitudinal neuropsychological measures in the Cache County Memory Study." (2006).
Advised: Sarah Schwartz

Master's Committee Chair, "Computational efficiency of exact family-based association tests." (2006).
Advised: Yanwei Ouyan

Supervised Research/URF, "Nutritional risk factors for cognitive decline among the elderly," Biology. (2006).
Advised: Angela Dunn

Dissertation Committee Chair, "Exact family based association tests." (2004).
Advised: Kady Schneiter

Supervised Research/URF, "Cognitive decline and antioxidant, Vitamin C, and Vitamin E intake among the elderly," Biology. (2003 - 2004).
Advised: Leila King

Supervised Research/URF, "Haplotypes of candidate genes as predictors of hip fracture in the elderly," Biology. (2003 - 2004).
Advised: Sara Anderson

Master's Committee Chair, "Use of classification methods for dementia screening." (2003).
Advised: Leslie Toone

Supervised Research/URF, "Using patient characteristics of the demented to classify dementia type," Mathematics & Statistics. (2003).
Advised: Kimberly Peterson

Supervised Research/URF, "Persistence of behavioral disturbances among the demented," Mathematics & Statistics. (2002 - 2003).
Advised: Craig Huber

Master's Committee Chair, "Correcting for left truncation bias when evaluating survival among the elderly with dementia." (2002).
Advised: Jennifer Harrick

Supervised Research/URF, "General advising for submitting abstract regarding NIH internship project to CUR Posters on the Hill," Mathematics & Statistics. (2002).
Advised: Randy Johnson

Supervised Research/URF, "Genetic factors in shortening time-to-onset of Alzheimer's disease," Mathematics & Statistics. (2002).
Advised: Sunni Mumford

Master's Committee Chair, "Operating characteristics of exact methods for corelated categorical data." (2001).
Advised: Shea Watrin

RESEARCH & OTHER CREATIVE ACTIVITIES

Published Intellectual Contributions

Book Chapters

Book, Chapter in Scholarly Book (Published)
Corcoran, C. D., Senchaudhuri, P., Mehta, C., Patel, N. (2010). Exact Methods for Categorical Data Analysis. In BS Everitt, CR Palmer (Ed.), *Encyclopaedic Companion to Medical Statistics*. London: Hodder Arnold.

Book, Chapter in Non-Scholarly Book (Published)

Corcoran, C. D. (2009). Analysis of Correlated Data. *StatXact Version 8.0 User Manual* (pp. 895-935).

Book, Chapter in Scholarly Book (Published)
Cutler, A., Corcoran, C. D., Toone, L. (2005). Bagging. *Encyclopedia of Statistics in Behavioral Science*. New York: Wiley & Sons.

Book, Chapter in Scholarly Book (Published)
Corcoran, C. D., Ryan, L. M. (2002). Exact Dose-Response Inference. In M Aerts, H Geys, G Molenberghs, and LM Ryan (Ed.), *Topics in Modelling of Clustered Data* (pp. 195-206). New York: Chapman and Hall.

Book, Chapter in Scholarly Book (Published)
Corcoran, C. D. (2002). Trend tests for binary data. In AH El-Shaarawi and WW Piegorsch (Ed.), *Encyclopedia of Environments* (vol. 4, pp. 2260-2264). Chichester: John Wiley & Sons.

Book, Chapter in Non-Scholarly Book (Published)
Corcoran, C. D., Kannappan, A. R., Senchaudhuri, P., Coull, B. (1999). *Egret User Manual.* Cytel Software Corporation.

Refereed Journal Articles

Journal Article, Professional Journal (Accepted)
Rattinger, G. B., Fauth, E. B., Behrens, S., Sanders, C., Schwartz, S., Norton, M. C., Corcoran, C. D., Mullins, C. D., Lyketsos, C. G., Tschanz, J. T. (in press). Closer caregiver and care recipient relationships predict lower informal costs of dementia care. *Alzheimer's & Dementia*.

Journal Article, Professional Journal (Accepted)
Matyi, J. A., Tschanz, J. T., Rattinger, G. B., Sanders, C., Vernon, E. K., Corcoran, C. D., Kauwe, J. S., Buhusi, M. C. (in press). Sex differences in risk for Alzheimer's Disease related to neurotrophin gene polymorphisms: the Cache County Memory Study. *Journal of Gerontology: Biological Sciences*.

Journal Article, Professional Journal (Published)
Sanders, C., Behrens, S., Schwartz, S., Wengreen, H., Corcoran, C. D., Lyketos, C. G., Tschanz, J. T. (2016). Nutritional status is associated with faster cognitive decline and worse functional impairment in the progression of dementia: The Cache County Dementia Progression Study. *Journal of Alzheimer's Disease*.

Journal Article, Professional Journal (Published)
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Journal Article, Professional Journal (Published)
Hippen, A. A., Ebbert, M. t., Norton, M. C., Tschanz, J. T., Munger, R. G., Corcoran, C. D., Kauwe, J. S. (2016). Presenilin E318G variant and Alzheiemr's disease risk: The Cache County Study. *BMC Genomics, 17*(Suppl 3), 438.

Journal Article, Professional Journal (Published)
Rattinger, G. G., Schwartz, S., Mullins, C. D., Corcoran, C. D., Zuckerman, I. H., Sanders, C., Norton, M. C., Fauth, E. B., Leoutsakos, J. M. S., Lyketsos, C. G., Tschanz, J. T. (2015). Dementia severity and the longitudinal costs of informal care in the Cache County population. *Alzheimer's & Dementia, 11*, 946-954.

Journal Article, Academic Journal (Published)
Snyder, C. M., Fauth, E. B., Wanzek, J., Piercy, K. W., Norton, M. C., Corcoran, C. D., Rabins, P. V., Lyketsos, C. G., Tschanz, J. T. (2015). Dementia caregivers' coping strategies and their relationship to health and well-being: The Cache County Study. *Aging & Mental Health, 19*(5), 390-399.

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Wang, L., Naj, A. C., Graham, R. R., Crane, P. K., Kunkle, B. W., Chrucaga, C., Murcia, J. D., Cannon-Albright, L., Baldwin, C. T., Zetterberg, H., Blennow, K., Kukull, W. A., Faber, K. M., Schupf, N., Norton, M. C., Tschanz, J. T., Munger, R. G., Corcoran, C. D., et al., Yu, L. (2015). Rarity of the Alzheimer Disease-Protective APP A673T Variant in the United States. *JAMA Neurology, 72*(2), 209-216. http://www.ncbi.nlm.nih.gov/pubmed/25531812

Journal Article, Academic Journal (Published)
Lythgoe, C., Perkes, A., Peterson, M., Schmutz, C., Leary, M., Ebbert, E. T. W., Ridge, P. G., M., J., Munger, R. G., Corcoran, C. D., Kauwe, J. S. K. (2015). Population-based analysis of cholesteryl ester transfer protein identifies association between I405V and cognitive decline: the Cache County Study. *Neurobiology of Aging, 36*(547), e1-3.

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Rattinger, G. B., Schwartz, S., Mullins, C. D., Corcoran, C. D., Zuckerman, I. H., Sanders, C., Norton, M. C., Fauth, E. B., Leoutsakos, J. M. S., Lyketsos, C. G., Tschanz, J. T. (2015). Dementia severity and the longitudinal costs of informal care in the Cache County population. *Alzheimer's & Dementia, 11*(8), 946-954.

Journal Article, Professional Journal (Published)
Greene, D., Tschanz, J. T., Smith, K. R., Østbye, T., Corcoran, C. D., Welsh-Bohmer, K. A., Norton, M. C. (2014). Impact of offspring death on cognitive health in late life: The Cache County Study. *American Journal of Geriatric Psychiatry, 22*(11), 1307-15.

Journal Article, Professional Journal (Published)
Chuang, Y.-f., Breitner, J. C., Chiu, Y. L., Khachaturian, A., Hayden, K., Corcoran, C. D., Tschanz, J. T., Norton, M. C., Munger, R. G., Welsh-Bohmer, K. A., Zandi, P., For the Cache County Investigators (2014). Use of diuretics is associated with reduced risk of Alzheimer's disease: The Cache County Study. *Neurobiology of Aging, 35*(11), 2429-35.

Journal Article, Professional Journal (Published)
Gilbert, M., Snyder, C., Corcoran, C. D., Norton, M. C., Lyketsos, C. G., Tschanz, J. T. (2014). The association of traumatic brain injury with rate of progression of cognitive and functional impairment in a population-based cohort of Alzheimer's disease: The Cache County Dementia Progression Study. *International Psychogeriatrics, 26*(10), 1593-1601.

Journal Article, Professional Journal (Published)
Snyder, C. M., Fauth, E., Wanzek, J., Piercy, K. W., Norton, M. C., Corcoran, C. D., Rabins, P. V., Lyketsos, C. G., Tschanz, J. T. (2014). Dementia caregivers' coping strategies and their relationship to health and well-being: The Cache County Study. *Aging Mental Health, 5*, 1-10.

Journal Article, Public or Trade Journal (Published)
Ridge, P. G., Maxwell, T. J., Foutz, S. J., Bailey, M. H., Corcoran, C. D., Tschanz, J. T., Norton, M. C., Munger, R. G., O'Brien, E., Kerber, R. A., Cawthon, R. M., Kauwe, J. S. (2014). Mitochondrial genomic variation associated with higher mitochondrial copy number: The Cache County Study on Memory Health and Aging. *BMC Bioinformatics, 15*(7), S6.

Journal Article, Public or Trade Journal (Published)
Sharp, A. R., Ridge, P. G., Bailey, M. H., Boehme, K. L., Norton, M. C., Tschanz, J. T., Munger, R. G., Corcoran, C. D., Kauwe, J. S., Alzheimer's Disease Neuroimaging Initiative (2014).

Population substructure in Cache County, Utah: The Cache County study. *BMC Bioinformatics, 15*(7), S8.

Journal Article, Professional Journal (Published)
Ebbert, M. T., Ridge, P. G., Wilson, A. R., Sharp, A. R., Bailey, M., Norton, M. C., Tschanz, J. T., Munger, R. G., Corcoran, C. D., Kauwe, J. S. (2014). Population-based analysis of Alzheimer's disease risk alleles implicates genetic interactions. *Biological Psychiatry, 75*(9), 732-737.

Journal Article, Professional Journal (Published)
Peterson, D., Munger, C., Crowley, J., Corcoran, C. D., Cruchaga, C., Goate, A. M., Norton, M. C., Green, R. C., Munger, R. G., Breitner, J. C., Welsh-Bohmer, K. A., Lyketsos, C. G., Tschanz, J. T., Kauwe, J. S. (2014). Variants in PPP3R1 and MAPT are associated with more rapid functional decline in Alzheimer's disease: The Cache County Dementia Progression Study. *Alzheimer's and Dementia, 10*(3), 366-371.

Journal Article, Professional Journal (Published)
Steinberg, M., Hess, K., Corcoran, C. D., Mielke, M. M., Norton, M. C., Breitner, J., Green, R., Leoutsakos, J.-M., Welsh-Bohmer, K., Lyketsos, C., Tschanz, J. T. (2014). Vascular risk factors and neuropsychiatric symptoms in Alzheiemr's disease: The Cache County Study. *International Journal of Geriatric Psychiatry, 29*(2), 153-159.

Journal Article, Professional Journal (Published)
Cruchaga, C., Karch, C. M., Jin, S. C., Benitez, B. A., Cai, Y., Guerreiro, R., Harari, O., Norton, J., Budde, J., Bertelsen, S., Jeng, A. T., Cooper, B., Skorupa, T., Carrell, D., Levitch, D., Hsu, S., Choi, J., Ryten, M., UK Brain Expression Consortium, Hardy, J., Ryten, M., Trabzuni, D., Weale, M. E., Ramasamy, A., Smith, C., Sassi, C., Bras, J., Gibbs, J. R., Hernandez, D. G., Lupton, M. K., Powell, J., Forabosco, P., Ridge, P. G., Corcoran, C. D., Tschanz, J. T., Norton, M. C., Munger, R. G., Schmutz, C., Leary, M., Demirci, F. Y., Bamne, M. N., Lopez, O. L., Ganguli, M., Medway, C., Turton, J., Lord, J., Braae, A., Barber, I., Brown, K., Alzheimer's Research UK Consortium, Passmore, P., Craig, D., Johnston, J., McGuinness, B., Todd, S., Heun, T., Kölsch, H., Kehoe, P. G., Hooper, N. M., Vardy, E. R., Mann, D. M., Pickering-Brown, S., Brown, K., Kalsheker, K., Lowe, J., Morgan, K., David Smith, A., Wilcock, G., Warden, D., Holmes, C., Pastor, P., Lorenzo-Betancor, O., Brkanac, Z., Scott, E., Topol, E., Morgan, K., Rogaeva, E., Singleton, A. B., Hardy, J., Kamboh, M. I., St. George-Hyslop, P., Cairns, N., Morris, J. C., Kauwe, J. S., Goate, A. M. (2014). Rare coding variants in the phospholipase D3 gene confer risk for Alzheimer's disease. *Nature, 505*(7484), 550-554.

Journal Article, Professional Journal (Published)
Gonzalez Murcia, J. D., Schmutz, C., Munger, C., Perkes, A., Gustin, A., Peterson, M., Ebbert, M. T. W., Norton, M. C., Tschanz, J. T., Munger, R. G., Corcoran, C. D., Kauwe, J. S. K. (2013). Assessment of TREM2 rs75932628 association with Alzheimer's disease in a population-based sample: The Cache County Study. *Neurobiology of Aging, 34*(12), 2889:e11-e13.

Journal Article, Professional Journal (Published)
Wengreen, H., Munger, R. G., Nelson, C., Corcoran, C. D., Tschanz, J. T., Norton, M. C., Welsh-Bohmer, K. A. (2013). Prospective Study of DASH- and Mediterranean-style Dietary Patterns and Age-related Cognitive Change. *98*(5), 1263-71.

Journal Article, Academic Journal (Published)
Wengreen, H., Munger, R. G., Cutler, A., Quach, A., Bowles, A., Corcoran, C. D., Tschanz, J. T., Norton, M. C., Welsh-Bohmer, K. (2013). Prospective study of dietary approaches to stop hypertension- and mediterranean-style dietary patterns and age-related cognitive change:

The Cache County Study on Memory, Health and Aging. *American Journal of Clinical Nutrition, 98*(5), 1263-1271.

Journal Article, Professional Journal (Published)
Piercy, K. W., Fauth, E. B., Norton, M. C., Pfister, R., Corcoran, C. D., Rabins, P. V., Lyketsos, C., Tschanz, J. T. (2013). Predictors of dementia caregiver depressive symptoms in a population: The Cache County Dementia Progression Study. *Journal of Gerontology: Psychological Sciences, 68*(6), 921-926.

Journal Article, Professional Journal (Published)
Norton, M. C., Clark, C., Fauth, E. B., Piercy, K. W., Pfister, R., Green, R. C., Corcoran, C. D., Rabins, P. V., Lyketsos, C. G., Tschanz, J. T. (2013). Caregiver personality predicts rate of cognitive decline in a community sample of persons with Alzheimer's Disease. The Dementia Progression Study. *International Psychogeriatrics, 25*(10), 1629-1637.

Journal Article, Academic Journal (Published)
Norton, M. C., Clark, C., Fauth, E. B., Piercy, K. W., Pfister, R., Green, R. C., Corcoran, C. D., Rabins, P. V., Lyketsos, C. G., Tschanz, J. T. (2013). Caregiver personality predicts rate of cognitive decline in a community sample of persons with Alzheimer's disease: The Cache County Dementia Progression Study. *International Psychogeriatrics, 25*, 1629-1637.

Journal Article, Professional Journal (Published)
Tschanz, J., Pfister, R., Steffens, D., Corcoran, C. D., Smith, K., Østbye, T., Schwartz, S., Welsh-Bohmer, K., Norton, M. C. (2013). Stressful events in late-life: Effects on cognitive decline: The Cache County Study. *International Journal of Geriatric Psychiatry, 28*, 821-830.

Journal Article, Academic Journal (Published)
Greene, D., Tschanz, J. T., Smith, K. R., Ostbye, T., Corcoran, C. D., Welsh-Bohmer, K. A., Norton, M. C. (2013). Impact of Offspring Death on Cognitive Health in Late Life: The Cache County Study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*.

Journal Article, Academic Journal (Published)
Tschanz, J. T., Pfister, R., Wanzek, J., Corcoran, C. D., Smith, K., Tschanz, B. T., Steffens, D. C., Østbye, T., Welsh-Bohmer, K. A., Norton, M. C. (2013). Stressful life events and cognitive decline in late life: moderation by education and age. The Cache County Study. *International journal of geriatric psychiatry, 28*(8), 821-30.

Journal Article, Academic Journal (Published)
Fauth, E. B., Schwartz, S., Tschanz, J. T., Ostbye, T., Corcoran, C. D., Norton, M. C. (2013). Baseline disability in activities of daily living predicts dementia risk even after controlling for global cognitive ability and depressive symptoms. *International Journal of Geriatric Psychiatry, 28*(6), 597-606.

Journal Article, Professional Journal (Published)
Peterson, D., Crowley, J., Munger, C., Corcoran, C. D., Cruchaga, C., Goate, A., Norton, M. C., Green, R., Munger, R. G., Breitner, J. C., Welsh-Bohmer, K., Lyketsos, C., Kauwe, J. S. (2013). Variants in PPP3R1 and MAPT are associated with more rapid functional decline in Alzheimer's disease: The Cache County Dementia Progression Study. *Alzheimer's and Dementia*.

Journal Article, Academic Journal (Published)
Rabins, P. V., Schwartz, S., Black, B. S., Corcoran, C. D., Fauth, E. B., Mielke, M., Christensen, J., Lyketsos, C., Tschanz, J. T. (2013). Predictors of progression to severe Alzheimer Disease in an incidence sample. *Alzheimer's and Dementia, 9*(2), 204-207.

Journal Article, Professional Journal (Published)
Piercy, K. W., Corcoran, C. D., Fauth, E. B., Norton, M. C., Rabins, P. V., Tschanz, B. T., Deberard, M. S., Snyder, C., Smith, C., Lee, L., Lyketsos, C. G. (2013). Caregiver coping strategies predict rate of cognitive and functional decline in dementia: The Cache County Dementia Progression Study. *American Journal of Geriatric Psychiatry, 21*(1), 57-66.

Journal Article, Academic Journal (Published)
Tschanz, J. T., Piercy, K. W., Corcoran, C. D., Fauth, E. B., Norton, M. C., Rabins, P. V., Tschanz, B. T., Deberard, M. S., Snyder, C., Smith, C., Lee, L., Lyketsos, C. G. (2013). Caregiver coping strategies predict cognitive and functional decline in dementia: The Cache County Dementia Progression Study. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry, 21*(1), 57-66.

Journal Article, Professional Journal (Published)
Ridge, P., Maxwell, T. J., Corcoran, C. D., Norton, M. C., Tschanz, J. T., O'Brien, E., Kerber, R. A., Cawthon, R. M., Munger, R. G., Kauwe, J. S. (2012). Mitochondrial genomic analysis of late onset Alzheimer's disease reveals protective haplogroups H6A1A/H6A1B. *PLoS, 7*(9), e45134.

Journal Article, Professional Journal (Published)
Leoutsakos, J. M., Han, D., Mielke, M., Forrester, S. N., Tschanz, J. T., Corcoran, C. D., Green, R., Norton, M. C., Welsh-Bohmer, K., Lyketsos, C. (2012). Effects of General Medical Health on Alzheimer Progression: the Cache County Dementia Progression Study. *International Journal of Psychogeriatrics, 24*(10), 1561-70.

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Leoutsakos, J. M., Han, D., Mielke, M. M., Forrester, S. N., Tschanz, J. T., Corcoran, C. D., Green, R. C., Norton, M. C., Welsh-Bohmer, K. A., Lyketsos, C. G. (2012). Effects of general medical health on Alzheimer's progression: the Cache County Dementia Progression Study. *International psychogeriatrics / IPA, 24*(10), 1561-70.

Journal Article, Academic Journal (Published)
Shao, H., Breitner, J. C., Whitmer, R., Wang, J., Hayden, K., Wengreen, H., Corcoran, C. D., Tschanz, J. T., Norton, M. C., Munger, R. G., Welsh-Bohmer, K., Zandi, P. (2012). Hormone Therapy and AD Dementia: New Findings from the Cache County Study. *Neurology, 79*(18), 1846-1852.

Journal Article, Professional Journal (Published)
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Rattinger, G. B., Behrens, S., Schwartz, S., Corcoran, C. D., Piercy, K. W., Norton, M. C., Fauth, E. B., Lyketsos, C., Tschanz, J. T., Alzheimer's Association International Conference, "How do neuropsychiatric symptoms in persons with Dementia affect caregiver physical and mental health over time? The Cache County Dementia Progression Study," Alzheimer's Association, Washington, D.C. (July 18, 2015 - July 23, 2015).

Matyi, J., Kauwe, J., Sanders, C., Rattinger, G. B., Corcoran, C. D., Norton, M. C., Munger, R. G., Buhusi, M. C., Tschanz, J. T., Alzheimer's Association International Conference, "Neurotrophin single nucleotide polymorphisms and cognitive functioning in older adults: The Cache County Study," Alzheimer's Association, Washington, DC. (July 18, 2015 - July 23, 2015).

Tschanz, J. T., Sanders, C. J., Wengreen, H., Schwartz, S., Behrens, S., Corcoran, C. D., Lyketsos, C., Alzheimer's Association International Conference, "Nutritional status and Neuropsychiatric symptoms in Dementia: The Cache County Dementia Study," Alzheimer's Association, Washington, D.C. (July 18, 2015 - July 23, 2015).

Sanders, C. J., Wengreen, H., Schwartz, S., Behrens, S., Corcoran, C. D., Lyketsos, C., Tschanz, J. T., Alzheimer's Association International Conference, "Nutritional status and severe Dementia, institutionalization and mortality: The Cache County Dementia Progression Study," Alzheimer's Association, Washington, D.C. (July 18, 2015 - July 23, 2015).

Sanders, C., Wengreen, H., Schwartz, S., Behrens, S., Corcoran, C. D., Lyketsos, C. G., Tschanz, J. T., Neuropsychological Society Meeting, "Nutritional status and neuropsychological functioning in persons with dementi: The Cache County Dementia Progression Study," Neuropsychological Society, Denver, CO. (February 2015).

Tschanz, J. T., Sanders, C., Wengreen, H., Schwartz, S., Behrens, S., Corcoran, C. D., Lyketsos, C., Annual Meeting of the Gerontological Society of America, "Nutritional status and neuropsychiatric symptoms in dementia: The Cache County Dementia Study," Gerontological Society of America, Washington DC. (November 2014 - 2014).

Milman, L., Faroqi-Shah, Y., Corcoran, C. D., Clinical Aphasiology Conference, "Normative data for the WAB-R: A comparison of monolingual English speakers, Asian Indian-English bilinguals, and Spanish-English bilinguals.," St. Simons Island, GA. (May 29, 2014).

Corcoran, C. D. (Invited Lecture), International Webinar, "Exact Nonparamatric Inference for Correlated Categorical Data," Cytel Software Corporation. (April 7, 2014).

Corcoran, C. D., Annual Meeting of the Utah Chapter of the American Statistical Association, "The Perils of P-Values: A Case Study in Statistical Genetics," American Statistical Association, Utah Chapter, Salt Lake City, UT. (March 25, 2014).

Corcoran, C. D. (Presenter & Author), Boston University Department of Biostatistics Seminar, "Permutation-Based Tests and Rare Variants in Genetic Association Studies," Department of Biostatics, Boston University, Boston University, Boston, MA. (March 20, 2014).

Corcoran, C. D. (Presenter & Author), Brigham Young University Department of Statistics Seminar, "Doctoral Research Programs in Statistics at Utah State University," Brigham Young University, Brigham Young University, Provo, UT. (February 2014).

Rattinger, G. B., Schwartz, S., Sanders, C., Corcoran, C. D., Fauth, E. B., Norton, M. C., Lyketsos, C. G., Tschanz, J. T., Annual Conference for the Gerontological Society of America, "Effect of caregiver relationship closeness and coping strategies on costs of care in the Cache County Dementia Progression Study Cohort," Gerontological Society of America, New Orleans, LA. (November 2013).

Corcoran, C. D. (Presenter & Author), Food and Drug Administration Workshop, "StatXact Training Course," Food and Drug Administration, Chevy Chase, MD. (September 19, 2013).

Corcoran, C. D. (Presenter & Author), Joint Statistical Meetings, "New StatXact Toolkit for Correlated Categorical Data," American Statistical Association and International Biometric Society, Montreal, Quebec, Canada. (July 2013 - August 2013).

Rattinger, G. (Presenter & Author), Schwartz, S. (Author Only), Corcoran, C. D. (Author Only), Zuckerman, I. (Author Only), Mullins, D. (Author Only), Norton, M. C. (Author Only), Fauth, E. B. (Author Only), Leoutsakos, J. (Author Only), Lyketsos, C. (Author Only), (Author Only), Alzheimer's Association International Conference, "How does dementia severity affect the costs of dementia care? Effect of dementia severity on costs of care in the Cache County Dementia Progression Study Cohort," Alzheimer's Association, Boston, MA. (July 2013).

Rattinger, G. B., Schwartz, S., Corcoran, C. D., Zuckerman, I. H., Mullins, C. D., Norton, M. C., Fauth, E. B., Leoutsakos, J. M., Lyketsos, C. G., Tschanz, J. T., Alzheimer's Association International Conference on Alzheimer's Disease, "Effect of dementia severity on costs of care in the Cache County Dementia Progression Study Cohort," Alzheimer's Association, Boston, MA. (July 2013).

Ebbert, M. T. W., Ridge, P. G., Wilson, A. R., Sharp, A. R., Bailey, M., Norton, M. C., Tschanz, J. T., Munger, R. G., Corcoran, C. D., Kauwe, J. S. K., Alzheimer's Association International Conference on Alzheimer's Disease, "Late-onset Alzheimer's disease risk alleles provide evidence of important gene-gene interactions," Alzheimer's Association, Boston, MA. (July 2013).

Norton, M. C., Munger, R. G., Tschanz, J. T., Corcoran, C. D., Smith, K. R., Alzheimer's Association International Conference on Alzheimer's Disease, "Multiple deaths of first-degree relatives during childhood predicts inflammation in late-life," Alzheimer's Association, Boston, MA. (July 2013).

Sanders, C., Wengreen, H., Corcoran, C. D., Schwartz, S., Norton, M. C., Lyketsos, C. G., Tschanz, J. T., Alzheimer's Association International Conference on Alzheimer's Disease, "Nutritional status and progression of dementia: The Cache County Dementia Progression Study," Alzheimer's Association, Boston, MA. (July 2013).

Tschanz, J. T., Schwartz, S., Gilbert, M., Wanzek, J., Sanders, C., Mielke, M., Corcoran, C. D., Norton, M. C., Lyketsos, C. G., Alzheimer's Association International Conference on Alzheimer's Disease, "Vascular factors as predictors of severe dementia and mortality in Alzheimer's disease," Alzheimer's Association, Boston, MA. (July 2013).

Corcoran, C. D. (Presenter & Author), Seventh International Workshop on Simulation, "Monte Carlo Sampling Using Parallel Processing for Multiple Testing in Genetic Association Studies," University of Bologna and University of Padova, Rimini, Italy. (May 22, 2013).

Fauth, E. B. (Presenter & Author), Schwartz, S. (Author Only), Norton, M. C. (Author Only), Corcoran, C. D. (Author Only), Piercy, K. W. (Author Only), Lyketsos, C. (Author Only), Tschanz, J. T. (Author Only), Gerontological Society of America Annual meeting, "Care Dyad Relationship Closeness Predicts Fewer Increases in Neuropsychiatric Symptoms over Time in Persons with Dementia," Gerontological Society of America, San Diego, CA. (November 17, 2012).

Corcoran, C. D. (Presenter & Author), Joint Statistical Meetings, "Twenty-Five Years of Cytel and StatXact: Where We've Been and Where We're Going," American Statistical Association and International Biometric Society, San Diego, CA. (July 2012 - August 2012).

Corcoran, C. D. (Presenter & Author), University of Utah Department of Family and Preventive Medicine Seminar, "Exact Tests for Correlated Data," University of Utah College of Family and Preventive Medicine, University of Utah, Salt Lake City, UT. (May 2012).

Corcoran, C. D. (Presenter & Author), University of Utah Department of Family and Preventive Medicine Seminar, "Exact Methods in Data Analysis," University of Utah Department of Family and Preventive Medicine, University of Utah, Salt Lake City, UT. (April 2012).

Norton, M. C., Hess, K., Corcoran, C. D., Piercy, K. W., Fauth, E. B., Rabins, P., Green, R., Lyketsos, C., Tschanz, J. T., International Conference on Alzheimer's Disease, "Caregiver Agreeableness, Neuroticism, Openness and Extraversion Associated with Rate of Cognitive Decline in Persons with Alzheimer's Disease.," Paris, France. (July 2011).

Tschanz, J. T., Corcoran, C. D. (Author Only), Norton, M. C., Piercy, K., Rabins, P. V., Fauth, E., DeBerard, M. S., Snyder, C., Smith, C., Lee, S., Morrison, A., Lyketsos, C. G., International Conference on Alzheimer's Disease and Other Disorders, "Caregiver Coping Strategies Predict Cognitive Decline in Dementia: The Cache County Dementia Progression Study," Honolulu, HI. (July 2010).

Treiber, K. A., Carlson, M., Corcoran, C. D. (Author Only), Foley, B., Stein, D., DeBerard, M. S., Norton, M., Piercy, K., Welsh-Bohmer, K. A., Breitner, J. S., Lyketsos, C. G., Tschanz, J., International Conference on Alzheimer's Disease and Other Disorders, "Cognitive Activity and Decline in Alzheimer's Disease: The Cache County Study," Honolulu, HI. (July 2010).

Norton, M. C., Fauth, E., Piercy, K., Corcoran, C. D. (Author Only), Hess, K., Morrison, A., Rabins, P. V., Lyketsos, C. G., Tschanz, J., International Conference on Alzheimer's Disease and Other Disorders, "Higher caregiver agreeableness predicts slower cognitive decline in persons with Alzheimer's Disease: the Dementia Progression Study," Honolulu, HI. (July 2010).

Munger, R. G., Cawthon, R. M., Corcoran, C. D. (Author Only), Tschanz, J., Norton, M. C., Smith, K., Zandi, P., Welsh-Bohmer, K., International Conference on Alzheimer's Disease and Other Disorders, "Prospective study of mitochondrial DNA copy number and incident dementia in Cach County, UTah," Honolulu, HI. (July 2010).

Corcoran, C. D., Pieper, C., Zandi, Z., Norton, M. N., Welsh-Bohmer, K., Breitner, J. S., Lyketsos, C. G., Tschanz, J. T., International Congress on Alzheimer's Disease, "A joint analysis of cognitive, functional, and neuropsychiatric symptom change in the Cache County Dementia Progression Study.," Honolulu, HI. (July 2010).

Corcoran, C. D. (Presenter & Author), Pieper, C., Zandi, Z., Norton, M. N., Welsh-Bohmer, K., Breitner, J. S., Lyketsos, C. G., Tschanz, J. T., International Congress on Alzheimer's Disease, "Predictors of decline in Alzheimer's: A joint analysis of cognitive, functional, and neuropsychiatric symptom change in the Cache County Dementia Progression Study," Honolulu, HI. (July 2010).

Corcoran, C. D. (Invited Lecture), Senchaudhuri, P., Mehta, C., Invited Seminar, University of Utah Medical School, "Using the StatXact Correlated Data Module for Exact Tests with Clustered Data," Salt Lake City, UT. (February 2010).

Corcoran, C. D. (Presenter & Author), Senchaundhuri, P., Mehta, C., Conference of the International Indian Statistical Association, "New Software Tools for Exact Tests with Correlated Data," Visakhapatnam, India. (January 2010).

Corcoran, C. D. (Invited Lecture), Senchaudhuri, P., Invited Seminar, Brigham Young University, "Exact Tests for Contingency Tables with Correlated Data," Department of Statistics, Provo, UT. (December 2009).

Norton, M. C., Smith, K. R., Ostbye, T., Tschanz, J. T., Corcoran, C. D. (Presenter Only), Schwartz, S., Piercy, K. W., Rabins, P. V., Steffens, D. C., Breitner, J. C., Welsh-Bohmer, K. A., International Conference on Alzheimer's Disease, "Spousal dementia caregiving as a risk factor for incident dementia," Vienna, Austria. (2009).

Tschanz, J. T., Corcoran, C. D., Green, R. C., Munger, R. G., Mielke, M. M., Norton, M. C., Rabins, P. V., Welsh-Bohmer, K. A., Buckley, T., Breitner, J. C., Lyketsos, C. G., International Conference on Alzheimer's Disease, "Interaction between C-Reactive Protein level and APOE genotype in predicting rate of progression in Alzheimer's disease," The Cache County Dementia Progression Study, Vienna, Austria. (2009).

Corcoran, C. D. (Invited Lecture), Munger, R. G., Cawthon, R., Invited Seminar, Harvard University, "Alzheimer's Disease Risk, Cognitive Decline, and Mitochondrial Function," Department of Biostatistics, Cambridge, MA. (October 2009).

Norton, M. C., Smith, K. R., Ostbye, T., Tschanz, J. T., Corcoran, C. D., Schwartz, S., Piercy, K. W., Rabins, P. V., Steffens, D. C., Breitner, J. C. S., Welsh-Bohmer, K. A., International Conference on Alzheimer's Disease, "Spousal dementia caregiving as a risk factor for incident dementia: The Cache County Study.," Vienna, Austria. (July 2009).

Corcoran, C. D. (Invited Lecture), Pieper, C., Tschanz, J., Invited Seminar, Brigham Young University, "Dynamical Correlations for Analyzing Multivariate Rates of Change, with Application to the Cache County Memory Study," Department of Statistics, Provo, UT. (January 2009).

Tschanz, J. T., Cook, L., Corcoran, C. D., Norton, M. C., Mielke, M., Rabins, P., Welsh-Bohmer, K. A., Treiber, K., Buckley, T., Breitner, J. C., Lyketsos, C., 36th Annual Meeting of the International Neuropsychological Society, "Gender Differences in the Trajectory of Cognitive Decline in Alzheimer's Disease in the Cache County Population," Waikola Hawaii. (2008).

Tschanz, J., Corcoran, C. D. (Author Only), Shao, H., Zandi, P., Norton, M., Mielke, M., Green, R., Rabins, P., Steinberg, M., Welsh-Bohmer, K., Breitner, J., Lyketsos, C., International Conference on Alzheimer's Disease, "Neuropsychiatric Symptoms and Mortality in a Populationbased Sample of Incident Alzheimer's Disease and other Dementias: The Cache County Dementia Progression Study," Chicago, IL. (2008).

Treiber, K., Shao, H., Zandi, P., Steinberg, M., Corcoran, C. D. (Author Only), Cook, L., Norton, M., Green, R., Piercy, K., Rabins, P., Breitner, J., Welsh-Bohmer, K., Lyketsos, C., Tschanz,

J., International Conference on Alzheimer's Disease, "Neuropsychiatric Syndromes in Alzheimer's disease: Relationship to Cognitive and Functional Progression: The Cache County Dementia Progression Study," Chicago, IL. (2008).

Treiber, K., Shao, H., Zandi, P., Steinberg, M., Corcoran, C. D., Cook, L., Norton, M. C., Green, R., Piercy, K. W., Rabins, P., Breitner, J. C. S., Welsh-Bohmer, K. A., Lyketsos, C., Tschanz, J. T., International Conference on Alzheimer's Disease, "Neuropsychiatric syndromes in Alzheimer's disease: Relationship to Cognitive and Functional Progression: The Cache County Dementia Progression Study.," The Cache County Dementia Progression Study, Chicago, IL. (2008).

Corcoran, C. D., Pieper, C., Zandi, p., Norton, M. C., Welsh-Bohmer, K., Breitner, J., Lyketsos, C., Tschanz, J. T., International Conference on Alzheimer's Disease, "Modeling dementia trajectories: An application of dynamical correlations to age-related traits: The Cache County Dementia Progression Study," The Cache County Dementia Progression Study, Chicago, IL. (2008).

Tschanz, J. T., Corcoran, C. D., Shao, H., Zandi, P., Norton, M. C., Mielke, M., Green, R., Rabins, P., Steinberg, M., Welsh-Bohmer, K., Breitner, J., Lyketsos, C., International Conference on Alzheimer's Disease, "Neuropsychiatric Symptoms and Mortality in a Population-based Sample of Incident Alzheimer's Disease and other Dementias: The Cache County Dementia Progression Study," The Cache County Dementia Progression Study., Chicago, IL. (2008).

Corcoran, C. D., Senchaudhuri, P., Joint Statistical Meetings, "Exact Trend Tests for Clustered 2 X C Tables," Denver, CO. (August 2008).

Corcoran, C. D. (Presenter & Author), Pieper, C., Zandi, P., Norton, M., Welsh-Bohmer, K., Breitner, J., Lyketsos, C., Tschanz, J., International Congress on Alzheimer's Disease, "Modeling dementia trajectories: An application of dynamical correlations to age-related traits in the Cache County Dementia Progression Study," Chicago, IL. (July 2008).

Corcoran, C. D. (Invited Lecture), Zandi, P., Pieper, C., Tschanz, J., Invited Seminar, Harvard University, "Assessing Multiple Trajectories of Dementia Symptoms: The Cache County Dementia Progression Study," Department of Biostatistics, Cambridge, MA. (May 2008).

Tschanz, J., Cook, L., Corcoran, C. D. (Author Only), Norton, M., Mielke, M., Rabins, P., Welsh-Bohmer, K. A., Trieber, K., Buckley, T., Breitner, J. S., Lyketsos, C., 36th Annual Meeting of the International Neuropsychological Society, "Gender Differeneces in the Trajectory of Cognitive Decline in Alzheimer's Disease in the Cache County Population," Waikola, Hawaii. (February 2008).

Breitner, J. C., Khachaturian, A., Zandi, P., Hayden, K., Skoog, I., Tschanz, J. T., Norton, M. C., Munger, R. G., Welsh-Bohmer, K., Rosenberg, P., Mielke, M., Corcoran, C. D., Lyketsos, C., Rabins, P., Green, R., 11th International Congress of the International Federation of Psychiatric Epidemiology, "Cardiovascular risk factors for incidence and/or progression of Alzheimer's disease: The Cache County Studies," The Cache County Studies, Göteborg, Sweden. (2007).

Mielke, M. M., Tschanz, J. T., Hayden, K. M., Rosenberg, P. B., Corcoran, C. D., Norton, M. C., Rabins, P. V., Green, R. C., Welsh-Bohmer, K. A., Breitner, J. C., Munger, R. G., Lyketsos, C. G., 2007 Vascular, Behavioural and Cognition (VAS-COG) Conference, "Interaction Between APOE ε4 and Vascular Factors Predict Rate of Cognitive and Functional Decline in Alzheimer's Disease," San Antonio, TX. (2007).

Mielke, M. M., Tschanz, J. T., Norton, M. C., Corcoran, C. D., Rabins, P., Steinberg, M., Carlson, M., Green, R., Breitner, J. C., Welsh-Bohmer, K., Lyketsos, C. G., Alzheimer Prevention Conference, "Use of acetylcholinesterase inhibitors and memantine in a population-based study of incident AD cases: Prevalence of use, characteristics, and relation to mortality," Washington, D.C. (2007).

Mielke, M. M., Tschanz, J., Norton, M., Corcoran, C. D. (Author Only), Rabins, P., Steinberg, M., Carlson, M., Green, R., Breitner, J. S., Welsh-Bohmer, K., Lyketsos, C. G., Alzheimer Prevention Conference, "Use of acetylcholinesterase inhibitors and memantine in a population-based study of incident AD cases: Prevalence of use, characteristics, and relation to mortality.," Washington D.C. (2007).

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Tschanz, J., Shao, H., Zandi, P., Steinberg, M., Corcoran, C. D. (Author Only), Norton, M., Green, R., Piercy, K., Rabins, P., Cook, L., Lyketsos, C., 60th Annual Scientific Meeting of the Gerontological Society of America, "Neuropsychiatric syndromes in Alzheimer's disease: Association with Rate of Cognitive Progression. The Cache County Study," San Francisco, CA. (November 2007).

Treiber, K., Tschanz, J., Corcoran, C. D. (Author Only), Stein, D., Steinberg, M., Norton, M., Green, R., Rabins, P., Piercy, K., Welsh-Bohmer, K., Lyketsos, C., 60th Annual Scientific Meeting of the Gerontological Society of America, "Point prevalence of neuropsychiatric symptoms in Alzheimer's disease and vascular dementia: The Cache County Study," San Francisco, CA. (November 2007).

Norton, M., Tschanz, J., Ostbye, T., Corcoran, C. D. (Author Only), Cook, L., Breitner, J., Welsh-Bohmer, K. A., 60th Annual Scientific Meeting of the Gerontological Society of America, "Stressful life events and cognitive decline - The Cache County Study," San Francisco, CA. (November 2007).

Norton, M. C., Tschanz, J. T., Ostbye, T., Corcoran, C. D., Cook, L., Breitner, J., Welsh-Bohmer, K., 60th Annual Scientific Meeting of the Gerontological Society of America, "Stressful life events and cognitive decline – The Cache County Study," The Cache County Study, San Francisco, CA. (November 2007).

Norton, M. C., Tschanz, J. T., Ostbye, T., Corcoran, C. D. (Author Only), Breitner, J. S., Welsh-Bohmer, K. A., World Conference of Stress, "Widow(er)hood increases risk for subsequent dementia, especially for women. The Cache County Study," Budapest, Hungary. (August 2007).

Norton, M. C., Tschanz, J. T., Ostbye, T., Corcoran, C. D., Zandi, P. P., Breitner, J. C., Welsh-Bohmer, K. A., World Conference of Stress, "Widow(er)hood increases risk for subsequent dementia, especially for women. The Cache County Study," The Cache County Study, Budapest, Hungary. (August 2007).

Corcoran, C. D. (Presenter & Author), Pieper, C., Zandi, P., Tschanz, J., Joint Statistical Meetings, "Invited Presentation," Salt Lake City, UT. (July 2007).

Breitner, J. S., Khachaturian, A., Zandi, P., Hayden, K., Skoog, I., Tschanz, J., Norton, M., Munger, R. G., Welsh-Bohmer, K., Rosenberg, P., Mielke, M., Corcoran, C. D. (Author Only), Lyketsos, C., Rabins, P., Green, R., 11th International Congress of the International

Federation of Psychiatric Epidemiology, "Cardiovascular risk factors for incidence and/or progression of Alzheimer's disease: The Cache County Studies," Goteborg, Sweden. (May 3, 2007 - May 6, 2007).

Buckley, T., Tschanz, J., Norton, M., Corcoran, C. D. (Author Only), Welsh-Bohmer, K. A., Breitner, J., International Neuropsychological Society Conference, "Metacognitive judgments and change in cognitive and functional abilities in a population of elderly individuals. The Cache County Study," Portland, OR. (February 2007).

Buckley, T., Tschanz, J. T., Norton, M. C., Corcoran, C. D., Welsh-Bohmer, K., Breitner, J., International Neuropsychological Society Conference, "Metacognitive judgments and change in cognitive and functional abilities in a population of elderly individuals. The Cache County Study," The Cache County Study, Portland OR. (February 2007).

Tschanz, J., Corcoran, C. D. (Author Only), Norton, M., Mielke, M., Rabins, P., Treiber, K., Welsh-Bohmer, K. A., Breitner, J., Lyketsos, C., International Neuropsychological Society Conference, "Rate of cognitive and functional decline in Alzheimer's disease in the Cache County Population," Portland, OR. (February 2007).

Tschanz, J. T., Corcoran, C. D., Norton, M. C., Mielke, M., Rabins, P., Treiber, K., Welsh-Bohmer, K. A., Breitner, J., Lyketsos, C., the International Neuropsychological Society Conference, "Rate of cognitive and functional decline in Alzheimer's disease in the Cache County Population," Portland OR. (February 2007).

Corcoran, C. D. (Invited Lecture), Invited Seminar, Harvard University, "Family-based Association Studies: The Cache County Study on Memory Health and Aging, and the Utah Population Database," Department of Biostatistics. (October 2006).

Corcoran, C. D. (Presenter & Author), Senchaudhuri, P., Coull, B., Joint Statistical Meetings, "Exact Inference for Correlated Categorical Data," Seattle, WA. (August 2006).

Corcoran, C. D. (Presenter & Author), Tschanz, J., Steinberg, M., Schwartz, S., Norton, M., Welsh-Bohmer, K., Breitner, J., Lyketsos, C., 10th International Conference on Alzheimer's Disease and Related Disorders, "Longitudinal Course of Neuropsychiatric Symptoms in Dementia. The Cache County Study," Madrid, Spain. (July 2006).

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Mielke, M. M., Rosenberg, P., Tschanz, J. T., Cook, L., Corcoran, C. D., Norton, M. C., Welsh-Bohmer, K. A., Breitner, J. C., Lyketsos, C., 10th International Conference on Alzheimer's Disease and Related Disorders, "Vascular Risk Factors and Functional Decline in Dementia," the Cache County Study. (July 2006).

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Corcoran, C. D. (Invited Lecture), Invited Seminar, University of Pennsylvania, "Family-based Association Studies: The Cache County Study on Memory Health and Aging, and the Utah Population Database," Department of Biostatistics. (March 2006).

Corcoran, C. D. (Invited Lecture), Invited Seminar, Cytel Software Corporation, "The Exact Family Based Association Test," Cambridge, MA. (February 2006).

Charoonruk, G., Munger, R. G., Wengreen, H., Corcoran, C. D., Hayden, K., Bastian, L., Tschanz, J. T., Norton, M. C., Welsh-Bohmer, K., Alzheiemr's Association International conference on Prevention of Dementia: Early diagnosis and intervention, "Diabetes Mellitus and risk of Alzheimer's disease in the Cache County Study on Memory, Health and Aging," the Cache County Study on Memory, Health and Aging, Washington, D.C. (2005).

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Wengreen, H. J., Munger, R. G., Corcoran, C. D. (Author Only), Zandi, P., Tschanz, J., Norton, M., Welsh-Bohmer, K., Alzheimer's Association International Conference on Prevention of Dementia: Early diagnosis and intervention, "Fruit and vegetable intake and cognitive function in the elderly: The Cache County Study on Memory, Health and Aging," Washington, D.C. (2005).

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Tschanz, J., Corcoran, C. D. (Author Only), Toone, L., Pfister, R., Welsh-Bohmer, K., Norton, M., Breitner, J., Lyketsos, C., International Neuropsychological Society Convention, "Head Injury and Trajectory of Cognitive Decline in Dementia. The Cache County Study," St. Louis, MO. (2005).

Tschanz, J. T., Corcoran, C. D., L, T., R., P., K., W.-B., Norton, M. C., J., B., C., L., Presented at the International Neuropsychological Society Convention, "Head Injury and Trajectory of Cognitive Decline in Dementia," Presented at the International Neuropsychological Society Convention The Cache County Study. (2005).

Wengreen, H., Munger, R. G., Corcoran, C. D., Zandi, P., Tschanz, J. T., Norton, M. C., Welsh-Bohmer, K., the Alzheiemr's Association International conference on Prevention of Dementia: Early diagnosis and intervention, "Fruit and vegetable intake and cognitive function in the elderly: The Cache County Study on Memory, Health and Aging," The Cache County Study on Memory, Health and Aging, Washington, D.C. (2005).

Schneiter, K., Corcoran, C. D., Laird, N., The Western North American Region of The International Biometric Soceity, "Exact Family Based-Association Tests for Multiallelic Data," International Biometric Soceity, Fairbanks, AK. (2005).

Corcoran, C. D., Canadian Society of Epidemiology and Biostatistics Annual Meeting, "Exact inference for epidemiology and statistics," Toronto, ON. (July 2005).

Norton, M., Steffens, D., Toone, L., Tschanz, J., Hayden, K., Corcoran, C. D. (Author Only), Klein, L., Zandi, P., Breitner, J. S., Welsh-Bohmer, K., Annual Meeting of the Gerontological Society of America, "Late-life Depression, Mild Cognitive Impairment, APOE and their Interactive Effects on 3-Year Conversion to Dementia.," Washington D.C. (November 2004).

Benson-Lensegrav, T., Tschanz, J., Masters, K. S., Carlson, M. C., Corcoran, C. D. (Author Only), Lykestos, C., Heath, E., Leslie, C., Munger, R. G., Ostbye, T., Welsh-Bohmer, K., Norton, M., Hayden, L., Annual Meeting of the American Psychological Association, "Sedentary Lifestyle Increases Dementia Risk: The Cache County Study.," Honolulu, HI. (July 2004).

Steinberg, M., Corcoran, C. D. (Author Only), Huber, C., Welsh-Bohmer, K., Zandi, P., Breitner, J. S., Tschanz, J., Lyketsos, C., International Conference on Alzheimer's Disease and Related Disorders, "A Longitudinal Model for Neuropsychiatric Symptoms in Dementia: The Cache County Study," Philadelphia, PA. (July 2004).

Toone, L., Tschanz, J., Rabins, P. V., Steinberg, M., Onyike, C., Corcoran, C. D. (Author Only), Norton, M., Welsh-Bohmer, K., Breitner, J., Zandi, P., Lykestos, C. G., International Conference on Alzheimer's Disease and Related Disorders, "A Population Based Study of Medical Co-Morbidity in Early Dementia and Mild Cognitive Syndrome: Association with Functional and Cognitive Impairment," Philadelphia, PA. (July 2004).

Wengreen, H., Munger, R. G., Corcoran, C. D. (Author Only), Zandi, P., Tschanz, J., Norton, M., Welsh-Bohmer, K., Skoog, I., Breitner, J., International Conference on Alzheimer's Disease and Related Disorders, "Antioxidant Intake and Cognitive Function of Elderly Participants in The Cache County, Utah Study on Memory, Health and Aging.," Philadelphia, PA. (July 2004).

Charoonruk, G., Munger, R. G., Wengreen, H., Corcoran, C. D. (Author Only), Tschanz, J., Norton, M., Bastian, L., Welsh-Bohmer, K., International Conference on Alzheimer's Disease and Related Disorders, "Diabetes Mellitus and Cognitive Decline in the Cache County Study on Memory, Helath and Aging," Philadelphia, PA. (July 2004).

Norton, M. C., Steffens, D. C., Toone, L., Tschanz, J. T., Hayden, K., Corcoran, C. D. (Author Only), Klein, L., Zandi, P., Breitner, J. S., Welsh-Bohmer, K. A., International Conference on Alzheimer's Disease and Related Disorders, "Late-life Depression, Mild Cognitive Impairment, APOE and their Interactive Effects on 3-Year Conversion to Dementia," Philadelphia, PA. (July 2004).

Tschanz, J., Klein, E., Trieber, K., Corcoran, C. D. (Author Only), Norton, M., Toone, L., Welsh-Bohmer, K., Steinberg, M., Munger, R. G., Pieper, C., Breitner, J., Zandi, P., Lyketsos, C., International Conference on Alzheimer's Disease and Related Disorders, "Neuropsychiatric Symptoms in Mild Cognitive Impairment and Dementia: Prevalence and Relationship to Cogntive and Functional Impairment," Philadelphia, PA. (July 2004).

Klein, E., Corcoran, C. D., Tschanz, J., Norton, M., Welsh-Bohmer, K., Breitner, J., Zandi, P., Lyketsos, C., International Conference on Alzheimer's Disease and Related Disorders, "Survival from Memory Symptom Onset: A Comparison of Individuals with Dementia and Cognitive Impairment. The Cache County Study," Philadelphia, PA. (July 2004).

Klein, E., Tschanz, J., Corcoran, C. D. (Author Only), Norton, M., Welsh-Bohmer, K., Breitner, J., Zandi, P., Lyketsos, C., Society of Epidemiological Research, "Estimating Survival Duration from Memory Symptom Onset: A Comparison of Methods. The Cache County Study," Salt Lake City, UT. (June 2004).

Norton, M., Skoog, I., Toone, L., Tschanz, J., Corcoran, C. D. (Author Only), Zandi, P., Hart, A., Breitner, J., Welsh-Bohmer, K., Steffens, D., Society of Epidemiological Research, "Improving Assessment of Incidence of First-Onset Geriatric Depression in Population-Based Studies," Salt Lake City, UT. (June 2004).

Lensegrav-Benson, T., Lisota, R., Tschanz, J., Masters, K., Norton, M., Carlson, M., Corcoran, C. D. (Author Only), Lyketsos, C., Heath, E., Leslie, C., Munger, R. G., Ostybe, T., Welsh-Bohmer, K., Annual Meeting of the Western Psychological Association, "Physical Activity is Associated with Better Cognitive Performance," Phoenix, AZ. (April 2004).

Corcoran, C. D. (Invited Lecture), Schneiter, K., Laird, N., Invited Seminar, University of Colorado Health Sciences Center, "Implementing an exact family based association test in the presence of two alleles," Denver, CO. (April 2004).

Lisota, R., Steffens, D., Toone, L., Tschanz, J. T., Norton, M., Corcoran, C. D. (Author Only), Welsh-Bohmer, K. A., Breitner, J. S., Annual AAGP Meeting, "Vascular Risk Factors Predict Chronicity of Depression in the Elderly," Baltimore, MD. (February 2004).

Schneiter, K., Corcoran, C. D., The Western North American Region of The International Biometric Soceity, "An Exact Approach to Family Based Association Tests Using a Network Algorithm.," The International Biometric Society, Golden, CO. (2003).

Corcoran, C. D. (Invited Lecture), Invited Seminar, Brigham Young University, "A network algorithm for exact family based association tests," Provo, UT. (September 2003).

Corcoran, C. D. (Author Only), Schneiter, K., Spring Meeting of the Western North America Region of the International Biometrics Society, "A Network Algorithm for Exact-Based Association Tests," Denver, CO. (June 2003).

Corcoran, C. D. (Presenter & Author), Senchaudhuri, P., Spring Meeting, Western North America Region, "Exact Dose-Response Estimation for Clustered Binary Data," International Biometrics Society, Denver, CO. (June 2003).

Huber, C., Steinberg, M., Tschanz, J., Corcoran, C. D. (Author Only), Posters on the Hill, "A Longitudinal Model for Behavioral Disturbances among the Elderly with Dementia: The Cache County Memory Study," Washington D.C. (April 2003).

Norton, M. C., Steffens, D. C., Skoog, I., Corcoran, C. D. (Author Only), Welsh-Bohmer, K. A., Breitner, J. S., American Association for Geriatric Psychiatry, "Prior Minor Depression Is More Predictive of Future Episodes of Depression in the Elderly than Gender, Age, or APOE status. The Cache County Study," Honolulu, HI. (March 2003).

Tschanz, J., Welsh-Bohmer, K., Norton, M., Corcoran, C. D. (Author Only), Breitner, J., International Neuropsychological Society 31st Annual Meeting, "Progression to Dementia in Diverse Types of Mild Cognitive Impairments of Aging," Honolulu, HI. (February 2003).

Corcoran, C. D. (Presenter & Author), Senchaudhuri, P., Mehta, C., Joint Statistical Meeting, "Order-restricted inference for several binomials," NYC, NY. (August 2002).

Norton, M., Tschanz, J., Corcoran, C. D., Mumford, S., Welsh-Bohmer, K., Breitner, J., International Conference on Alzheimer's Disease and Related Disorders, "Apolipoprotein E4 interacts with mild cognitive deficit to shorten time to dementia onset," Stockholm, Sweden. (July 2002).

Tschanz, J., Norton, M., Corcoran, C. D., LaCaille, R., Welsh-Bohmer, K., Breitner, J., International Conference on Alzheimer's Disease and Related Disorders, "Cognitive screening and self-perception of memory problems predict mild cognitive impairment and dementia," Stockholm, Sweden. (July 2002).

Corcoran, C. D. (Author Only), International Conference on Alzheimer's Disease and Related Disorders, "Differential impact of genetic and demographic variables on clinical course of dementia and Alzheimer's disease," Stockholm, Sweden. (July 2002).

Hayden, K., Khachaturian, A., Breitner, J., Tschanz, J., Corcoran, C. D. (Author Only), Norton, M., International Conference on Alzheimer's Disease and Related Disorders, "Evaluation of performance of a two-stage screen for incident dementia," Stockholm, Sweden. (July 2002).

Wengreen, H. J., Munger, R. G., West, N., Cutler, D., Corcoran, C. D., Zhang, J., Sassano, N. E., International Conference on Nutrition and Aging, "Protein Intake and Risk of Osteoporotic Hip Fracture in Elderly Utah Residents," Paris, France. (July 2001).

Corcoran, C. D. (Presenter & Author), WHO Meeting for the Prevention of Craniofacial Anomalies, "Deisgn consideration for dose-response studies.," Park City, UT. (May 2001).

West, N., Tschanz, J., Welsh-Bohmer, K., Corcoran, C. D., Wyse, B., Weight, C., Breitner, J., Annual Meeting of the International Neuropsychological Society, "Genetic and nongenetic risk factors for cognitive decline in the normal elderly," Chicago, IL. (February 2001).

Contracts, Grants and Sponsored Research

Contract

Kauwe (Brigham Young University), Keone (Principal), Munger, Ronald G. (Supporting), Corcoran, Christopher D (Supporting), "Alzheimer's disease candidate gene genotyping: The Cache County Study," Sponsored by USTAR, State, $42,000.00. (February 1, 2011 - May 30, 2011).

Grant

Tschanz, Joann T (Principal), Corcoran, Christopher D (Supporting), Munger, Ronald G. (Supporting), Lefevre, Michael (Supporting), "Epidemiology of Alzheimer's Disease resilience and risk pedigrees," Sponsored by NIH, Federal, $1,067,869.00. (September 1, 2016 - August 31, 2021).

Corcoran, Christopher D (Supporting), Stevens, John R. (Supporting), "miRNA and colorectal cancer: Associations with tumor phenotype and survival," Sponsored by National Institutes of Health, Federal, $1,250,000.00. (July 2012 - June 2017).

Corcoran, Christopher D (Supporting), "Pleiotropic and interaction effects on Alzheimer's disease risk and progression," Sponsored by National Institutes of Health, Federal, $1,250,000.00. (July 2012 - June 2017).

Corcoran, Christopher D (Supporting), "Prenatal and Neonatal Biologic Markers for Autism," Federal, $576,008.00. (July 2010 - June 2015).

Intellectual Contributions in Submission

Refereed Journal Articles

Milman, L., Faroqi-Shah, Y., Corcoran, C. D., Damele, D. Interpreting MMSE scores in highly proficient bilingual Asian Indian-English and Spanish-English speakers: Demographic adjustments, item analyses, and supplemental measures.

SERVICE

General Service

Department

Chairperson, Graduate Committee, August 2012 - Present.

Undergraduate Statistics Advisor, 1999 - Present.

Committee Member, Undergraduate Curriculum Committee, 2003 - 2005.

Committee Member, Graduate Committee, 2002 - 2003.

Committee Member, Undergraduate Committee, 2001 - 2002.

Other

Committee Chair, Computing Committee, 2005 - 2009.

Professional/Public

Officer, Secretary, American Statistical Association, Utah Chapter. 2002 - 2006.

Member, Sunrise Elementary School Community Council. 2002 - 2006.

Committee Member, Cache School District Building Task Force. 2003 - 2004.

Program Organizer, Bioinformatics Working Group. 2002 - 2003.

Contribuing Author of User Manuals. 1999 - 2003.

Program Organizer, Statistics Brown Bag Seminar Series. 2000 - 2001.

Utah State University

Committee Member, Promotion and Tenure Central Committee, September 2014 - Present.

Committee Member, Utah State University Faculty Senate, 2007 - Present.

Committee Chair, Utah State University Faculty Senate Committee on Committees, 2008 - 2009.

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	**PLAINTIFFS' NOTICE TO TAKE ORAL AND VIDEOTAPED DEPOSITION OF DR. CHRISTOPHER D. CORCORAN**

To: Monsanto Company, by and through their counsel, Hollingsworth, LLP.

Please take notice that, pursuant to Rule 30 and Rule 45 of the Federal Rules of Civil Procedure, Plaintiffs' Counsel shall take the videotaped deposition upon oral examination of **Dr. Christopher D. Corcoran on September 20, 2017** before a person duly authorized to administer oaths. The deposition shall commence at **9:00 a.m. ET at Hampton Inn, 1665 N. Main St., Logan, UT.** The conduct of the deposition, including its continuation if necessary, shall be governed by Pretrial Order No. 7: Deposition Protocol (ECF No. 103) and Rule 30 of the Federal Rules of Civil Procedure. Dr. Foster shall produce any documents identified in Schedule A attached to his Document Subpoena, at least 10 days prior to the deposition.

Dated: September 6, 2017

Respectfully submitted,

/s/ Robin Greenwald
Robin Greenwald
rgreenwald@weitzlux.com
Weitz & Luxenberg
700 Broadway
New York, NY 10003

/s/ Aimee Wagstaff
Aimee Wagstaff

aimee.wagstaff@andruswagstaff.com
Andrus Wagstaff, P.C.
7171 West Alaska Drive
Lakewood, CO 80226

/s/ Mike Miller
Michael Miller
mmiller@millerfirmllc.com
The Miller Firm LLC
108 Railroad Ave
Orange, VA 22960

Co-Lead Counsel for Plaintiffs in MDL No. 2741

AO 88B (Rev. 02/14) Subpoena to Produce Documents, Information, or Objects or to Permit Inspection of Premises in a Civil Action

UNITED STATES DISTRICT COURT

for the

Northern District of California

IN RE: ROUNDUP PRODS. LIABILITY LITIG.

Plaintiff

v.

MONSANTO COMPANY

Defendant

Civil Action No. 16-md-2741-VC

SUBPOENA TO PRODUCE DOCUMENTS, INFORMATION, OR OBJECTS OR TO PERMIT INSPECTION OF PREMISES IN A CIVIL ACTION

To: Dr. Christopher D. Corcoran

(Name of person to whom this subpoena is directed)

☑ *Production:* **YOU ARE COMMANDED** to produce at the time, date, and place set forth below the following documents, electronically stored information, or objects, and to permit inspection, copying, testing, or sampling of the material: SEE ATTACHED SCHEDULE A

Place:	Date and Time:
Weitz & Luxenberg, P.C., 700 Broadway, New York, NY 10003	09/16/2017 5:00 pm

☐ *Inspection of Premises:* **YOU ARE COMMANDED** to permit entry onto the designated premises, land, or other property possessed or controlled by you at the time, date, and location set forth below, so that the requesting party may inspect, measure, survey, photograph, test, or sample the property or any designated object or operation on it.

Place:	Date and Time:

The following provisions of Fed. R. Civ. P. 45 are attached – Rule 45(c), relating to the place of compliance; Rule 45(d), relating to your protection as a person subject to a subpoena; and Rule 45(e) and (g), relating to your duty to respond to this subpoena and the potential consequences of not doing so.

Date: 09/06/2017

CLERK OF COURT

OR

Signature of Clerk or Deputy Clerk

/s/ Robin Greenwald

Attorney's signature

The name, address, e-mail address, and telephone number of the attorney representing *(name of party)* Plaintiffs, who issues or requests this subpoena, are:

Robin Greenwald, 700 Broadway, New York, NY 10003, rgreenwald@weitzlux.com, 212-558-5802

Notice to the person who issues or requests this subpoena

If this subpoena commands the production of documents, electronically stored information, or tangible things or the inspection of premises before trial, a notice and a copy of the subpoena must be served on each party in this case before it is served on the person to whom it is directed. Fed. R. Civ. P. 45(a)(4).

Civil Action No. 16-md-2741-VC

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 45.)

I received this subpoena for *(name of individual and title, if any)* _____

on *(date)* _____ .

❒ I served the subpoena by delivering a copy to the named person as follows: _____

_____

_____ on *(date)* _____ ; or

❒ I returned the subpoena unexecuted because: _____

_____ .

Unless the subpoena was issued on behalf of the United States, or one of its officers or agents, I have also tendered to the witness the fees for one day's attendance, and the mileage allowed by law, in the amount of $ _____ .

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____

_____
Server's signature

_____
Printed name and title

_____
Server's address

Additional information regarding attempted service, etc.:

Federal Rule of Civil Procedure 45 (c), (d), (e), and (g) (Effective 12/1/13)

(c) Place of Compliance.

(1) ***For a Trial, Hearing, or Deposition.*** A subpoena may command a person to attend a trial, hearing, or deposition only as follows:

(A) within 100 miles of where the person resides, is employed, or regularly transacts business in person; or

(B) within the state where the person resides, is employed, or regularly transacts business in person, if the person

(i) is a party or a party's officer; or

(ii) is commanded to attend a trial and would not incur substantial expense.

(2) ***For Other Discovery.*** A subpoena may command:

(A) production of documents, electronically stored information, or tangible things at a place within 100 miles of where the person resides, is employed, or regularly transacts business in person; and

(B) inspection of premises at the premises to be inspected.

(d) Protecting a Person Subject to a Subpoena; Enforcement.

(1) ***Avoiding Undue Burden or Expense; Sanctions.*** A party or attorney responsible for issuing and serving a subpoena must take reasonable steps to avoid imposing undue burden or expense on a person subject to the subpoena. The court for the district where compliance is required must enforce this duty and impose an appropriate sanction—which may include lost earnings and reasonable attorney's fees—on a party or attorney who fails to comply.

(2) ***Command to Produce Materials or Permit Inspection.***

(A) *Appearance Not Required.* A person commanded to produce documents, electronically stored information, or tangible things, or to permit the inspection of premises, need not appear in person at the place of production or inspection unless also commanded to appear for a deposition, hearing, or trial.

(B) *Objections.* A person commanded to produce documents or tangible things or to permit inspection may serve on the party or attorney designated in the subpoena a written objection to inspecting, copying, testing, or sampling any or all of the materials or to inspecting the premises—or to producing electronically stored information in the form or forms requested. The objection must be served before the earlier of the time specified for compliance or 14 days after the subpoena is served. If an objection is made, the following rules apply:

(i) At any time, on notice to the commanded person, the serving party may move the court for the district where compliance is required for an order compelling production or inspection.

(ii) These acts may be required only as directed in the order, and the order must protect a person who is neither a party nor a party's officer from significant expense resulting from compliance.

(3) ***Quashing or Modifying a Subpoena.***

(A) *When Required.* On timely motion, the court for the district where compliance is required must quash or modify a subpoena that:

(i) fails to allow a reasonable time to comply;

(ii) requires a person to comply beyond the geographical limits specified in Rule 45(c);

(iii) requires disclosure of privileged or other protected matter, if no exception or waiver applies; or

(iv) subjects a person to undue burden.

(B) *When Permitted.* To protect a person subject to or affected by a subpoena, the court for the district where compliance is required may, on motion, quash or modify the subpoena if it requires:

(i) disclosing a trade secret or other confidential research, development, or commercial information; or

(ii) disclosing an unretained expert's opinion or information that does not describe specific occurrences in dispute and results from the expert's study that was not requested by a party.

(C) *Specifying Conditions as an Alternative.* In the circumstances described in Rule 45(d)(3)(B), the court may, instead of quashing or modifying a subpoena, order appearance or production under specified conditions if the serving party:

(i) shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship; and

(ii) ensures that the subpoenaed person will be reasonably compensated.

(e) Duties in Responding to a Subpoena.

(1) ***Producing Documents or Electronically Stored Information.*** These procedures apply to producing documents or electronically stored information:

(A) *Documents.* A person responding to a subpoena to produce documents must produce them as they are kept in the ordinary course of business or must organize and label them to correspond to the categories in the demand.

(B) *Form for Producing Electronically Stored Information Not Specified.* If a subpoena does not specify a form for producing electronically stored information, the person responding must produce it in a form or forms in which it is ordinarily maintained or in a reasonably usable form or forms.

(C) *Electronically Stored Information Produced in Only One Form.* The person responding need not produce the same electronically stored information in more than one form.

(D) *Inaccessible Electronically Stored Information.* The person responding need not provide discovery of electronically stored information from sources that the person identifies as not reasonably accessible because of undue burden or cost. On motion to compel discovery or for a protective order, the person responding must show that the information is not reasonably accessible because of undue burden or cost. If that showing is made, the court may nonetheless order discovery from such sources if the requesting party shows good cause, considering the limitations of Rule 26(b)(2)(C). The court may specify conditions for the discovery.

(2) ***Claiming Privilege or Protection.***

(A) *Information Withheld.* A person withholding subpoenaed information under a claim that it is privileged or subject to protection as trial-preparation material must:

(i) expressly make the claim; and

(ii) describe the nature of the withheld documents, communications, or tangible things in a manner that, without revealing information itself privileged or protected, will enable the parties to assess the claim.

(B) *Information Produced.* If information produced in response to a subpoena is subject to a claim of privilege or of protection as trial-preparation material, the person making the claim may notify any party that received the information of the claim and the basis for it. After being notified, a party must promptly return, sequester, or destroy the specified information and any copies it has; must not use or disclose the information until the claim is resolved; must take reasonable steps to retrieve the information if the party disclosed it before being notified; and may promptly present the information under seal to the court for the district where compliance is required for a determination of the claim. The person who produced the information must preserve the information until the claim is resolved.

(g) Contempt.

The court for the district where compliance is required—and also, after a motion is transferred, the issuing court—may hold in contempt a person who, having been served, fails without adequate excuse to obey the subpoena or an order related to it.

For access to subpoena materials, see Fed. R. Civ. P. 45(a) Committee Note (2013).

SCHEDLUE A

DEFINITIONS

1. The term "Communication," as used in Schedule A shall include, but not be limited to, any contact or act by which information or knowledge is transmitted or conveyed between two or more persons and includes, without limitation: (1) written contact, including but not limited to letters, memoranda, PowerPoint presentations, email, text message, facsimile, internet-based meetings, or other written or electronic documents or files; (2) oral contact, whether by face-to-face meetings, internet-based meetings, video conferences, telephonic conversations, or otherwise; and (3) nonverbal acts intended to communicate or convey any meaning, understanding or other message.

2. "Documents" shall include, but not be limited to, the original and/or any non-conforming copies of any and all written, printed, typed, graphic, photographic, visual or otherwise recorded material, and all microfilm, or electronic sound recording or transcripts thereof however produced or reproduced, including non-identical copies, whether different from the original by reason of any notation made on such copies or otherwise, writings, drawings, records and recordings of every kind and description, whether inscribed by hand or by mechanical, electronic, microfilm, photographic or other means, as well as audio or visual reproduction of all statements, conversations or events including, but not limited to, agreements, bids, bonds, bulletins, calendars and appointment books, checks, circulars, communications, contracts, correspondence, statements, telegrams, receipts, returns, summaries, data books, accounting records, including ledgers, vouchers and books of account, computer printouts, information storage, media diaries and diary entries, drawings and charts,

including additions and revisions, estimates, evaluations, financial statements and records, instructions, inter- and intra-office communications, invoices, job site reports, investigative reports, audits, logs, memoranda of any type, minutes of all meetings, notes of all types, orders, including change, proceed and purchase orders questionnaires and surveys, photographs, price sheets, records, results of investigations, schedules including additions and revisions, statistical records, reports, analyses and studies of any kind, tape recordings, including any form of any recording of any telephone or other conversation, interview, conference, or meeting, and all contract and working papers as well as drawings, papers and files. A reference herein to any one or more of these types of documents shall be construed to include all other types of documents without limitations.

3. Words used in the singular shall, where the context permits, include the plural, and words used in the plural shall, where the context permits, include the singular.

4. "You" and "your" refers to the person served with and responding to these requests.

5. "Roundup® litigation" refers to the multidistrict litigation captioned, *In re Roundup Products Liability Litigation,* Case No. 3:16-md-02741-CV (N.D. Cal.), in which individuals have asserted or will assert a claim against Monsanto Company ("Monsanto") asserting that the use of Monsanto's Roundup®-branded products has caused their non-Hodgkin's lymphoma ("NHL").

REQUESTS FOR PRODUCTION

As stated in the foregoing Notice, you are required to produce the following documents:

1. All documents provided to you, or that you have, related to the Roundup® and/or glyphosate and cancer including, but not limited to, NHL, that are not publicly available.

2. All studies, literature, materials, research files, publications, treatises or any other documents that are not publicly available that you have reviewed and upon which you rely and/or intend to rely upon as a basis for, or in any other way support, the opinions that you intend to offer in general causation phase of the Roundup® litigation, MDL 2741, or that were reviewed and/or considered by you in the course of formulating your opinions.

3. Your most recent curriculum vitae.

4. All billing records, invoices, or other documents reflecting time spent and/or fees and expenses charged by you (either directly or through your employer or other entity) in connection with the general causation phase of the Roundup® litigation, MDL 2741, and/or other consulting work regarding glyphosate, IARC Monograph 112, Roundup®, Intertek Scientific & Regulatory Consultancy, other glyphosate- based products.

5. Any retainer letter, contract, agreement, or other document setting forth the retention of you to work in the Roundup® litigation, MDL 2741.

6. A copy of all abstracts, articles, draft articles, books or book excerpts, presentations, power points of which you are an author, co-author, drafter or editor which has as all or part of its subject matter NHL, glyphosate, Roundup®, other glyphosate-based products

and/or IARC that are not publicly available. With respect to documents in this request relating to IARC, the time frame for the request is limited to 2014 to the present.

7. All documents and communications regarding glyphosate, NHL, Roundup®, and/or other glyphosate-based products with any of the following people, agencies and/or entities: Exponent, Failure Analysis Associates, CropLife America, Reuters, Glyphosate Task Force, Glyphosate Expert Advisory Panel, Food and Chemical Toxicology Journal, Critical Reviews in Toxicology, Joint Glyphosate Task Force, Toxicology Technical Working Group, Environmental Protection Agency (EPA), European Union (EU), European Food Safety Administration (EFSA), Intertek Scientific and Regulatory Consultancy, Intertek Expert Panel, International Agency for Research on Cancer (IARC), , Dr. William Fleming, Dr. Warren G. Foster, Dr. Jay Goodman, Dr. Lorelei Mucci, Dr. Jennifer Rider, and Dr. Thomas Rosol.

8. All draft and final spreadsheets, notes, tables, graphs or other documents showing the mathematical computations that form the bases in the report for the p-Values set forth in Appendix A, Tables A.1, A.2, A.3(i), A.4A, A.5, A.6. and A.7; the p-Values set forth in Appendix B, Tables B.1, B.2, B.3, B.4, B.5, B.6; the Exact Trend P-values and "P-Value[s] Adjusted for False Discovery Rate" set forth in Appendix C, Table C.1; and the Exact Trend P-values and "P-Value[s] Adjusted for False Discovery Rate" set forth in Appendix D, Table D.1.

9. Any documents and/or correspondence related to a statistical analysis or reanalysis carried out by Dr. Klaus Weber of data from the Kumar mouse study, as referenced on page 11 of the report, as well as any data used for those analyses that is not contained in the report or otherwise publicly available.

Dated: September 6, 2017

Respectfully submitted,

/s/ Robin Greenwald

Hollingsworth LLP

Eric G. Lasker
dir 202 898 5843
elasker@hollingsworthllp.com

August 31, 2016

PRIVILEGED AND CONFIDENTIAL

VIA ELECTRONIC MAIL

Dr. Chris Corcoran
Utah State University
3900 Old Main Hill
Logan, UT 84322

Re: Monsanto Roundup® Litigation

Dear Dr. Corcoran:

This letter confirms that Hollingsworth LLP ("HLLP"), on behalf of Monsanto Company ("Monsanto"), has retained you to provide expert consulting services to HLLP, for the purpose of assisting HLLP in representing Monsanto in connection with potential and/or actual litigation against Monsanto involving injuries allegedly caused by Roundup® and/or glyphosate ("the Litigation"). You acknowledge that you have received, and/or likely will receive, confidential information from HLLP and that you likely will generate work product (orally and/or in writing) to assist us in representing Monsanto in the Litigation. You agree that you will maintain all information exchanged between HLLP and you (whether orally or in writing) as strictly confidential and privileged, unless we inform you, at some time in the future, that certain information needs to be disclosed in the Litigation. You also agree to maintain the fact that you have been retained by HLLP as strictly confidential and privileged, unless we inform you, at some time in the future, that your identity as HLLP's expert has been disclosed in the Litigation. Furthermore, you agree to not do any consulting or other work for any other corporation, law firm, or person with respect to any actual or potential legal claims involving Roundup® and/or glyphosate. You will be compensated at your standard hourly rate for time spent working with HLLP on the Litigation, namely $250.00 per hour.

Hollingsworth LLP

If you agree to these terms, please sign the letter below and send it back to me. We look forward to working with you.

Sincerely,

Eric G. Lasker /JB

Eric G. Lasker

SEEN AND AGREED:

By: _____
Dr. Chris Corcoran

INVOICE

Christopher D. Corcoran
[redacted]

Date: 01/20/17
INVOICE #

Hollingsworth LLC
1350 I Street, N.W.
Washington, D.C. 20005

Hollingsworth contacts	Job	Hourly Rate	SS# or Tax ID
John Kalas, Eric Lasker	Glyphosate – Statistical Consulting	$250	[redacted]

Date	Description	Hours	Line Total
08/16/16	Teleconference	1	$250
09/14/16	Research/Reading	4	$1000
09/17/16	Research/Reading	4	$1000
09/19/16	Teleconference	1	$250
10/15/16	Research/Reading	4	$1000
10/20/16	Research/Reading	4	$1000
10/22/16	Research and Data Analysis	6	$1500
11/01/16	Teleconference	1	$250
11/05/16	Data Analysis and Report	4	$1000
11/10/16	Data Analysis and Report	5	$1250
11/17/16	Data Analysis and Report	3	$750
11/18/16	Data Analysis and Report	4	$1000
11/22/16	Teleconference	1	$250
12/06/16	Data Analysis and Report	6	$1500
12/09/16	Data Analysis and Report	5	$1250
12/10/16	Data Analysis and Report	5	$1250
12/13/16	Data Analysis and Report	5	$1250
12/14/16	Reading and Research	5	$1250
12/15/16	Meeting in SLC UT with Eric L.	3	$750
12/17/16	Research/Data Analysis	5	$1250
12/21/16	Research/Data Analysis	3	$750
12/22/16	Research/Data Analysis	4	$1000
12/27/16	Research/Data Analysis	3	$750
01/17/17	Research/Data Analysis	6	$1500
01/18/17	Research/Data Analysis	4	$1000
01/20/17	Teleconference	1	$250
		Total	$24,250

EXHIBIT 21-4
WIT: Corcoran
DATE: 9-20-17
C. Campbell, RDR CRR CSR #13921

INVOICE

Christopher D. Corcoran
[redacted]

Date 05/20/17
INVOICE #002

Hollingsworth LLC
1350 I Street, N.W.
Washington, D.C. 20005

Hollingsworth contacts	Job	Hourly Rate	SS# or Tax ID
John Kalas, Eric Lasker	Glyphosate – Statistical Consulting	$250	[redacted]

Date	Description	Hours	Line Total
02/10/17	Data Analysis and Report	2	$500
02/24/17	Data Analysis and Report	4	$1000
02/25/17	Data Analysis and Report	4	$1000
03/01/17	Data Analysis and Report	3	$750
03/03/17	Data Analysis and Report	2	$500
03/07/17	Data Analysis and Report	4	$1000
03/08/17	Data Analysis and Report	5	$1250
03/09/17	Data Analysis and Report	8	$2000
03/10/17	Meeting in SLC UT with John K	4	$1000
03/15/17	Data Analysis and Report	6	$1500
03/20/17	Data Analysis and Report	8	$2000
04/08/17	Data Analysis and Report	9	$2250
04/10/17	Data Analysis and Report	8	$2000
04/12/17	Teleconference	1	$250
04/18/17	Data Analysis and Report	6	$1500
04/20/17	Data Analysis and Report	5	$1250
04/22/17	Data Analysis and Report	5	$1250
04/24/17	Data Analysis and Report	6	$1500
04/25/17	Teleconference	1	$250
04/27/17	Data Analysis and Report	6	$1500
04/28/17	Teleconference	1	$250
05/04/17	Plaintiff Expert Report – Research and Data Analysis	4	$1000
05/05/17	Teleconference	1	$250
05/06/17	Plaintiff Expert Report – Research and Data Analysis	4	$1000
05/08/17	Plaintiff Expert Report – Research and Data Analysis	5	$1250
05/12/17	Plaintiff Expert Report – Research and Data Analysis	3	$750
05/15/17	Data Analysis and Report	8	$2000
05/16/17	Data Analysis and Report	10	$2500

05/17/17	Data Analysis and Report	8	$2000
05/18/17	Data Analysis and Report	9	$2250
05/19/17	Data Analysis and Report	10	$2500
05/20/17	Data Analysis and Report	10	$2500
		Total	$42,500

INVOICE

Christopher D. Corcoran
[redacted]

Date 05/20/17
INVOICE #002

Hollingsworth LLC
1350 I Street, N.W.
Washington, D.C. 20005

Hollingsworth contacts	Job	Hourly Rate	SS# or Tax ID
John Kalas, Eric Lasker	Glyphosate – Statistical Consulting	$250	[redacted]

Date	Description	Hours	Line Total
05/21/17	Data Analysis and Report	8	$2000
05/22/17	Data Analysis and Report	10	$2500
05/23/17	Data Analysis and Report	10	$2500
05/24/17	Data Analysis and Report	12	$3000
05/25/17	Meeting with John and Eric, D.C.	6	$1500
05/25/17	Data Analysis and Report	5	$1250
05/26/17	Data Analysis and Report	8	$2000
05/27/17	Data Analysis and Report	8	$2000
05/31/17	Teleconference with John and Eric	1	$250
06/05/17	Data Analysis and Report	8	$2000
06/07/17	Data Analysis and Report	8	$2000
06/09/17	Teleconference with John and Eric	1	$250
06/10/17	Data Analysis and Report	5	$1250
06/12/17	Data Analysis and Report	3	$750
06/14/17	Data Analysis and Report	5	$1250
06/15/17	Data Analysis and Report	6	$1500
06/16/17	Data Analysis and Report	4	$1000
06/17/17	Data Analysis and Report	5	$1250
06/19/17	Teleconference with John and Eric	1	$250
06/25/17	Data Analysis and Report	4	$1000
06/26/17	Meeting with John, Logan UT	5	$1250
07/10/17	Teleconference with John and Eric	1	$250
07/11/17	Data Analysis and Report	5	$1250
07/14/17	Teleconference with John and Eric	1	$250
07/14/17	Data Analysis and Report	4	$1000
07/15/17	Data Analysis and Report	4	$1000
07/16/17	Data Analysis and Report	5	$1250
07/17/17	Data Analysis and Report	4	$1000

07/18/17	Data Analysis and Report	7	$1750
07/19/17	Data Analysis and Report	4	$1000
07/20/17	Meeting with John and Eric, SLC UT	4	$1000
		Total	$40,500

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REVIEW ARTICLE

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

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

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

Abstract

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

Keywords

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

History

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Table of Contents

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Introduction

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

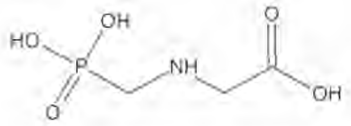

Figure 1. Structure of glyphosate acid.

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

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

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

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

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

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

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

DOI: 10.3109/10408444.2014.1003423

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

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

Absorption, distribution, metabolism and excretion of glyphosate

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

Toxicological properties of glyphosate

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

Genotoxicity

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

Epidemiology

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

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

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

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

Chronic toxicity studies

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

Dog chronic studies

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

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

Rat chronic studies

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

DOI 10.3109/10408444.2014.1003423

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

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

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

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

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

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

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

Carcinogenicity studies

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

Rat carcinogenicity

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

Study 1 (Monsanto 1981)

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

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

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

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

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

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Table 4. Study 1 – Pituitary tumor findings.

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

B benign, *M* malignant

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

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

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

Study 2 (Monsanto 1990)

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

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

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

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

B benign, *M* malignant

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

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

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

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

Study 3 (Cheminova 1993a)

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

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

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

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

B benign, *M* malignant

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

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

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

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

Study 4 (Feinchemie Schwebda 1996)

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

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

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

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

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

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

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

B benign, *M* malignant

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

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

Study 5 (Excel 1997)

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

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

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

Study 6 (Arysta Life Sciences 1997b)

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

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

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

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

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

Study owner:	Arysta Life Sciences (1997b)			
Reliability/Justification:	1 Study performed according to GLP and OECD guideline requirements, with no deviations.			
Substance:	Glyphosate (94.6–97.6% pure)			
Species/Strain:	Rat/Sprague-Dawley, groups of 50 ♂ and 50 ♀; satellite groups of 30 ♂ and 30 ♀for interim investigations			
Administration route:	Diet			
Concentration:	0, 3000, 10 000, 30 000 ppm diet (♂ about 0, 104, 354, 1127 mg/kg bw/day; ♀ about 0, 115, 393, 1247 mg/kg bw/day)			
Duration:	2 years			
Findings:	3000 ppm diet: NOAEL (♂+♀)			
	10 000 ppm diet: cecum weight↑, distension of cecum, loose stool, follicular hyperkeratosis and/or folliculitis/follicular abscess of the skin, body weight ↓			
Select neoplasms:	Pituitary adenoma, skin keratoacanthoma (males), mammary gland fibroadenoma (females)			
Tumor		Dose (mg/kg bw/day)		
Males	0	104	354	1127
Findings for dead and moribund sacrificed animals (Table 25–10)				
Pituitary anterior adenoma – B	22/32 (69%)	21/30 (70%)	*14/32 (44%)	18/21 (86%)
Skin keratoacanthoma – B	2/32 (6%)	1/30 (3%)	0/32	1/21 (5%)
Findings for animals sacrificed at termination (after 104 weeks, Table 25–8)				
Lung adenoma – B	0/18	2/20 (10%)	1/18 (6%)	3/29 (10%)
Pituitary anterior adenoma – B	13/18 (72%)	14/20 (70%)	13/18 (72%)	21/29 (72%)
Pituitary adenoma in intermediate part – B	0/18	1/20 (5%)	0/18	0/29 (0%)
Skin keratoacanthoma – B	1/18 (6%)	2/20 (10%)	0/18	6/29 (21%)
Tumor		Dose (mg/kg bw/day)		
Females	0	115	393	1247
Findings for dead and moribund sacrificed animals				
Pituitary anterior adenoma – B	34/35 (97%)	29/31 (94%)	28/33 (82%)	31/36 (86%)
Thyroid follicular adenoma – B	0/35	2/31 (6%)	0/32	0/36
Mammary gland fibroadenoma – B	13/35 (37%)	14/31 (45%)	12/34 (35%)	20/36 (56%)
Findings for animals sacrificed at termination				
Pituitary anterior adenoma – B	12/15 (80%)	19/19 (100%)	12/16 (75%)	13/14 (93%)
Mammary gland fibroadenoma – B	10/15 (67%)	13/19 (68%)	12/16 (75%)	10/14 (71%)

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

Study 7 (Syngenta 2001)

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

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

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

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

Study 8 (Nufarm 2009b)

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

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

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

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

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

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

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

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

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

B benign, *M* malignant

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

Study 9 Publication (Chruscielska et al. 2000a)

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

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

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

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

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

Mouse carcinogenicity

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

Study 10 (Monsanto 1983)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Study 11 (Cheminova 1993b)

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

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

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

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

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

B benign, *M* malignant

Study 12 (Arysta Life Sciences 1997a)

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

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

Study 13 (Feinchemie Schwebda 2001)

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

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

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

B benign, *M* malignant

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

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

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

	Historical controls		Dose (mg/kg bw/day)			
			0	15.0	151	1467
Females						
Mortality	12/50–20/50		16/50 (7)	16/50 (7)	20/50 (2)	20/50 (3)
Findings for dead and moribund sacrificed animals						
Bronchiolar/alveolar adenoma – B	–	–	0/16	0/16	1/20 (5%)	2/20 (10%)
Lymphoma – M	49/77	63.6% [0–100]	9/16 (56.0%)	10/16 (63.0%)	13/20 (65.0%)	12/20 (60.0%)
Findings in animals sacrificed at termination						
Bronchiolar/alveolar adenoma – B			1/34 (3%)	0/0	1/1 (100%)	1/30 (3%)
Lymphoma – M	50/175	28.9% [2043]	9/34 (26.5%)	10/30 (29.4%)	6/30 (20.0%)	*13/28 (43.3%)
Total animals						
Bronchiolar/alveolar adenoma – B			1/50 (2%)	0/16	2/21 (10%)	3/50 (6%)
Lymphoma – M	99/250	39.6% [1458]	18/50 (36.0%)	20/50 (40.0%)	19/50 (38.0%)	*25/50 (50.0%)

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

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

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

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

Study 14 (Nufarm 2009a)

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

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

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

B benign, *M* malignant

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

Select neoplasm	Tumor Incidence/number of animals examined, by dose (mg/kg bw/day)							
	[b]300	[a]814	[c]838	[c]946	[b]1000	[d]1454	[c]4348	[a]4841
Bronchiolar-alveolar adenoma	11/50	9/50	[§]13/50	[§]4/51	13/50	1/50	[§]11/50	9/50
Bronchiolar-alveolar adenocarcinoma	NF	2/50	[§]6/50	[§]11/51	NF	NF	[§]4/50	1/50
Bronchiolar-alveolar carcinoma	8/50	NF	NF	NF	9/50	1/50	NF	NF
Hepatocellular adenoma	11/50	1/50	15/50	2/51	9/50	3/50	7/50	0/50
Hepatocellular carcinoma	6/50	0/50	3/50	4/51	7/50	2/50	1/50	2/50
Malignant lymphoma	1/1	[#]4/50	0/50	5/51	6/8	19/50	6/50	[#]2/50
Myeloid leukemia	NF	NF	NF	0/51	NF	1/50	NF	NF

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

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

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

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

Select neoplasm	Tumor incidence/number of animals examined, by dose (mg/kg bw/day)							
	[b]300	[c]787	[c]946	[a]955	[b]1000	[d]1467	[c]4116	[a]5874
Bronchiolar-alveolar adenoma	3/50	[§]12/50	[§]2/51	10/49	6/50	3/50	[§]5/50	1/50
Bronchiolar-alveolar adenocarcinoma	NF	[§]3/50	[§]3/51	4/49	NF	NF	[§]1/50	4/50
Bronchiolar-alveolar carcinoma	1/50	NF	NF	NF	5/50	0/50	NF	NF
Malignant lymphoma	9/12	8/50	11/51	[#]6/50	13/14	25/50	7/50	[#]10/50
Myeloid leukemia	NF	0/50	0/51	NF	NF	1/50	1/50	NF
Pituitary adenoma	0/23	0/50	2/51	0/44	[–]3/50	1/48	0/50	0/37

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

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

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

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

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

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

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

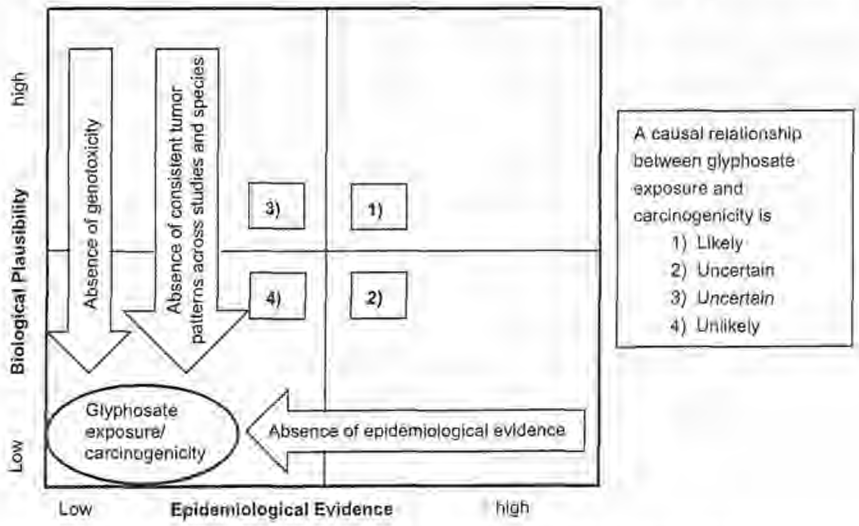

Figure 2. Likelihood of glyphosate carcinogenicity based on experimental and epidemiological data; a causal inference grid as proposed by Adami et al. (2011) to utilize both toxicological and epidemiological data

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

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

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

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Declaration of interest

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

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Supplementary material available online

Data Supplementary Study 1–14.

Utah State University

Cytel STATISTICAL SOFTWARE & SERVICES

New StatXact Toolkit for Correlated Data

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Example 1 – Developmental Toxicology Experiment with Multinomial Response

Response counts for 48 litters of mice with respect to (Dead, Malformed, Normal):

Dose=0.0 g/kg			Dose=3.0 g/kg		
(1,0,7)	(0,0,14)	(0,0,13)	(0,4,3)	(1,9,1)	(0,4,8)
(0,0,10)	(0,1,15)	(1,0,14)	(1,11,0)	(0,7,3)	(0,9,1)
(1,0,10)	(0,0,12)	(0,0,11)	(0,3,1)	(0,7,0)	(0,1,3)
(0,0,8)	(1,0,6)	(0,0,15)	(0,12,0)	(2,12,0)	(0,11,3)
(0,0,12)	(0,0,12)	(0,0,13)	(0,5,6)	(0,4,8)	(0,5,7)
(0,0,10)	(0,0,10)	(1,0,11)	(2,3,9)	(0,9,1)	(0,0,9)
(0,0,12)	(0,0,13)	(1,0,14)	(0,5,4)	(0,2,5)	(1,3,9)
(0,0,13)	(0,0,13)	(1,0,14)	(0,2,5)	(0,1,11)	
(0,0,14)					

TOTAL: (2.3%, 0.3%, 97.4%) (3.0%, 55.6%, 41.5%)

Example 2 – Genetics of Alzheimer's Disease (AD)

Sibships of size 3 from the Cache County Study on Memory, Health, and Aging.
Question: dose-response effect with respect to number of APOE ε4 alleles?

		# $\epsilon 4$ Alleles		
Family		0	1	2
1	AD	0	0	0
	No AD	1	2	0
2	AD	0	1	0
	No AD	0	2	0
⋮				
20	AD	0	0	1
	No AD	2	0	0

Overall: 1/33 (2.6%) AD rate for 0 ε4, 8/21 (38.1%) for 1 ε4, and 1/1 (100.0%) for 2 ε4.

Example 3 – Congenital Ophthalmologic Defects

Number of rejected corneal grafts out of total grafts received among 9 children with congenital hereditary endothelial dystrophy (CHED). With all four rejections observed in the older age group, what can we say about the effect of age on the probability of rejection?

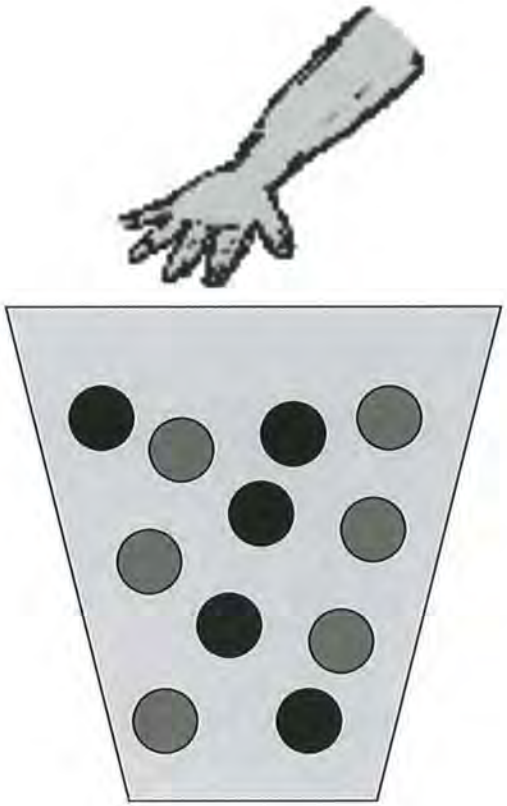
Age at Diagnosis (years)	
< 3	≥ 3
0/2	0/2
0/2	1/2
0/2	1/2
0/2	1/1
	1/1

Fisher's Exact Test

R.A. Fisher (1890-1962)

An analogue of the chi-square test of independence for a two-way table. With an exact test, we do not need to rely on the assumption of large-sample normality (in particular, a large-sample chi-square distribution).

Sampling and Permutation Tests



Question: What's the probability that you reach into this bin to pull out 4 balls at random, and two of them are red?

Answer: There a ${}_{11}C_4$ total ways of choosing 4 balls from 11, where order doesn't matter. Of these possibilities, there are $({}_6C_2)({}_5C_2)$ ways of choosing exactly two red and two black. So

$$P(\text{Two Red}) = \frac{({}_6C_2)({}_5C_4)}{({}_{11}C_4)}.$$

Hypergeometric Distribution

In general, suppose that we have a bin with N balls, of which r are red and $N - r$ are black. We select m balls from the bin. What's the probability that we observe exactly x balls in this sample?

From the previous slide, we can see the answer is

or the hypergeometric mass function.

The Tea-Tasting Experiment

How does this relate to exact inference? While having tea with some colleagues, a woman in Fisher's company claimed that she could tell by taste if a cup of tea had been prepared with the tea poured first or the milk.

Fisher proposed the following experiment: present the woman with 8 cups of tea in random order, four of which had tea added first and four milk.

What if she picked four correctly? Three? Would either case provide evidence that her claim had merit?

Computing a Probability for this Experiment

To summarize the result of this experiment, we can use a 2 x 2 table, like this:

Truth	Decision		Total
	Tea first	Milk first	
Tea First	3	1	4
Milk First	1	3	4
Total	4	4	8

What's the probability of this result? Suppose we assume the number of tea-first cups is fixed. If the woman's claim is false, then picking tea-first cups correctly is like picking four red balls at random out of a bag containing a fixed number of red and black.

What's the "exact" p-value?

Assuming that the taster can't tell the difference (the null hypothesis), each possible table has associated with it a hypergeometric probability.

Note that assuming a fixed number of tea-first cups, these are the following potential outcomes of the experiment:

0	4	1	3	2	2	3	1	4	0
4	0	3	1	2	2	1	3	0	4
0.014		0.229		0.514		0.229		0.014	

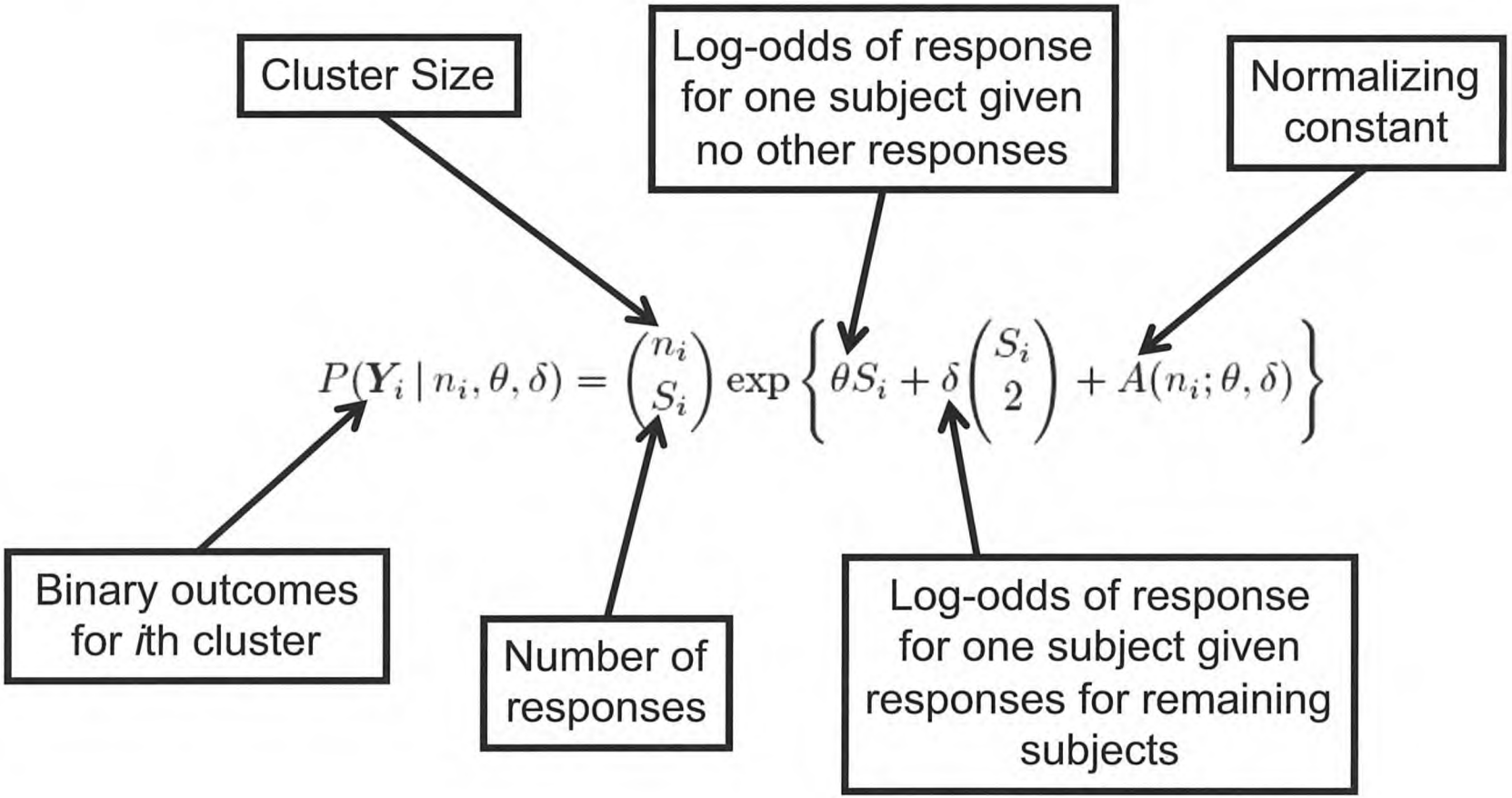
As always, the p-value represents the probability that an outcome is as extreme as the observed result, given the null hypothesis is true. In this case:

P-value = P(Pick 3 correctly) + P(Pick 4 Correctly) = 0.229 + 0.014 = 0.243.

Quadratic Exponential Model (QEM)

Gourieroux (1984), Zhao and Prentice (1990)

- Loglinear model with all three-way and higher association parameters set to zero.
- For clustered binomial data (with N clusters, indexed by i):



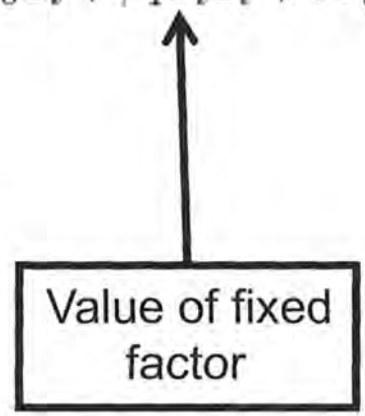
Comparing Response Rates With Respect to Fixed Factors

- Alternative formulation using -1/1 coding for failure/success (Molenberghs and Ryan, 1999):

$$P(\boldsymbol{Y}_i \mid n_i, \theta, \delta) = \binom{n_i}{S_i} \exp\{\theta S_i + \delta S_i(n_i - S_i) + A(n_i; \theta, \delta)\}$$

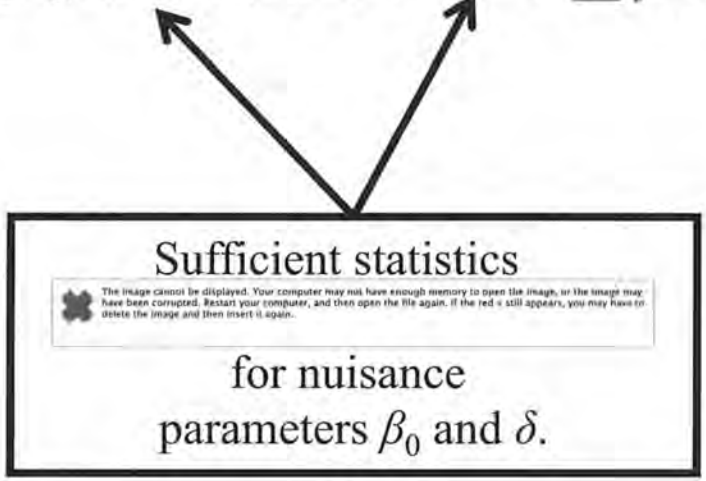
- Using logit link:

$$P(\boldsymbol{Y}_i \mid n_i, x_i, \beta_0, \beta_1, \delta) = \binom{n_i}{S_i} \exp\{\beta_0 S_i + \beta_1 x_i S_i + \delta S_i(n_i - S_i) + A(n_i, x_i; \beta_0, \beta_1, \delta)\}$$



Likelihood and Conditioning

$$\left[\prod_{i=1}^{N}\binom{n_i}{S_i}\right]\exp\{\beta_0 T_0+\beta_1 T_1+\delta U+\textstyle\sum_i A(n_i,x_i;\beta_0,\beta_1,\delta)\}$$



EXACT TEST (Corcoran et al., 2001):

- Condition on sufficient statistics T_0 and U (and cluster sizes) to eliminate nuisance parameters β_0 and δ. Denote this set of tables by Γ.
- Order all tables in Γ according to test statistic $T_1 = \Sigma_i x_i S_i$.
- Under the hypothesis of no group differences (i.e., $\beta_1 = 0$), distribution of T_1 is a hypergeometric distribution, free of all unknown parameters.

Illustration: Corneal Graft Data

Reject	Age Group, or $I\{< 3$ years$\}$									Total
	0	0	0	0	1	1	1	1	1	
Yes	0	0	0	0	0	1	1	1	1	4
No	2	2	2	2	2	1	1	0	0	12
Total	2	2	2	2	2	2	2	1	1	16

Observed Sufficient Statistics: $t_0 = 4$, $t_1 = 4$, $u = 2$

2	2	0	0	0	0	0	0	0
0	0	2	2	2	2	2	1	1

→ $t_0 = 4$, $u = 0$ X

1	2	0	0	1	0	0	0	0
1	0	2	2	1	2	2	1	1

→ $t_0 = 4$, $u = 2$ ★

Comparing Two Ordered Multinomials with Clustering

- We have C categories, with N clusters.
- An exponential-family likelihood (adapted from Heagerty and Zeger, 1996):

$$\left[\prod_{i=1}^{N}\binom{n_i}{y_{i1}\ldots y_{iC}}\right]\exp\left\{\sum_{j=1}^{C}\beta_j\sum_{i=1}^{N}y_{ij}+\sum_{j<k}\delta_{jk}\sum_{i=1}^{N}y_{ij}y_{ik}+\sum_{i=1}^{N}A_i(\beta_1,\ldots,\beta_C,\delta_{12},\ldots,\delta_{C-1,C},n_i)\right\}$$

Multinomial counts within cluster

- Use Wilcoxon-type test statistic $T = \Sigma_{i,j}\, u_j y_{ij}\, I(i\text{th cluster in treatment group})$.
  - u_j's represent increasing scores across multinomial categories.
  - $I(\cdot)$ is an indicator function.

Within-Cluster Covariates

- For both ordered binomials and multinomials, conditioning on the sufficient statistics is the same.

- Need to also condition on numbers of subjects within each cluster assigned to each treatment group.

- Test statistics change slightly: for both binomials and multinomials we need to sum over subgroups within cluster – defined by treatment level.

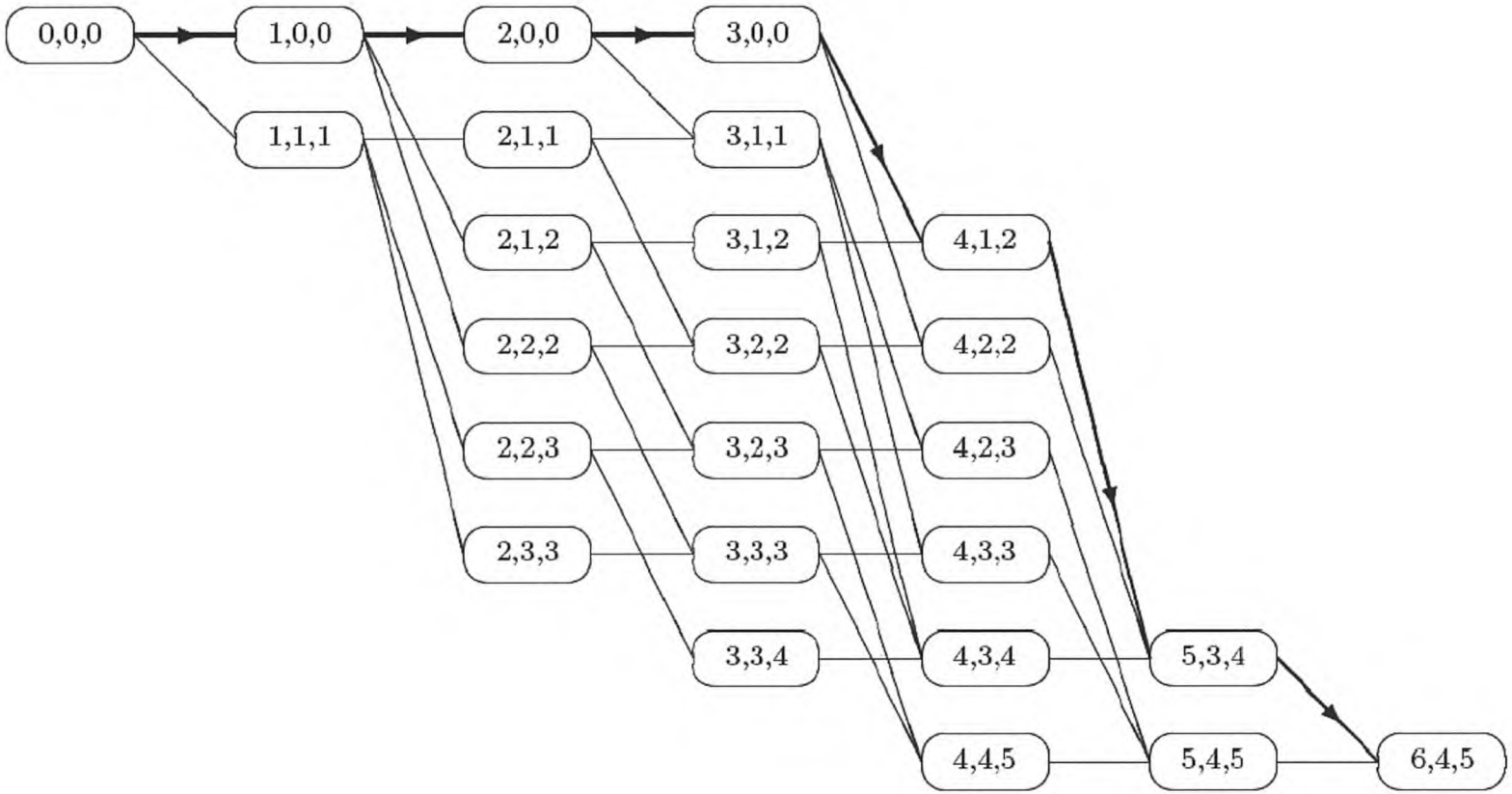
Computational Efficiency

- For dementia data: thousands of tables.
- Explicit enumeration too inefficient.
- Implicit enumeration: network algorithm.

Network Example

Suppose there are 6 clusters, divided equally in three dose groups, with cluster sizes (1,2,1,2,2,1), and observed number of responses (0,0,0,1,2,1).

Sufficient statistics are given by $T_0 = 4$ and $U = 5$. For dose scores of 0, 1, and 2, the test statistic is given by $T_1 = 6$.



Correlated Data Procedures in StatXact

SBIR Phases I and II: correlated data module for StatXact.

Clustered-data analogues:

- trend tests for ordered binomials and two ordered multinomials,
- Kruskal-Wallis test,
- Fisher's exact test,
- stratified 2 x 2 tables.

Also:

- Exact test for clustering,
- Exact trend test for multiple binomial outcomes.

Example 1 – Developmental Toxicology Experiment with Multinomial Response

Response counts for 48 litters of mice with respect to (Dead, Malformed, Normal):

Dose=0.0 g/kg			Dose=3.0 g/kg		
(1,0,7)	(0,0,14)	(0,0,13)	(0,4,3)	(1,9,1)	(0,4,8)
(0,0,10)	(0,1,15)	(1,0,14)	(1,11,0)	(0,7,3)	(0,9,1)
(1,0,10)	(0,0,12)	(0,0,11)	(0,3,1)	(0,7,0)	(0,1,3)
(0,0,8)	(1,0,6)	(0,0,15)	(0,12,0)	(2,12,0)	(0,11,3)
(0,0,12)	(0,0,12)	(0,0,13)	(0,5,6)	(0,4,8)	(0,5,7)
(0,0,10)	(0,0,10)	(1,0,11)	(2,3,9)	(0,9,1)	(0,0,9)
(0,0,12)	(0,0,13)	(1,0,14)	(0,5,4)	(0,2,5)	(1,3,9)
(0,0,13)	(0,0,13)	(1,0,14)	(0,2,5)	(0,1,11)	
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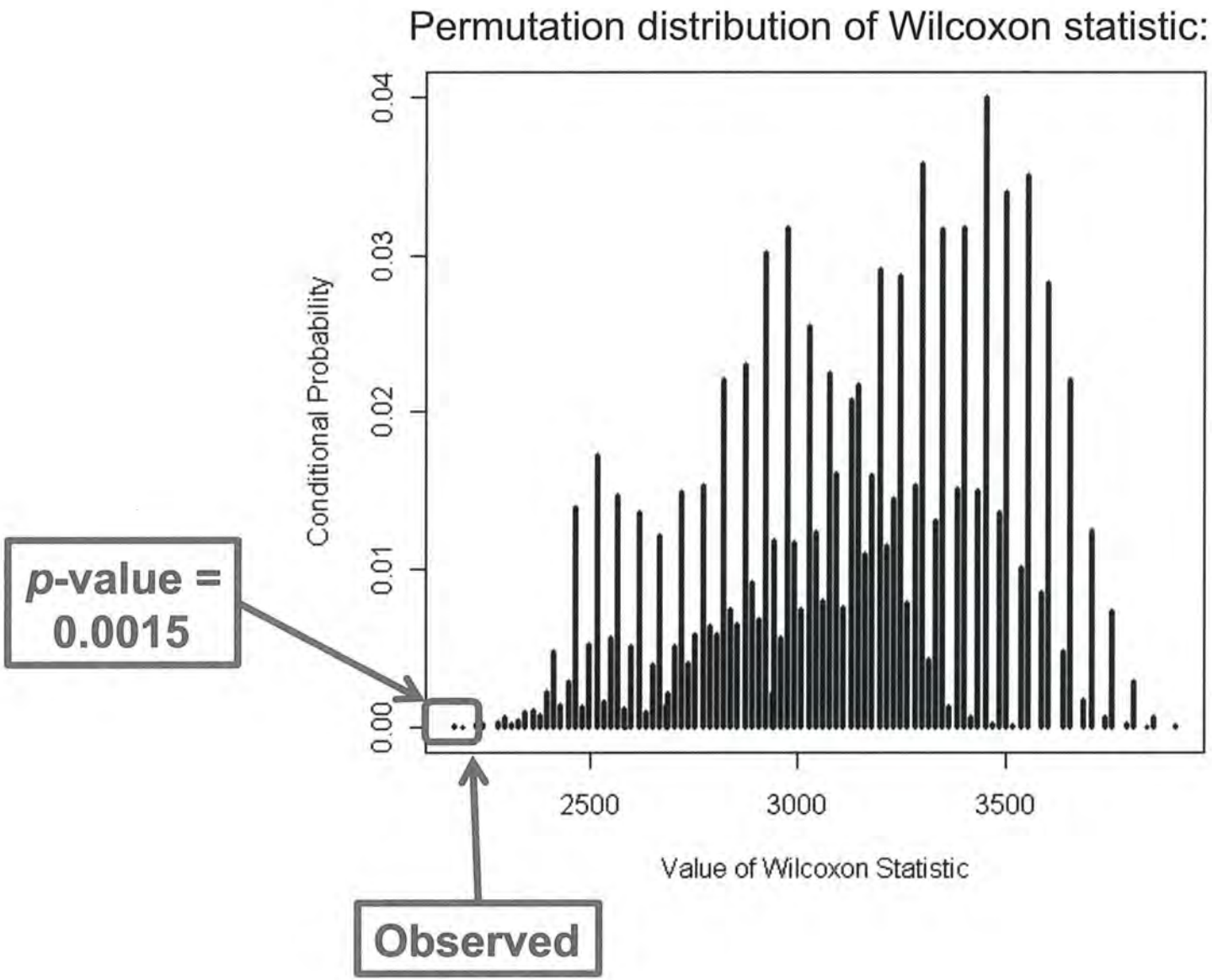
TOTAL: (2.3%, 0.3%, 97.4%) (3.0%, 55.6%, 41.5%)

Example 1 – Developmental Toxicology



Example 2 – Genetics of Alzheimer's Disease (AD)

Sibships of size 3 from the Cache County Study on Memory, Health, and Aging.
Question: dose-response effect with respect to number of APOE ε4 alleles?

		# $\epsilon 4$ Alleles		
Family		0	1	2
1	AD	0	0	0
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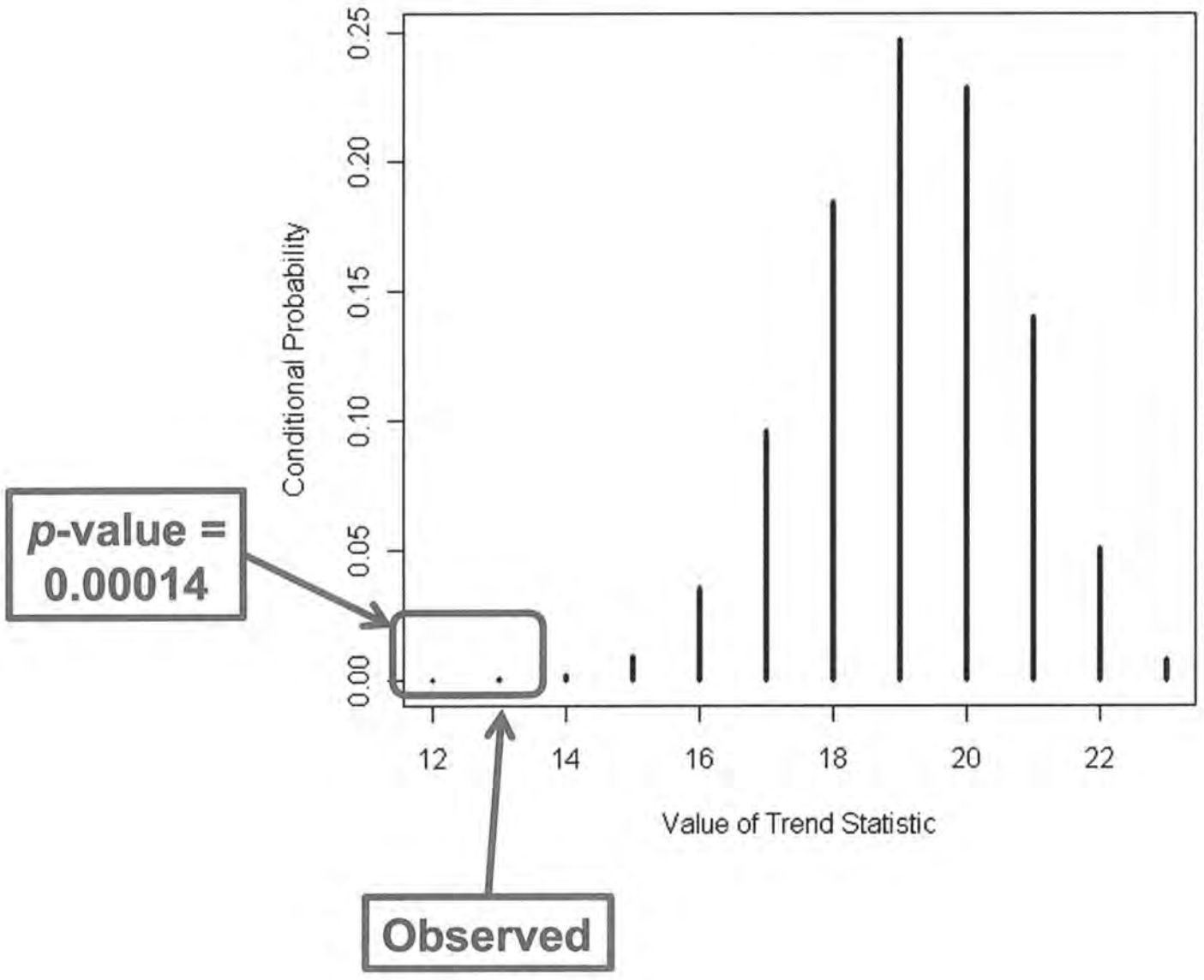
⋮				
20	AD	0	0	1
	No AD	2	0	0

Overall: 1/33 (2.6%) AD rate for 0 ε4, 8/21 (38.1%) for 1 ε4, and 1/1 (100.0%) for 2 ε4.

Example 2 – Genetics of Alzheimer's

Permutation distribution of trend statistic:



Alternatives

- Under independence:
  - *p*-value is 1.92E-12 for toxicology data.
  - *p*-value is 0.00011 for Alzheimer's data.

- What if we stratify on cluster?
  - *p*-value is 0.012 for Alzheimer's data.

Do we still have to worry about small samples and asymptotic approximations?

Many "big data" problems are really just a large samples of small data problems

Genomewide association studies with high-density SNP panels:

- *1M (or more) hypothesis tests – none* of these two-way tables produce highly discrete testing distributions?

- *Bonferroni-corrected p-values* – is it reasonable to use a chi-square approximation for a critical region of 10^{-8}?

Thanks to…

- The NIH: National Institute of Research Resources award RR019052.

- Cytel Software Corporation.

Expert Report
Christopher J. Portier, Ph.D.

Charge

Glyphosate acid is a colorless, odorless, crystalline solid. Glyphosate is the term used to describe the salt that is formulated by combining the deprotonated glyphosate acid and a cation (isopropylamine, ammonium, or sodium). This expert report is intended to review the available scientific evidence relating to the potential of glyphosate and glyphosate-based formulations (GBFs), including Roundup®, to cause Non-Hodgkin's Lymphoma (NHL) in humans.

Qualifications

I received an undergraduate degree in mathematics in 1977 from Nicholls State University and a Master's degree and Ph.D. in biostatistics from the University of North Carolina School of Public Health in 1979 and 1981 respectively. My Ph.D. thesis addressed the optimal way to design a two-year rodent carcinogenicity study to assess the ability of a chemical to cause cancer[1, 2]; the optimal dosing pattern from my thesis is still used by most researchers. My first employment following my doctoral degree was a joint appointment at the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) to conduct research on the design and analysis of experiments generally employed in toxicology. After 5 years with NIEHS/NTP, I developed my own research group which eventually became the Laboratory of Quantitative and Computational Biology and then the Laboratory of Computational Biology and Risk Assessment (LCBRA). One highlight during this period was the development of the Poly-3 Test for survival adjustment of data from two-year carcinogenicity studies in rodents[3, 4]; this test is used as the main method of analysis of these studies by the NTP and many others. We also did a complete analysis of the historical controls animals from the NTP studies[5, 6]. The LCBRA focused on the application of computational tools to identify chemicals that are toxic to humans, to develop tools for understanding the mechanisms underlying those toxicities and to quantify the risks to humans associated with these toxicities. The main toxicological focus of the LCBRA was cancer and my laboratory developed many methods for applying multistage models to animal cancer data and implemented the use of these models in several experimental settings[7-19]. In my last few years at the NIEHS/NTP, my research focus expanded to the development of tools for evaluating the response of complex experimental and human systems to chemicals[20-24] and the name of the laboratory shifted to Environmental Systems Biology.

Over my 32 years with the NIEHS/NTP, I was involved in numerous national priority issues that went beyond my individual research activities. After Congress asked NIEHS to work with the Vietnamese government to address the hazards associated with Agent Orange use during the Vietnamese War, I was given the responsibility of working with

my counterparts in Vietnam to build a research program in this area[25]. Congress also tasked NIEHS with developing a research program (EMF-RAPID) to address concerns about the risks to humans from exposure to power lines and to report back to Congress on what we found. I was in charge of evaluating all research developed under this program and was responsible for the final recommendations to Congress on this issue[26-28].

While at the NIEHS/NTP, I also had administrative positions that relate to my qualifications. From 2000 to 2006 I was the Director of the Environmental Toxicology Program (ETP) at NIEHS. The ETP included all of the toxicology research laboratories within the NIEHS Intramural Research Program. It was my responsibility to ensure the research being done was pertinent to the mission of the NIEHS, addressing high priority concerns about toxic substances and human health and that the NIEHS had adequate resources to complete this research.

During this time I was also Associate Director of the NTP, a position in which I was the scientific and administrative director of the NTP (The Director of the NTP was also the NIEHS Director and gave me complete autonomy in the management and science of the NTP). These two positions were historically always combined at the NIEHS and the NTP so that one person was in charge of all toxicological research at the NIEHS/NTP. The NTP is the world's largest toxicology program, routinely having 15 to 25 active two-year carcinogenicity studies, numerous genetic toxicology studies and many other toxicological studies being conducted at any given time. The NTP two-year carcinogenicity studies and their technical reports are also considered the "gold standard" of cancer studies due to their extreme high quality, their tremendous utility in evaluating human health hazards and the rigor and transparency they bring to the evaluation of the data. All data from NTP two-year cancer studies are publicly available including data on individual animals and images from the pathology review of each animal. The NTP is also home to the Report on Carcinogens, the US Department of Health and Human Services official list of what is known or reasonably anticipated to be carcinogenic to humans. It was my responsibility to decide what items eventually went onto this list while I was Associate Director of the NTP. In 2006, I became an Associate Director of the NIEHS, a senior advisor to the director and the director of the Office of Risk Assessment Research (ORAR). ORAR focused on stimulating new research areas on the evaluation of health risks from the environment and addressed major risk assessment issues on behalf of the NIEHS/NTP. For example, in this capacity, I lead a multiagency effort to understand the health risks to humans from climate change and to develop a research program in this area[29].

I left the NIEHS/NTP in 2010 to become the Director of the National Center for Environmental Health (NCEH) at the Centers for Disease Control and Prevention and simultaneously Director of the Agency for Toxic Substances and Disease Registry (ATSDR). NCEH does research and supports activities aimed at reducing the impact of environmental hazards on public health. One well-respected research effort of the NCEH is the National Biomonitoring Program. This program tests for the presence of hundreds of chemicals in human blood and urine in a national sample of people in the

United States. ATSDR advices the Environmental Protection Agency (EPA) and communities on the potential health impacts from toxic waste dump sites (superfund sites). ATSDR is required by law to produce ToxProfiles. These are comprehensive reviews of the scientific literature for specific chemicals generally found at superfund sites. They also provide an assessment of the safety of these chemicals. As part of my activities at ATSDR, I began a modernization of the ToxProfiles to use systematic review methods in their assessments; this effort was linked to a similar effort that I had helped to implement at the NIEHS/NTP.

Aside from my official duties in my various federal jobs, I also served on numerous national and international science advisory panels. Most notable, for my qualifications for this statement, are my serving as Chair from 2005 to 2010 of the Subcommittee on Toxics and Risk of the President's National Science and Technology Council, member and chair of EPA'S Science Advisory Panel from 1998 to 2003 (focused specifically on advising their pesticides program) and chair of the International Agency for Research on Cancer (IARC) advisory group that updated and improved its rules for reviewing scientific data to ensure that conclusions on the carcinogenicity of human exposures are the best possible (Preamble)[30]. As part of my work on science advisory panels, I have served on EPA's Science Advisory Board, as an advisor to the Australian Health Council on risk assessment methods, as an advisor to the Korean Food and Drug Administration on toxicological methods, and served on several World Health Organization (WHO) International Program on Chemical Safety scientific panels dealing with risk assessment. Besides the guidelines for evaluating cancer hazards used by the IARC, I have either chaired or served as a member of scientific panels developing guidance documents for other organizations including the EPA.

I have received numerous awards, most notably the Outstanding Practitioner Award from the International Society for Risk Analysis and the Paper of the Year Award (twice) from the Society of Toxicology Risk Assessment Specialty Section. I am a fellow of the American Statistical Association, the International Statistical Institute, the World Innovation Foundation and the Ramazinni Institute. I have published over 250 peer-reviewed scientific papers, book chapters and technical documents on topics in toxicology and risk assessment.

Finally, I have served on numerous national and international committees tasked with evaluating the risk and/or hazard of specific environmental chemicals, including glyphosate. For example, I have contributed to risk assessments for EPA, the Food and Drug Administration, the Centers for Disease Control and Prevention, the National Institutes of Health, the WHO and IARC.

Reliance List

During the course of my preparation for this report, I have reviewed the following materials:

a. All epidemiological data relating to the ability of glyphosate formulations to cause NHL in humans.

b. Scientific papers on the cellular origins of NHL
c. Peer-reviewed scientific data relating to the carcinogenicity, genotoxicity and oxidative stress caused by glyphosate
d. Technical reports relating to the carcinogenicity of glyphosate provided by the defendant to the lawyers for the plaintiff
e. The USEPA, the European Food Safety Authority (EFSA), the German Federal Institute for Risk Assessment, the European Chemical Agency, the IARC and the WHO/Food and Agriculture Organization Joint Meeting on Pesticide Residues reviews of the scientific literature relating to the potential for glyphosate to cause cancer.
f. Technical documents available from EFSA regarding animal carcinogenicity data on glyphosate prepared by organizations other than the defendant
g. Various other documents produced in the litigation

A complete list of my reliance materials is at the end of this report.

Methodology for Causality Evaluation

The evaluation of whether glyphosate and/or GBFs can cause NHL in humans requires the review and synthesis of scientific evidence from studies of human populations (epidemiology), animal cancer studies, and studies investigating the mechanisms through which chemicals cause cancer. Many different approaches[31, 32] are used to synthesize these three areas of science to answer the question "Does this chemical cause cancer in humans?" In any of these three science areas, the quality of the individual studies has to be assessed and summarized to make certain the studies included in the overall assessment are done appropriately. Once the quality of the individual studies has been assessed, a judgment needs to be made concerning the degree to which the studies support a finding of cancer in humans. To do this, the EPA, IARC, the European Chemical Agency (EChA), the US Report on Carcinogens, and many others use guidelines[30, 33-35] that rely upon aspects of the criteria for causality developed by **Hill (1965)**[36].

Hill listed nine (9) aspects of epidemiological studies and the related science that one should consider in assessing causality. The presence or absence of any of these aspects is neither sufficient nor necessary for drawing inferences of causality. Instead, the nine aspects serve as means to answer the question of whether other explanations are more credible than a causal inference. As noted by Hill:

> *"None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"*

The nine aspects cited by Hill include consistency of the observed association, strength

of the observed association, biological plausibility, biological gradient, temporal relationship of the observed association, specificity of the observed association, coherence, evidence from human experimentation and analogy. These are briefly described below.

An inference of causality is strengthened when several of the studies show a **consistent positive association** between cancer and the exposure. This addresses the key issue of replication of studies which is critical in most scientific debates. If studies are discordant, differences in study quality, potential confounding, potential bias and statistical power are considered to better understand that discordance.

An inference of causality is strengthened when the **strength of the observed association** in several studies are large and precise. These large, precise associations lessen the possibility that the observed associations are due to chance or bias. A small increase in risk of getting cancer does not preclude a causal inference since issues such as potency and exposure level may reduce the ability of a study to identify larger risks. Meta-analyses provide an objective evaluation of the strength of the observed association across several studies with modest risks to help clarify strength of the observed associations.

An inference of causality is strengthened when there is data supporting **biological plausibility** demonstrated through experimental evidence. Animal carcinogenicity studies, in which tumor incidence is evaluated in experimental animals exposed to pure glyphosate, play a major role in establishing biological plausibility. There are numerous types of mechanisms that can lead to cancer[37], most of which can be demonstrated through experimental studies in animals, human cells, animal cells, and/or other experimental systems. Occasionally, occupational, accidental or unintended exposures to humans allow researchers to evaluate mechanisms using direct human evidence.

An inference of causality is strengthened when there is a **biological gradient** showing a reasonable pattern of changing risk with changes in exposure (e.g. risk increases with increasing exposure or with longer exposure). In many epidemiological studies, this aspect cannot be examined due to limitations in the study design or due to a lack of clarity in the presentation of the results. When a study does address an exposure-response relationship, failure to find a relationship can be due to a small range of exposures, insufficient sample size or a changing exposure magnitude over time that has not been accounted for.

An inference of causality is strengthened when there is a **temporal relationship** in which the exposure comes before the cancer. This aspect is necessary to show causality; if it is not present, a causal inference is not plausible. Because the latency period for cancers can be long (years), evaluation of studies should consider whether the exposure occurred sufficiently long ago to be associated with cancer development.

An inference of causality is strengthened when the exposure is **specific** for a given cancer. This would mean that the disease endpoint being studied is only due to the cause being assessed. This issue is seldom applicable and, since NHL has other causes, specificity is not applicable to the determination of causality for glyphosate.

An inference of causality is strengthened when other lines of experimental evidence are **coherent** with a causal interpretation of the association seen in the epidemiological evidence. To evaluate coherence, information from animal carcinogenicity studies, mechanistic investigations and information on the metabolism of the chemical being studied would be considered.

An inference of causality is strengthened when there is **experimental evidence in humans** supporting a causal interpretation. Seldom is this type of information available when addressing the toxicity of chemicals. However, experiments in which an individual reduces or limits exposures and the risk of cancer is reduced would carry considerable weight in the evaluation (e.g. studies evaluating the cancer risks of people who stop cigarette smoking compared with continuing smoking have demonstrated reduced lung cancer risks). No such data are available for glyphosate.

Finally, an inference of causality is strengthened when there are other chemical agents with **analogous** structures showing similar effects in humans and/or animals and/or showing similar biological impacts in mechanistic studies. No such data are available for glyphosate.

The most logical approach to developing an inference of causality is to step through each of the aspects of causality developed **by Hill (1965)**[36] and apply them to the available data for glyphosate and for glyphosate formulations. This is done in the sections that follow.

Consistency of the Associations seen in Human Epidemiological Studies

Relevant Epidemiology Studies

In their meta-analysis, **Chang and Delzell (2016)**[38] performed a systematic literature search of all scientific literature up to June, 2015, to identify all epidemiological studies that were pertinent to evaluating an association between glyphosate and NHL. They identified 12 relevant epidemiology studies[39-50]. Their search agrees with all current reviews of glyphosate and I will use their findings from the literature up until 2015. To cover from June 2015 to the present (April 1, 2017), I used their searching algorithm and identified 117 additional published studies, none of which were new epidemiology studies. These same 12 studies will be considered for use in this evaluation. Other experts will be discussing the studies as well as their strengths and their weaknesses; I will focus on using the results of these studies in evaluating causality so I will only briefly describe each study.

Cantor et al. (1992)[39] did an in-person interview study comparing 622 white men, newly diagnosed with NHL, to 1245 population-based controls in Iowa and Minnesota. They originally identified 780 cases, of which 694 (89%) were interviewed. After pathology review, only 622 were found to have NHL, the remaining cases having leukemia or other diseases. Three different sources of controls were used, random digit dialing (76.7% response rate), Health Care Financing Administration rolls (79% response

rate) and deceased controls with eligible proxies (77% response rate). Both cases and controls were questioned regarding their use of agricultural products including Roundup® and any other glyphosate-based formulations. For deceased or incompetent controls (184) and cases (number not given), proxy interviews were done with a close relative. When cases in farmers were compared to cases in non-farmer controls, 26 cases (out of 266) and 49 controls (out of 547) had handled herbicides containing glyphosate yielding an odds ratio[1] (OR) of 1.1 (95% confidence interval 0.7-1.9). This analysis controlled for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations and high-risk exposures in a logistic analysis. The authors noted there was "minimal evidence for confounding of results for any single pesticide by exposure to pesticides belonging to other chemical families." Because the exposure is determined based on interviews in cases and controls, this study has the potential for recall bias[2]. However, the authors note that the bias could both increase or decrease the OR because of non-differential exposure misclassification[3] because of difficulties in accurate recall of past pesticide exposures for both controls and treated individuals. This study will not be included separately into the evaluation since it overlaps with **De Roos et al. (2003)**[43]

Two additional studies conducted by **Zahm et al. (1990)**[51] in Nebraska and **Hoar et al. (1986)**[52] in Kansas collected information on pesticide and herbicide use, but did not report specifically on the effects of glyphosate. **De Roos et al. (2003)**[43] pooled the data from these two studies with the data from **Cantor et al. (1992)**[39] to examine pesticide exposure to glyphosate in farming as risk factors for NHL. The three case-control studies[39, 51, 52] had slightly different designs. The design for the Minnesota study[39] is

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[1] The odds ratio (OR) is calculated as the proportion of exposed cases with disease to exposed controls divided by the proportion of non-exposed cases to non-exposed controls. For rare diseases, this value approximates the population risk ratio (PRR) which is the probability of having the disease in exposed individuals divided by the probability of having the disease in non-exposed individuals. If the PRR is 1, then there is no difference in the probability of having the disease regardless of your exposure. Values of PRR greater than 1 imply the risk is higher in the exposed population. Because the OR is an estimate of the PRR for rare diseases, it is usually accompanied by a 95% confidence interval that describes the probable range of the estimate. If the OR is greater than 1, then the exposure is associated with the disease. If the lower 95% confidence bound for the OR is greater than 1, this is typically used to say the association is statistically significant.

[2] Recall bias occurs when cases are more likely to say they are exposed to glyphosate than controls or when controls are more likely to say they are exposed to glyphosate than cases. The recall must be different for the cases than the controls for this to cause a bias; errors in recalling past exposures that happen for both cases and controls would not be recall bias.

[3] Non-differential exposure misclassification occurs when the probability of an error in determining whether an individual is exposed or not is the same for both cases and controls.

provided directly above. In Nebraska[51], the cases were identified through the Nebraska Lymphoma Study Group and area hospitals for 66 counties and included all white men and women diagnosed with NHL between July 1, 1983 and June 30, 1986. Controls were obtained by random-digit dialing, Medicare records or state mortality files depending upon age and vital status. All study participants were over age 21 and even though this study included a few women, they were excluded from the **De Roos et al. (2003)** analysis. The response rates for cases and controls were 91% and 87% respectively. In Kansas[52], cases were randomly sampled from a registry at the University of Kansas of white men, over age 21, diagnosed between 1979 and 1981. The response rates for cases and controls were 96% and 94% respectively. Controls were population-based matched on age and vital status. As for the Nebraska study, controls for live cases were obtained from Medicare records for cases 65+ and by random-digit dialing for cases <65 years; controls for deceased patients came from state mortality records. The resulting pooled case-control study had 870 cases and 2569 controls (for analyzing the relationship between glyphosate and NHL, there were only 650 cases and 1933 controls following exclusion of subjects with missing data). For any glyphosate exposure, there were 36 exposed cases and 61 exposed controls with an OR (95% confidence interval) of 2.1 (1.1-4.0) in a logistic regression analysis controlling for all other pesticides reported, age and study site. The authors also analyzed the data using a Bayesian hierarchical regression analysis yielding an OR (95% confidence interval) of 1.6 (0.9-2.8) controlling for the same parameters as the logistic regression. They also conducted an analysis of "potentially carcinogenic" pesticides which included glyphosate. When just one of these pesticides was used by subjects, the logistic regression OR was 1.6 (0.8-3.1), two to four pesticides yielded an OR of 2.7 (0.7 to 10.8) and when more than five were used, the OR was 25.9 (1.5-450.2) in the logistic regression analysis and 1.1 (0.8-1.7), 1.3 (0.7-2.3) and 2.0 (0.8-5.2) respectively for the Bayesian analysis. Removing glyphosate from the list of "potentially carcinogenic" pesticides yielded equivalent ORs of 1.2 for one pesticide, 1.2 for two to four pesticides and 1.1 for five or more pesticides. The authors note that the positive results seen in their study are not likely due to recall bias since there were few associations seen over the 47 pesticides they studied. Also, although some of the positive results could be due to chance, the use of the hierarchical regression analysis theoretically decreases the chance of false positive findings. In the Kansas study[52], suppliers for 110 subjects with farming experience were identified and provided information on the subjects' crops and pesticide purchases. In general, the suppliers reported less pesticide use than the subjects of the study with no consistent differences in agreement rates between cases and controls. The agreement between suppliers and subjects improved when pesticide use during the last 10 years was considered. This supports a reduced role of recall bias in these studies and a possible role of non-differential exposure misclassification. The reduced ORs when using the Bayesian analysis as compared to the logistic regression is not surprising because the authors used a non-informative prior rather than a less conservative prior. In addition, adjustment for 47 pesticides is also likely to reduce the significance of the observed ORs for pesticides that are associated with NHL as demonstrated by the analysis of "potentially carcinogenic" pesticides (this model is possibly over-parameterized since it

includes over 47 dependent variables for only 36 exposed cases; this can significantly reduce the ORs and increase the confidence bounds). This pooled case-control study is the strongest study with sufficient power (3.8% of subjects exposed) and will be included in the evaluation of causation.

Lee et al. (2004)[44] pooled data from **Zahm et al. (1990)**[51] and **Cantor et al. (1992)**[39] (previously described) to evaluate whether asthma acts as an effect modifier of the association between glyphosate exposure and NHL. Women were included in this analysis whereas **De Roos et al. (2003)**[43] excluded women. The final study published by Lee included 872 cases and 2336 controls of which 45 cases and 132 controls had been told by their doctors they had asthma. The OR of association between glyphosate and NHL in non-asthmatics was 1.4 (0.98-2.1) and 1.2 (0.4-3.3) in asthmatics when controlling for age, vital status and state (geographical location). This study completely overlaps with the study by **De Roos et al. (2003)**[43] with the exception of the inclusion of the few women in the study by **Zahm et al. (1990)**[51]. Since this study only looks at effect modification due to asthma, it does not contribute to the overall evaluation of causality and it will be excluded from further evaluations.

Nordstrom et al. (1998)[40] conducted a population-based case-control study of hairy cell leukemia (HCL); a subtype of B-cell NHL) in Sweden that included an evaluation of exposures to glyphosate. The study included 111 men with NHL reported to the Swedish Cancer Registry between 1987 and 1992 (with one patient from 1993 accidentally included). Controls (400 in total) were drawn from the National Population Registry matched for age and county with the cases. The response rates were 91% for cases (10 refused to participate out of the original 121) and 83% (84 controls refused to participate out of 484 selected). Almost all questionnaires were answered by the subject of the study (4 cases and 5 controls were answered by proxies). The study reported an OR for glyphosate exposure and HCL of 3.1 (0.8-12) controlling only for age. This study had very limited power for detecting an association because there were only four cases and five controls with glyphosate exposure (1.8% of the total study population). In addition, because they failed to adjust for other exposures, the potential for confounding in this study is greater than those presented previously. The authors noted that they attempted to minimize recall bias by only using living cases in the analysis. Also, even though matching was performed to identify the controls, this matching was not used in the final analysis. This study was later used in a pooled analysis of HCL and NHL[42] and will not be considered independently in the evaluation for causation but will be used in the context of the pooled analysis.

Hardell and Eriksson (1999)[41] conducted a population-based case-control study of all male patients older than 25 years diagnosed with NHL between 1987 and 1990 in the four most northern counties of Sweden. After excluding misdiagnosed cases, they included 442 cases of which 404 answered their questionnaire (most by proxy) for a response rate of 91%; 192 of these cases were deceased. For each living case, two male matched controls were chosen from the National Population Registry and matched on age and county. For each deceased case, two male controls were chosen from the National Registry for Causes of Death, matched for age and year of death. The response

rate for the controls was 84% (741 out of 884 identified). Study subjects were sent a detailed questionnaire and, in most cases, this was supplemented with a phone interview. A complete working history was obtained with questions regarding exposure to numerous chemicals to avoid a focus on pesticides and organic solvents, the focus of the study. Exposure was defined as at least one full day of exposure more than one year before diagnosis. For glyphosate exposure, the authors identified four cases and three controls with exposures and a univariate OR of 2.3 (0.4-13). A multivariate analysis of both glyphosate and phenoxy herbicides produced an OR of 5.8 (0.6-54). The study has limited power for detecting an effect because the exposure frequency is very low (0.6% exposed). This study was later used in a pooled analysis of HCL and NHL[42] and will not be considered independently in the evaluation for causation but will be used in the context of the pooled analysis.

Hardell et al. (2002)[42] conducted a pooled analysis of NHL and HCL by combining the studies of **Nordstrom et al. (1998)**[40] and **Hardell and Eriksson (1999)**[41]. This study fully overlaps with the previous two studies. The analysis controlling for age, study, county and vital status yielded an OR of 3.04 (1.08-8.52) based on eight exposed cases and eight exposed controls. A more extensive analysis additionally controlled for other pesticides and yielded a smaller OR of 1.85 (0.55-6.20). As for the study by **De Roos et al. (2003**), the analysis may be over-parameterized (more than eight dependent variables with only eight exposed cases) which could lead to a reduction in the ORs and larger confidence bounds. Even with the pooled data, **Hardell et al. (2002)** had limited power to detect an effect because the exposure frequency for cases and controls was very low (1% exposed). This study is a valid case-control study and will be used in the evaluation of causality.

In a later study, **Eriksson et al. (2008)**[46] conducted a population-based case-control study where cases were identified as NHL patients aged 18-74 years diagnosed in four major hospitals in Sweden from December 1, 1999 until April 30, 2002. In total, 995 cases were identified as matching the study parameters with 910 (91%) answering the questionnaire shortly after diagnosis. All cases were classified into subgroups with 810 B-cell, 53 T-cell, and 38 unspecified lymphomas. Controls (1,108) were randomly selected from the population registry and matched on health service, region, sex and age and interviewed in several periods during the conduct of the study; 1,016 controls responded to the questionnaire (92% response rate). Study subjects were sent a detailed questionnaire and, in many cases, a phone interview followed. Exposure was defined as at least one full day of exposure more than one year before diagnosis. The univariate analysis, adjusting for age, sex and year of diagnosis (cases) or enrollment (control) yielded an OR of 2.02 (1.10-3.71) based on 29 exposed cases and 18 exposed controls. When cases and controls were divided into those with ≤10 days per year exposure and those with >10 days per year exposure, the ORs were 1.69 (0.70-4.07) and 2.36 (1.04-5.37) respectively. When diagnoses were grouped into various subtypes of NHL, the results did not change dramatically except for small lymphocytic lymphoma and chronic lymphocytic lymphoma which showed an increased OR of 3.35 (1.42-7.89). A multivariate analysis of glyphosate controlling for other agents with statistically

increased odds ratios and/or odds ratios greater than 1.5 yielded an OR of 1.51 (0.77-2.94). In a similar analysis to the multivariate analysis, latency periods of one to ten years showed an OR of 1.11 (0.24-5.08) and >10 years had an OR of 2.26 (1.16-4.40). This study was much larger than the previous Swedish studies (2.3% exposed) and, although there may have been confounding from other pesticides, this was addressed in the multivariate analysis and the latency analysis. This study is a valid case-control study and will be used in the evaluation of causality.

McDuffie et al. (2001)[50] recruited incidence cases of NHL in men 19 years or older from six Canadian provinces with a first diagnosis between September 1, 1991 and December 31, 1994. Each provincial Cancer Registry or, in the case of Quebec, hospital, had a target number of cases and ended recruitment when the case number was reached. Controls were men 19 years or older selected at random from provincial health insurance records, computerized telephone listings or voter registration lists, depending upon the province. Cases and controls were sent questionnaires with surrogates ineligible to answer the questionnaires for deceased cases or controls. Each subject who reported 10 hours per year or more of pesticide exposure and a random sample of 15% who reported less exposure were interviewed by telephone to obtain details on pesticide use. A pilot study was conducted to obtain an improved version of the telephone interview questionnaire used by **Hoar et al. (1986)**[52] and **Zahm et al. (1990)**[51] that would provide accurate pesticide exposure assessment in the form of a screening questionnaire and a telephone interview questionnaire. This was followed by a validation study (27 farmers) where the final questionnaires used to screen and include potential cases and controls were administered and the answers regarding pesticide usage showed excellent concordance with purchases through their local agrochemical supplier. The screening questionnaire was returned by 517 cases of NHL (67.1% response rate) and 1506 controls (48% response rate). Following analysis of the screening questionnaire, the telephone interview was administered to 179 cases and 456 controls to obtain more detailed exposure information. The OR for glyphosate exposure and NHL was 1.26 (0.87-1.80) stratified by age group and province of residence and the OR was 1.20 (0.83-1.74) when the analysis also controlled for significant medical variables (51 exposed cases and 133 exposed controls). An exposure-response evaluation was performed where the OR for exposure between zero to two days per year was 1.0 (0.63-1.57) and for greater than two days per year was 2.12 (1.20-3.73) with the latter group having 23 exposed cases and 36 exposed controls. This study had excellent sample size and power (8.1% of subjects exposed), but a low response rate to the screening questionnaire. Also, by adjusting for significant medical variables, this study ruled out many confounders but did not adjust for other pesticide exposures. The effort to validate the recall of pesticide usage for farmers supports a lack of recall bias in the study. This study is a valid case-control study and will be used in the evaluation of causality.

Hohenadel et al. (2011)[48] re-analyzed the data of **McDuffie et al. (2001)**[50] to specifically investigate the impact of exposure to multiple pesticides on NHL. Four cases of NHL were excluded from this evaluation following a pathology review. They reported associations with the use of glyphosate with and without malathion but not with

glyphosate overall. The OR for glyphosate (ever used) without malathion (ever used) was 0.92 (0.54-1.55) and the OR for glyphosate (ever used) with malathion (ever used) was 2.1 (1.31-3.37). **Chang and Delzell (2016)**[38] combined the ORs from the glyphosate only analysis with the glyphosate and malathion analyses using random-effects meta-analysis to get a combined OR for glyphosate of 1.4 (0.62-3.15). This study was specifically targeted to interactions of various pesticides and does not substantively contribute to an evaluation of glyphosate. Since it is a refined analysis of **McDuffie et al. (2001)**[50], it will be included in the evaluation of causation only in the context of the combined analysis provided by **Chang and Delzell (2016).**

Orsi et al. (2009)[47] conducted a hospital-based case-control study of men and women diagnosed with lymphoid neoplasms in five hospitals in France between 2000 and 2004 who were aged 20-75 years (the abstract gives the age range as 18-75 years). All diagnoses were cytologically or histologically confirmed. The evaluation only included men and questionnaires/interviews were completed by 491 cases (95.7% response rate) which included 244 cases with NHL. Controls were patients in the same hospital (mostly orthopedic or rheumatological patients) with no prior history of lymphoid neoplasms and excluding patients admitted to the hospital for cancer or a disease directly related to occupation, smoking or alcohol abuse. The controls were matched to cases by hospital and age. Of the 501 candidate controls, 456 participated (91% response). Exposure was evaluated differently for subjects who had non-occupational exposures from those who had occupational exposures. For both, the subjects had to fill out a questionnaire/interview on occupations and home gardening pesticide exposures. For those who had worked professionally as farmers or gardeners for at least 6 months, a specific agricultural occupational questionnaire/interview was administered and exposure was determined on the basis of this extra data. The OR for occupational use of glyphosate and NHL was 1.0 (0.5-2.2) with 12 exposed cases and 24 exposed controls stratified by age and center category. A further analysis was done by individual subtypes of NHL with an OR of 1.0 (0.3-2.7) for diffuse large cell lymphoma, 1.4 (0.4-5.2) for follicular lymphoma, 0.4 (0.1-1.8) for chronic lymphocytic leukemia (CLL) and 1.8 (0.3-9.3) for HCL. No separate analysis of non-occupational use of glyphosate was provided, nor does it seem specific data on glyphosate usage was ascertained for subjects who were not professional farmers or gardeners. This could lead to non-differential misclassification of exposure which could reduce the ORs of the study. Barring this, the sample size was sufficient to detect an effect (5.3% with occupational exposure) and this study will be included in the evaluation of causality.

Cocco et al. (2013)[49] evaluated data from a multi-center case-control study of lymphoid neoplasms in six European countries from 1998 to 2004. Cases included only adult patients diagnosed with lymphoma during the study period drawn from participating centers. Controls were either selected by sampling from the general population on sex, age group, and residence area (Germany, Italy), or from hospital controls matched to the patient excluding patients with cancer, infectious diseases, and immunodeficiency diseases (Czech Republic, France, Ireland, Spain). The study included 2348 lymphoma cases (88% participation) and 2462 controls (81% response rate in hospital-based controls and 52% in population-based controls). Exposures were derived using an

occupational exposure matrix developed by industrial hygienists and occupational experts from the research centers. Only 35 individuals (cases and controls not broken out) in the study were exposed to carbamates (glyphosate was grouped with the carbamates). No results were provided for NHL and the only OR provided for glyphosate was for B-cell lymphoma where the OR was 3.1 (0.6-17.1) based on four exposed cases and two exposed controls. No information was provided on the total number of cases for each type of lymphoma evaluated. This study has very limited power to evaluate an association between NHL and glyphosate and provides only information on B-cell lymphomas with very few exposed cases and controls. As has been done by most researchers evaluating these data, this study will receive very little weight in the evaluation of causality.

De Roos et al. (2005)[45] reported results on the association of glyphosate and cancer incidence from the Agricultural Health Study (AHS), a prospective cohort study in Iowa and North Carolina, which included 57,311 private and commercial applicators who were licensed to apply restricted-use pesticides at the time of enrollment. Recruitment occurred between 1993 and 1997 and cohort members were matched to cancer registry files to identify cases and the National Death Index (1999) to ascertain vital status. Incident cancers were identified from the date on enrollment until 31 December, 2001, with the average follow-up time being 6.7 years. Comprehensive use data was obtained by self-administered questionnaire for 22 pesticides, ever/never use for 28 additional pesticides, and general information on work practices. Applicators were given a second self-administered questionnaire on occupational exposures and lifestyle factors. They used three exposure metrics in their analyses: a) ever personally mixed or applied pesticides containing glyphosate; b) cumulative exposure days of use of glyphosate (years of use times days per year); and c) intensity weighted cumulative exposure days (years of use times days per year times intensity of use). Persons whose first primary tumor occurred before the time of enrollment (1074) were excluded from the analysis as were those who were lost to follow-up (298), did not provide age information (7) or information on glyphosate use (1678) leaving 54,315 subjects for inclusion. There were 92 cohort members with a diagnosis of NHL during the study period of which 77.2% had ever used glyphosate resulting in a rate ratio[4] (RR) of 1.2 (0.7-1.9) when controlling for age and an RR of 1.1 (0.7-1.9) when controlling for age, lifestyle factors, demographics and five other pesticides for which cumulative-exposure-day variables were most highly associated with glyphosate cumulative-exposure-days (2,4-D, alachlor, atrazine, metalochlor, and trifluralin) or, for chemicals with only ever/never exposure information that were most highly associated with glyphosate ever/never use (benomyl, maneb, paraquat, carbaryl and diazinon). When cumulative exposure days in exposed individuals are divided into tertiles and RRs examined using the lowest exposed tertile as

[4] The rate ratio (RR) is estimated as the incidence in the exposed population divided by the incidence in the unexposed population. Incidence is calculated as the number of events in a fixed period of time divided by the person years at risk. Unlike the OR, the RR does not require the assumption of a rare disease to serve as a good estimate of the population risk ratio (PRR).

the reference group, the RRs drop with values of 0.7 (0.4-1.4) and 0.9 (0.5-1.6) for tertiles 2 and 3 respectively controlling for demographic and lifestyle factors and other pesticides (30,699 subjects). When intensity-weighted exposure days are examined again using exposed tertile 1 as the reference group, the RRs drop with values of 0.6 (0.3-1.1) and 0.8 (0.5-1.4) for tertiles 2 and 3 intensity-weighted exposure days respectively controlling for demographic and lifestyle factors and other pesticides (30,699 subjects). Analyses are not shown for the evaluation of the exposed tertiles against never exposed because the authors felt that never exposed and exposed subjects differed in terms of socio-economic factors and other exposures like smoking[45].

This is a typical cohort study, but has some limitations in terms of its interpretation. The majority (75.5%) of subjects in the cohort reported having ever personally mixed or applied products containing glyphosate and was composed primarily of male, middle-aged, private applicators. For glyphosate, reliability of the answers by subjects on the use of glyphosate between the first and second questionnaire were evaluated in the AHS[53]: 82% agreement for whether they had ever mixed or applied glyphosate, 53% agreement on years mixed or applied, and 62% agreement on days per year mixed or applied and 62% agreement on decade first applied. They saw no differences in over versus under reporting between the two questionnaires suggesting this could lead to non-differential exposure bias and reduce the RRs in this study. Another weakness, noted by the authors, is that the small number of incident cases during follow-up period hindered precise effect estimates. Also, the high frequency of exposure to many pesticides (e.g. 73.8% were exposed to 2,4-D) means subjects unexposed to glyphosate were likely to be exposed to other agents that may also induce NHL, reducing the RRs. Also, as noted by the EPA's FIFRA Science Advisory Panel (SAP)[54] in their review of the EPA's issue paper on the carcinogenicity of glyphosate and as noted in a critique[55] of the European Food Safety Agency's risk assessment for glyphosate, the follow-up time in this cohort study may not be long enough to produce a sufficient sample size for evaluation of the association between NHL and glyphosate. Like other studies, this study has few exposed cases and controls, but the authors adjust their analysis for many other pesticides which could reduce ORs and increase confidence bounds limiting the ability of the study to show positive results. This study could also suffer from a survival bias because pesticide applicators were recruited as case participants after their exposure had begun and those with a cancer prior to enrollment were excluded.

This study will be included in the evaluation of causality.

Consistency of Associations

Hill (1965)[36] defines consistency as the answer "yes" to the question "Has it repeatedly been observed by different persons, in different places, circumstances and times?" For these studies, the answer is indeed yes.

If the population relative risk (PRR) for an association of glyphosate with NHL were equal to 1 (no effect), then one would expect very few statistically significant results in multiple studies and that about half of the studies would have ORs or RRs below one

and half above one. As noted by both the **IARC Monograph 112 (2015)**[56] and by **Chang and Delzell (2016)**[38], when comparing studies, the most reasonable comparison is to use the most-fully-adjusted risk estimates. I will mostly limit my comments to these most-fully-adjusted risk estimates.

Consistency 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 responses. Figure 1 shows a forest plot of all ORs and RRs from the epidemiology studies discussed previously. Each horizontal line in the forest plot shows the mean estimate of the OR/RR as a black square and the 95% confidence interval around this estimate as whiskers extending left and right from the black square.

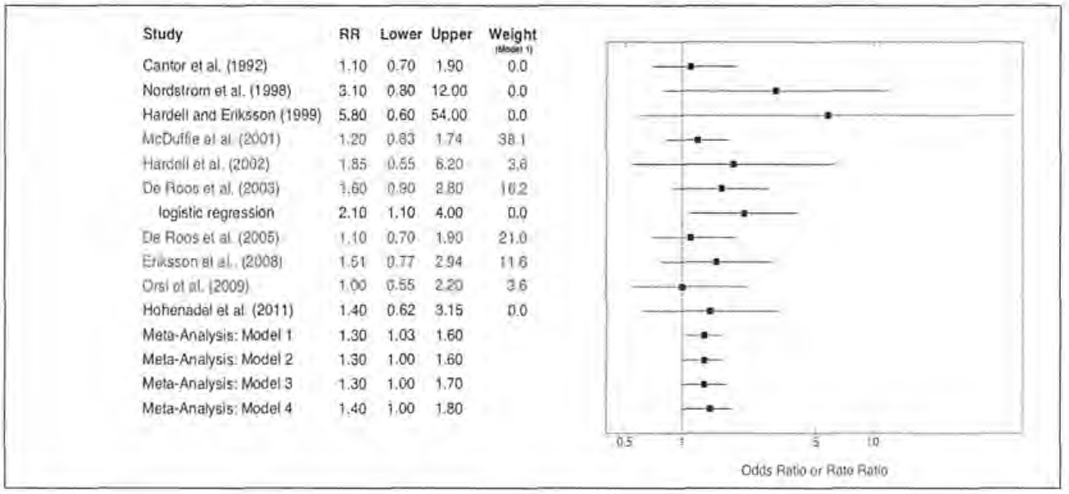
The first obvious conclusion to be drawn from Figure 1 is that all of the mean OR/RR estimates (black squares) are consistently ≥1. This implies that all of the studies are pointing in the same direction toward a positive effect. In their meta-analyses, **Schinasi and Leon (2014)**[57], **IARC (2015)**[56] and **Chang and Delzell (2016)**[38] all identified 6 papers (highlighted in red in Figure 1) as being the most reliable for evaluation of the ability for glyphosate to induce NHL in people: **McDuffie et al. (2001)**[50], **Hardell et al. (2002)**[42], **De Roos et al. (2003)**[43] and **(2005)**[45], **Eriksson et al. (2008)**[46] and **Orsi et al. (2009)**[47]. I will refer to these papers as the six core epidemiology studies. As noted above, if 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. Using only the results from the 6 core studies, you can see that all are ≥1; the probability of this happening is $(0.5)^6$ or 0.016, strongly suggesting the studies do not agree with an underlying PRR=1 and that they consistently support a positive effect.

A second way in which consistency can be evaluated is to combine the individual studies using meta-analysis to obtain a combined analysis using both the ORs and the RR (CRR) and test for heterogeneity in the studies. The meta-analysis done by **Chang and Delzell (2016)** includes the same analysis as that done by the **IARC (2015)** and is an improvement over **Schinasi and Leon (2014),** so I will focus my comments on using the **Chang and Delzell (2016)** meta-analysis. **Chang and Delzell (2016)** did four separate meta-analyses on the glyphosate epidemiology studies using two different methods (random-effects and fixed-effects models). In their first analysis (model 1)[5], they combined the most-fully-adjusted risk estimates from the six core studies to yield a CRR of 1.27 (1.01-1.59) for both random-effects and fixed-effects models supporting an association between NHL and glyphosate exposure in these studies. In a second analysis (model 2), they replace the results of the Bayesian analysis in **De Roos et al. (2003)** with the results of the logistic regression analysis and get the same CRR of 1.30 (1.03-1.64) for both random-effects and fixed-effects models. In a third analysis (model 3), they replace from model 1 the **McDuffie et al. (2001)** results in with a combined meta-

[5] **Chang and Delzell (2016)** provided only one significant digit to the right of the decimal point in their confidence bounds; the EPA SAP (2017) re-calculated models 1-4 of **Chang and Delzell (2016)** to provide two significant digits – these are presented here.

analytic result they derived from analyses by **Hohenadel et al. (2011)** (this study reanalyzed the same data as **McDuffie et al. (2001)**, splitting results between asthmatics and non-asthmatics) resulting in a CRR of 1.32 (1.00-1.73) for both random-effects and fixed-effects models. Finally, in a fourth analysis (model 4), they use model 3 but replaced the Bayesian analysis in **De Roos et al. (2003)** with the logistic regression analysis yielding a CRR of 1.37 (1.04-1.82) for both random-effects and fixed-effects models. In essence, none of the different meta-analyses rejected the notion of a combined, statistically significant positive effect.

Figure 1: Odds Ratios and Rate Ratios from the most-fully-adjusted risk estimates from selected epidemiology studies and from the meta-analyses of **Chang and Delzell (2016)**[38]. "RR" refers to the OR or RR from the study, "Lower" refers to the 95% lower bound, "Upper" to the 95% upper bound and "Weight" refers to the weight applied to that specific study in Model 1 of the meta-analysis (Table 3 in Chang and Delzell). For **De Roos et al. (2003)**, the first row is for the Bayesian model analysis and the second row, labelled "logistic regression" is from the logistic model analysis.



As stated above, another way to evaluate consistency in the epidemiological data would be to evaluate the heterogeneity in the studies. Heterogeneity may be due to differences in participants, outcomes, exposure metrics, methods for questioning study subjects, sex of the subjects, etc. **Chang and Delzell (2016)** formally tested for heterogeneity of the responses from the six core studies using Cochran's Q statistic and the I^2 statistic[58]. For models 1 to 4, the p-values from Cochran's Q test are 0.84, 0.59, 0.85, and 0.63 respectively (typically you reject the concept of homogenous studies in favor of heterogeneous studies if $p<0.10$). The I^2 statistic for all four models are 0.0% (values for I^2 can range from 0-100% with concern for heterogeneity above 50%). The fact that the fixed-effects models and random-effects models gave the same results also supports a lack of heterogeneity in the data. There is no indication of heterogeneity in these six core studies. Lack of heterogeneity supports the interpretation of the meta-analyses as showing a positive association and strong consistency of the findings across the six core studies.

Chang and Delzell (2016) also evaluated the association between subtypes of NHL and glyphosate exposure where possible. For B-cell lymphomas, they combined the results of **Eriksson et al. (2008)**[46] with those of **Cocco et al. (2013)**[49] and saw a CRR (random-effects and fixed-effects) of 2.0 (1.1-3.6) with an I^2 of 0 and a Cochran's Q test p-value of 0.58. For diffuse large B-cell lymphomas, they combined the results of **Eriksson et al. (2008)**[46] with those of **Orsi et al. (2009)**[47] and saw a CRR (random-effects and fixed-effects) of 1.1 (0.5-2.3) with an I^2 of 0 and a Cochran's Q test p-value of 0.79. For combined chronic lymphocytic leukemia and small lymphocytic lymphoma, they combined the results of **Eriksson et al. (2008)**[46] with those of **Orsi et al. (2009)**[47] and saw a CRR using the random-effects model of 1.3 (0.2-10) and for the fixed effects model 1.9 (0.9-4.0) with an I^2 of 83.7% and a Cochran's Q test p-value of 0.01. For follicular lymphomas, they combined the results of **Eriksson et al. (2008)**[46] with those of **Orsi et al. (2009)**[47] and saw a CRR (random-effects and fixed-effects) of 1.7 (0.7-3.9) with an I^2 of 0 and a Cochran's Q test p-value of 0.73. And finally, for HCL, they combined the results of **Nordstrom et al. (1998)**[40] with those of **Orsi et al. (2009)**[47] and saw a CRR (random-effects and fixed-effects) of 2.5 (0.9-7.3) with an I^2 of 0 and a Cochran's Q test p-value of 0.63. These subtype analyses are based upon small numbers of cases and only two studies making them unreliable, when considered individually, to address the question of consistency in the data. However, when they are combined with the results for the meta-analyses of the core studies of NHL, these studies add support to the conclusion that these data are consistent.

Chang and Delzell (2016) also performed a sensitivity analysis by only doing meta-analyses on studies with similar characteristics. Using only the five case-control studies, the CRR was 1.3 (1.0-1.7). Breaking them into the type of control used, there were four studies using population controls with a CRR of 1.4 (1.0-1.8). There were four studies with males only with a CRR of 1.3 (1.0-1.7) and two studies with males and females with a CRR of 1.2 (0.8-1.8). Three studies were done in North America with a CRR of 1.2 (1.0-1.6), three in Europe with a CRR of 1.3 (0.8-2.1); two of the three studies were in Sweden with a CRR of 1.6 (0.9-2.8). All of the resulting meta CRRs were the same for the fixed-effects model and the random-effects model. This sensitivity analysis shows that the results do not differ significantly from the main CRR for the six core studies combined adding support to the findings being consistent across the different studies.

In case-control studies, selection bias arises when the reasons cases and controls choose to participate in the study could lead to systematic biases that might result in a positive or negative finding independent of the exposure being studied. For example, if cases with exposure are more likely to participate than controls with exposure, the result would be higher OR values; however, this difference has to be differential and not simply a difference in participation rates. It is possible that in a few of these studies, the method by which controls were selected could contribute to selection bias that might lead to increased ORs. However, given the diverse types of cases and controls used in the five core case-control studies, this is unlikely to explain the consistent findings seen from these studies. It is also possible that the lack of complete data on cases versus controls could result in selection bias if the reasons for not completing the questionnaire/interview are different between cases and controls and relates to

exposure. There is no indication of this type of selection bias in these reports, and this is unlikely to explain the consistency seen in these data.

Exposure misclassification can lead to increases or decreases in the OR or RR values seen in both case-control and cohort studies. For example, in case-control studies, if cases are more likely to say they were exposed to glyphosate than controls, this would inflate the OR values; this is one type of recall bias. This type of bias is less likely in cohort studies. In all six of the core studies, this issue was discussed by the authors. In every case, they concluded there was bound to be some exposure misclassification, but that it was most likely non-differential, meaning that the misclassification was random; this would likely reduce the OR/RRs seen in the studies rather than increase them.

Confounding occurs when there is an exposure or some other factor that is tightly associated with both glyphosate exposure and NHL diagnosis that, if controlled for, could explain the results. The most likely source of confounding in these studies would be exposures to other pesticides. Four[42, 43, 45, 46] of the six core studies controlled for exposure to other pesticides and saw basically the same findings as the other two studies. Another concern for confounding would be if the cases had immune deficiencies that could be linked to NHL; in all of the case-control studies, such cases were excluded. Finally, other agricultural exposures (e.g. animals, other chemicals, infectious agents) could be correlated with glyphosate exposure and may be linked to NHL; none of the studies controlled for these factors. However, not all exposed cases were farmers; if confounding via other agricultural exposures is occurring, it is not possible to determine the magnitude or direction of such an effect from these data.

In conclusion, we have six core epidemiology studies done on two different continents by four different research groups using different designs, questionnaires and study populations that are highly consistent with no obvious bias or confounding that would explain the results. **There is a consistency of associations across the six core studies.**

Strength of the Association seen in Human Epidemiological Studies

To explain strength of association, **Hill (1965)** gives the classic example of John Snow and the cholera epidemic of 1855 where the risk ratio of dying if you drank water from the Southwark and Vauxhall Company (polluted by sewage) compared to drinking from the Lambeth Company water (sewage free) was 14. Yet, for the six core studies, the OR/RR ranges from 1.0 to 1.85 for the most-fully-adjusted risk estimates and to 2.1 if you include the fully adjusted risk estimate from De Roos et al. (2003)[45] using logistic regression. These are moderate OR/RR estimates making it conceivable they are individually due to either chance or bias. Thus, with the exception of the logistic regression analysis in **De Roos et al. (2003)**[45], none of the core studies demonstrate large, precise risks as envisioned by **Hill (2016)**[36]. However, **Hill (1965)** was not expressing himself in statistical terms where the significance of an association is dependent upon the precision of the observations. If the statistical variation around an OR/RR estimate is large relative to the estimate itself, the estimate is not very precise

and generally would not be statistically significant. The result from the study by **Hardell and Eriksson (1999)** shown in Figure 1 is an example of an estimate with very large statistical variation. On the other hand, a very small (in value), precise OR or RR estimate could be statistically significant and prove important in deciding causation. The meta-analyses shown in Figure 1 all demonstrate estimates of OR/RR that are significantly different from 1 rejecting the concept that the overall association is due to chance. The statistically significant estimate of the OR/RR for B-cell lymphomas in the meta-analysis support this finding as well.

In summary, we have six core epidemiology studies that all show approximately the same, modest increase in OR/RR that, when combined, demonstrate a significant strength of association. **There is a strong association across the six core studies**

Biological Plausibility

The range of data one can use to determine biological plausibility is quite diverse and can be exceptionally complicated. For simplicity, it can be divided into the types of assays that can be used in this evaluation: animal cancer bioassays, toxicokinetic studies, studies from accidental exposures in humans, and studies of specific biological mechanisms in animals or cells derived from humans or animals. Animal cancer bioassays are intended to test whether glyphosate can cause cancers in mammals, thus supporting the concept that the chemical could cause cancer in humans. Toxicokinetic studies provide insight into the degree to which glyphosate is absorbed by humans, distributed to various organs in the body, what happens to the chemical once it is in the body (metabolism), and, finally, how it is eliminated from the body. Studies from accidental exposures in humans can provide some information on the effects of glyphosate through changes in the chemistry and cellular structure of human blood. Studies of biological mechanisms are generally addressing what effects the chemical may have on human and animal cells under controlled, laboratory conditions. Some of the studies in this section were done with technical grade (virtually pure) glyphosate and some with the glyphosate formulations that humans encounter in occupational and environmental settings. I will summarize the literature in each of these areas and offer an opinion to their support of biological plausibility of NHL in humans.

Animal Cancer Bioassays

Typical animal cancer bioassays will expose animals (generally rats or mice) to a chemical for a substantial proportion of the animal's life (generally 2 years) then kill the animal and examine its organs and tissues for tumors. There are guidelines on how to conduct and analyze these studies. Typically, chemical registrants conduct cancer bioassays for pesticide approval pursuant to guidelines developed under the guidance of the Organization for Economic Cooperation and Development (OECD[59]). Other groups[30, 33, 34] provide guidance on how to analyze these studies based upon methodology papers from the published literature. These studies are conducted in a way that controls for everything in the animal's environment (e.g., food type, water quality, how often the animals are handled) leaving only the exposure to explain

differences in tumor formation between control and exposed animals. Even then, non-cancer endpoints can also be modified by the chemical and these may have an impact on tumor rates in the animals (e.g., survival, death from some other toxic effect of the chemical); these must be accounted for when reaching conclusions from the study.

Studies generally use four groups of animals, one group receiving no exposure (control) and the remaining three groups are test animals, with each group receiving different dose exposures to the chemical[60]. 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 because even the best known human carcinogens do not cause cancer in large fractions (say 20%) of the human population. The basic underlying premise of this design consideration is that, as the dose increases, so does the risk of getting a tumor. By exposing animals to the highest dose possible, you increase the ability of the study to identify a risk if one is present. However, one must be careful not to use a dose that is so high it will cause cancers by processes that would never work at lower doses. To avoid this, studies are designed around a maximum tolerated dose (MTD) or limit dose. This dose is generally determined based upon a subchronic study (90 days) in the same animals and is usually the maximum dose that can be tolerated by the animals without any signs of significant toxicity in the exposed animals (e.g., weight loss, tissue damage). The OECD and EPA provide guidelines[33, 59] on how to choose this top dose. These guidelines are in general agreement with the scientific literature[60].

The guidelines also address the methods by which the data should be analyzed. For example, the EPA guidelines[61] state that:

"A trend test such as the Cochran-Armitage test (Snedecor and Cochran, 1967) asks whether the results in all dose groups together increase as dose increases. A pairwise comparison test such as the Fisher exact test (Fisher, 1950) asks whether an incidence in one dose group is increased over that of the control group. By convention, for both tests a statistically significant comparison is one for which p is less than 0.05 that the increased incidence is due to chance. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."

In fact, most guidelines and peer-reviewed publications come to the same conclusion[30, 59, 60, 62] on what tests to use, as did EPA's FIFRA Scientific Advisory Panel (SAP) in their review of the EPA's issue paper of the carcinogenicity of glyphosate[54]. The US National Toxicology Program (NTP) uses both a trend test[3, 4, 63] and Fisher's exact test for analyzing carcinogenicity data. Unless otherwise noted in this document, all p-values presented in this section on animal cancer studies were recalculated on my computer and are the exact one-sided p-values for the Fisher test (p_{Fisher}) and/or the Cochran-Armitage linear trend test (p_{Trend}) where appropriate. In cases where the data is pooled and the numbers of tumors are large, the approximate p-value based upon the normal distribution is used for the trend test to avoid excessive computation time; these are noted as p_{TrendA}. The approximation (p_{TrendA}) is generally equivalent to the exact p-value (p_{Trend}) when there are more than 10 animals with tumors[64].

To avoid doing large numbers of tests and over-analyzing the data, my comments will generally rely upon the use of the trend test with the results from Fisher's exact test serving as a descriptive discussion of the findings. This is in agreement with SAP comments[54] and is generally accepted in the evaluation of animal cancer studies.

Even with the high doses used in these studies, it is sometimes necessary to use "historical controls" to evaluate a given response. Historical controls are generally the historical collection of tumor responses from untreated control groups from studies in the same laboratory within two to three years of the study being evaluated[30, 34, 59, 65, 66]. Evaluation of the data using the historical controls should be done rigorously to correctly evaluate the responses seen in a given study. Where a valid historical control dataset was available, I used the mean tumor response in the controls to calculate the probability of observing the trend seen in the study or a more significant trend if the true probability of response is the historical control average; this is labeled p_{Hist}. In all cases, the guidelines and literature support the use of the control in the current study as the most appropriate control group to use unless there is a specific need to address historical responses. Many guidelines[30, 33, 34, 67] suggest historical controls be used for evaluating rare tumors and findings in assays that appear to be unusual. It is explicitly noted that significant increases in tumors over what is seen in the concurrent control should not be rejected simply because the tumors are in the range of the historical controls[30]. Nor is it recommended to reject significant increases in tumor responses because the control response is on the low end of the historical range. Animals are randomly assigned to control and exposure groups and any low response in controls is likely to also reflect similar response patterns in treated animals. This is in agreement with SAP comments[54] on the EPA issue paper on glyphosate[61] and with all guidelines for analyzing animal carcinogenicity data.

There are 13 animal carcinogenicity studies in rats[68-80] and eight in mice[81-88]. Only two studies[71, 77] appear in the peer-reviewed literature; the remaining studies are partially available through several sources. For three of the rat studies[70, 74, 78] and two mouse studies[83, 86], technical reports from the performing laboratory are available from documents provided by the registrant. For the remaining unpublished studies, data was obtained from the EPA review of glyphosate[61], the European Food Safety Authority review of glyphosate[89, 90] and supplemental material from a review of the carcinogenicity of glyphosate by a panel of scientists on behalf of Monsanto[91].

Many additional endpoints, other than cancer incidence and related toxicities, were evaluated in these studies; I will only provide comments on the tumor incidence data and related data where relevant to the cancer findings.

It is unusual to have multiple carcinogenicity studies in the same experimental animal model arising from different laboratories. Methods for the combined analysis of multiple animal cancer bioassays are not available in the scientific literature. However, pooled analyses, as conducted in epidemiology[92, 93] are applicable for combining animal carcinogenicity studies. The basic concept is to pool all data from the same sex/species/strain into one study and analyze it appropriately. The basic steps are: 1) select the studies to be pooled; 2) merge the data for analysis; 3) estimate study specific

effects; 4) estimate pooled effects; 5) explain the differences between the pooled effects and the individual study effects; 6) do a sensitivity analysis if possible. These steps will be used to analyze pooled data from animal carcinogenicity studies where pooling is done by sex, species, strain and duration of exposure to limit heterogeneity across pooled studies. In their recommendations to the EPA regarding EPA's issue paper on the carcinogenicity of glyphosate[54], the FIFRA Science Advisory panel strongly supported the use of a pooled analysis to address the question of consistency citing my comments to the EPA[94].

Rat Studies

Reyna and Gordon (1974)[76] exposed Albino rats (probably Sprague-Dawley) to ammonium salt of glyphosate (13.85% purity) in a two-year chronic feeding study. Only EPA[61] reported on this study and provided no details other than to report there were approximately 70 animals per group and there was insufficient reporting on the histopathology findings. Insufficient detail is available on this study.

This study is inadequate for use in deciding on causality.

Burnett et al. (1979)[70] exposed male and female albino rats to an aqueous monosodium salt solution of glyphosate by oral intubation (purity not given). There were 90 animals per group and doses were 0, 3, 10 and 30 mg/kg/day for 24 months. EPA[61] reported that no histopathological alterations were observed; no additional information was available on this study. This study had severely reduced sensitivity to observe any cancer findings because the highest dose used in this study is very low compared to the MTDs in the other rat studies. This study does not contribute to the evaluation of cancer causation in laboratory animals and will be excluded from any further discussion.

Lankas et al. (1981)[74] exposed groups of 50 male and 50 female Sprague-Dawley rats to glyphosate (98.7% purity) in feed (see Table 1 for doses) for 26 months. This study is not in concordance with OECD guidelines (they were not available at the time of this study), but as noted by EFSA[89], it was in general accordance with the 1981 OECD guidelines. Information on this study was available from EPA[61], EFSA[89], Greim et al.[91], the original study report from Bio/dynamics Inc.[95] and memos from Monsanto to EPA provided by Monsanto.

There were no survival differences in this study and there was no indication that the highest dose used exceeded the maximum-tolerated dose.

Table 1 shows the statistically significant trend in testicular interstitial cell tumors that was observed (p_{Trend}=0.009). Historical controls were provided in the study report for five studies with response rates of 4/116, 5/75, 4/113, 6/113 and 5/118 for a mean response of 4.5% (24/535). Comparing this historical control mean to the observed response yields p_{Hist}=0.006, showing that this result is significant, even when comparing it to the historical control dataset. **Lankas et al. (1981)** argued that the tumor rates at sacrifice were not statistically significant from control suggesting this finding is not related to glyphosate. However, by reducing the numbers of animals to only those at

terminal sacrifice, the power to find an effect was significantly reduced. Also, if the tumor increases the animal's chances of dying, then some animals with tumors will die early, which could bias results only seen at terminal sacrifice. This type of analysis is simply never done; it appears to have been developed for this case to dismiss the effects seen in the study. **Lankas et al. (1981)** also suggested the control response was low compared to the historical rates, but the concurrent control is always the best control group to use unless it is clearly flawed[33, 34, 59]; in this case, there was no apparent problem with the controls because the probability of seeing 0/50 if the true background response is 4.5% is about 10% and this control group is not significantly different than the historical controls. **EFSA**[89] noted rates for interstitial cell hyperplasia (a potential precursor for the interstitial cell tumors) and saw no dose-response trend (Table 1). However, these very low rates would suggest that the tumors arising in the 10 animals that did get interstitial cell tumors are independent of a mechanism involving interstitial cell hyperplasia. The tumor response for interstitial cell tumors was not monotonic (tumor rates increasing as dose increases), but was still within statistical variation. The EPA SAP agrees, concluding that "requiring visual confirmation of a monotonic trend in scatter plots of data ... is known to be a poor way of assessing trend"[54].

An increase in Thyroid C-cell carcinomas (Table 1) was observed in female rats (p_{Trend}=0.003) but combining adenomas and carcinomas was only marginally significant (p_{Trend}=0.072). Independent pathologists brought in by Monsanto argued these tumors were not treatment related. The authors provided historical control data for both carcinomas and carcinomas combined with adenomas from nine control groups with mean responses of 4/453=0.9% for carcinomas and 46/453=10.2% for the combined tumors. The significance of both results was unchanged using the historical control data.

The authors also mentioned that the incidence of lymphocytic hyperplasia in the thymus and lymph nodes were slightly elevated above controls (p_{Trend}=0.143). The middle dose group was significantly different from controls (p_{Fisher}=0.018).

This study also had a statistically significant increase in pancreatic islet cell tumors in the lowest dose (p_{Fisher}=0.028) in males (Table 1), but not any of the other doses; the trend test was not significant (p_{Trend}=0.312).

The highest dose used in this study in Sprague-Dawley rats is far below the MTD. Even though EFSA[89] noted that this study was in general accordance with the 1981 OECD guidelines, they dismissed it for not meeting current guidelines due to the low-doses used. EPA[61] also excluded this study from consideration. However, the study saw an increase in testicular tumors in males and Thyroid C-cell carcinomas in females that should be carefully evaluated in determining causality. Also, this is the study with the longest exposure (26 months) and provides unique information to the overall evaluation.

Additional tumors seen to have significant increases in other studies using Sprague-Dawley Rats are also included in Table 1.

Table 1: Tumors of interest in male and female Sprague-Dawley rats the 26-month feeding study of **Lankas (1981)**[74]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	3.05	10.30	31.49	
	Female	0	3.37	11.22	34.02	
Testicular interstitial cell tumors	Male	0/50	3/50	1/50	6/50**	P_{Trend}=0.009 P_{Hist}=0.006
Interstitial cell hyperplasia	Male	1/50	1/50	1/50	0/50	P_{Trend}=0.830
Thyroid C-cell Carcinomas	Female	1/47	0/49	2/50	6/47	P_{Trend}=0.003 P_{Hist}=<0.001
Thyroid C-cell Adenomas and Carcinomas	Female	6/47	3/49	8/50	9/47	P_{Trend}=0.072 P_{Hist}=0.072
Pancreas Islet Cell Tumors	Male	0/50	5/50*	2/50	3/50	P_{Trend}=0.312
lymphocytic hyperplasia, thymus and lymph nodes	Female	27/50	35/50	38/50*	35/50	P_{Trend}=0.143
Thyroid C-cell Adenomas and Carcinomas	Male	1/47	2/49	4/49	4/49	P_{Trend}=0.122
Thyroid Follicular-cell Adenoma	Male	5/47	1/49	2/49	2/49	P_{Trend}=0.748
Liver Neoplastic Nodule	Male	3/50	5/50	1/50	3/10	P_{Trend}=0.630
Kidney Adenoma	Male	1/50	5/50	0/50	0/50	P_{Trend}=0.979

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

In conclusion, this study shows positive result for testes interstitial cell tumors and hepatocellular adenomas in male Sprague-Dawley rats and a positive response for thyroid c-cell carcinomas in female Sprague-Dawley rats and will be included in the overall evaluation of causation.

Stout and Ruecker (1990)[78] exposed groups of 50 male and 50 female Sprague-Dawley rats to glyphosate (98.7% purity) in feed (see Table 2 for doses) for 24 months. This study was done under OECD guidelines.

There were no survival differences in this study and there was no indication that the highest dose used exceeded the maximum-tolerated dose.

Pancreatic islet cell tumors were increased in all dose groups relative to the controls in male rats and statistically significant for the lowest (p_{Fisher}=0.015) and highest (p_{Fisher}=0.032) dose groups (Table 2). However, these rates include the 10 animals that were sacrificed at one year. Due to the short duration of exposure, the rats terminated at one year were likely not at risk of developing this tumor; it is very unusual to include these animals in the final tumor counts (EPA[61] also excluded these animals). In the pathology tables for this study, there were no tumors in any of the 10 animals at the interim sacrifice. Removing these 10 animals does not alter the p-values for trend or

Fisher's exact test. Historical control data for this tumor in this laboratory was reported as 23/432 or 5.3%[96] and a trend comparison against this control rate was not significant (p_{hist}=0.15). The lack of a trend is driven by the up and down nature of the response. Assuming the historical rate of 5.3% is correct, the chances of seeing eight or more tumors in 47 animals is 0.003. Similarly, for the mid- and high-doses, this probability is 0.124 and 0.014, respectively. Females did not show an increase in this tumor. The authors provided a table with the combined results for pancreatic islet-cell adenomas and carcinomas from this study with the tumor counts from the **Lankas et al. (1981)**[74] study arguing the results do not show a dose-related increase. Animals studied for 26 months versus 24 months can have very different responses to the same chemical and very different control incidence.

In male rats, there was a statistically significant trend (p_{Trend}=0.015) after removal of interim-sacrificed animals for hepatocellular adenomas but a significant increase for adenomas and carcinomas combined (p_{Trend}= 0.05, Table 2) and not in females (not shown). Liver carcinomas are generally also provided in a separate analysis, but these data were not provided by the authors (the data would suggest the hepatocellular carcinomas would have a negative trend).

There was also a significant increase in thyroid C-cell adenomas in the female rats (p_{Trend}=0.049) and a marginal increase[6] in adenomas and carcinomas combined (p_{Trend}=0.052) regardless of whether interim sacrificed animals are included (Table 2). In males, the trend for adenomas was p_{Trend}=0.084 and for adenomas and carcinomas was p_{Trend} =0.091. Adenomas were seen in male rats at the interim sacrifice demonstrating that male rats at the interim sacrifice were at risk for this tumor. If these animals are added back into the analysis, the trend test in males has p_{Trend}=0.063 for adenomas and p_{Trend}=0.068 for adenomas and carcinomas combined.

Several other tumors demonstrating significant findings in other studies of Sprague-Dawley rats are included in Table 2 and do not show significant effects.

In conclusion, the finding of an increased incidence of pancreatic islet-cell tumors in this study cannot easily be ruled out as a chance finding. Findings of significant increases in liver adenomas in male rats with no increases in carcinomas could be due to chance. The findings of significant increases in thyroid c-cell tumors in males and females should be compared with other studies. This study will be included in the overall evaluation of causation.

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[6] In statistics, it is common to refer to p-values in the range of 0.10>p-value>0.05 as marginal when the target p-value is ≤0.05; this is done to avoid missing trends in data reflected by almost significant findings

Table 2: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of Stout and Ruecker (1990)[78]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	89	362	940	
	Female	0	113	457	1183	
Pancreas Islet Cell Tumors (with interim sacrifice)	Male	1/58	8/57*	5/60	7/59*	P_{Trend}=0.147 P_{Hist}=0.140
Pancreas Islet Cell Tumors (without interim sacrifice)	Male	1/48	8/47*	5/50	7/49*	P_{Trend}=0.147 P_{Hist}=0.150
Hepatocellular adenomas (without interim sacrifice)	Male	3/50	2/50	3/50	8/50	P_{Trend}=0.015
Hepatocellular Adenomas and Carcinomas (without interim sacrifice)	Male	6/50	4/50	4/50	10/50	P_{Trend}=0.050
Thyroid C-Cell Adenomas (with interim sacrifice)	Female	2/60	2/60	6/60	6/60	P_{Trend}=0.050
Thyroid C-Cell Adenomas (without interim sacrifice)	Female	2/50	2/50	6/50	6/50	P_{Trend}=0.049
Thyroid C-Cell Adenomas and Carcinomas (with interim sacrifice)	Female	2/60	2/60	7/60	6/60	P_{Trend}=0.053
Thyroid C-Cell Adenomas and Carcinomas (without interim sacrifice)	Female	2/50	2/50	7/50	6/50	P_{Trend}=0.052
Thyroid C-Cell Adenomas (with interim sacrifice)	Male	2/60	4/60	8/60	7/60	P_{Trend}=0.063
Thyroid C-Cell Adenomas (without interim sacrifice)	Male	0/50	4/50	8/50**	5/50*	P_{Trend}=0.084
Thyroid C-Cell Adenomas and Carcinomas (with interim sacrifice)	Male	2/60	6/60	8/60*	8/60*	P_{Trend}=0.068
Thyroid C-Cell Adenomas and Carcinomas (without interim sacrifice)	Male	0/50	6/50*	8/50**	6/50*	P_{Trend}=0.091
Testis Interstitial Cell Tumors	Male	2/50	0/50	3/50	2/50	P_{Trend}=0.296
Kidney Adenomas	Males	0/50	2/50	0/50	0/50	P_{Trend}=0.813
Thyroid Follicular Adenoma/Carcinoma	Males	2/50	1/48	3/48	3/50	P_{Trend}=0.225

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Atkinson et al. (1993)[68] conducted a combined chronic toxicity/carcinogenicity study of glyphosate (98.9% pure). They used 50 Sprague-Dawley rats in each group for both sexes with dietary exposures given in Table 3. An additional 35 rats/sex/dose were included for interim sacrifices.

There were no survival differences in this study and there was no indication that the highest dose used exceeded the maximum-tolerated dose.

Table 3: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of Atkinson et al. (1993)[68]

Tumor	Sex	Doses (mg/kg/day)					p-values
	Male	0	11	112	320	1147	
	Female	0	12	109	347	1134	
Thyroid Follicular Adenomas and Carcinomas	Male	0/50	0/21	0/17	2/21	2/49	P_{Trend}=0.099
Thyroid Follicular Adenomas and Carcinomas (adding terminal sacrifice animals to denominator)	Male	0/50	0/50	0/50	2/50	2/49	P_{Trend}=0.034
Thyroid C-cell Adenomas and Carcinomas	Female	8/50	1/27	1/29	1/29	7/49	P_{Trend}=0.197
Thyroid C-cell Adenomas and Carcinomas	Male	9/50	1/21	1/17	2/21	9/49	P_{Trend}=0.183
Testes Interstitial Cell Tumors	Male	3/50	1/25	0/19	0/21	2/50	P_{Trend}=0.580
Kidney Adenomas	Males	1/50	0/50	0/50	0/50	0/50	p_{Trend}=1
Hepatocellular Adenomas	Males	2/50	1/50	1/50	2/50	3/50	P_{Trend}=0.155
Pancreas Islet-Cell Adenoma	Male	0/50	0/50	0/50	0/50	1/50	P_{Trend}=0.200

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

The authors reported no significant effects, as do **EPA**[61] and **EFSA**[89]. The study did not do detailed histopathological examination on all animals in all groups for every tumor type, but did examine all control and high dose animals, all animals that died before study termination and animals showing macroscopic tumors at study termination; liver, kidney and lungs were examined for all animals. This severely weakens the study for addressing dose-response trends. However, in reviewing the pathology tables provided in **Greim et al. (2015)**[91], thyroid follicular adenomas and carcinomas were found to be marginally significant (p_{Trend}=0.099) by the trend test. If the three middle exposure groups had seen no other tumors and the denominators were the entire 50 animals on study, the trend analysis becomes significant (p_{Trend}=0.034).

Without examination of the animals free of gross tumors at terminal sacrifice, the findings from this study will be given less weight in the overall evaluation of causation.

Brammer (2001)[69] conducted a two-year carcinogenicity study in Wistar rats in which groups of 52 animals were exposed to glyphosate (97.6% pure) at doses provided in

Table 4 . An additional 12 animals were sacrificed at one-year.

A significant positive trend in survival was noted by the EPA (p=0.03), however this trend was not accomplished using a Kaplan-Meir test[97] (the appropriate test), but simply a test relating to the percent surviving to terminal sacrifice. There was no indication that the highest dose used exceeded the maximum-tolerated dose.

EPA[61], but not **EFSA**[89], noted there was a statistically significant trend of hepatocellular adenomas in male rats with the highest dose also being statistically significant from the control. Trend analysis gives p_{Trend}=0.008 and the Fisher's exact test comparison of high dose to control is p_{Fisher}=0.027. EPA dismissed this finding as potentially due to a slight difference in the number of animals at the terminal sacrifice in this study versus controls. However, no formal statistical evaluation of survival is provided and it cannot be assumed from these numbers that survival was significantly impacted in these animals. **Greim et al. (2015)**[91] used slightly different numbers for this tumor because three animals (one in the control group, one in the low-dose group and one in the mid-dose group) in the interim sacrifice group died before their sacrifice time and, from the pathology tables provided in their paper, these could not be separated from others. These numbers have been included in Table 4, but it does not change the significance of the findings. **Greim et al. (2015)**[91] dismissed these findings, partly because of the same survival argument used by the EPA and partly because they had a historical control dataset where the range of historical response was from 0-11.5%; they did not provide the mean response or the individual tumor responses for these historical controls. As mentioned earlier, dismissing results because they are in the range of the historical controls is an unacceptable method for using historical controls to evaluate a study, and in this case, there is no reason to question the concurrent controls.

Table 4: Tumors of interest in male and female Wistar rats from the 24-month feeding study of Brammer (2001)[69]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	121	361	1214	
	Female	0	145	437	1498	
Hepatocellular Adenoma	Male	0/52	2/52	0/52	5/52*	P_{Trend}=0.008
Hepatocellular Adenoma (from Greim et al., 2015[91])	Male	0/53	2/53	0/53	5/52*	P_{Trend}=0.008 P_{Hist}=0.006
Mammary Gland Adenomas and Adenocarcinomas	Female	3/51	2/51	0/51	2/51	P_{Trend}=0.575
Skin Keratocanthoma	Male	1/51	0/51	1/51	1/51	P_{Trend}=0.392

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

I obtained historical control data from 16 control groups in Wistar rats from Charles River Laboratories for the years 2003 to 2011[98]. Although these are outside of the optimal time range for the animals used in the **Brammer (2001)** study, they can serve as an illustration of why using a range can be misleading. There were 52 liver adenomas

seen in 1217 control animals for a mean response of 4.27% with a range of 0% to 17.5% (individual study findings of 6/100, 0/60, 1/60,1/50,1/80, 14/112, 1/65, 0/60, 21/120, 0/50, 1/50, 2/60, 0/50, 1/100, 1/150, 2/50; 13 studies with ≤2% response). Assuming the underlying probability of having a tumor in controls is 4.27%, p_{Hist}=0.006 (Table 4). Thus, even though the responses seen in **Brammer (2001)** are in the range of the historical controls, the trend is highly significant when historical controls are used appropriately. **Greim et al. (2015)** also mentioned findings of increased toxicity at the high dose for which they provided numbers for only hepatocyte fat vacuolation and hepatitis; none of these findings were statistically significant by any test.

In conclusion, this study shows a positive result for hepatocellular adenomas in male Wistar rats and will be included in the overall evaluation of causation.

Pavkov and Wyand (1987)[75] exposed Sprague-Dawley rats to glyphosate trimesium salt (sulfosate, 56.2% pure) in feed for two years. Eighty animals/sex were tested in the control, low-dose and mid-dose groups, and 90/sex were tested in the high dose group. Doses of 0, 4.2, 21.2 and 41.8 mg/kg/day were used in males and 0, 5.4, 27, and 55.7 mg/kg/day in females. This study showed no significant findings according to EPA[61]. No details were given beyond that simple statement and no others reported on this study. The doses in this study are far below the MTD so this study would have reduced sensitivity to detect an effect if one existed. This study also used a different chemical than the other Sprague-Dawley rat studies and is not comparable on that basis.

This study is not acceptable for use in the evaluation of causality due to the lack of details about the study.

Suresh, (1996)[79] exposed Wistar rats to glyphosate (96.8% pure) in feed for two years. Fifty animals/sex were tested in four exposure groups shown in Table 5.

There were no survival differences in this study and there was no indication that the highest dose used exceeded the maximum-tolerated dose.

EPA[61] concluded there were no tumors increased due to glyphosate exposure in this study and **EFSA**[89] concluded that, "[n]one of the significant microscopic changes, increased and decreased incidences (in liver, spleen, lymph nodes, adrenals, thymus, gonads, uterus, mammary gland) observed have shown dose relationship, hence appeared to be incidental and not related to the treatment with the test compound." (page 491). **Greim et al. (2015)**[91] provided data on hepatocellular adenomas and carcinomas in both sexes but none of these showed significant trends or pairwise tests (Table 5). However, there was another study with a strong significant trend in hepatocellular adenomas in Wistar rats[69] so these are also included in Table 5 for comparison. No other tumors were mentioned by any other group and an examination of the grouped pathology tables provided by **Greim et al. (2015)** show an increase in mammary gland adenomas at the mid-dose (p_{Fisher}=0.017) but no significant trend. However, there was another study with a strong significant trend in mammary gland adenomas and adenocarcinomas combined in Wistar rats[80] so these are also included in Table 5 for comparison. Like the **Atkinson et al. (1993)**[68] study, **Suresh (1996)** did not do full pathology on all of the animals in the interim exposure groups making

interpretation of this study problematic.

This study will be included in the overall evaluation of causation.

Table 5: Tumors of interest in male and female Wistar rats from the 24-month feeding study of Suresh(1996)[79]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	6.3	59.4	595.2	
	Female	0	8.6	88.5	886	
Mammary Gland Adenoma and Carcinoma	Female	5/40	3/28	8/33	2/48	P_{Trend}=0.970
Hepatocellular Adenoma	Male	24/50	22/50	10/50	21/50	P_{Trend}=0.374
Skin Keratocanthoma	Male	0/50	0/50	0/50	0/50	P_{Trend}=1

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Enemoto (1997)[72] exposed Sprague-Dawley rats to glyphosate (95.7% pure) in feed for two years. Fifty animals/sex were tested in four exposure groups (see Table 6). In addition, 10 animals per exposure group were exposed for 1 year and another 10 for 18 months at which point they were sacrificed and examined. These interim sacrifice animals (1 year and 18 months) are included in the analysis if tumors were seen in these groups.

There were no survival differences in this study and there was no indication that the highest dose exceeded the maximum-tolerated dose.

EPA and EFSA both found no significant changes in tumors in any group. **Greim et al. (2015)** again provide tables for a number of tumors, none of which show significant effects except for the incidence of kidney adenomas in male rats (p_{Trend}=0.004, Table 6). Examining the pathology tables provided in **Greim et al. (2015)** reveals no additional tumors showing an increase in tumor incidence with dose. A different study[74] in Sprague-Dawley rats demonstrated a strong significant trend in mammary gland adenomas, thyroid C-cell carcinomas, skin Keratocanthomas and testicular interstitial cell tumors so these are also included in Table 6 for comparison.

This study showed a significant increase in kidney adenomas and will be included in the overall evaluation of causation.

Table 6: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of Enemoto (1997)[72]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	104	354	1127	
	Female	0	115	393	1247	
Mammary Gland Adenoma	Female	23/50	27/50	24/50	30/50	P_{Trend}=0.106
Kidney Adenoma	Male	0/50	0/50	0/50	4/50	P_{Trend}=0.004
Thyroid C-cell Adenomas/Carcinomas	Female	4/60	7/60	8/60	4/60	P_{Trend}=0.692
Thyroid C-cell Adenomas/Carcinomas	Male	8/70	10/70	6/70	7/70	P_{Trend}=0.697
Thyroid Follicular-cell Adenomas/Carcinomas	Male	4/70	2/70	1/70	0/70	P_{Trend}=0.990
Testes Interstitial Cell Tumors	Male	3/49	2/50	0/50	2/50	P_{Trend}=0.594
Hepatocellular Adenomas	Male	1/60	0/60	2/60	1/60	P_{Trend}=0.371
Skin Keratocanthoma	Male	3/50	3/50	0/50	6/50	P_{Trend}=0.065
Pancreas Islet-Cell Adenoma	Male	4/50	1/50	2/50	1/50	P_{Trend}=0.844

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Wood et al. (2009)[80] exposed Wistar rats to glyphosate (94.7% to 97.6% pure) in feed for two years. Fifty-one animals/sex were tested in four exposure groups at doses shown in Table 7.

No survival differences were seen in this study.

EFSA[89] found no dose-related tumor increases while **EPA**[61] noted an increase in mammary gland adenomas and adenocarcinomas combined with p_{Trend}=0.062 for adenomas, p_{Trend}=0.042 for adenocarcinomas and p_{Trend}=0.007 for the combined tumors (Table 7). EPA concluded there was no progression from adenoma to adenocarcinoma and argued the increase was not glyphosate related. This conclusion is contradicted by the fact that 6 animals in control and the lower dose groups got carcinomas with no adenomas in any of the animals in these groups. It seems likely that, in this case, mammary gland adenocarcinomas can arise without the presence of any adenomas. **Greim et al (2015)**[91] also noted an increase in skin keratoacanthoma in males (p_{Trend}=0.030). Review of the pathology tables identified no other tumors with increased tumor rates as a function of dose. There was another study with a strong significant trend in hepatocellular adenomas in Wistar rats[69] so this tumor is also included in Table 7 for comparison.

This study showed an increase in mammary tumors in females and skin keratoacanthomas in males and will be used in the evaluation of causality.

Table 7: Tumors of interest in male and female Wistar rats from the 24-month feeding study of Wood et al. (2009)[80]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	85.5	285.2	1077.4	
	Female	0	104.5	348.6	1381.9	
Mammary Gland Adenomas	Female	0/51	0/51	0/51	2/51	P_{Trend}=0.062
Mammary Gland Adenocarcinomas	Female	2/51	3/51	1/51	6/51	P_{Trend}=0.042
Mammary Gland Adenomas and Adenocarcinomas	Female	2/51	3/51	1/51	8/51*	P_{Trend}=0.007
Skin Keratocanthoma	Male	2/51	3/51	0/51	6/51	P_{Trend}=0.030
Hepatocellular Adenoma	Male	0/51	2/51	1/51	1/51	P_{Trend}=0.418

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Excel (1997)[73] exposed Sprague-Dawley rats to glyphosate (purity not given) in feed for two years. Fifty-one animals/sex were tested in four exposure groups at doses of 0, 150, 780 and 1290 mg/kg/day in males and 0, 210, 1060 and 1740 mg/kg/day in females. **EPA**[61], **EFSA**[89] and **Greim et al. (2015)**[91] had concerns with the quality of this study, the characterization of the chemical being used and with tumor rates in this strain of animals being too low. The Supplemental Material from **Greim et al. (2015)** on this study shows no significant increase in any tumor and virtually all animals having no tumors in controls and treated animals.

This study is inadequate for use in deciding on causality for the same reasons given by the **EPA**, **EFSA** and **Greim et al. (2015)**.

Chruscielska, K. (2000)[71] exposed Wistar rats to glyphosate as a 13.8% solution (purity not given) in drinking water for two years. According to **Greim et al. (2015)**[91], this appears to be the glyphosate formulation Perzocyd. Eighty-five animals/sex were tested in four exposure groups. The authors listed the doses as control, 300 mg/L, 900 mg/L and 2700 mg/L in drinking water. **Greim et al. (2015)**[91] estimated the intake of glyphosate to be 0, 1.9, 5.7 and 17 mg/kg/day for females and 0, 2.2, 6.5, and 19 mg/kg/day in males. There was a slight increase in malignant adenomas of the pituitary gland and an opposite decrease in pituitary adenomas suggesting no effect or potentially a promotional effect in which adenomas are promoted to carcinomas by glyphosate. No other increased tumor responses were reported in the manuscript. Because of the low exposures, this study is an inadequate challenge to the animals (the highest dose is far below the MTD). The reporting of this study is very limited and it the overall quality of the work cannot be evaluated.

This study is inadequate for use in deciding on causality.

Seralini, G. E., et al. (2014)[77] exposed Sprague-Dawley rats to the glyphosate formulation Roundup in drinking water for two years as part of a broader experiment on

Roundup-Ready Corn. Ten animals/sex were tested in four exposure groups at doses of 0, 0.00005, 400 and 22500 mg/L in females. The authors reported an increase in the incidence of mammary gland tumors (mainly fibroadenomas and adenocarcinomas) in female rats with incidences of 5/10 for control and 9/10, 10/10, 9/10 (p_{Fisher}=0.016) in the low-, mid- and high-doses groups respectively. It is difficult to assess the quality of this study due to limited reporting on the histopathological descriptions of the tumors and the very small sample size.

This study will not be used in the evaluation of causality.

Joint Analysis - Rats

Table 8 summarizes the significance for all tumors of interest in rats.

Brammer (2001)[69] saw a significant increase in hepatocellular adenomas in male Wistar rats with increasing dose (p_{Trend}=0.008, Table 4). The other two acceptable studies in Wistar rats (**Wood et al. (2009)**[80] and **Suresh (1996)**[79] did not see significant increases (Tables 5 and 7). On the basis of statistical significance, these studies are inconsistent. To reject these findings based upon only 1/3 being positive is the same as rejecting a coin as being fair if, in three flips of the coin, the result is one head and two tails; it simply is not possible and there is a better way to address these findings. Given different doses and different sample sizes, we need to formally test for consistency in these studies. **Suresh (1996)** saw 48% response for hepatocellular adenomas in controls whereas the other two studies saw no tumors in the control animals. Thus, although all three studies are in Wistar rats, **Suresh (1996)** has a significantly different control response from the other two. **Suresh (1996)** did not give a substrain for the Wistar rats used, but **Brammer (2001)** and **Wood et al. (2009)** used different substrains. All three studies used different diets and were conducted in different facilities. Thus, there is no obvious explanation for the dramatically different rates in **Suresh (1996).** It is known that the same strain of rats from different laboratories can have markedly different control tumor responses. Because they have similar control response, **Brammer (2001)** and **Wood et al. (2009)** can be pooled into a single study to ask the question "Does the significant trend for **Brammer (2001)** disappear when it is pooled with the negative study of **Wood et al. (2009)**?" The analysis of the pooled studies yields p_{Trend}=0.013 supporting the conclusion that glyphosate causes hepatocellular adenomas in Wistar rats with similar background responses.

Wood et al. (2009)[80] saw a significant increase in mammary gland adenomas and adenocarcinomas (p_{Trend}=0.007, Table 7) in females that was not seen in the other two studies (Tables 4 and 6). The background rates in these studies differ only slightly and a pooled analysis of all three studies yields p_{TrendA}=0.459, suggesting that combining the data eliminates the dose-response trend seen in **Wood et al. (2009)**. However, if the Wistar rats used in **Suresh (1996)** differed in their response for hepatocellular adenomas, they may differ for this tumor as well. Combining only **Wood et al. (2009)** with **Brammer (2001)** results in p_{Trend}=0.037. Given the mixed results from the pooling for this tumor I conclude there is limited support for the notion that glyphosate can cause mammary gland adenomas and adenocarcinomas in Wistar rats.

Wood et al. (2009)[80] saw a significant increase in skin keratocanthomas (p_{Trend}=0.030, Table 7) in males that was not seen in the other two studies (Tables 4 and 6). The background rates in these studies differ only slightly and a pooled analysis of all three studies yields p_{TrendA}=0.010, suggesting that combining the data does not eliminate the dose-response trend seen in **Wood et al. (2009)**. Combining only **Wood et al. (2009)** with **Brammer (2001)** results in p_{Trend}=0.053. Given the results from the pooling for this tumor I conclude there is support for the notion that glyphosate can cause skin keratocanthomas in Wistar rats.

In Sprague-Dawley rats, there were four studies that were acceptable for inclusion in the evaluation of causality with one[74] yielding strong positive responses for thyroid C-cell carcinomas in females and testicular interstitial tumors and hepatocellular adenomas in males and another[72] yielding a strong result for kidney adenomas in males. **Lankas (1981)**[74] saw a significant increase in thyroid C-cell carcinomas in female rats exposed to glyphosate (p_{Trend}=0.003, Table 1) and a marginal increase in C-cell adenomas and carcinomas combined (p_{Trend}=0.072, p_{hist}=0.072, Table 1; two of the other three studies also saw marginal results for thyroid C-cell adenomas and carcinomas in females (Tables 2 and 3). A pooled analysis using all four studies yields p_{TrendA}=0.390. This pooled analysis does not support the results seen in **Lankas (1981)**. However, the **Lankas (1981)** study was for 26 months and the other three were for 24 months; the C-cell carcinomas could be a result of the longer exposure period even though the dose is substantially lower in this study compared to the other two. From these data, I conclude that the evidence is weak that glyphosate causes thyroid C-cell tumors in female Sprague-Dawley rats.

Thyroid C-cell adenomas and carcinomas combined, in males, show marginally significant dose-response trends in **Stout and Ruecker (1990**, Table 2) but not in the remaining three studies. Pooling all four studies yields a significant trend of p_{TrendA}=0.041. From these data, I conclude that there is evidence is that glyphosate causes thyroid C-cell tumors in male Sprague-Dawley rats.

Thyroid follicular-cell adenomas and carcinomas combined, in males, show a significant dose-response trend in **Atkinson et al. (1993**, Table 3) but not in the remaining three studies;. Pooling all four studies yields no significant trend with p_{TrendA}=0.618. From these data, I conclude that there is no evidence that glyphosate causes thyroid follicular-cell tumors in male Sprague-Dawley rats.

Hepatocellular adenomas, in males, show a significant dose-response trend in **Stout and Ruecker (1990**, Table 2) but not in the remaining three studies. Pooling all four studies yields a marginally significant trend with p_{Trend}=0.073. From these data, I conclude that there is limited evidence that glyphosate causes thyroid follicular-cell tumors in male Sprague-Dawley rats.

Table 8: Summary of significance tests for 5 tumors from 7 studies in Rats

Study	Strain	Neoplasm							
		Hepato-cellular Adenomas (males)	Mammary Gland Tumors (females)	Skin Kerato-canthoma (males)	Thyroid C-Cell Tumors (females)	Thyroid C-Cell Tumors (males)	Thyroid Follicular Cell Tumors (males)	Testis Inter-stitial Cell Tumors (male)	Kidney Adenomas (males)
Brammer (2001)[69]	Wistar	+++[1]	-						
Wood (2009)[80]		-	+++	++					
Suresh (1996)[79]		-	-						
Pooled Wistar Rats		++[2]	++[2]	+++					
Lankas (1981)[74]	Sprague Dawley	-[3]			+	-	-	+++	-
Enemoto (1997)[72]		-			-	-	-	-	+++
Atkinson et al. (1993)[68]		-			-	-	++	-	-
Stout and Ruecker (1990)		++			-	+	-	-	-
Pooled Sprague-Dawley Rats		+			-	++	-	-	++[4]

[1]entries are p_{Trend}/p_{Hist} with values: – p>0.1, + 0.1≥p>0.05, ++ 0.05≥p>0.01, +++ p≤0.01; [2]pooling results from **Brammer (2001)** and **Wood (2009)** only; [3]liver neoplastic nodules; [4]excluding **Lankas (1981)**

Another significant trend seen in Sprague-Dawley rats is the finding of testes interstitial cell tumors from **Lankas (1981)**[74] (P_{Trend}=0.009, Table 1); the other three studies were negative for this tumor (Tables 2, 3 and 6). Combining the other three studies with that of **Lankas (1981)** for testes interstitial tumors results in a p-value for trend that is clearly non-significant (p_{TrendA}=0.608). However, as noted above, the **Lankas (1981)** study was for 26 months and the other two were for 24 months; the tumors could be a result of the longer exposure period even though the dose is substantially lower in this study compared to **Stout and Ruecker (1990)**, **Atkinson et al.(1993)** and **Enemoto (1997)**.

The final tumor in Sprague-Dawley rats showing a strong significant trend is kidney

adenomas in males from the study by **Enemoto (1997)**[72] (P_{Trend}=0.004, Table 6). The kidney tumor data is not significant for the studies by **Lankas (1981)**[74] (Table 1), **Atkinson et al. (1993)**[99] (Table 3) and **Stout and Ruecker (1990)**[78] (Table 2). Pooling the **Enemoto (1997)** study with that of **Lankas (1981)**[74], **Stout and Ruecker (1990)** and **Atkinson et al. (1993)** yields p_{TrendA}=0.201. Removing the 26-month study by **Lankas (1981)**[74] yields a p-value for the three combined 24-month studies of p_{Trend}=0.031; thus, the association between glyphosate and kidney adenomas in male Sprague-Dawley rats is supported by these data, even with the difficulty associated with interpreting the results in the low- and mid-doses in the **Atkinson et al. (1993)** study. There is evidence to support an increase in kidney tumors in male Sprague-Dawley rats exposed to glyphosate.

In summary, there is evidence that glyphosate causes hepatocellular adenomas and skin keratocanthomas in male Wistar rats, mammary gland adenomas and adenocarcinomas in female Wistar rats and kidney adenomas and thyroid C-cell adenomas and carcinomas in male Sprague-Dawley rats. There is limited evidence glyphosate causes hepatocellular adenomas in male Sprague-Dawley rats.

Mouse Studies

Reyna and Gordon (1974)[86] exposed Swiss White mice to glyphosate (>97% purity) in feed for 16 months in males and 18 months in females. Fifty animals/group/sex were tested in three exposure groups; control, 17 mg/kg and 50 mg/kg. Only 10 animals per group were examined for histopathological changes.

There was no impact on survival of administration of glyphosate and no indication that the high dose exceeded the MTD.

No significant increases were seen in any tumor from this study. However, given the small sample size for histopathological evaluation and the low doses used for this study, this study is inadequate.

This study will not be used in the evaluation of causality.

Knezevich and Hogan, (1983)[83] exposed CD-1 mice to glyphosate (99.8% pure) in feed for two years. Fifty animals/group/sex were tested in four exposure groups (see Table 9).

There were no survival differences in this study and there was no indication that the highest dose used exceeded the MTD.

EPA[100] found a significant increase in kidney tubular cell adenomas in male mice based upon the original pathology done from the study and this analysis is shown in Table 9 (p_{Trend}=0.019). Kidney tubular cell adenomas are very rare tumors in CD-1 mice so it is important to compare these results with the historical controls. No historical controls were available from the laboratory that conducted **Knezevich and Hogan, (1983)** so IARC, EPA and EFSA all used historical control databases from published studies in the

literature[101-103]. These studies have virtually identical rates for the important tumors seen in CD-1 mice; I will use the study by **Giknis and Clifford (2000)**[102] since it best covers the range of studies we have for CD-1 mice. For studies of approximately two years, the mean historical tumor response in controls is 0.27%. Applying this control response rate to the kidney adenomas yields p_{Hist}=0.005, strengthening the significance of the evaluation against the concurrent control. EPA originally used a similar analysis and reached the same conclusions. However, in 1985, the registrant had a group of pathologists review the kidney slides. Using additional kidney sections from this study, the pathologists identified an additional adenoma in the control animals and changed the classification for three adenomas to carcinomas (Table 9). With these changes, the adenomas no longer have a significant trend (P_{Trend}=0.442, P_{Hist}=0.121) but carcinomas have a marginally significant trend against concurrent controls and a clearly significant trend using historical controls (p_{Trend}=0.063, p_{Hist}=0.002, historical control rate of 0.15%). These historical control rates may not apply to this analysis because the reevaluation of the kidney tumors considered additional sections and no information is available on how additional sections affect historical control rates in this strain of mice; differences have been seen in other settings[104]. The incidence of combined carcinomas and adenomas has the same marginal significance against the concurrent control and significance against the historical controls (p_{Trend}=0.065, p_{Hist}=0.011, historical control rate of 0.44%). However, there was considerable disagreement on whether the one adenoma in the control group was correctly diagnosed[105]. Removing this one adenoma from the control group results in p_{Trend}=0.019 and p_{Hist}=0.005.

Other CD-1 mouse studies have seen increases in malignant lymphomas, hemangiosarcomas and lung adenocarcinomas (males) and hemangiomas (females). Evaluations of those tumors for this study yields results that are not significant; for malignant lymphoma, p_{Trend}=0.754, p_{Hist}=0.767, with the historical control rate equal 6.2%, for hemangiosarcomas p_{Trend}=0.503, p_{Hist}=0.591, with the historical control rate equal to 2.5%, for lung adenocarcinomas p_{Trend}=0.918, p_{Hist}=0.899, with the historical control rate equal to 9.2% and for hemangiomas p_{Trend}=0.631. No other tumors were found in this study.

The **EPA**[61] has produced many different arguments to dismiss the findings of renal tumors from this study. One argument is that the pathology working group requested by the EPA in 1986 concluded these lesions were not glyphosate related because "*1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the concurrent controls and there was no evidence of a statistically significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound-related nephrotoxic lesions, including pre-neoplastic changes, were not present in male mice in this study.*" Reason number one no longer exists as there are two very good historical control databases for CD-1 mice[101, 102]. The second reason, while technically correct, is not supportable since the Agency's own guidelines for evaluating carcinogenicity studies state that "*Significance in*

either kind of test [trend or pair-wise] *is sufficient to reject the hypothesis that chance accounts for the result."* The third reason is also weak since one would not expect (nor require) multiple tumors to appear when dealing with a rare tumor. For the fourth point, EPA provides data on the rate of bilateral chronic interstitial nephritis in the study which it considers to show no statistically significant results although the trend test is highly significant (p_{Trend}=0.006, Table 9). EPA then states, without reference, that *"chronic interstitial nephritis is not considered to be a precursor lesion for tubular neoplasms"*. I could find no published research to either support or refute this statement. However, chronic interstitial nephritis is an inflammation of the interstitial tissue surrounding the glomeruli and tubules in the kidney. Inflammation is well known

Table 9: Tumors of interest in male and female CD-1 mice from the 24-month feeding study of **Knezevich and Hogan (1983)**[83]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	157	814	4841	
	Female	0	190	955	5874	
Kidney Adenoma[1] (original pathology)	Male	0/49	0/49	1/50	3/50	P_{Trend}=0.019 P_{Hist}=0.005
Kidney Adenoma (EPA pathology)	Male	1/49	0/49	0/50	1/50	P_{Trend}=0.442 P_{Hist}=0.121
Kidney Carcinoma[2] (EPA pathology)u	Male	0/49	0/49	1/50	2/50	P_{Trend}=0.063 P_{Hist}=0.002
Kidney Adenoma and Carcinoma Combined[3] (EPA pathology)	Male	1/49	0/49	1/50	3/50	P_{Trend}=0.065 P_{Hist}=0.011
Malignant Lymphoma[4]	Male	2/49	5/49	4/50	2/50	P_{Trend}=0.754 P_{Hist}=0.767
Hemangiosarcoma[5]	Male	0/50	0/49	1/50	0/50	P_{Trend}=0.503 P_{Hist}=0.591
Bilateral Chronic Interstitial Nephritis	Male	5/49	1/49	7/50	11/50	P_{Trend}=0.006
Hemangiooma[6]	Female	0/49	1/49	1/50	0/50	P_{Trend}=0.631
Lung Adenocarcinoma[7]	Male	4/48	3/50	2/50	1/50	P_{Trend}=0.918 P_{Hist}=0.899

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.27%, [2]historical rate=0.15%, [3]historical rate=0.44%, [4]historical rate=6.2%, [5]historical rate=2.5%, [6]No Historical Controls, [7]Historical rate=9.2%

to play an important role in kidney cancer[106] and many other cancers so this argument also fails to support rejection of these findings.

In summary, this study shows a positive result for kidney tumors in male CD-1 mice and will be included in the overall evaluation of causation.

Atkinson, et al., (1993)[81] exposed CD-1 mice to glyphosate (>97% purity) in feed for two years. Fifty animals/group/sex were tested in four exposure groups (see Table 10).

There was no impact on survival of administration of glyphosate and no indication that the high dose exceeded the MTD.

Table 10: Tumors of interest in male and female CD-1 mice from the 24-month feeding study of **Atkinson et al. (1993)**[81]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	98	297	988	
	Female	0	102	298	1000	
Kidney Adenoma and Carcinoma Combined[1]	Male	2/50	2/50	0/50	0/50	P_{Trend}=0.981 P_{Hist}=1
Malignant Lymphoma[2]	Male	4/50	2/50	1/50	6/50	P_{Trend}=0.087 P_{Hist}=0.085
Hemangiosarcoma[3]	Male	0/50	0/50	0/50	4/50	P_{Trend}=0.004 P_{Hist}=0.001
Hemangioma[4]	Female	0/50	0/50	0/50	0/50	P_{Trend}=1
Lung Adenocarcinoma[5]	Male	10/50	7/50	8/50	9/50	P_{Trend}=0.456 P_{Hist}=0.449

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=6.2%, [3]historical rate=2.5%, [4]No historical control rate, [5]Historical rate=9.2%

Hemangiosarcomas were the only tumors showing a significant trend in this study (P_{Trend}=0.004, P_{Hist}=0.001, Table 10). Also shown in Table 10 are the results for malignant lymphomas, kidney tumors and lung adenocarcinomas (males) and hemangioma (females); there is a marginal trend for malignant lymphomas (P_{Trend}=0.087, P_{Hist}=0.085) and no trend for kidney tumors.

The **EPA**[61] concluded the findings in this study were not treatment related based upon the tumors appearing only in the high dose group, a lack of statistical significance between the response in this group and control response and that these tumors are commonly observed in mice as both spontaneous and treatment related effects. There is no scientific support for excluding positive findings in the highest dose group, a view also held by the **SAP**[54]. I have already commented on how EPA's guidelines treat trend tests and Fisher's Exact test results, although in this case, the value of the comparison of the highest exposure group to controls, p_{Fisher}=0.059, is marginally significant. The argument regarding the frequency of this tumor in controls is addressed directly by the evaluation against the historical control rates; if these rates were high enough to exclude this finding, P_{Hist} would have be above 0.05 instead of 0.001. The mean

historical control incidence of hemangiosarcomas in controls from two-year cancer bioassays in CD-1 mice is 2.5% and the response seen in the high-dose group is 8.9%. The **SAP**[54] stated very clearly that the practice, being used by the EPA, of negating a positive finding because of historical control data was not acceptable[54]. (page 63). The EPA Cancer Guidelines[33] state this very clearly "*...statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average.*"

In summary, this study shows a positive result for hemangiosarcomas in male CD-1 mice and will be included in the overall evaluation of causation.

Wood et al., (2009)[88] exposed CD-1 mice to glyphosate (95.7% pure) in feed for 80 weeks. Fifty-one animals/groups/sex were tested in four exposure groups (see Table 11).

There was no effect on survival and no information suggesting the study exceeded the MTD.

No increase in kidney tumors or hemangiosarcomas (males) or hemangiomas (females) were seen in this study. There was a monotonic increase in lung adenocarcinomas (p_{Trend}=0.028, p_{Hist}=0.031) in males and a monotonic increase in malignant lymphomas (p_{Trend}=0.007, p_{Hist}=0.007) in males. The historical control incidence for this study is different from the earlier studies because this study is only for 80 weeks instead of 104 weeks (two years); the historical control rate for malignant lymphomas in CD-1 mice after 80 weeks is 2.6% instead of 6.2%, the historical control rate at two years[102].

For lung adenocarcinomas, the **EPA**[61] again argued a lack of significance for pairwise comparisons (in violation of its guidelines) and that there was no evidence of progression from adenomas to carcinomas. Even though there was no increase in lung adenomas as a function of exposure, it is possible to have an increase in lung adenocarcinomas without an associated increase in adenomas[107]. For malignant lymphomas, EPA notes that there was a statistically significant response and that the high dose was significantly different from control (p_{Fisher}=0.028), but then uses an argument based upon the number of analyses done in this study to adjust the Fisher Exact test p-value to 0.082 (an adjustment for multiple comparisons is indeed warranted in evaluating the outcomes of these animal cancer studies, this will be addressed later in my report in the evaluation of all of the studies combined).

The **EPA**[61] uses historical control data[103, 108] to exclude the malignant lymphomas and cite a mean response of 4.5% and a range of 1.5% to 21.7%. **Son and Gopinath (2004)**[108] saw 21 animals out of 1453 examined prior to 80 weeks with lung adenocarcinomas (1.4%). **Giknis and Clifford (2005)**[103] saw a mean rate of 4.5% with a range of 0% to 21.7% in 52 studies which included mostly 78 week controls (26 studies) and 104 week controls (21 studies). Including only studies of 80 weeks or less, the rate in **Giknis and Clifford (2005)** is 37/1372=2.7% with a range of 0% to 14%. **Giknis and Clifford (2000)**[102] (the reference I have been citing) did a similar evaluation, using mostly the same data as their 2005 paper and saw an average tumor incidence before

80 weeks of 2.6% with a range of 0% to 14%. Based upon its flawed interpretation of the **Giknis and Clifford (2005)** historical controls, EPA argues that the incidence of concurrent controls in the study was low (it was 0%) and rejected the positive finding. In fact, of the 26 studies in the 18-month control groups evaluated by **Giknis and Clifford (2005),** eight (31%) had response of 0% and eight (31%) had only one tumor. The evaluation used by the EPA is incorrect. In addition, as noted earlier, the use of historical control data to negate a positive finding is not supported by **EPA's guidelines**[33, 54] or its **SAP**[54].

There was an increase in the number of animals with multiple malignant tumors (P_{Trend}=0.046)

In summary, this study shows a positive result for malignant lymphomas and lung adenocarcinomas in male CD-1 mice and will be included in the overall evaluation of causation.

Table 11: Tumors of interest in male and female CD-1 mice from the 18-month feeding study of **Wood et al. (2009)**[88]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	71.4	234.2	810	
	Female	0	97.9	299.5	1081.2	
Kidney Adenoma[1]	Male	0/51	0/51	0/51	0/51	P_{Trend}=1
Malignant Lymphoma[2]	Male	0/51	1/51	2/51	5/51*	P_{Trend}=0.007 P_{Hist}=0.007
Hemangiosarcoma	Male	0/51	0/51	0/51	0/51	P_{Trend}=1
Lung Adenocarcinoma[3]	Male	5/51	5/51	7/51	11/51	p_{Trend}=0.028 P_{Hist}=0.031
Hemangioma[4]	Female	0/51	2/51	0/51	1/51	p_{Trend}=0.438
Animals with Malignant Neoplasms	Male	14/51	20/51	17/51	20/51	P_{Trend}=0.203
Animals with Malignant Neoplasms	Female	23/51	15/51	17/51	18/51	P_{Trend}=0.628
Animals with multiple malignant tumors	Male	1/51	2/51	3/51	5/51	P_{Trend}=0.046

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=2.6%, [3]Historical rate=2.5%, [4]No Historical Control Rate

Sugimoto (1997)[87] exposed CD-1 mice to glyphosate (94.61-95.67% pure) in feed for two years. Fifty animals/group/sex were tested in four exposure groups (see Table 12).

There were no effects of treatment on survival and no indication the highest dose had exceeded the MTD.

Kidney adenomas (p_{Trend}=0.062, p_{Hist}=0.005), malignant lymphomas (p_{Trend}=0.016,

p_{Hist}=0.017) and hemangiosarcomas (p_{Trend}=0.062, p_{Hist}=0.004) in male mice and hemangiomas (p_{Trend}=0.002) in female mice all showed increased tumor incidence with increasing dose. The evaluation of lung adenocarcinomas in males showed no significant dose-related trend (p_{Trend}=0.148, p_{Hist}=0.140). This study also had an increase in animals with any malignancy in males (p_{Trend}=0.001) but not in females (p_{Trend}=0.362). Note that no hemangiosarcomas were seen in the 26 control groups evaluated by **Giknis and Clifford (2000)** so the development of an estimate of the historical control response is difficult (if the historical control rate is 0, then any observed response other than 0 has a p-value of 0). The fact that this tumor was never seen in the historical controls should strongly support any positive finding as being significant. However, to still allow for a test using historical control data, I used the historical control estimate of the mean response that would result in a 5% chance of seeing no tumors in 1149 animals. This estimated historical control response value was 0.0026. This value was used in the analysis for hemangiosarcomas in male CD-1 mice exposed for 18 months (p_{Hist} <0.001).

Table 12: Tumors of interest in male and female CD-1 mice from the 18-month feeding study of **Sugimoto (1997)**[87]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	165	838.1	4348	
	Female	0	153.2	786.8	4116	
Kidney Adenoma[1]	Male	0/50	0/50	0/50	2/50	P_{Trend}=0.062 P_{Hist}=0.005
Malignant Lymphoma[2]	Male	2/50	2/50	0/50	6/50	P_{Trend}=0.016 P_{Hist}=0.017
Hemangiosarcoma[3]	Male	0/50	0/50	0/50	2/50	P_{Trend}=0.062 P_{Hist}=0.004
Hemangioma[4]	Female	0/50	0/50	2/50	5/50*	P_{Trend}=0.002
Lung Adenocarcinoma[5]	Male	1/50	1/50	6/50	4/50	P_{Trend}=0.148 P_{Hist}=0.140
Number of animals with Malignant Neoplasms	Male	5/50	5/50	11/50	16/50**	P_{Trend}=0.001
Number of animals with Malignant Neoplasms	Female	9/50	13/50	16/50	13/50	P_{Trend}=0.362

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=2.6%, [3]historical rate=0/1424 (0.26% - 95% confidence limit), [4]No Historical Control Rate, [5]Historical rate=2.5%

EPA[61] only addressed the hemangiomas in the female mice and did not note any other significant effects. For the females, EPA argued that the high dose was approximately four times higher than the current recommended high dose from the **OECD guidelines**[109]. This study was correctly designed under the previous guidelines (the limit was <5% in feed) and there is no indication that this dose exceeded the MTD. The EPA also argued that when the p-value for Fisher's Exact test was adjusted for multiple comparisons, the new p-value for the high-dose group for hemangiomas was 0.055.

For the hemangiosarcomas in males, none of the 26 historical control groups examined by **Giknis and Clifford (2000)** had hemangiosarcomas, making this a very rare tumor in males prior to 80 weeks on study. The malignant lymphomas in males are statistically significant against both the concurrent controls and the historical controls. Finally, there is clearly an overall increase of malignancies in the males.

In summary, this study shows a positive result for kidney adenomas, malignant lymphomas and hemangiosarcomas in male CD-1 mice, hemangiomas in female CD-1 mice and an overall increase in malignancies as a function of exposure in male CD-1 mice. This study will be included in the overall evaluation of causation.

Kumar (2001)[84] exposed Swiss Albino mice to glyphosate (>95% purity) in feed for two years. Fifty animals/group/sex were tested in four exposure groups (see Table 13).

The survival was decreased in the highest exposure group but this was not statistically significant and there was no other data indicating the MTD was exceeded for this study.

Kidney adenomas (p_{Trend}=0.062) and malignant lymphomas (p_{Trend}=0.064, p_{Hist} =0.070) in male mice demonstrated marginal statistical significance and hemangiosarcomas (p_{Trend}=0.500) in male mice demonstrated no statistical significance. In this study, not all animals in the low- and mid- dose groups were evaluated for kidney tumors, so a second analysis was done based on only the animals examined in these two groups (p_{Trend}=0.088). No historical control data was available for hemangiosarcomas and kidney adenomas in Swiss Albino mice. For the malignant lymphomas, EFSA provided a historical control data set showing a mean response of 46/250=0.184 (18.4%) with a range of 6% to 30%. Using this historical control data, the trend is only marginally significant (p_{Hist}=0.070). I have some concern that the responses at two of the doses are outside of the historical control range and the third dose is at the upper limit of the historical control range. However, this is a small historical control dataset for a tumor with a relatively high background tumor rate, thus placing too much emphasis on this historical control population is not warranted.

In a recent memo, Martens (2017) [110] asserts that the incidence counts for malignant lymphomas and kidney adenomas appearing in Greim et al. (2015)[91] and EFSA (2013)[89] are incorrect and provides different rates (shown in Table 13). The p-values for both of these tumors are reduced using the incidence counts from the Martens memo. However, it should be noted that if the counts for malignant lymphomas in the Martens (2017) memo are correct, then all three exposure groups have responses outside of the range of the historical controls. It is unclear from Greim et al. (2015), EFSA or Martens (2017) which tumor incidence counts are correct.

There was a significant increase in hemangiomas (any tissue) in female mice (p_{Trend}=0.004).

In summary, this study shows support for an increase for malignant lymphomas and kidney adenomas as a function of exposure in male Swiss Albino mice and an increase in hemangiomas in female Swiss Albino mice. This study will be included in the overall

Table 13: Tumors of interest in male and female Swiss Albino mice from the 18-month feeding study of **Kumar (2001)**[84]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	14.5	149.7	1453	
	Female	0	15	151.2	1466.8	
Kidney Adenoma (only tissues examined microscopically)	Male	0/50	0/26	1/22	2/50	P_{Trend}=0.088
Kidney Adenoma (as reported by Greim et al.)	Male	0/50	0/50	1/50	2/50	P_{Trend}=0.062
Kidney Adenoma (as reported by Martens)	Male	0/50	0/50	0/50	1/50	P_{Trend}=0.250
Malignant Lymphoma[1] (as reported by Greim et al.)	Male	10/50	15/50	16/50	19/50	P_{Trend}=0.064 P_{Hist}=0.070
Malignant Lymphoma[1] (as reported by Martens)	Male	10/50	16/50	18/50	19/50*	P_{Trend}=0.141 P_{Hist}=0.150
Hemangiosarcoma	Male	0/50	0/50	2/50	0/50	P_{Trend}=0.500
Hemangioma (any tissue)	Female	1/50	0/50	0/50	5/50	P_{Trend}=0.004

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]Historical control rate=0.184 (46/250 mice)

evaluation of causation.

Pavkov and Turner (1987)[85] exposed CD-1 mice to glyphosate trimesium salt (56.2%) and 1% propylene glycol (wet weight vehicle) in feed for two years. Eighty animals/sex/group were tested in control, low- and mid-dose groups and 90 animals/sex were tested at the high dose. Exposure levels were 0, 11.7, 118 and 991 mg/kg/day in males and 0, 16, 159 and 1341 mg/kg/day in females. **EPA**[61] lists this study as completely negative for any cancer findings. No details on this study are provided by the EPA nor is it listed in the **Greim et al. (2015)**[91] manuscript. There was limited information on this study in a Data Evaluation Report from EPA (accession number 4021 40-06) that discussed findings from this study. EPA noted that body weight and food consumption were reduced in the highest exposure group, but the actual amounts of these reductions were not available. They also noted that the authors failed to make it clear that the tumors reported in the study had been histopathologically validated. Data was presented for tumors in the livers and lungs of male mice and the lungs of female mice. No other data is provided.

This study is not acceptable for inclusion in the evaluation of causation due to the lack of information on the tumor incidence in tissues other than liver and lung.

George et al. (2010)[82] exposed groups of 20 male Swiss Albino mice to a glyphosate

formulation (Roundup Original, 36g/L glyphosate) at a dose of 25 mg/kg (glyphosate equivalent dose) topically three times per week, topically once followed one week later by 12-o-tetradecanoylphorbol-13-acetate (TPA) three times per week, topically three times per week for three weeks followed one week later by TPA three times per week, or a single topical application of 7,12-dimethyl-benz[a]anthracene (DMBA) followed one week later by topical application of glyphosate three times per week for a total period of 32 weeks. Appropriate untreated, DMBA-treated, and TPA-treated controls were included. The group exposed to DMBA followed by glyphosate demonstrated a significant increase ($p<0.05$) in the number of animals with tumors (40% of the treated animals versus no tumors in the controls) indicating glyphosate has a promotional effect on carcinogenesis in the two-stage model in skin. This study addresses the question of whether glyphosate is more likely to cause skin tumors through initiation (starting the cancer process) or promotion (moving the process along after it starts). This study supports the overall concept that glyphosate can have an impact on tumor incidence.

EPA[61] discounted this study because it included only 20 animals per group, tested only males and did not conduct a histopathological analysis. It is hard to understand how EPA could reject a positive finding using 20 mice; typically one would ignore a negative study that had too few animals as not having sufficient statistical power to see an effect but never reject positive findings for this reason. Also, 20 animals per group is common for skin-painting initiation-promotion studies like the one presented here. Doing a study in only males is not a reason to ignore the positive findings in a study. Finally, in initiation-promotion studies of mouse skin, histopathological evaluation would be done if one were interested in separating papillomas from carcinomas. It is highly unlikely that the lesions seen in 40% of the DMBA/glyphosate treated mice were not papillomas or carcinomas.

Some members of the EPA SAP noted[54] that the rodent data were consistent with glyphosate acting as a tumor promoter but, because "*[t]here has been no direct test of this hypothesis (such as in a standard initiation-promotion bioassay)...,*" this "*conclusion was speculative.*" (page #). Because the EPA dismissed this study without any discussion, the SAP did not recognize there was an initiation-promotion supporting a promotional effect of glyphosate.

This study is included in the evaluation of causality as support for a promotional effect of glyphosate on some tumors.

Joint Analysis - Mouse

In their evaluation of the mouse studies, **EPA**[61] and **EFSA**[89] chose to challenge the results in each study separately, dismiss the studies as showing no effect, and never compared results across the various studies. In response to the evaluation done by the **IARC**[30], **EFSA**[90] extracted the original data and did trend tests on kidney tumors, malignant lymphomas and hemangiosarcomas in male mice in five of the mouse studies, the same five studies I consider acceptable for a causation analysis. Rather than formally evaluate these cancer responses for consistency by pooling the data where appropriate, EPA and EFSA simply produced a table with the responses for each dose

group in each study and concluded (subjectively) they were inconsistent. In addition, EPA and EFSA argued that doses above 1000 mg/kg/day (there are only two of these) were outside the range of what would be tested today under OECD guidelines and should be excluded. I will now address both points.

In CD-1 mice, there are four useful animal carcinogenicity studies and one study in Swiss Albino mice. As with the rats, consistency across studies can be addressed in two ways. The first is by simply looking at the overall findings to evaluate where they agree or disagree in terms of statistical significance. Table 14 summarizes the positive and negative findings for all five cancers in which at least one study in CD-1 mice showed a significant trend. It is clear that not every tumor shows a positive trend with glyphosate exposure in every study. For hemangiosarcomas in males, there are clear positive findings in the studies by **Sugimoto (1997)** and **Atkinson et al. (1993)** and non-significant responses in **Wood et al. (2009)** and **Knezevich and Hogan (1983)**. In females, hemangiosarcomas are only present in the study by **Sugimoto (1997)**. Malignant lymphomas in males are clearly positive in two studies[87, 88] and marginally positive in a third[81] but negative in the fourth[83]. Both of the strong positive studies exposed animals for 18 months. Kidney tumors in males are positive in two studies[83, 87] and negative in the remaining two[81, 88]. Lung adenocarcinomas in males are only positive in the study by **Wood et al. (2009)**. **Sugimoto (1997)** had four clearly positive associations between tumors and glyphosate while the others had two or less.

Table 14: Summary of significance tests for 5 tumors from 4 studies in CD-1 Mice

Study	Months on Study	Neoplasm				
		Hemangio-sarcoma (male)	Hemangioma (female)	Malignant Lymphoma (male)	Kidney Tumor (male)	Lung Adeno-carcinoma (male)
Sugimoto 1997[87]	18	+/+++[1]	+++	++/++	+/+++	-/-
Wood 2009[88]	18	-/-	-	+++/+++	-/-	++/++
Sugimoto & Wood Pooled		++/+++	+++	+++/+++	++/+++	-/-
Atkinson 1993[81]	24	+++/+++	-	+/+	-/-	-/-
Knezevich 1983[83]	24	-/-	-	-/-	+/++	-/-
Atkinson & Knezevich Pooled		-/-	-	-/-	+/+	-/-
All CD-1 Studies Pooled		++/++	++/++	+/+	+++/+++	-/-

[1]entries are p_{Trend}/p_{Hist} with values: – p>0.1, + 0.1≥p>0.05, ++ 0.05≥p>0.01, +++ p≤0.01

As seen for the rat studies, this simple evaluation of the positive versus negative findings fails to resolve the issue of which findings are driving the overall responses in these data. To do this, I will again pool the studies. Table 14 summarizes the pooled analyses.

For kidney tumors in males, pooling the two 18-month studies yields significant increases in incidence (p_{Trend}=0.015, p_{Hist}=0.003) and pooling of the two year studies shows marginal significance (p_{Trend}=0.081, p_{Hist}=0.054). Pooling all four studies results in (p_{Trend}=0.005, p_{Hist}=0.007), thus the positive trend remains. **Knezevich and Hogan (1983)** saw a 4% response for kidney carcinomas in their highest exposure group. The largest response seen for kidney carcinomas in controls in 48 studies by **Giknis and Clifford (2000)** and in 52 studies by **Giknis and Clifford (2005)** was 2% and in the control groups from 11 two-year cancer studies, **Chandra and Frith (1992)**[101] saw only one animal out of 725 with a kidney carcinoma. In 46 control datasets, **Giknis and Clifford (2000)** saw 39 control groups with no adenomas, five with one adenoma and two with two adenomas; both 24-month studies saw two adenomas in the highest exposure group, a very rare finding. To better illustrate, there are 16 groups of animals in the four studies. For any one group, there is a 2/44 or 4.3% chance of getting a response 4% or larger. The chances of randomly getting 3 or more such responses in 16 groups is 2.9% and the chances of two of these being in any two of the four highest exposure groups is 0.01. In summary, the strong finding in two of the four studies, the positive finding when all four studies are pooled and the very low probability that this is due to chance when compared to historical controls support the conclusion that glyphosate causes kidney tumors in male mice.

For malignant lymphomas in males, pooling the two 18-month studies, **Sugimoto (1997)** and **Wood et al. (2009)**, results in a significant trend (p_{Trend}=0.005, p_{Hist}=0.006). Pooling the two 24-month studies, **Knezevich and Hogan (1983)** and **Atkinson et al. (1993)**, yields (p_{Trend}=0.653, p_{Hist}=0.649). The main differences between these two findings is in the control response; the pooled control response at 24 months is 6/99 (6%) versus 2/101 at 18 months (2%). This is expected since, in the absence of any exposure, tumor rates increase as a function of age[5]. **Giknis and Clifford (2000)** show a control response at 18 months of 4% and a control response at 24 months of 6% (matching the value for the pooled studies). Pooling all four studies results in (p_{TrendA}=0.073, p_{Hist}=0.080). However, the responses seen for malignant lymphomas in controls by **Giknis and Clifford (2000)** show only one historical control group in twenty-six 18-month groups with 10% or higher response. The responses at the high doses (10% and 12%) in the two 18-month studies are very unlikely to have arisen by chance. There are eight groups of animals in the two studies. For any one group, there is a 1/26 or 3.8% chance of getting a response of at least 10% based on the 26 control groups from **Giknis and Clifford (2000)**. The chances of getting two or more such responses in eight groups is 0.035 and the chances of these being in three of the four highest exposure groups is 0.004. For the 24-month studies, the higher background rate makes it difficult to identify a small change in incidence, thus the findings in the 24-month studies and the 18-month studies are not inconsistent. In summary, the very strong findings in the 18-month studies, the very strong positive findings when the two 18-month studies are pooled, the low probability that the responses seen in the 18-month studies are due to chance, and the

marginal increase in malignant lymphomas in the 18-month study in Swiss Albino mice[84] support the conclusion that glyphosate causes malignant lymphoma in male mice.

For hemangiosarcomas in males, pooling the two 18-month studies results in a significant trend (p_{Trend}=0.015, p_{Hist}=0.002). Pooling the two 24-month studies yields (p_{Trend}=0.490, p_{Hist}=0.429). The main difference between these two findings is the 0/50 response in animals exposed at 4841 mg/kg/day in the study by **Knezevich and Hogan (1983)**. Removing this one exposure group in the pooled 24-month analysis yields (p_{Trend}<0.001, p_{Hist}<0.001). Pooling all four studies results in (p_{Trend}=0.045, p_{Hist}=0.043). No hemangiomas were seen in controls groups from twenty-six 18-month studies by **Giknis and Clifford (2000)** so the two hemangiosarcomas seen in the high dose group in the study by **Sugimoto (1997)** are biologically very significant. For the 24-month historical controls, only two out of 20 control groups had a response greater than 8%. In summary, the very strong findings in the 18-month studies, the positive finding when all four studies are pooled and the low probability that the responses seen in the 18-month studies are due to chance support the conclusion that glyphosate causes hemangiosarcomas in male CD-1 mice.

For hemangiomas in females, pooling the two 18-month studies results in a significant trend (p_{Trend}=0.001). Pooling the two-year studies results in p_{Trend}=0.424. Pooling all four studies results in p_{Trend}=0.018. In summary, the very strong findings in one 18-month study, the positive finding when all four studies are pooled and the low probability that the responses seen in the **Sugimoto (1997)** study are due to chance, support the conclusion that glyphosate causes hemangiomas in female CD-1 mice.

For lung adenocarcinomas in male CD-1 mice, pooling the two 18-month studies results shows no significant trend (p_{Trend}=0.417, p_{Hist}0.126). Pooling the two 24 month studies yields (p_{TrendA}=0.985, p_{Hist}=0.993). Pooling all four studies results in (p_{TrendA}=0.937, p_{Hist}=0.744). In summary, the moderate findings in one 24 month study, and the negative finding when any studies are pooled suggest that the linkage between glyphosate and lung adenocarcinomas in male CD-1 mice is due to chance.

The one study in Swiss Albino mice[84] was effectively negative for all endpoints except malignant lymphomas and kidney adenomas where marginally significant tumor responses were seen. Considering the findings for kidney adenomas in CD-1 mice, glyphosate may also cause kidney adenomas in male Swiss Albino mice from the study of **Kumar (2001)**.

To summarize the findings in mice, glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice and hemangiomas in female CD-1 mice after 18 months of exposure, kidney tumors in male CD-1 mice after 24 months exposure and possibly kidney adenomas in male Swiss albino mice. When 18-month and 24-month studies are pooled, there is a significant increase in hemangiosarcomas in male mice, hemangiomas in female mice and kidney tumors in male mice.

Discussion and Summary Animal Carcinogenicity Studies

As noted earlier, there has been a suggestion that using doses substantially larger than 1000 mg/kg/day exceeds the current limit dose set by the OECD. The only place in the **OECD guidance**[67] that addresses a dose of 1000 mg/kg/day is in paragraph 23 which reads:

> *"For the chronic toxicity phase of the study, a full study using three dose levels may not be considered necessary, if it can be anticipated that a test at one dose level, equivalent to at least 1000 mg/kg body weight/day, is unlikely to produce adverse effects. This should be based on information from preliminary studies and a consideration that toxicity would not be expected, based upon data from structurally related substances. A limit of 1000 mg/kg body weight/day may apply except when human exposure indicates the need for a higher dose level to be used."*

This language does not preclude the use of a dose exceeding 1000 mg/kg/day nor does it advocate ignoring such doses when evaluating the results of an animal carcinogenicity study. In fact, the reasons for excluding a dose in an animal carcinogenicity study are clearly outlined in paragraph 90 within **OECD guidance**[59] and reads:

> *"If the main objective of the study is to identify a cancer hazard, there is broad acceptance that the top dose should ideally provide some signs of toxicity such as slight depression of body weight gain (not more than 10%), without causing e.g., tissue necrosis or metabolic saturation and without substantially altering normal life span due to effects other than tumours. Excessive toxicity at the top dose level (or any other dose level) may compromise the usefulness of the study and/or quality of data generated. Criteria that have evolved for the selection of an adequate top dose level include: (in particular) toxicokinetics; saturation of absorption; results of previous repeated dose toxicity studies; the MOA and the MTD."*

While one study has a slight decrease in body-weight gain, there are no indications in any other studies of an exceedance in dose that would support ignoring the findings from any exposure group.

EPA[33] uses a slightly different criteria to determine which dose to include or exclude based on an earlier OECD document. These are spelled out in EPA's guideline document for carcinogenicity risk assessment[33]

> *"Other signs of treatment-related toxicity associated with an excessive high dose may include (a) significant reduction of body weight gain (e.g., greater than 10%), (b) significant increases in abnormal behavioral and clinical signs, (c) significant changes in hematology or clinical chemistry, (d) saturation of absorption and detoxification mechanisms, or (e) marked changes in organ weight, morphology, and histopathology. It should be noted that practical upper limits have been established to avoid the use of excessively high doses in long-term carcinogenicity studies of environmental chemicals (e.g., 5% of the test substance in the feed for dietary studies or 1 g/kg body weight for oral gavage studies [OECD, 1981])."* As before, this applies to only one study presented in this review.

Both of these guidelines make good scientific sense. In the 12 acceptable rodent carcinogenicity studies included in this evaluation, no study had sufficient toxicity at the highest dose to justify removing the highest dose from the analysis. Hence, the analyses presented here did not drop the doses >1000 mg/kg/day. This is also supported by one member of the **EPA's SAP**[54].

Twenty chronic rodent carcinogenicity studies have been done using glyphosate as the test compound. Eight of these studies are unacceptable for use in an evaluation of causality leaving seven studies in rats and five studies in mice. Because of the large number of evaluations done in an individual animal carcinogenicity study, there is concern that the false-positive rates could be exaggerated. For example, if 20 evaluations are done and a finding is deemed significant if $p_{Trend}<0.05$, then you would expect that 20*0.05=1 evaluation would be positive simply due to chance.

Table 15: Observed versus expected tumor sites with significant trends in the 12 acceptable rodent carcinogenicity studies using glyphosate.

Species	Strain	Sex	Total Sites[1]	Exp. <0.05	Obs. <0.05	Tumors[2] p<0.05	Exp. <0.01	Obs. <0.01	Tumors p<0.01
Rat (7 studies)	Sprague-Dawley (4 studies)	M	86	4.3	4	TICT, TFAC, KA, HA	0.9	2	TICT, KA
		F	102	5.1	1	TCCC	1.0	1	TCCC
	Wistar (3 studies)	M	64.5	3.2	2	HA, SK	0.6	1	HA
		F	76.5	3.8	2	MC, MAC	0.8	1	MAC
Mouse (5 studies)	CD-1 (4 studies)	M	42	2.1	8	KA, KC, KAC, HS(2)[3], ML(2), LAC	0.4	5	KA,KC, HS(2), ML
		F	60	3	1	H	0.6	1	H
	Albino (1 study)	M	10.5	0.5	0		0.1	0	
		F	15	0.8	1	H	0.2	1	H
Rats (7 studies)	All (7 studies)	M	150.5	7.5	6	TICT, KA, HA(2), TFAC, SK	1.5	3	TICT, KA, HA
		F	178.5	8.9	3	TCCC, MC, MAC	1.8	2	TCCC, MAC
		Both	329	16.5	9	TICT, KA, HA(2), TFAC, SK, TCCC, MC, MAC	3.3	5	TICT, KA, HA, TCCC, MAC
Mice (5 studies)	All (5 studies)	M	52.5	2.6	8	KA, KC, KAC, HS(2), ML(2), LAC	0.5	5	KA,KC, HS(2), ML
		F	75	3.8	2	H(2)	0.7	2	H(2)
		Both	127.5	6.4	10	KA, KC, KAC, HS(2)[3], H(2), ML(2), LAC	1.3	7	KA,KC, HS(2), H(2), ML
All (12 studies)	All (12 studies)	M	203	10.1	14	TICT, KA(2), HA(2), TFAC, SK, KC, KAC, HS(2), ML(2), LAC	2.0	8	TICT, HA, KA(2),KC, HS(2), ML
		F	253.5	12.7	5	TCCC, MC, MAC, H(2)	2.5	4	TCCC, MAC, H(2)
		Both	456.5	22.8	19	TICT, KA(2), HA(2), TFAC, SK, KC, KAC, HS(2), H, ML(2), LAC, TCCC, MC, MAC	4.6	12	TICT, HA, KA(2), KC, HS(2), H(2), ML, TCCC, MAC

[1]Number of sites examined is based upon suggestions by Dr. J. Haseman in his written testimony to the EPA; male mice – 10.5 sites; female mice – 15 sites; male rats – 21.5 sites; female rats – 25.5 sites

[2]Tumor abbreviations are: KA – kidney adenoma; KC – kidney carcinoma; KAC – kidney adenoma or carcinoma; HS – hemangiosarcoma; H – hemangioma; HA – hepatocellular adenoma; LAC – lung adenoma or adenocarcinoma; ML – malignant lymphoma; MC – mammary gland carcinoma; MAC – mammary gland adenoma or carcinoma; TCCC – thyroid C-cell carcinoma; TFAC

– thyroid follicular cell adenoma or carcinoma; TICT – testes interstitial cell tumor; SK – skin keratocanthoma
[3](x): x studies with this result

The EPA asked the SAP to comment on its evaluation of glyphosate[61] at a meeting in Washington, DC in December 2016[54]. Many comments were received from outside experts at this meeting; one such set of comments came from Dr. J. K. **Haseman (2016)**[111]. **Haseman (2016)** directly addressed the false-positive error rate and concluded that the results seen in these studies were due to chance. He did this by deciding how many evaluations were likely for each study (broken into sex-by-species groups) and then aggregating the findings. He concluded that the effective number of analyses were 10.5 in male mice, 15 for female mice, 21.5 for male rats, and 25.5 for female rats. **Haseman (2016)** made two assumptions in his analysis that are not valid. The first was that all of the possible trend tests had been done on all of the sites he considered reasonable for such an evaluation. He identified eight positive findings. However, EPA had not evaluated all of the sites nor had they considered doing a formal analysis using historical control data. EPA identified eight sex/species groups that had at most one positive tumor finding using the trend test with $p_{Trend} \leq 0.05$. In Tables 1-14 above, I have identified 19 tumors with $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ and 12 with $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ (Table 15). Secondly, Dr. Haseman assumed one could aggregate all the studies into one large analysis of Type-1 error. However, inference in these studies is always made by sex/species/strain (e.g. glyphosate causes hemangiosarcomas in male CD-1 mice; not glyphosate causes cancer in rodents), and the analysis should have been done by grouping each separately. Table 15 shows these analyses as well as the aggregated analysis for all of the acceptable studies.

With the exception of male Sprague-Dawley rats, the observed number of tumors are at or near the expected number for the different sex/strain groups in rats (Table 15). For male Sprague-Dawley rats, 0.8 cases with $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ are expected and two were observed ($p=0.21$). In female CD-1 mice and Swiss Albino mice, the expected and observed numbers are approximately equal. However, in male CD-1 mice, there were 2.1 tumors expected for $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ and eight were observed ($p<0.001$) and there were 0.4 expected for $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ and five were observed ($p<0.001$). This clearly could not have occurred by chance alone. Even if one incorrectly groups all sexes and species together, there are 4.6 expected responses for $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ and 12 observed ($p<0.001$). Thus, chance does not explain the positive results seen in these studies.

Conclusion for Animal Carcinogenicity Studies

There are several general issues that pertain to all animal carcinogenicity studies. There is considerable genetic variability across animal strains both over time and space. It is difficult to compare experiments done in different laboratories even when using the same strain of animal. This is obvious when you examine the rates for hepatocellular adenomas in Wistar rats across the three studies using this strain. Thus, each study

should be considered separately with regard to the findings in that study before being compared across studies.

The use of a p-value of 0.05 as the cut off for increasing tumor incidence does not account for trends in the data across multiple studies. Three studies with marginal responses of 6-8% in a given tumor could, when pooled for analysis, lead to highly significant findings. This issue is well-recognized in epidemiology but not usually considered in toxicology because of a lack of replicate studies. This case is fairly unique because of the larger number of studies available for analysis and requires a more rigorous evaluation of the data such as the pooled analysis presented in this report.

Pooling of the data for the evaluation of replicate studies makes sense as it addresses the question "Does the data as a whole support a finding of increased cancer incidence in these studies?" Some toxicologists may argue that the studies are not replicates and hence cannot be pooled. But if they are not replicates, then they cannot be compared to see if there is consistency across the studies. This is because there may be some subtle change from one study to another that leads to a positive finding in one study but a negative finding in other studies. Thus, either the studies are not good replicates so you cannot compare across studies and you cannot pool them, or they are good replicates so you can compare across studies and you can pool them. There is no argument that would support a comparison across studies that is appropriate when pooling is inappropriate.

There were seven rat studies and five mouse studies that were of sufficient quality and with sufficient details available for inclusion in this evaluation.

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, to a lesser degree, in male Sprague-Dawley rats, mammary gland adenomas and adenocarcinomas in female Wistar rats, skin keratocanthomas in male Wistar rats, and kidney adenomas and thyroid C-cell adenomas and carcinomas in male Sprague-Dawley rats. Glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice and hemangiomas in female CD-1 mice and possibly causes malignant lymphomas, kidney adenomas in male Swiss albino mice and hemangiomas in female Swiss albino mice. Thus, glyphosate causes cancer in mammals.

Mechanisms Relating to Carcinogenicity

Many human carcinogens act via a variety of mechanisms causing various biological changes, taking cells through multiple stages from functioning normally to becoming invasive with little or no growth control (carcinogenic). **Hanahan and Weinberg (2011)**[112] identified morphological changes in cells as they progress though this multistage process and correlated these with genetic alterations to develop what they refer to as the "hallmarks of cancer." These hallmarks deal with the entire process of carcinogenesis and not necessarily with the reasons that cells begin this process or the early stages in the process where normal protective systems within the cells remove

potentially cancerous cells from the body. While tumors that arise from a chemical insult to the cell may be distinct from other tumors by mutational analysis, they all exhibit the hallmarks as described by **Hanahan and Weinberg (2011)**.

Systematic review of all data on the mechanisms by which a chemical causes cancer is complicated by the absence of widely accepted methods for evaluating mechanistic data to arrive at an objective conclusion on human hazards associated with carcinogenesis. Such systematic methods exist in other contexts[113], but are only now being accepted as a means of evaluating literature in toxicological evaluations[114-117].

In this portion of the report, I am focusing on the mechanisms that can cause cancer. **Smith et al. (2015)**[37] discussed the use of systematic review methods in identifying and using key information from the literature to characterize the mechanisms by which a chemical causes cancer. They identified 10 "Key Characteristics of Cancer" useful in facilitating a systematic and uniform approach to evaluating mechanistic data relevant to carcinogens. These 10 characteristics are presented in Table 16 (copied from Table 1 of **Smith et al. (2015)**[37]). While there is limited evidence on glyphosate for most of the key characteristics, genotoxicity (characteristic two) and oxidative stress (characteristic five) have sufficient evidence to warrant a full review.

Genotoxicity

Genotoxicity refers to the ability of an agent (chemical or otherwise) to damage the genetic material within a cell, thus increasing the risks for a mutation. Genotoxic substances interact with the genetic material, including DNA sequence and structure, to damage cells. DNA damage can occur in several different ways, including single- and double-strand breaks, cross-links between DNA bases and proteins, formation of micronuclei and chemical additions to the DNA.

Just because a chemical can damage DNA does not mean it will cause mutations. So, while all chemicals that cause mutations are genotoxic, all genotoxic chemicals are not necessarily mutagens. Does that mean that the genotoxicity of a chemical can be ignored if all assays used for identifying mutations in cells following exposure to a chemical are negative? The answer to that question is no and is tied to the limitations in tests for mutagenicity (the ability of a chemical to cause mutations in a cell). It is unusual to see an evaluation of the sequence of the entire genome before exposure with the same sequence after exposure to determine if the genome has been altered (mutation). There are assays that can evaluate a critical set of genes that have previously been associated with cancer outcomes (e.g. cancer oncogenes), but these are seldom applied. In general, mutagenicity tests are limited in the numbers of genes they actually screen and the manner in which these screens work.

Because screening for mutagenicity is limited in scope, any genetic damage caused by chemicals should raise concerns because of the possibility of a mutation arising from that genetic damage. In what follows, I will systematically review the scientific findings available for evaluating the genotoxic potential of glyphosate. This will be divided into six separate sources of data based on the biological source of that data: (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 (non-human) in the laboratory, (5) data from non-mammalian animals and others, and (5) data from cells from non-mammalian animals and others. These six areas are based upon the priorities one would apply to the data in terms of impacts. Seeing genotoxicity in humans is more important than seeing genotoxicity in other mammals, which is more important than seeing genotoxicity in non-mammalian systems. In addition, seeing genotoxicity in whole, living organisms (*in vivo*) carries greater weight than seeing responses in cells in the laboratory (*in vitro*). Basically, the closer the findings are to real, living human beings, the more weight they should be given.

Table 16: Key characteristics of carcinogens, **Smith et al. (2016)**[37]

Characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

The data being included in this review come from the peer-reviewed scientific literature, the summaries of reports in regulatory documents that are proprietary and for which I have limited access to the original work, and reports from industry that are proprietary to which I have been given greater access. All of these studies are included in the overall evaluation of causation.

Genotoxicity in Humans *in-vivo*

Three studies have evaluated the potential genotoxicity of glyphosate formulations in exposed humans. **Paz-y-Miño et al. (2007)**[118] analyzed the blood of 24 exposed individuals (living within 3 kilometers of spraying) and 21 unexposed individuals (living 80 kilometers away from the spraying area) for DNA damage using the comet assay. All study subjects were from Ecuador and none of the controls or exposed individuals smoked, drank alcohol, took non-prescription drugs or had been exposed to pesticides during the course of their normal daily lives. Exposed and control individuals did some cultivating and harvesting but without pesticides or herbicides. Exposed individuals were analyzed within two months of spraying for the eradication of plants associated with illegal narcotics. An average of 200 cells per person were ranked between 0-400 depending on the amount of DNA in the comet's tail in order to calculate the mean amount of DNA damage. There was a significant difference between the mean total migration level of exposed individuals to controls ($p<0.001$). Data was given for each individual classified into five groups based upon the amount of DNA in the comet's tail. There was clearly a shift in the distribution of DNA in cells with the controls never seeing scores in the top two categories while all but three exposed had some scores in the top two categories. In essence, some of the DNA had been fragmented by the exposure.

In a second study by the same group, **Paz-y-Miño et al. (2011)**[119] evaluated the karyotypes (the chromosome count of the individuals and any alterations to the chromosomes as seen under a microscope) of 92 people living in 10 communities in northern Ecuador. Controls were from areas without spraying and both controls and exposed subjects had no history of exposure to smoking or other genotoxic compounds. This study saw no changes between controls and exposed subjects for 182 karyotypes evaluated.

Bolognesi et al. (2009)[120] studied women of reproductive age and their spouses in five areas of Colombia, four of which are subject to spraying for either narcotics control or sugar cane growing. There were 60 subjects from the Santa Marta area (organic coffee is grown without the use of pesticides), 52 from Boyaca (manual spraying for illicit drugs), 58 from Putumayo (aerial spraying for illicit drugs using a glyphosate formulation), 63 from Nariño (same exposure as Putumayo) and 28 from Valle del Cauca (aerial spraying of Roundup 747 (74.7% glyphosate) without additional adjuvant for sugar cane maturation). All subjects were interviewed with a standardized questionnaire designed to obtain information about current health status, health history, lifestyle and potential exposure to possible confounding factors (smoking, use of medicinal products, severe infections or viral diseases during the last six months, recent vaccinations, presence of known indoor/outdoor pollutants, exposure to diagnostic x-rays, and previous radio- or chemotherapy). In Santa Marta, blood samples were taken

once, during the initial interview. In Boyaca, blood samples were taken at the initial interview and 1 month later. In Nariño, Putumayo and Valle del Cauca, blood samples were taken at the initial interview, within five days after spraying and 4 months later. In lymphocytes, binucleated cells with micronuclei (BNMN) were lowest in Santa Marta and similar in the four exposed regions prior to exposure. Statistically significant increases in BMNM in Nariño, Putumayo and Valle del Cauca were seen between first and second sampling. The mean BNMN in Nariño and Putumayo was greater in respondents who self-reported direct contact with sprayed fields, but differences were not statistically significant. Multiple linear regression demonstrated statistically significant increases in BMNM in all four exposed regions post exposure when compared to pre-exposure and controlling for all other variables ($p<0.001$). The largest total change in mean BMNM values pre-exposure compared to immediate post exposure occurred in Valle del Cauca where spraying is done using Roundup with no additional adjuvant.

Kier (2015)[121] identified 16 additional studies of pesticide use that included some exposure to glyphosate. Eleven of the 16 studies demonstrated some degree of genotoxicity in the human populations studied but did not adequately attribute the exposure primarily to glyphosate so they are not included in this review.

In summary, two of the three studies in which genotoxicity endpoints were evaluated in humans in areas with exposure to glyphosate spraying showed statistically increased changes in DNA damage in blood. In the strongest study, in three areas where chromosomal damage (micronuclei) was examined in individuals pre- and post-spraying (<5 days) showed statistically significant increases. In one other area where post-exposure damage was measured one month after exposure, there was little change.

Genotoxicity in Human Cells (*in vitro*)

Studies have explored the *in vitro* genotoxicity of glyphosate using a variety of different cell types (lymphocytes, fibroblasts, and immortalized cells from cancers of the larynx, mouth, blood and liver) using several different assays for markers of genotoxicity with or without metabolic activation.

Mladinic et al. (2009)[122] induced DNA strand breaks (comet assay) from exposure to glyphosate (purity not given) in lymphocytes from three healthy human donors (questionnaire used to exclude genotoxic exposures) at concentrations of 3.5, 92.8 and 580 µg/ml with S9 activation and saw effects at only the highest doses for cells without S9 activation.

Alvarez-Moya et al. (2014)[123] conducted a similar study using lymphocytes from human volunteers (questionnaire used to exclude genotoxic exposures) and exposure to glyphosate (96% purity) at concentrations of 0.12, 1.2, 12 and 120 µg/ml. A significant increase in DNA strand breaks (comet assay) was seen for all exposure groups with a clear dose-response relationship without metabolic activation (metabolic activation was not tested).

Using human HEP-2 cells, **Manas et al. (2009)**[124] induced DNA damage (comet assay) by

glyphosate (96% pure) at all concentrations ranging from 676 µg/ml to 1270 µg/ml (no S9 activation tested). Cell viability at the highest concentration was below 80% and values at the other concentrations were not given.

Monroy et al. (2005)[125] induced significant DNA damage (comet assay) in fibroblast GM 38 cells at concentrations of glyphosate (technical grade, purity not given) ranging from 676 µg/ml to 1000 µg/ml with a clear dose-response pattern. Over this same concentration range, they also saw concentration-dependent decreases in cell viability at all doses making the comet assay results difficult to interpret. In a similar analysis in the same paper, using fibrosarcoma HT1080 cells, they also saw concentration-dependent DNA damage and loss of cell viability. Activation by S9 was not used in either experiment.

Lueken et al. (2004)[126] induced DNA damage (comet assay) in fibroblasts GM 5757 at a concentration of glyphosate (98.4% purity) of 12,680 µg/ml in combination with exposure to 40 or 50 mM H_2O_2. Activation by S9 was not used in this experiment. According to the authors, cell viability at this exposure level was above 80%.

Koller et al. (2012)[127] significantly induced DNA damage (comet assay) in human TR146 cells (buccal carcinoma cells) from exposure to glyphosate (>95% purity) in a dose-dependent fashion at concentrations of 20 and 40 µg/ml. Above 40 µg/ml, there was a significant increase in tail intensity relative to controls, but the actual amount increased did not change as the dose increased (plateau). Using Roundup (Ultra Max) the authors saw virtually the same level of DNA damage at 20 and 40 µg/ml, but the concentration response continued to increase above that exposure. These experiments did not use S9 activation. They also used the CBMN assay in the same system to evaluate the total number of micronuclei in binucleated cells (MNI), the number of binucleated cells with micronuclei (BN-MNI), the number of nuclear buds (NB) and the number of nucleoplasmic bridges (NPB) caused by glyphosate and Roundup exposure. Two endpoints (NB, NPB) had significant increases at concentrations of 10, 15 and 20 µg/ml and two (MNi, BN-MNi) were significantly elevated for concentrations of 15 and 20 µg/ml. Equivalent Roundup exposures resulted in significant increases in all four measures of DNA damage at 10, 15 and 20 µg/ml. The results for the Roundup were greater than for glyphosate alone.

Gasnier at al. (2009)[128] exposed cells from the hepatoma cell line HepG2 to glyphosate (purity not given) and four glyphosate formulations. Only one glyphosate formulation was tested for DNA damage (comet assay) and they saw significant effects at equivalent concentrations of 0.05 µ/ml to 4 µg/ml of glyphosate (p-values not given). No p-values are provided and presentation of the results does not provide a clear means to compare these results with other studies. This study will not be used in the evaluation.

Manas et al. (2009)[124] obtained human blood samples from three healthy, non-smoking women and three healthy men with no history of pesticide exposure. Lymphocytes were cultured with glyphosate (96% purity) at concentrations of 34, 203, and 1015 µg/ml with no statistically significant changes in chromatid breaks,

chromosome breaks, chromatid gaps, chromosome gaps, dicentrics, acentric fragments, or endoreduplication.

Mladinic et al. (2009)[129] used blood from three non-smoking, healthy volunteers to evaluate the formation of micronuclei, nuclear buds and nucleoplasmic bridges as a function of exposure to glyphosate (98% purity). Significant changes in micronuclei were seen following exposure to glyphosate at 92.8 and 580 µg/ml in S9 activated cells, but not those without metabolic activation. Changes in nuclear buds were seen at 580 µg/ml for both S9 activated and non-activated cells while significant changes in nucleoplasmic bridges were seen only at 580 µg/ml in S9 activated cells. This study contained a positive control (ethyl methanesulfonate at 200 µg/ml) which was also negative in all assays, many times showing effects below that seen for glyphosate.

Bolognesi et al. (1997)[130] obtained blood from two healthy female donors and exposed it to glyphosate (99.9% purity) or a Roundup formulation (30.4% glyphosate). At concentrations of 1000, 3000 and 6000 µg/ml of glyphosate and at 100 and 330 µg/ml of glyphosate formulation, significant changes in sister chromatid exchanges (SCEs) were seen. At 330 µg/ml, a non-significant increase in SCEs was seen for glyphosate alone that was approximately 20% below that seen for an equivalent glyphosate exposure from the Roundup formulation. This study did not consider S9 activation.

Lioi et al. (1998)[124, 131] obtained blood from three healthy donors and exposed it to glyphosate (>98% purity). At concentrations of 1.4, 2.9, and 8.7 µg/ml of glyphosate, significant changes in sister chromatid exchanges (SCEs) and chromosomal aberrations were seen. This study did not consider S9 activation.

Vigfusson and Vyse (1980)[132] exposed cultured human lymphocytes from two people to Roundup (% glyphosate unknown) at concentrations of 250, 2500 and 25000 µg/ml. Results for the highest concentration were not provided due to lack of cell growth in culture. SCEs were shown to be significantly increased for the remaining two concentrations in one donor and only for the lowest concentration in the other. While the relative SCE counts seen in this paper are similar to those from **Bolognesi et al. (1997),** the absolute counts in the controls are roughly three times higher in this study. This study did not consider S9 activation.

Genotoxicity in Non-Human Mammals (*in vivo*)

Bolognesi et al. (1997)[130] exposed groups of three Swiss CD-1 male mice by Intraperitoneal (IP) injection with a single dose of glyphosate (99.9% purity, 300 mg/kg) or Roundup (900 mg/kg, equivalent to 270 mg/kg glyphosate). Animals were sacrificed at four and 24 hours after injection and livers and kidney were removed to obtain crude nuclei from the adhering tissues. Both tissues demonstrated significant increases in DNA single-strand breaks ($p<0.05$) at four hours for both glyphosate and Roundup with no discernable difference between the responses. At 24 hours, the presence of strand breaks was reduced and no longer statistically significant from controls.

Peluso et al. (1998)[133] exposed groups of six (controls, lowest doses of glyphosate-salt and Roundup) or three Swiss CD-1 mice (males and females, specific numbers not

specified, liver and kidney tissues combined for analysis) to the isopropylammonium salt of glyphosate or Roundup (30.4% isopropylammonium salt of glyphosate) for 24 hours. DNA adducts (^{32}P-DNA post labeling) were not evident in mice exposed to the glyphosate-salt alone in either liver or kidney, but were present in liver and kidney at all tested doses of Roundup showing a dose-response pattern.

Rank et al. (1993)[134] exposed male and female NMRI mice (three to five per sex) to glyphosate isopropylamine salt (purity not specified) and Roundup (480 g glyphosate isopropylamine salt per liter) by intraperitoneal injection. After 24 or 48 hours (only 24 hours for Roundup), polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 1000 cells. No significant increases were seen for any concentration in glyphosate-exposed animals (100, 150 and 200 mg/kg) or Roundup-exposed animals (133 and 200 mg/kg glyphosate equivalent dose). The positive controls, while not statistically significant, showed an increase in micronuclei.

Bolognesi et al (1997)[130] exposed groups of three, four or six male Swiss CD-1 mice to glyphosate (99.9% purity) and Roundup (30.4% glyphosate) by intraperitoneal injection in two equal doses given 24 hours apart. After six or 24 hours following the last exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 1000 cells. Mice given two doses of 150 mg/kg of glyphosate showed a non-significant increase in micronuclei at 6 hours and a significant increase at 24 hours. In contrast, mice given two doses of 225 mg/kg glyphosate equivalent of Roundup showed a significant increase in micronuclei at both six and 24 hours. The relative differences in mean absolute increase (subtract mean response in controls) in micronucleii between glyphosate and Roundup at 24 hours was 3.6 whereas the relative difference in glyphosate equivalent dose was 1.5 indicating a greater effect of the glyphosate formulation.

Manas et al. (2009)[124] exposed groups of male and female Balb C mice (group size not given, tissues combined for analysis) to glyphosate (96% purity) by intraperitoneal injection in two equal doses given 24 hours apart. Twenty-four hours post exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 1000 cells. No significant increases were seen at doses of 50 mg/kg and 100 mg/kg in glyphosate-exposed animals but a significant increase was seen at 400 mg/kg. The positive controls showed a statistically significant increase in micronuclei (roughly three times the control rate).

Dimitrov et al. (2006)[135] exposed groups of eight male C57BL mice (tissues combined for analysis) to Roundup (41% glyphosate) via gavage at a dose of 1080 mg/kg. At 6, 24, 72, 96, or 120 hours post exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 4000 cells (500 per animal). No significant increases were seen. They also looked for chromosomal damage in these animals and saw no significant increases. The positive controls showed a statistically significant increase in micronuclei.

Prasad et al. (2009)[136] exposed groups of 15 male Swiss CD-1 mice to Roundup (30.4% glyphosate) by IP injection at doses of 25 and 50 mg/kg. At 24, 48 or 72 hours post

exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 2000 cells per animal, five animals per sacrifice. Micronucleii counts were significantly increased ($p<0.05$) at all doses at all times relative to controls. In addition, the number of cells with chromosomal aberrations was significantly increased for all doses at all times. The control rate of micronuclei was similar to that of **Bolognesi et al. (1997),** but about 50% greater response for a dose that was approximately 10 times smaller.

Grisolia et al. (2002)[137] exposed groups of Swiss mice (sex and sample size not given) to Roundup (480 g glyphosate isopropylamine salt per liter) by IP injection at doses of 50, 100 and 200 mg/kg Roundup in two doses separated by 24 hours. At 24 hours post exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 2000 cells per animal. Micronuclei counts were not increased at any dose. This exposure appears to be the same formulation of Roundup used in the study by **Rank et al. (1993)** which was also negative.

Coutinho do Nascimento and Grisolia (2000)[138] exposed groups of six male mice (strain not given) to Roundup (% glyphosate not given) by IP injection at doses of 50, 100 and 200 mg/kg in two doses separated by 24 hours. At 24 hours post exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 1000 cells per animal. A significant increase in micronuclei were seen at a dose of 85 mg/kg. No increase was seen at 42 or 170 mg/kg.

Cavusoglu et al. (2011)[139] exposed groups of six Swiss albino mice by IP injection with a single dose of glyphosate formulation (RoundupUltra Max, 450 g/l glyphosate, 50 mg/kg glyphosate equivalent dose). Animals were sacrificed at three days after injection. Micronuclei in normochromatic erythrocytes were counted from a sample of 1000 cells per animal. There was a significant increase in micronuclei in erythrocytes ($p<0.05$). *G. bilboa* eliminated these effects.

Chan and Mahler (1992)[140] exposed groups of 10 male and female B6C3F$_1$ mice to glyphosate (98.6% purity) in feed at doses of 0, 507, 1065, 2273, 4776, and 10780 mg/kg in males and 0, 753, 1411, 2707, 5846, and 11977 mg/kg in females for 13 weeks. At sacrifice, polychromatic erythrocytes from peripheral blood were extracted and micronuclei counted from a sample of 10,000 cells. No significant increases were seen at any of the tested doses.

Li and Long (1988)[141] exposed groups of 18 male and female Sprague-Dawley rats to glyphosate (98% purity) by IP injection at a dose of 1000 mg/kg. At 6, 12 and 24 hours post treatment, 6 animals of each sex were sacrificed and polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 50 cells per animal. The percentage of cells with chromosomal aberrations was not increased at any time point following exposure.

Genotoxicity in Non-Human Mammalian Cells (*in vitro*)

Li and Long (1988)[141] incubated Chinese hamster ovary cells (CHO-K1BH4) with glyphosate (98% purity) for three hours at concentrations of 5, 10, 50 and 100 mg/ml.

Cells were then plated using 200 cells per sample in triplicate and incubated for 8-12 days. Colonies were then counted and results expressed as mutant frequency. No positive results were seen in any experimental group with or without S9 activation. It is not clear why there is such a large difference in the incubation times in the various groups in this experiment, nor is it clear which groups incubated longer. In a second study in the same publication, non-induced primary rat hepatocytes (Fischer 344) were incubated with seven concentrations of glyphosate (12.5 ng/ml to 125 µg/ml) for 18-20 hours. No significant increases were seen for net grains per nucleus at any exposure concentration. There was a four-fold increase in the lowest exposure groups relative to controls and then every other treated group was below the control response. This is a very unusual finding and could be due to the way in which the data is adjusted for net grains in cytoplasm. The authors calculated net grains per nucleus by subtracting the highest cytoplasmic count from the nuclear count; if cytoplasmic count is increased by glyphosate this could bias the findings making any increase in nuclear count disappear. No data is provided to resolve this issue.

Roustan et al. (2014)[142] incubated Chinese hamster ovary cells (CHO-K1) with glyphosate (purity not provided) for three hours at concentrations of 2, 5, 10, 15, 17.5, 20, and 22.5 mg/ml. Cells were then plated using 200 cells per sample in triplicate and incubated for 24 hours. For each exposure concentration, 2000 bi-nucleated cells were examined for micronuclei. No positive results were seen in any experimental group without S9 activation but the four highest exposure groups were significant with a clear concentration-response pattern when S9 activation was present.

Lioi et al. (1998)[131] exposed lymphocytes from three unrelated healthy cows to glyphosate (>98% purity) for 72 hours to concentrations of 3, 14.4 and 28.7 µg/ml without S9 activation. Chromosomal aberrations scored from 150 cells were significantly increased ($P<0.05$) for all exposure concentrations of glyphosate with a clear concentration-response pattern. Similarly, SCEs per cell were increased at all concentrations ($p<0.05$) but no concentration response pattern was evident.

Sivikova and Dianovsky (2006)[143] exposed lymphocytes from two healthy young bovine bulls to glyphosate formulation (62% glyphosate) for 2, 24 and 48 hours using concentrations of 4.7, 9.5, 23.6, 47.3, 94.6 and 190 µg/ml without S9 activation. Chromosomal aberrations scored from 100 cells were not significantly increased ($P<0.05$) without S9 activation for any 24-hour exposure concentration of glyphosate (2- and 48-hours exposures were not done). SCEs per cell were increased at all 24-hour exposure concentrations ($p<0.05$) except the lowest concentration. At 48-hours, significant increases of SCEs per cell were seen at concentrations at or above 47.3 µg/ml (2-hour exposures were not done). Finally, after two hours of exposure with S9 activation, significant effects were seen at 5 and 10 µg/ml but not at 15 µg/ml (24- and 48-hour exposures were not done for S9 activation).

Holeckova (2006)[144] exposed lymphocytes from two healthy young bovine bulls to glyphosate formulation (62% glyphosate) for 24 hours to concentrations ranging from 28 to 1120 µmol/L without S9 activation. A significant increase in polyploidy was observed at 56 µmol/L, all other comparisons were without significance. However, this

one finding cannot be easily dismissed because all exposure groups above this concentration had too few cells for evaluation. This study did not consider S9 activation.

Genotoxicity in Non-Human Systems (*in vivo* and *in vitro*)

Four studies[123, 145-147] in fish have seen positive results for genotoxicity (DNA strand breaks, different assays) following exposure to glyphosate. In addition, one study[148] in oyster sperm and embryos exposed to glyphosate saw no increase in DNA damage (comet assay) and one study[149] in two strains of Drosophila melanogaster showed an increase in mutations (wing spot test) at the higher doses of exposure.

Fourteen studies[137, 145, 147, 150-160] in multiple fish species evaluated the relationship between various glyphosate formulations and genotoxicity with all studies showing positive results for various endpoints (DNA strand breaks, micronucleus formation, and chromosomal aberrations). Two of the studies[150, 152] were negative for micronucleus formation after exposure to glyphosate formulations and one of these[150] was also negative for chromosomal aberrations but both were positive in other markers of genotoxicity. Two studies[161, 162] demonstrated genotoxicity (DNA strand breaks, micronuclei) in caiman from *in-vivo* exposure to a glyphosate formulation. Three studies[163-165] demonstrated genotoxicity (DNA strand breaks, micronucleus formation) in frogs or tadpoles from exposure to glyphosate formulations. One study[148] in oyster sperm and embryos, one study[166] in clams and one study[167] in mussels exposed to a glyphosate formulation saw no increase in DNA damage (comet assay). One study[168] in snails saw increased DNA damage (comet assay) following exposure to a glyphosate formulation. Two studies[169, 170] in worms saw mixed results for DNA damage (comet assay) with one of these studies[169] showing a positive result for micronucleus formation. One study[171] in Drosophila melanogaster showed an increase in sex-linked recessive lethal mutations.

In the published literature, five studies evaluated the impact of glyphosate in *in vitro* systems. Two of these studies[172, 173] looked at genotoxicity of glyphosate in combination with UVB radiation and saw significant increases in DNA strand breaks (FADU assay) in bacteria without metabolic activation. One study[174] in eukaryote fish saw a significant increase in DNA strand breaks (comet assay) without S9 activation. Another study[141] showed no increase in reverse mutations in two strains of bacteria with and without S9 activation.

Williams et al. (2000)[175] summarized the literature regarding the use of reverse mutation assays in *S. typhimurium* (Ames Test). Four studies using glyphosate and five studies of glyphosate formulations were all negative. They cited one study[134] of a glyphosate formulation that was positive with S9 activation and negative without S9 activation. However, this study was positive with S9 activation in TA100 cells, negative with S9 activation in TA98 cells, negative without S9 activation for TA100 cells and positive without activation for TA98 cells. They also summarized two studies of glyphosate in *e. coli* that were negative with and without activation.

Two additional studies[141, 176] of glyphosate using reverse mutation assays are available

from the scientific literature, both of which are negative.

Regulatory Studies

EFSA[89] cited 14 reverse mutation assays in *S. typhimurium* (Ames Test), most of which were tested in strains TA 98, 100, 1535, 1537 (Table B.6.4-1). All 14 studies are listed as negative by EFSA. Actual data is provided for only one of the 14 studies and this study is clearly negative. **EPA**[61] cited 27 reverse mutation assays in *S. typhimurium* (Ames Test), most of which were tested in strains TA 98, 100, 1535, 1537 (EPA Table 5.1). All 27 studies are listed as negative. No data is provided for any of the studies. **Kier and Kirkland (2013)**[177] cited results from 18 bacterial reverse mutation assays of glyphosate and 16 of glyphosate formulations. Tabulated results and background information were provided for all 34 studies. Six studies of glyphosate alone demonstrated positive findings in one or more groups.

EFSA[89] cites three studies of gene mutations in mammalian cells, all of which are listed as negative (EFSA Table B.6.4-5), two use the mouse lymphoma assay, and one uses the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) mutation assay. **EPA**[61] cites four studies, three of which appear to be the same as those cited by EFSA (EPA Table 5.2) and the fourth is another mouse lymphoma assay. All four are listed as negative. **Kier and Kirkland (2013)**[177] cite two of the mouse lymphoma studies and provide tabulated data. Neither study shows any indication of a statistically significant increase in mutation frequency at the thymidine kinase locus of L5178 mouse lymphoma tk(+/-) cells.

EFSA[89] cites one *in vitro* study of DNA damage and repair in mammalian cells which is listed as negative (EFSA Table B.6.4-6). This study is of unscheduled DNA synthesis (UDS assay) in primary rat lymphocytes. They also list five studies of chromosome aberrations (EFSA Table B.6.4-8), which are characterized as negative. Two studies are in human lymphocytes and two are in Chinese hamster lung (CHL) cells. Data for one of the studies in CHL is provided in tabular form and is clearly negative. **EPA**[61] cites eight *in vitro* studies of chromosome aberrations in mammalian cells (EPA Table 5.3); two of these studies match studies in the EFSA report. Four of the studies are from the literature[124, 131, 143, 178] and are reviewed above. Surprisingly, EPA refers to the study by **Manas et al. (2009)**[124] as negative although it was clearly positive in the comet assay., Additionally, EPA refers to the study by **Sivikova and Dainovsky (2006)**[143] as negative even though they saw clear effects of glyphosate on SCEs. Basically, all four of the literature studies cited by EPA are positive yet EPA lists only two of the four as positive. The remaining four studies are noted as negative; however, no data is supplied for these studies. **Kier and Kirkland (2013)**[177] cites eight literature studies (all reviewed above) and three regulatory studies with glyphosate exposure. The three regulatory studies are listed as negative, and the data are available as a table in the supplement material to **Kier and Kirkland (2013)**; these studies are negative at all tested concentrations in CHL cells; one matches the study data provided by EFSA[89].

EFSA[89] cites nine micronucleus assays, three in Swiss Albino mice, two in NMRI mice, two in CD-1 mice, one in Sprague-Dawley rats, and one in CD rats (EFSA Table B.6.4-12). They list one study in Swiss Albino mice as weakly positive in males, one study in CD-1 mice as positive at the highest dose (data for this study is provided) and all other studies as negative. They discard one study with low doses in male Swiss mice, but the tables provided for this study show a clearly significant result at the highest dose used (30 mg/kg) and clear dose-response. They provide data for two of the negative studies which indicate these studies were indeed negative. **EPA**[61] (EPA Table 5.5) cites 20 micronucleus assays, four are available in the scientific literature and three are reviewed above (the fourth reference[179] was unavailable to me at the time of preparation of this report). The remaining 16 studies include six studies in Swiss Albino mice, four studies in CD-1 mice, three studies in NMRI mice, two studies in Sprague-Dawley rats and one study in Wistar rats. Since EFSA does not provide names associated with their micronucleus studies, I cannot determine if any of the studies cited by the EPA are the same as those cited by EFSA. EPA lists two of the literature studies as positive and two as negative (matching my reviews for the three studies I have access to) and all but one of the regulatory studies as negative (the one positive study was in Swiss-Albino mice). **Kier and Kirkland (2013)**[177] cite 12 regulatory micronucleus assays of glyphosate and provide data tables for all 12. All 12 of these studies are cited by EPA. **Kier and Kirkland (2013)** list 11 studies as negative and one as inconclusive. However, four of the studies show positive effects in at least one sex-by-treatment group. One of these four studies they list as inconclusive and the remaining three studies are determined to be negative because the response is within the range of the historical controls. As was discussed for the animal carcinogenicity studies, the correct group to use is the concurrent control. **Kier and Kirkland (2013)**[177] also cite 12 regulatory studies and three literature studies where animals are exposed to a glyphosate formulation. Two of the literature studies are reviewed above and the remaining study[179] was unavailable. Data for the 12 regulatory studies are all provided in tables by **Kier and Kirkland (2013)** and show two positive studies in CD-1 mice and negative studies for the remaining 10.

Summary for Genotoxicity

This is a complicated area from which to draw a conclusion due to the diversity of the studies available (there are multiple species, multiple strains within a species, multiple cell types from multiple species, differing lengths of exposure, differing times of evaluation after exposure, differing exposures, numerous markers of genotoxicity, and finally both glyphosate and multiple different glyphosate formulations). There are three studies that evaluate the genotoxicity of glyphosate in humans directly, 36 experiments in eight strains of mice, three studies in rats, nine studies in human lymphocytes and four studies in other human cells, 12 studies in non-human mammalian cell lines (two using mouse cells, five using hamster cells, two using rat cells and three using cells from cows), a large number of studies in a wide variety of non-mammalian species, and a plethora of studies, mostly identical, in bacteria.

Some conclusions are straightforward"; glyphosate does not appear to cause reverse mutations for histidine synthesis in *Salmonella typhimurium*, regardless of whether

these reverse mutations are due to frameshift mutations or point mutations. I am cautious in this determination because there were several studies with positive results, but no clear pattern is evident. There is ample evidence supporting the conclusion that glyphosate formulations and glyphosate can cause genotoxicity in non-mammalian animal species. This clearly indicates that both glyphosate and the formulations are able to cause injury to DNA. So while findings of genotoxicity in these species do not speak directly to the hazard potential in humans, they do support a cause for concern.

The more important studies are those that have been done using mammalian systems, human cells and direct human contact. Table 16 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.

Clearly, for *in vitro* evaluations in human cells, the majority of the studies have produced positive results. There was only one regulatory study evaluating glyphosate genotoxicity in human lymphocytes from healthy volunteers and that study was negative. The study was not significantly different from the other six studies in this category, five of which produced positive results. The majority of these studies used either the comet assay (a simple way for measuring any type of DNA strand break) or methods that counted specific types of strand breaks in the cells (e.g. SCEs, micronuclei, nuclear buds and nucleoplasmic bridges). From these assays, we can conclude there is DNA damage. For glyphosate formulations, there are only three studies in humans *in vivo*, two of which were positive.

The magnitude of the concentrations used in these studies could potentially lead to false positives if the glyphosate is causing cytotoxicity in the cells. All six studies using the comet assay were positive with no study showing a negative response below 10 µg/ml and mixed results below that with positive results at 0.12 and 3.5 µg/ml and negative results at 2.91 and 10 µg/ml. In general, the comet assays provide strong support for genotoxicity.

The four studies that directly addressed specific types of strand breaks in cells following exposure to glyphosate showed markedly different responses across the various concentrations used. **Manas et al. (2009)** saw no changes in chromatid breaks, chromosome breaks, chromatid gaps, chromosome gaps, dicentrics, acentric fragments or endoreduplication over the range of concentrations 3.4-1015 µg/ml. In contrast, **Lioi et al. (1998)** saw changes in SCEs over concentrations ranging from 1.4 to 8.7 µg/ml. Both studies were done in lymphocytes from volunteers. **Mladinic et al. (2009)** saw significant changes in micronuclei above 92.8 µg/ml and **Bolognesi et al. (1997)** saw positive changes in SCEs above 1000 µg/ml but not at 330 µg/ml. While changes have been seen in three of the four studies, the actual concentrations in which the changes are seen is not consistent across studies. I conclude that glyphosate causes DNA strand breaks, which is indicative of genotoxicity.

The micronucleus assays in rodents examining glyphosate genotoxicity are either all positive in one strain or all negative in one strain with the exception of the three studies

in CD-1 mice and four studies in Swiss Albino mice. For the positive studies, we can ask the question of whether, in this strain, the actual number of micronuclei are consistent.

Table 17: Summary of *in vivo* and *in vitro* genotoxicity studies of glyphosate and glyphosate formulations in mammals[1]

In vivo or *in vitro*	Species	Cell type or tissue	Glyphosate[2]		Glyphosate Formulations	
			Number Positive	Number Negative	Number Positive	Number Negative
In vivo	Humans	Peripheral blood			2	1
in vitro	Humans	lymphocytes	5	2(1)	2	
		Hep 2	1			
		GM 38 HT1080	1			
		GM 5757	1			
		TR146	1		1	
In vivo	Swiss CD-1 Mouse	Liver/Kidney	1	1	2	
In vivo (micro-nucleus assay)	NMRI mouse	Erythrocytes		4(3)		2(1)
	Swiss CD-1 mouse		1		2	
	Balb C mouse		1			
	$B6C3F_1$ mouse			1		
	Swiss mouse		1(1)			3(2)
	CD-1 mouse		2(2)	1(1)	2 (2)	6 (6)
	Swiss albino mouse		1(1)	3(3)	1	
	C57BL mouse					1
	Mouse (not specified)				1	
	Rats (all)			2(1)		1(1)
In vitro	Mouse	L5178 lymphoma		2(2)		
	Chinese hamster	Lung		3(3)		
	Chinese hamster	ovary	1	1		
	Fischer rat	liver		1		

	Rat	Lymphocytes		1(1)		
	Bovine	Lymphocytes	1		2	

[1]each entry in the table corresponds to a single study where a study is positive if at least one valid positive finding emerged from the study $p<0.05$; entries in the table are only for studies where data was available to review including data from EFSA[89] and Kier and Kirkland (2000)[177]; [2]numbers are the total number of studies in this category, numbers in parentheses are the subset of studies that are regulatory studies

In Swiss Albino mice, all four studies were done with males and females. Exposures were by oral gavage for the positive study (in female mice) and IP injection by the negative studies. The positive study was at 5000 mg/kg and the highest dose in any of the negative studies was 3024 mg/kg. Finally, the control response in the positive study was 6.7 micronucleated PCE per 1000 PCE whereas the controls in the three negative studies were between 0 and 0.6 micronucleated PCE per 1000 PCE. Any of these differences could easily explain the differences in response so the positive result in Swiss Albino mice should be accepted.

For CD-1 mice, the one negative micronucleus study was by oral gavage in males and females at a single dose of 5000 mg/kg. One of the positive studies was also by oral gavage in males at a single dose of 2000 mg/kg. Because of the nature of statistical noise, these two studies could both occur whether there is a true effect or not. For the other positive study, the dose was by IP injection in male mice with a positive response at 600 mg/kg that was more than double the response of the controls. These data support the finding that glyphosate can cause micronuclei in male CD-1 mice, which is indicative of genotoxicity.

The remaining *in vitro* assays in mammalian cells exposed to glyphosate show mixed results. The mouse lymphoma assay and the Chinese hamster ovary assays are looking for specific mutations that will allow these cells to grow in culture. The Chinese hamster lung, the two rat assays and the assay in bovine lymphocytes are measuring DNA damage and provide mixed results. In general, these responses appear to be negative with the exception of those seen in bovine lymphocytes that appear to show a positive increase in SCEs following exposure to glyphosate.

For glyphosate formulations, the main difference between the findings for glyphosate and those for the glyphosate formulations is the direct evidence for genotoxicity in humans and the micronucleus assays in Swiss mice. The observation of genotoxicity in humans following exposure to glyphosate formulations must carry the greatest weight in the overall analysis and two of the three studies were positive with the strongest study by **Bolognesi et al. (2009)**[120] showing the strongest response.

For the Swiss mouse studies of micronuclei, the fact that all three studies are negative for glyphosate formulations while one study is positive for glyphosate creates a clear disagreement. The positive study is an oral gavage study with an effect seen in male mice at 30 mg/kg/day. The two negative regulatory studies for glyphosate formulations were done at 2000 mg/kg (about 500 mg/kg glyphosate equivalent), were also oral

gavage studies and were replicates done in the same laboratory at different times. The remaining negative study used glyphosate formulation doses of 50-200 mg/kg (25-100 mg/kg glyphosate equivalent) but was done by intraperitoneal injection. With the exception of the different routes of exposure, the differences between these studies cannot be resolved.

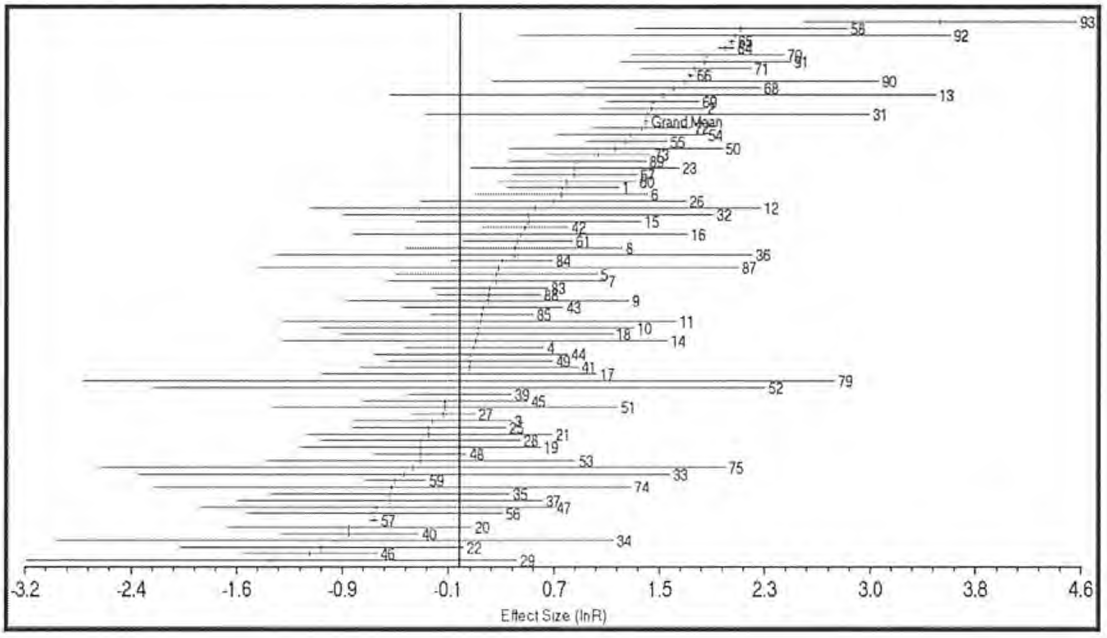
In this case, a pooled analysis of the data is not possible because in almost every case, no one study is a clear replicate of another. Instead, the appropriate approach would be to do a meta-analysis and evaluate which aspects of the experimental designs are important to producing positive findings of genotoxicity. The studies with the most data for this type of analysis are the various *in vivo* assays of micronucleus formation. **Ghisi et al. (2016)**[180] did a systematic search to identify all published studies evaluating the ability of glyphosate or glyphosate formulations to induce micronuclei *in vivo*. The authors also used the data from **Kier and Kirkland (2013)**[177] summarized above. An experiment, in their evaluation, was defined by sex/species/route/form of glyphosate so that some studies doing both sexes using glyphosate and a glyphosate formulation will enter multiple times into the analysis. They identified 93 experiments from which it was possible to do a meta-analysis. Data were extracted for each study and the log ratio of the mean of each experimental group to the mean control response (E+) was used to evaluate effect sizes in the meta-analysis. For this meta-analytic mean, a value below zero suggests no genotoxicity while a value above zero suggests increased genotoxicity. A test of heterogeneity (Cochran's Q statistic discussed earlier for the epidemiological data) was also evaluated.

Figure 2 is a reprint of Figure 1 from the study by **Ghisi et al. (2016)**[180] and is a forest plot from all studies they evaluated for glyphosate and glyphosate formulations. It is clear from this plot that the predominant response is positive in these data with an overall grand mean response across all studies of E+=1.37 and a 95% confidence interval of (1.356-1.381) (this is highly statistically significant with a $p<0.0001$). The Qt value for the grand mean was also statistically significant suggesting there are other explanatory variables in the data that would help to explain the overall variance.

Categorical variables were then used to make comparisons across the various strata in the data to identify which experimental conditions show the largest impacts on the mean response. Mammalian species presented a higher mean effect (E+=1.379; 1.366-1.391) than non-mammalian species (E+=0.740; 0.641-0.840). Glyphosate formulations showed a greater mean response (E+=1.388; 1.375-1.400) than did glyphosate (E+=0.121; 0.021-0.221), but both were significantly greater than zero. The mean response in studies using only male animals (E+=1.833; 1.819-1.847) was significantly different from zero as were studies using both males and females (E+=0.674;0.523-0.825) whereas the mean response in studies using only females (E+0.088; -0.153-0.328) was not. Peer-reviewed studies had higher mean response (E+=1.394; 1.381-1.407) compared to regulatory studies (E+=0.114; 0.027-0.202), but both means were significantly greater than zero, indicating an overall genotoxic effect. Other variables were examined such as length of exposure and magnitude of exposure that had very little impact on the overall findings.

The meta-analysis by **Ghisi et al. (2016)**[180] provides strong support for the hypothesis that exposure to glyphosate and glyphosate formulations increases the formation of micronuclei *in vivo*. This means that glyphosate and glyphosate formulations are damaging DNA in living, functioning organisms with intact DNA repair capacity strengthening the finding that glyphosate is genotoxic to humans.

Figure 2: Forest plot of studies evaluating micronucleus frequency in glyphosate exposure, arranged by effects size. The plot shows the estimate of the response ratio and 95% confidence interval (CI) of each experiment included in the meta-analysis. The number beside the bars represents the reference number of each experiment as in Table 1 of Ghisi et al. (2016)[180]. Grand Mean is the overall mean effects size of all studies. [Reprinted from Ghisi et al. (2016)[180]]



From a simply statistical perspective, there is another way in which one can decide if the positive findings in the micronucleus assays in the mice are due to chance. For the glyphosate studies, if one adds up all of the individual experimental groups, there are 79 total groups which correspond to 79 statistical tests. Assuming the critical testing level is 0.05 for all of the tests, one would expect to see just under four positive findings, yet six are observed. For the glyphosate formulations, there were 70 experimental groups so one expects 3.5 positive findings yet 12 are observed ($p<0.01$). Overall, there were a total of 149 experimental groups examined in mice for micronucleus formation and we observed 18 (7.5 expected, $p<0.01$). Repeating this analysis on the basis of studies instead of experimental groups, there were 15 studies for glyphosate (expected number is 0.75 positive) yet six positive were observed ($p<0.01$). For the glyphosate formulations, there were 18 studies (expected number is 0.9 positive) yet six positive

are observed ($p<0.01$). Now expanding to all 69 studies presented in Table 17, there were 33 positive studies, but the expectation is a mere 3.5 ($p<0.01$).

It is clear that both glyphosate and glyphosate formulations have genotoxic potential. But which is worse? Of the 69 experiments in Table 17, there were eight experiments from five research publications that addressed both glyphosate and a glyphosate formulation in the same laboratory. Of these, two were negative for both glyphosate and the formulation and do not contribute to a discussion of relative potency. The remaining six can provide some guidance on the relative potency of glyphosate to glyphosate formulations. In **Koller et al. (2007)**[127], tail intensity for the comet assay were virtually identical when the amount of glyphosate in the formulation was compared to the results using glyphosate alone. In the same paper, micronuclei and related biomarkers were consistently higher in the glyphosate formulation by 10-20%. In **Bolognesi et al. (1997),** DNA strand breaks in liver and kidney in Swiss CD-1 mice were virtually identical under equivalent doses of glyphosate and glyphosate formulations. In their micronucleus assay, the glyphosate formulation was approximately 50% more potent. Finally, **Bolognesi et al. (1997),** in their analysis of SCEs in human lymphocytes, the glyphosate formulation was approximately twice as effective as glyphosate alone. In **Peluso et al. (1988)**[133], DNA adducts in livers and kidneys were only seen in mice treated with the glyphosate formulation, so these findings are not likely to be due to glyphosate. The data suggest a small increase in the potential for genotoxicity for glyphosate formulations relative to the genotoxicity one would see with glyphosate alone.

In summary, the data support a conclusion that both glyphosate and glyphosate formulations are genotoxic. Thus, there is a reasonable mechanism supporting the increases in tumors caused by glyphosate and glyphosate formulations in humans and animals.

Oxidative Stress

Oxidative stress refers to an imbalance between the production of reactive oxygen species (free radicals) in a cell and the antioxidant defenses the cell has in place to prevent this. Oxidative stress has been linked to both the causes and consequences of several diseases[181-186] including cancer[37, 187-191]. Multiple biomarkers exist for oxidative stress; the most common being the increased antioxidant enzyme activity, depletion of glutathione or increases in lipid peroxidation. In addition, many studies evaluating oxidative stress used antioxidants following exposure to glyphosate to demonstrate that the effect of the oxidative stress can be diminished.

Oxidative Stress in Human Cells (*in vitro*)

Mladinic et al. (2009)[122] examined the induction of oxidative stress from exposure to glyphosate (98% purity) in lymphocytes from three healthy human donors (questionnaires were used to exclude other genotoxic exposures) at concentrations of 0.5, 2.91, 3.5, 92.8 and 580 µg/ml. Cells with and without S9 activation saw increases in total antioxidant capacity at only the highest dose for cells without S9 activation although a clear concentration response pattern was seen with S9 activation.

Kwiatkowska et al. (2014)[192] examined the induction of oxidative stress from exposure to glyphosate (purity not given) in erythrocytes obtained from healthy donors in the Blood Bank of Lodz, Poland. Erythrocytes were exposed to concentrations of 1.7, 8.4, 17, 42.3, 85 and 845 µg/ml and incubated for 1 hour. Oxidative stress (oxidation of dihydrorhodamine 123) was significantly increased at 42.3, 85 and 845 µg/l with a clear concentration-response pattern.

Chaufan et al. (2014)[193] examined the induction of oxidative stress from exposure to glyphosate (95% purity) and Roundup UltraMax (74.7% glyphosate) in HepG2 cells (human hepatoma cell line). Exposure concentrations were 900 µg/ml for glyphosate and 40 µg/ml for the glyphosate formulation. After incubation for 24 hours, oxidative stress (expressed as the activity of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and glutathione-S-transferase (GST)) was significantly increased ($p<0.0-5$) for the glyphosate formulation (increased SOD activity) but not for glyphosate alone.

Coalova et al. (2014)[194] examined the induction of oxidative stress from exposure to a glyphosate formulation (Atanor, 48% glyphosate) or with a surfactant (Impacto) in Hep-2 cells (human epithelial cell line). Exposure concentrations were 376.4 µg/ml for Atanor, 12.1 µg/ml for Impacto and 180.2 µg/ml for a mixture of the two. After incubation for 24 hours, oxidative stress (measured as activity of SOD, CAT, GSH, and GST) was significantly increased for Impacto, Atanor and the mixture (CAT and GSH only, $p<0.05$ or $p<0.01$).

Gehin et al. (2005)[195] examined the induction of oxidative stress from exposure to glyphosate (purity unknown) and a glyphosate formulation (Roundup 3 plus, 21% glyphosate) in HaCaT cells (human keratinocyte cell line). Glyphosate induced cytotoxicity in the cells which was reduced or eliminated by antioxidants. The authors attributed the cytotoxicity to oxidative stress.

Elie-Caille et al. (2010)[196] examined the induction of oxidative stress from exposure to glyphosate (purity unknown) in HaCaT cells (human keratinocyte cell line). Exposure concentrations ranged from 1700 µg/l to almost 12,000 µg/ml. Glyphosate induced cytotoxicity in the cells and increased hydrogen peroxide H_2O_2 (dichlorodihydrofluorescein diacetate assay). This study used exceptionally high concentrations that may be inducing cytotoxicity by means that are independent of the oxidative stress observed. Measuring oxidative stress using the dichlorodihydrofluorescein diacetate assay has limitations[197, 198].

George and Shukla (2013)[199] examined the induction of oxidative stress from exposure to a glyphosate formulation (Roundup Original, 41% glyphosate) in HaCaT cells (human keratinocyte cell line). Exposure concentration ranged from 1.7 µg/ml to 17,000 µg/ml and exposure was for 24 hours. Glyphosate significantly induced the formation of reactive oxygen species (dichlorodihydrofluorescein diacetate assay) at all exposures in a concentration-dependent fashion. Prior treatment of the cells with N-Acetylcysteine reduced the impact of glyphosate, but did not eliminate it. Measuring oxidative stress using dichlorodihydrofluorescein diacetate has limitations[197, 198] that affect the clear

interpretation of these results.

Oxidative Stress in Non-Human Mammals (*in vivo*)

Bolognesi et al. (1997)[130] exposed groups of three Swiss CD-1 male mice by IP injection with a single dose of glyphosate (99.9% purity, 300 mg/kg) or Roundup (900 mg/kg, equivalent to 270 mg/kg glyphosate). Animals were sacrificed at eight and 24 hours after injection and livers and kidney were removed to obtain crude nuclei from the adhering tissues. Samples of liver and kidneys from these mice were evaluated for levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) which is a biomarker of oxidative stress[200]. There was a significant increase in the liver of 8-OHdG at 24 hours following glyphosate exposure, but not at eight hours and not in the kidney. At both eight hours and 24 hours, Roundup increased 8-OHdG in the kidneys, but the mild increase seen in the liver at 24 hours was not significant.

Cavusoglu et al. (2011)[139] exposed groups of six Swiss albino mice by IP injection of a glyphosate formulation (RoundupUltra Max, 450 g/l glyphosate, 50 mg/kg formulation). At the end of dosing, animals were fasted overnight then sacrificed. There was a significant increase in malondialdehyde in both liver and kidney and a significant decrease in GSH in liver and kidney from exposure to the glyphosate formulation. *G. bilboa* eliminated these effects.

Jasper et al. (2012)[201] exposed groups of 10 male and 10 female Swiss albino mice via oral gavage for 15 days to a glyphosate formulation (Roundup Original, 41% glyphosate, 50 mg/kg glyphosate equivalent dose). Animals were sacrificed at three days after injection. There was a significant increase in thiobarbituric acid-reactive substances (TBARS) in the liver for both male and female mice at both doses ($p<0.05$). The concentration of non-protein thiols was elevated in both dose groups for males and for the high dose only in females (no dose-response was seen for this endpoint).

Astiz et al. (2009)[202] exposed groups of four male Wistar rats by IP injection to a single dose of glyphosate (purity unknown, 10 mg/kg). Animals were injected three times per week for five weeks and then sacrificed. Thiobarbituric acid-reactive substances (TBARS assay), protein carbonyls (PCOSs), total glutathione levels, individual glutathione levels, SOD and CAT were all measured as biomarkers for oxidative stress in plasma, brain, liver and kidney. Glyphosate significantly increased TBARS in all tissues ($p<0.01$), total glutathione in brain ($p<0.01$), SOD in liver and brain ($p<0.01$) and CAT in brain. In a follow-up report[203], they demonstrate that lipoic acid eliminates or severely reduces the impacts of glyphosate on the brain.

Cattani et al. (2014)[204] exposed groups of four pregnant Wistar rats to glyphosate formulation (Roundup Original, 360 g/L glyphosate) in drinking water from gestational days 5-15 at a dose of 71.4mg/kg. Fifteen day-old pups (2 per dam) were examined for oxidative stress markers in the hippocampus. Pups had a significant increase in TBARS ($p<0.05$) and a significant decrease in GSH ($p<0.01$).

George et al. (2010)[82] exposed groups of four Swiss albino mice to a glyphosate formulation (Roundup Original, 36g/L glyphosate) at a dose of 50 mg/kg (glyphosate

equivalent dose) via a single topical application. Proteomic analysis of skin from the treated animals saw alterations in SOD1, CA III and PRX II, proteins known to play a role in the management of oxidative stress.

Oxidative Stress in Non-Mammalian Systems

As for genotoxicity, oxidative stress from exposure to glyphosate and glyphosate formulations have been studied in various aquatic organisms; reviewed in **Slaninova et al. (2009)**[205]. Many of the studies reviewed by **Slaninova et al. (2009)** showed associations with glyphosate and oxidative stress in various organs. Since that review, additional studies have been completed that also demonstrate a positive association between glyphosate and oxidative stress[147, 156-159, 206-217].

Summary for Oxidative Stress

Seven studies addressed oxidative stress in human cells and another six studies addressed it in mammalian systems. In lymphocytes and erythrocytes from healthy donors, oxidative stress was detected as low as 580 µg/ml in lymphocytes and at 42.3 µg/ml in erythrocytes. In Hep-G2 cells, no increased oxidative stress was seen for a single concentration of 900 µg/l. In two studies in HaCat cells, glyphosate induced oxidative stress in a continuous model fit to the results in one study and at the lowest concentration (1700 µg/ml) in the other. The most convincing studies in human cells for oxidative stress are the two studies in human blood.

In Swiss CD-1 male mice, increased oxidative stress was seen in the liver at 24 hours, but not at four hours after injection of 300 mg/kg glyphosate. No increase was seen in the kidney. In Wistar rats, repeated IP dosing with glyphosate lead to increased oxidative stress in multiple organs using multiple biomarkers. Thus, all of the laboratory studies demonstrated oxidative stress with a significant finding in the rat study.

In Hep-G2 cells, a glyphosate formulation demonstrated a robust increase in oxidative stress at 40 µg/ml. Given the negative response in this cell line for glyphosate alone, it must be concluded that this response is not due to glyphosate. In HEP-2 cells, a glyphosate formulation demonstrated a robust increase in oxidative stress via multiple biomarkers at 376 µg/ml and when a surfactant is added, at 180.2 µg/ml. In HaCaT cells, a glyphosate formulation demonstrated significant increases in oxidative stress from doses starting as low as 1.7 µg/ml in a concentration-dependent fashion. No studies were available in human lymphocytes.

In Swiss CD-1 mice, a glyphosate formulation significantly increased oxidative stress in the kidney but only demonstrated a mild (non-significant) increase in the liver. This study evaluated oxidative stress at two different time points following exposure and saw responses that differed over time. The strong increase in the liver for glyphosate but not glyphosate formulation, suggests a complicated response pattern for pure glyphosate versus the formulation that could be linked to the time since exposure. In Swiss Albino mice, a glyphosate formulation demonstrated increased oxidative stress by two separate biomarkers in both the liver and the kidney. In a second study in Swiss albino mice using a different biomarker but a similar dose, increased oxidative stress

was seen in both the liver and the kidney. In Wistar rat pups exposed in utero, an increase in oxidative stress was seen in the hippocampus. In Swiss albino mice, topical application of a glyphosate formulation to the skin resulted in a proteomic fingerprint suggesting oxidative stress was increased.

Though there are fewer studies for oxidative stress than there are for genotoxicity, the robust response seen here in human cells and in rodent studies clearly supports a role for both glyphosate and glyphosate formulations in inducing oxidative stress. Thus, there is a second reasonable mechanism through which the tumors seen in humans and those seen in animals can be caused by glyphosate and glyphosate formulations.

Summary for Biological Plausibility

In the evaluation of causality, the evidence for biological plausibility is overwhelming. Glyphosate clearly causes multiple cancers in mice, two cancers in the hematopoietic system similar to what is seen in humans, causes cancer in rats, is genotoxic and induces oxidative stress. The findings are clear for both glyphosate alone and for glyphosate formulations. **There is strong support for biological plausibility in support of a causal association of glyphosate and glyphosate formulations with NHL.**

Biological Gradient

Only three of the epidemiological studies provided information on biological gradients in their publications.

Eriksson et al. (2008)[46] divided their cases and controls into those with ≤10 days per year of exposure and those with >10 days per year of exposure. The ORs were calculated using a multivariate analysis that included agents with statistically significant increased OR, or with an OR > 1.50 and at least 10 exposed subjects. ORs for glyphosate were 1.69 (0.70-4.07) for ≤10 days per year and 2.36 (1.04-5.37) for >10 days per year. In their multivariate analysis, latency periods of 1-10 years showed an OR of 1.11 (0.24-5.08) and >10 years had an OR of 2.26 (1.16-4.40). Thus, they show an increase with intensity of exposure and with latency.

McDuffie et al. (2001)[50], using a conditional logistic regression analysis controlling for major chemical classes of pesticides and all other covariates with $p<0.05$, the OR for ≤2 days per year of exposure was 1.0 (0.63-1.57) and for >2 days per year, the OR was 2.12 (1.20-3.73). Thus, they show an increase with intensity of exposure.

De Roos et al. (2005)[45] used three exposure metrics in their analyses: a) ever personally mixed or applied pesticides containing glyphosate; b) cumulative exposure days of use of glyphosate (years of use times days per year); and c) intensity weighted cumulative exposure days (years of use times days per year times intensity of use). For exposure measurements b and c, they divided the respondents into tertiles chosen *a priori* to avoid having sparse data when dealing with rare tumors. For cumulative exposure days and using the lowest exposed tertile as the reference group, the RRs drop with values of 0.7 (0.4-1.4) and 0.9 (0.5-1.6) for tertiles 2 and 3 respectively adjusted for demographic and lifestyle factors and other pesticides (30,699 subjects). When

intensity-weighted exposure days are examined, the RRs drop with values of 0.6 (0.3-1.1) and 0.8 (0.5-1.4) for tertiles 2 and 3, respectively adjusted for demographic and lifestyle factors and other pesticides (30,699 subjects). Thus, they do not see a biological gradient in their responses. However, the high frequency of exposure to many pesticides (e.g. 73.8% were exposed to 2,4-D) means subjects with low exposure to glyphosate were likely to be exposed to other agents that may also induce NHL; this could reduce the RRs in the higher exposure classes because it would inflate the RR in the low-exposure referent group.

Eriksson et al. (2008)[46] and **McDuffie et al. (2001)**[50] had consistent results for intensity of exposure per year (≤2 days per year, OR=1.0; ≤10 days per year, OR=1.69; >2 days per year, OR=2.12; >10 days per year, OR=2.26). It is not possible to resolve the remaining differences between these three studies nor is it easy to argue that one study has more weight on this question than any other. The studies use different measures of exposure or time since exposure, are done on different populations and have different statistical power to detect a trend.

In rodent carcinogenicity studies, there is clear evidence of a biological gradient.

In general, there is support that a biological gradient exists for the epidemiological data and thus support from this aspect of the Bradford-Hill evaluation.

Temporal Relationship

Exposure must come before the cancers occur otherwise the epidemiology studies are useless. In this case, it is clear that exposure came before the onset of NHL. **The need for a temporal relationship in the data supporting a causal association between glyphosate and NHL is satisfied.**

Specificity

There are other causes of NHL[218-221] so this group of cancers is not specific to glyphosate. **There is little support for specificity.**

Coherence

Humans, coming into contact with glyphosate, can absorb the compound into their bodies where it has been measured in blood and in urine[56, 222-226]. In laboratory animals, absorption, distribution and elimination of glyphosate and glyphosate compounds have been studied[140, 227] and show that glyphosate gets into the animal's bodies, distributes to numerous organs and is eliminated in urine. The animal cancer studies clearly demonstrate that glyphosate in mammals can have toxic effects.

Mouse models have long served as surrogates for humans in understanding and developing treatments for many diseases. The same holds true for lymphoid tumors seen in humans. For over 30 years, mouse models have been studied and evaluated as surrogates for NHL[228-232]. These publications and the associated classification systems for humans and mice indicate a close linkage between the diseases in humans and mice.

Thus, coherence is supported by 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.

There is strong support for coherence in the data supporting a causal association of glyphosate and glyphosate formulations with NHL.

Experimental Evidence in Humans

There is no experimental evidence in humans since purposely exposing humans to a pesticide, especially one that is probably carcinogenic, is not ethical and would never pass review by a human subject's advisory board.

Analogy

I am unaware of any analogous compounds from the scientific literature. This, however, is not an area where I have sufficient background to express an opinion.

Summary

Table 18 summarizes the information for each of Hill's aspects of causality. For these data, causality is strengthened because the available epidemiological studies show a consistent positive association between cancer and the exposure. The studies do not show different responses with some studies being positive and others negative, nor do they show any heterogeneity when analyzed together. And, in answer to Hill's question, the relationship between NHL and glyphosate exposure has been observed by different persons, in different places, circumstances, and times.

Causality is strengthened for these data because the strength of the observed associations, when evaluated simultaneously, are statistically significant, the findings are uni-directional and the results are unlikely to be due to chance. Even though none of the individual studies provide relative risks or odds ratios that are large and precise, the meta-analysis has objectively shown that the observed association across these studies is significant and supports a positive association between NHL and glyphosate.

Biological plausibility is strongly supported by the animal carcinogenicity data and the mechanistic data on genotoxicity and oxidative stress. When addressing biological plausibility, the first question generally asked is "Can you show that glyphosate causes cancers in experimental animals?" In this case, the answer to that question is clearly yes. Glyphosate has been demonstrated to cause cancer in two strains of rats and one strain of mice. 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, to a lesser degree, in male Sprague-Dawley rats, mammary gland adenomas and adenocarcinomas in female Wistar rats, skin keratocanthomas in male Wistar rats, and kidney adenomas and thyroid C-cell adenomas and carcinomas in male Sprague-Dawley rats. Glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice and hemangiomas in female CD-1 mice and possibly

causes malignant lymphomas, kidney adenomas in male Swiss albino mice and hemangiomas in female Swiss albino mice. Thus, glyphosate causes cancer in mammals. Thus, it is biologically plausible that glyphosate alone can cause cancer in mammals.

The next question generally asked is "Does the mechanism by which glyphosate causes cancer in experimental animals also work in humans?" The best understood mechanism by which chemicals cause cancer in both humans and animals is through damaging DNA that leads to mutations in cells that then leads to uncontrolled cellular replication and eventually cancer. It is absolutely clear from the available scientific data that both glyphosate and glyphosate formulations are genotoxic. This has been amply demonstrated in humans that were exposed to glyphosate, in human cells *in vitro*, in experimental animal models and their cells *in vitro* and *in vivo*, and in wildlife. One way in which DNA can be damaged is through the presence of free oxygen radicals that overwhelm a cell's antioxidant defenses. Glyphosate induces this type of oxidative stress, providing additional support for a biological mechanism that works in humans.

Table 18: Summary conclusions for Hill's nine aspects of epidemiological data and related science

Aspect	Conclusion	Reason
Consistency of the observed association	Strong	Multiple studies, all are positive, meta-analysis shows little heterogeneity, different research teams, different continents, different questionnaires, no obvious bias or confounding
Strength of the observed association	Strong	Six core epidemiology studies all show the same modest increase, significant meta-analyses
Biological plausibility	Very Strong	Multiple cancers in multiple species, not due to chance, increased risk of rare tumors, convincing evidence for genotoxicity and oxidative stress
Biological gradient	Moderate	Clearly seen in the two case-control studies that evaluated it, not seen in the cohort study
Temporal relationship of the observed association	Satisfied	Exposure clearly came before cancers
Specificity of the observed association	Not needed	NHL has other causes, this does not subtract from the causal argument
Coherence	Strong	Glyphosate is absorbed, distributed and excreted from the body, cancers seen in the mice have strong similarity to human NHL
Evidence from human experimentation	No data	No studies are available
Analogy	No data	No studies available in the literature

In general, there is support that a biological gradient exists for the epidemiological data and thus support from this aspect of the Bradford-Hill evaluation. Glyphosate ORs increased with time since first exposure and with intensity of use per year in the two case-control studies that evaluated at least one of these issues.

There is clearly the proper temporal relationship with the exposure coming before the cancers.

The human evidence is coherent. The basic findings in humans agree with the animal evidence for absorption, distribution and elimination of glyphosate. Also, one of the tumors seen in mice has almost the same etiology as NHL.

NHL is not specific to glyphosate exposure. There is no experimental evidence in humans and I did not find any references where researchers looked for analogous compounds with similar toxicity.

Hill (1965)[36] asks *"is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"* There is no better way of explaining the scientific evidence relating glyphosate to an increase in NHL in humans than cause and effect.

In 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.

The IARC Assessment of Glyphosate

In March 2015, the International Agency for Research on Cancer (an agency of the World Health Organization) brought together seventeen scientists (the Working Group) to evaluate the scientific evidence on whether glyphosate can cause cancer in humans. This group also contained one invited specialist (myself) to aid the Working Group (WG) in going through the science but who was not allowed to join discussions on the final conclusion or write any part of the document. The Working Group concluded that glyphosate falls in the category *"probably carcinogenic to humans (Group 2A)"*[56].

The IARC preamble[30] guides Working Groups on how to evaluate scientific literature to determine if something is a hazard. All Working Groups follow these guidelines and this process is accepted worldwide as a proper way to evaluate the literature for a hazard (e.g., the European Chemical Agency cites the IARC review process as guidance and then uses the exact same wording as IARC does to guide their own hazard evaluation process[34]).

The WG examined the epidemiological data and classified it as *"limited evidence of carcinogenicity,"* which is defined to mean *"a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with*

reasonable confidence." This is a precise and clear description of the strength of the evidence from the epidemiological studies.

The WG examined the evidence from animal carcinogenicity studies and classified it as "*sufficient evidence of carcinogenicity,*" which IARC defines as: "*a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites*." Based on the data available to IARC at the time of their review and the restrictions placed on the studies they can review by the Preamble, this conclusion is justified and correct.

One of the major criticisms of the WG review was that the WG did not review all of the animal carcinogenicity data that was available to the regulatory bodies and thus came to the wrong conclusions on the animal cancer data. In this review, I evaluated all 19 animal carcinogenicity experiments that have been collectively mentioned by any agency that reviews glyphosate. Where possible, I have analyzed the original data and used sound statistical methods to test for significant increases in cancer incidence in animals exposed to glyphosate. My conclusion is that the WG would have called this data "*sufficient evidence*" to support their findings despite not reviewing the additional studies analyzed herein. Despite the fact the industry kept these studies confidential, nothing contained in the withheld studies would have changed the WG conclusion.

On the mechanistic data, the IARC Working Group reviewed the same data that I reviewed, but I also evaluated, where possible, the proprietary data supporting the regulatory decisions. Where possible, I reanalyzed that data to be certain the results being presented were accurate. The IARC Working Group, using the guidelines set forth in their Preamble, declared strong support for the biological mechanisms of genotoxicity and oxidative stress. As I have shown here, there is strong support for these two mechanisms, even with the proprietary evidence from the industry studies. Thus, the IARC Working Group reached the correct conclusion.

To decide on a final classification for a compound, the IARC Preamble provides guidance on how the classification of the three areas are to be used. If the data in humans is "*limited*" and the data from animal carcinogenicity studies is "*sufficient*," the discussions should begin with Class 2A, "*the agent is probably carcinogenic to humans.*" Then, given the overall quality of the data set, the strength of the evidence from the mechanistic studies and any additional scientific issues that need to be considered, the Working Group will determine whether the data justifies a different category. In this case, the Working Group concluded 2A was the right category and I still believe the evidence supports that finding.

The EPA Assessment of Glyphosate

Like IARC, the EPA has guidelines that are to be followed when evaluating scientific literature and making a determination about the carcinogenic potential of a chemical. Those guidelines have been developed over many years and are based on sound scientific guidance that myself and many other scientists have provided to the Agency. For their evaluation of glyphosate, the Agency did not follow their own guidelines, nor did they follow sound scientific practice. This opinion is consistent with the review done by the **EPA FIFRA Scientific Advisory Panel**[54]. In addition, the Agency failed to find all of the relevant animal cancer studies and misinterpreted several of them. The major problems with the Agency evaluation are:

- Misinterpretation of the epidemiological evidence, confusing the potential for bias and potential for confounding with real bias and real confounding, allowing them to give almost no weight to the case-control studies in favor of the one cohort study;
- Misinterpretation of the findings in the meta-analysis;
- Failure to properly use historical controls in the analysis of the animal carcinogenicity studies; declaring a significant finding as not due to the compound if it is in the range of the historical controls;
- Failure to analyze all tumors in all studies relying upon the industry submissions to have done this correctly;
- Failure to follow their guidelines on what constitutes a positive finding, disregarding significant trend tests when no corresponding pairwise comparisons are also significant;
- Disregarding positive findings in doses that are clearly not above the maximum dose the animals could be given with compromising the integrity of the study;
- Using unreasonable arguments about the overall false positive rates in the study without actually doing an analysis of this issue;
- Failing to recognize the similar findings in similar studies and to do a pooled analysis to determine if the negative effects in one study cancel out the positive effects in another;
- Giving very little weight to studies from the literature and relying almost entirely on studies provided by industry that have not undergone peer review for both quality and, more importantly in some cases, interpretation of the findings; and
- Comparing results across different species and strains for the animal cancer studies and the mechanistic studies with little regard for unique findings in any one study and consistent findings across multiple studies.

Similar comments apply to the evaluation done by the **European Food Safety Authority**[89] and the **European Chemical Agency**[233]. My detailed comments to these

agencies on their risk assessments are attached. There were comments to my comments to EPA by other scientists and I also responded to those comments in the EPA docket for glyphosate. These are also included in the attached Appendices.

Dr. Christopher J. Portier

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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	

REBUTTAL REPORT OF DR. CHRISTOPHER J. PORTIER IN SUPPORT OF GENERAL CAUSATION ON BEHALF OF PLAINTIFFS

This rebuttal report addresses the reports of Dr. Corcoran and Dr. Foster. Because they address different issues, I address their statements separately, Dr. Corcoran first and Dr. Foster second. I do not address each issue with which I disagree; rather I identify those that I understand are appropriate for rebuttal.

REBUTTAL TO DR. CORCORAN

I. INTRODUCTION

Dr. Corcoran, in his response to my evaluation of glyphosate, demonstrates a lack of understanding of and experience with animal carcinogenicity studies. In addition, he seems to have missed some of the critical points that were made in my Expert Report, dated June 27, 2017 (hereinafter "Expert Report"). Further, he suggests an alternate analysis of the pooled data than the one I used in the Expert Report; this alternate analysis is also based on sound statistical methodology and when applied to the data set at issue here, yields effectively identical results to those in the Expert Report. These points are addressed below.

II. RESPONSE TO DR. CORCORAN'S p-VALUE COUNT

Dr. Corcoran claims that there are 1,016 p-values evaluated in the 12 animal bioassays considered acceptable for the evaluation. (Corcoran Report, at p. 9 & Tables 1 and 2). He arrives at this number by his evaluation of every neoplastic endpoint provided in the tables by **Greim et al. (2015)**[1]. Where did these 1,016 p-values come from?

Primary tumors are cancers that develop at the anatomical site where the cancer begins. Many cancers, after developing at their primary site, can metastasize and invade other anatomical sites leading to what are referred to as secondary or metastatic tumors. In evaluating the potential for a chemical to cause cancer, the predominant interest is in the increased incidence of primary tumors, not increases in secondary tumors that arise in one place (e.g. the liver) and metastasize to invade another organ (e.g. the lung). Tumors have a specific signature, so secondary tumors found in the lung that arose from the liver will be identified as a metastatic tumor in the lung but generally would not be included in an analysis of primary tumors. Eighty-one (81) of the tumor sites appearing in Dr. Corcoran's Tables A.1-7 and B.1-5 in his Appendix are metastatic secondary tumors and should not be included in the p-value count for this analysis.

Some tumors in animal bioassays are organ-specific (e.g. hepatocellular carcinomas in liver) and some are systemic (e.g. malignant lymphomas). Systemic tumors are not analyzed separately; instead, results are combined and a single analysis is conducted on the combined results. Thus, an analysis of malignant lymphomas that are found in the lung would not be done separately from those found in a particular lymph node. There are numerous examples in Dr. Corcoran's analysis where he fails to combine systemic tumors. Instead, Dr. Corcoran erroneously conducts multiple individual analyses. Engaging in this type of data analysis is incorrect, inflates the total p-values evaluated, and fails to appreciate the significance of the reported systemic tumors that

a combined analysis demonstrates. Of special importance are the malignant lymphomas, hemangiomas, and hemangiosarcomas in mice.

Some organs in the body are made up of pairs of separate organs (e.g. kidneys, lungs, ovaries). In some of the studies analyzed by Dr. Corcoran, tumors in these organs are presented as unilateral (affecting only one side of the body) or as bilateral (affecting both sides) with separate counts given for each category. It is uncommon to analyze these categories separately, and animals with either unilateral or bilateral tumors are simply grouped together as having the tumor. Similarly, for some of the studies, Dr. Corcoran also counts animals that have a single tumor of a specific type separately from animals with multiple tumors of that same type. These also should be combined in analyses where the interest is in whether an animal got a tumor of a specific type or did not. In both of these cases, by not combining the information into a single category, important chemical-related effects can be missed and the total number of p-values is inflated.

In every well-conducted animal bioassay, the pathology generally involves the evaluation of over 40 tissues in each sex/species group from the study. Given the different types of tumors in different tissues that might arise from such a study (e.g. thyroid follicular cell carcinomas and thyroid c-cell carcinomas), there is the potential to have more than 200 different evaluations of the data from each sex/species group. A majority of these potential tumor type-by-site combinations have no tumors. In addition, many sites have only one or two tumors in all of the animals evaluated; statistical tests simply cannot detect the effect of a chemical to increase tumors in cases where so few animals have a tumor. Without the use of historical control data, it is common practice not to evaluate the tumor sites with less than three tumors and only analyze those sites with three or more tumors.

Table 1 shows the total number of primary tumor sites evaluated by Dr. Corcoran, but adjusts his data to match common practice in analyzing cancer bioassays. Table 1 adds several tumor sites that were missed by Dr. Corcoran in his tables. Table 1 also eliminates secondary tumors, combines separate counts for unilateral and bilateral tumors, combines separate counts for single and multiple tumors and eliminates individual sites for systemic tumors using only one analysis for each systemic tumor. Once the data is adjusted to correct the omissions and analytical errors, the 1,016 p-values observed by Dr. Corcoran are shown to be an inflated count of tumor analyses. As exemplified in Table 1, there are 847 possible evaluations that could have been performed on these data. Of the possible evaluations, only 319 have three or more animals with tumors and, thus, should be analyzed.

III. APPROPRIATE USE OF HISTORICAL DATA

Dr. Corcoran criticizes the application of the numbers provided by Dr. Haseman in the Expert Report since historical control data was used to evaluate some of the studies, especially those in mice. Twenty sites were evaluated using historical control data and in exactly four of those sites, the historical data changed the resulting p-value from non-significant to significant. These four are kidney carcinomas (p_{Trend}=0.063, p_{Hist}=0.002) and adenomas and carcinomas

(p_{Trend}=0.065, p_{Hist}=0.011) in the study by **Knezevich and Hogan (1983)**[2], and kidney adenomas (p_{Trend}=0.062, p_{Hist}=0.005) and hemangiosarcomas (p_{Trend}=0.062, p_{Hist}=0.004) in the **Sugimoto (1997)**[3] study. In all four cases, the tumors are rare and all were at or close to the statistical limit of the exact trend test to identify an effect; this is the correct condition for historical control animals to make a difference in the analysis. Regardless, Dr. Corcoran implies that there is double the number of evaluations in the analysis because of the historical control evaluations. In fact, there are only 20 extra, 16 of which did not change the p-value at all.

Dr. Haseman's numbers are reasonable and come close to matching what is seen in the actual data. In male rats, there were on average 17.1 evaluations of single tumor findings in each study. Given that one would also combine tumor findings like liver adenomas and carcinomas, this is likely to add four to five additional analyses per bioassay giving 21 or 22 evaluations; Dr. Haseman chose 21.5. For female rats, there were an average of 13.4 analyses at individual sites and Dr. Haseman chose to use 25.5; this appears to be too high. Considering that females have a few more combined tumor analyses than males, I believe that 20 analyses in female rats would be more appropriate than 25.5; **Modified Table 15** (Appendix) now uses 20 tests for female rats. For male and female mice, the averages are 8.4 and 12.6, respectively, with Dr. Haseman choosing to use 10.5 and 15, again in reasonable agreement with the data. Using this arithmetic, a total of 418 possible evaluations would be done in all of these studies combined (**Modified Table 15**, Appendix), allowing almost 100 more sites than the actual count of sites with three or more animals shown in **Table 1**.

Dr. Corcoran criticizes the test used for the historical control analyses on the grounds that it does not take into account the heterogeneity that might exist across the various control groups. He references several other methods based upon statistical literature. There are several problems with this suggestion. In many cases, the methods outlined by Dr. Corcoran require the individual tumor counts from each historical control group; in many cases, only the average of the data from the historical controls is available. Where a valid historical control dataset was available, I used the mean tumor response in the controls to calculate the conditional probability of observing the trend seen in the study or a more significant trend if the true probability of response is the historical control average. Additionally, Dr. Corcoran references the manuscript by **Fung et al. (1996)**[4] as support for his approach to historical control analysis. However, one of the analysis methods used in the Fung article is similar to the one used in the Expert Report. This method has been shown to have sound and reliable statistical characteristics when there is no extra-binomial heterogeneity in the data and to be conservative when there is heterogeneity. For hemangiosarcomas, **Giknis and Clifford (2000)**[5] saw no tumors in 26 historical control studies (1,202 male CD-1 mice); there is no heterogeneity in these data. For kidney tumors, only the mean was provided for 46 historical control groups and only 11 animals out of 2,569 had a kidney tumor. This is broken down into seven adenomas seen in five studies and four adenocarcinomas seen in four studies; there is no heterogeneity in these data either. For the data presented here, the historical control test applied in the Expert Report was appropriate and methodologically sound. Any other reasonable statistical test applied to the four cases where historical controls changed a non-significant response to a significant response will yield effectively the same results.

IV. APPLYING LOGISTIC REGRESSION MODELING TO THE DATA SET

Dr. Corcoran criticized the pooled analysis of the data suggesting there should have been a correction for heterogeneity in the results. His long discussion of this issue, while perhaps relevant to epidemiology studies, would simply not work for animal carcinogenicity studies. In animal studies, one controls for all of the factors within a study that might make one exposure group different from any other. In pooling across multiple studies, I examined the individual experiments and only pooled data when it was clear the studies were close to identical. However, the approach suggested by Dr. Corcoran is also reasonable and it would be of value to see if the method of analysis suggested by Dr. Corcoran provides different results than the one used in the Expert Report. Thus, I reanalyzed the pooled data treating each experiment as a replicate while allowing for an effect of experiment in the evaluation (**Tables 2 and 3**). As suggested by Dr. Corcoran, the procedure used involved logistic regression modeling.

Table 2 shows four cases (highlighted in red) where the pooled analysis and the analysis using logistic regression differed in significance ($p<0.05$). In three of the four cases, the logistic regression provided a statistically significant finding where the pooled analysis was either marginal (two cases) or not significant (one case). For thyroid C-cell tumors in male Sprague-Dawley rats, the original significant finding is no longer supported and would suggest that the marginal statistically positive finding in **Lankas (1981)**[6] does not hold when compared to the other studies in the same sex and species and strain. In contrast, the lack of statistical significance for the pooled analyses of kidney adenomas and hepatocellular adenomas in male Sprague-Dawley rats and skin keratoacanthomas in male Wistar rats when combining **Brammer (2001)**[7] and **Wood et al. (2009)**[8] are reversed using logistic regression. This suggests a significant impact of glyphosate on the incidence of kidney adenomas and hepatocellular adenomas in male Sprague-Dawley rats and strengthens the finding of an increase in skin keratoacanthomas in male Wistar rats. Since kidney effects were also seen in the CD-1 mice, this strengthens the overall finding of an effect on kidney cancer rates in these animals. Since hepatocellular adenomas were also seen in Wistar rats, this strengthens that finding as well.

Four tumors in **Table 2** were not evaluated in the pooled analysis in the Expert Report; adrenal cortical carcinomas in female Sprague-Dawley rats and pituitary adenomas in male and female Wistar rats. These tumors did not appear in the Expert Report. Dr. Corcoran analyzed each of the individual tumor sites from all of the studies whereas the analysis in the Expert Report focused on tumors that were identified by regulatory authorities as increased in at least one study. Dr. Corcoran saw seven statistically significant tumor sites that were not discussed in the Expert Report. These are as follows: adrenal cortical carcinomas in female rats in the study by **Stout and Ruecker (1990)**[9]; skin intracutaneous cornifying epitheliomas (these are the same as keratoacanthomas) in male rats from the study by **Atkinson et al. (1993)**[10]; basal cell tumors in male rats in the study by **Enemoto (1997)**[11]; pituitary adenomas in both male and female rats in the study by **Wood et al. (2009)**[8]; splenic lymphosarcomas in female mice from the study by **Knezevich and Hogan (1983)**[2]; and Harderian gland adenomas in female mice from the study by **Sugimoto (1997)**[3]. In addition, after reviewing all of the findings in the Expert Report, it was

clear that the tumor incidence rates for skin keratoacanthomas in male rats from the study by **Enemoto (1997)**[11] were incorrect and an additional animal with this tumor was seen in the highest exposure group. Modifications to the original tables are provided as **Modified Tables 1-7** (rats) and **Modified Tables 9-12** (mice) in the Appendix. As before, where possible, any significant increase in a tumor as a function of dose seen in one study is analyzed in all remaining studies using the same sex, species, and strain. The new statistically significant findings are highlighted in the modified tables.

Returning to **Table 2**, after pooling all of the data for adrenal cortical carcinomas in female Sprague-Dawley rats, the exact trend test statistic is not significant. Logistic regression is also not significant with a p-value of 0.984. The lack of significance in this tumor is due to the high rates for this tumor in the **Lankas (1981)**[5] study and low rates in the remaining studies. The **Lankas (1981)**[5] study exposed rats for 26 months and the other three studies for only 24 months explaining, to some degree, the higher background rate in the **Lankas (1981)**[6] study (only six of the 25 cortical adenomas seen in this study occurred in rats dying before 730 days). Removing the **Lankas (1981)**[6] study and only pooling the three 24-month studies yields a significant trend in both tests. The significant trend seen for adrenal cortical adenomas cannot be easily discarded and suggest a potential for glyphosate to also affect adrenal cortical tumors.

For pituitary tumors in female Wistar rats, the pooled analysis was significant (p=0.005) and logistic regression was not significant (p=0.123). As noted in the Expert Report, the **Suresh (1996)**[12] study has very different control rates for pituitary tumors when compared with the other two studies. For this tumor, the categorical variable linked to the experiment by **Suresh (1996)**[12] was statistically significant (p<0.001). As before, if we remove the **Suresh (1996)**[12] study from the analysis and only pool the studies by **Brammer (2001)**[7] and **Wood et al. (2009)**[8], the results are statistically significant by both tests (**Table 2**). For pituitary tumors in male Wistar rats, none of the pooled analyses were significant (**Table 2**). These results would suggest there is limited support for an effect of glyphosate on pituitary adenomas in female Wistar rats.

Pooling the remaining new findings in Sprague-Dawley rats across the studies shows positive results for skin keratoacanthomas ($p_{pooling}$=0.010; $p_{logistic}$ =0.033) and basal cell tumors ($p_{pooling}$=0.011; $p_{logistic}$=0.020) in males. Since the pooled results for skin keratoacanthomas in male Wistar rats was also significant ($p_{pooling}$≤0.001; $p_{logistic}$ =0.008), there is strong support for an impact of glyphosate on skin keratoacanthomas in both male Sprague-Dawley rats and male Wistar rats.

Table 3 shows the pooled analyses for mice. None of the significant findings in the pooled analysis shown in the Expert Report were altered by the logistic regression analysis. For both hemangiosarcomas and kidney adenomas and carcinomas when pooling the 18-month studies by **Sugimoto (1997)**[3] and **Wood et al. (2009)**[3], the logistic regression model had difficulty

estimating the parameter for control response[1] so logistic regression was replaced with a simple linear model.

The Harderian gland adenomas seen in the study by **Sugimoto (1997)**[3] remain significant when combined with data from the other 18-month study by **Wood et al. (2009)**[13]. As seen in **Modified Table 11** (Appendix), there is a slight increase in Harderian gland tumors in the **Wood et al. (2009)**[13] study. The results remain statistically significant when combined with the results from **Knezevich and Hogan (1983)**[2]; **Atkinson (1993)**[10] did not evaluate Harderian glands.

The one remaining significant finding when applying logistic regression is an increase in composite lymphosarcomas in the spleen in female mice in the study by **Knezevich and Hogan (1983)**[2]. In the **International Classification of Diseases, Revision 9 (1975)**[14] (ICD-9), lymphosarcomas were classified under the heading of "Lymphosarcoma and reticulosarcoma". This was changed in **Revision 10 (1990)**[15] (ICD-10) where they are no longer classified[15]. In ICD-10, lymphosarcomas are approximately equal to lymphomas in the category of "Other specified types of non-Hodgkin lymphoma". This is a highly relevant finding for the causality argument for non-Hodgkin lymphoma in humans. This systemic tumor should be aggregated over all tissue sites with this tumor from this study. However, that is not possible without the individual animal pathology data from the study since, like malignant lymphomas, this tumor is aggressive and any animal with one tumor of this type is likely to have many other tumors of this same type; data summarized by organ cannot be used to obtain tumor incidence of at least one tumor in each animal. The remaining studies in CD-1 mice did not use this tumor classification for any of the lymphoid tumors identified; this is probably due to the classification change identified in ICD-10.

The new **Modified Table 15** (Appendix) includes all of the tumors identified in the Expert Report and those of Dr. Corcoran. In the original **Table 15**, when an increase occurred in both adenomas and in adenomas and carcinomas, only the more malignant finding was listed. In the **Modified Table 15**, that is no longer the case and each of these tumors is counted separately. With the exception of male Sprague-Dawley rats, the observed number of tumors are at or near the expected number for the different sex/strain groups in rats (**Modified Table 15**). For male Sprague-Dawley rats, 4.3 positive tumor findings with $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ are expected and 10 are observed (p=0.01) while 0.8 cases with $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ are expected and two were observed (p=0.21). In female CD-1 mice and Swiss Albino mice, the expected and observed numbers are approximately equal. However, in male CD-1 mice, there were 2.1 tumors expected for $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ and eight were observed (p<0.001) and there were 0.4 expected for $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ and five were observed (p<0.001). The findings

[1] In logistic regression, modeling is done using the logit(p) where p is the probability of response and modeling is done using $log\left(\frac{p}{1-p}\right) = \alpha + \beta \times dose$. If the control tumor response is 0, then $log\left(\frac{p}{1-p}\right) = -\infty$ and so the best estimate for α is also negative infinity. In these cases, numerical fitting algorithms have difficulty with estimating α which can effect the estimate and standard error of β. The general linear model has the form $p = \alpha + \beta \times dose$ and α can easily be estimated to be zero for the control response.

for male Sprague-Dawley rats and male CD-1 mice in these studies could not have occurred by chance alone. Even if one incorrectly groups all sexes and species together, there are 20.9 expected responses for $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ and 30 observed (p=0.032) and 4.2 expected responses for $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ and 12 observed (p=0.001). Thus, chance does not explain all of the positive results seen in these studies.

Dr. Corcoran makes only one comment relating to **Table 15** suggesting that the historical control evaluations explain the difference between **Table 15** and his results. As noted earlier, the use of historical control data in this instance is justified and based on sound and accepted methodology given the rarity of the four tumor sites where the historical control data made a difference. If the historical control evaluations are included in **Modified Table 15**, that adds three additional evaluations to the male rats (one with p<0.01), 1 to female rats (p<0.001), 0 to female mice and 18 to male mice (five with p<0.01 and eight with p<0.05). The number of evaluations for each group would then become 22 for male rats, no real change for female rats or female mice, and a change to 13.5 for male mice. The number of findings in the **Modified Table 15** that were significant at p≤0.05 by either test would change from 30 (expected 20.9) out of 418 reasonable analyses (p=0.032) to 38 (expected 22) out of 440 (p<0.001). Similarly, the number of findings in the **Modified Table 15** that were significant at p≤0.01 by either test would change from 12 (expected 4.2) out of 418 reasonable analyses (p=0.001) to 18 (expected 4.4) out of 440 (p<0.001). It is clear that incorporation of the tests using historical controls into **Modified Table 15** would make it even less likely that all of these findings are due to chance.

V. CONCLUSION

Dr. Corcoran has raised certain issues relating to the pooling of experiments that have been addressed in this response. There is no significant difference between the results from the methods proposed by Dr. Corcoran and those in the Expert Report. Both are sound methods for evaluating the overall significance of multiple animal carcinogenicity studies. Dr. Corcoran also identified several tumors that were not evaluated in the Expert Report, which are now included in my expert opinion as updated in this response. Dr. Corcoran also expressed concerns about the number of analyses and the effect of all of these analyses on false-positive error rates. As explained above, Dr. Corcoran misunderstood how analyses are conducted for animal cancer studies.

In summary, Dr. Corcoran's concerns have led to additional analyses that strengthen the case that glyphosate causes cancers in rodents, especially lymphatic and hematological cancers in male mice. The new analyses strengthen the biological plausibility, biological gradient, and coherence arguments developed by **Hill (1965)**[16] supporting the conclusion that glyphosate can cause non-Hodgkin lymphoma in humans.

Table 1: Number of tumor sites with one, two, and three or more tumors in all dose groups combined from the 12 rodent studies of glyphosate

Study	Numbers of Sites with Specified Number of Tumors in All Exposure Groups					
	Exactly 1 Tumor		Exactly 2 Tumors		3 or More Tumors	
	Males	Females	Males	Females	Males	Females
Lankas (1981) S-D Rats	16	17	4	2	22	25
Stout and Ruecker (1990) S-D Rats	21	24	7	4	16	12
Atkinson et al. (1993) S-D Rats	20	16	5	3	15	9
Brammer (2001) Wistar Rats	20	20	5	5	16	13
Suresh (1996) Wistar Rats	17	20	2	3	11	9
Enemoto (1997) S-D Rats	29	18	3	5	21	12
Wood et al. (2009) Wistar Rats	27	17	2	8	19	14
Totals Rats	150	132	28	30	120	94
Average Rats	21.5	18.9	4	4.3	17.1	13.4
Knezevich and Hogan (1983) CD-1 Mice	20	44	5	7	9	17
Atkinson et al. (1993) CD-1 Mice	10	11	4	2	9	14
Wood et al. (2009) CD-1 Mice	8	14	2	2	10	13
Sugimoto (1997) CD-1 Mice	10	14	5	5	6	11
Kumar (2001) Swiss Albino Mice	4	16	3	2	8	8
Total Mice	52	99	19	18	42	63
Average Mice	10.4	19.8	3.8	3.6	8.4	12.6

Table 2: Comparison of pooled analyses with and without a correction for experiment in Rats

Studies	Sex	Tumor	General Linear Model		Original Pooled Analysis
			Slope (se)	P-value	
Lankas (1981)[6] Enemoto (1997)[11] Atkinson et al. (1993)[10] Stout and Ruecker (1990)[9] Sprague-Dawley Rats	M	Testicular Interstitial Cell Tumors	0.513 (0.517)	0.461	0.608
	F	Thyroid C-cell Adenomas and Carcinomas[2]	2.95 (2.79)	0.145	0.390
	M	Thyroid C-cell Adenomas and Carcinomas	2.29 (2.78)	0.205	0.041
	M	Thyroid Follicular-cell Adenomas and Carcinomas[2]	0.930 (5.49)	0.433	0.618
	M	Pancreas Islet-Cell Tumors[2]	3.02 (4.07)	0.260	0.275
	M	Hepatocellular Adenomas[2]	9.65 (4.30)	0.012	0.073
	M	Kidney Adenomas[2]	14.3 (8.27)	0.042	0.200
	M	Kidney Adenomas (excluding Lankas, 1981)	14.7 (8.29)	0.038	0.031
	F	Adrenal Cortical Carcinoma[2]	26.5 (13.6)	0.984	0.997
	M	Skin Keratoacanthoma	11.1 (4.61)	<0.001	<0.001
	M	Basal Cell Tumors	23.3 (11.4)	0.020	0.011
Brammer (2001)[7] Wood (2009)[8] Suresh (1996)[12] Wistar Rats	M	Hepatocellular Adenomas[2]	40.0 (20.9)	0.030	0.051
	F	Mammary Gland Adenomas and Adenocarcinomas[2]	2.11 (3.25)	0.258	0.459
	M	Skin Keratoacanthoma[2]	10.4 (5.65)	0.033	0.010
	M	Pituitary Adenomas[2]	0.266 (2.32)	0.454	0.177
	F	Pituitary Adenomas[2]	1.89 (1.64)	0.123	0.005
Brammer (2001)[7] Wood (2009)[8] Wistar Rats	M	Hepatocellular Adenomas	1.32 (6.11)	0.015	0.013
	F	Mammary Gland Adenomas and Adenocarcinomas[2]	7.00 (3.62)	0.027	0.037
	M	Skin Keratoacanthoma[2]	10.4 (5.65)	0.033	0.053
	M	Pituitary Adenomas	0.146 (2.38)	0.476	0.503
	F	Pituitary Adenomas[2]	3.34 (1.76)	0.029	0.017

Entry is multiplied by 10^4 for ease in presentation; [2]at least one of the categorical variables for experiment in the logistic regression analysis for these tumors was statistically significant ($p<0.05$)

Table 3: Comparison of pooled analyses with and without a correction for experiment in CD-1 Mice

Studies	Sex	Tumor	General Linear Model		Original Pooled Analysis
			Slope (se)	P-value	
Sugimoto 1997[3], Wood 2009[13] 18 Month	M	Hemangiosarcoma[1]	7.91e-2 (1.81e-7)	<0.001	0.015
	M	Kidney Adenoma and Carcinoma[1]	7.91e-2 (1.81e-7)	<0.001	0.015
	M	Malignant Lymphoma	4.24 (1.67)	0.005	0.005
	M	Lung Adenocarcinoma[2]	2.24 (1.47)	0.063	0.417
	F	Hemangioma (any tissue)	5.92 (2.293)	0.005	<0.001
	F	Harderian Gland Adenoma	3.66 (1.81)	0.021	0.005
Atkinson 1993[17], Knezevich 1983[2] 24 Month	M	Hemangiosarcoma	3.58 (4.32)	0.204	0.490
	M	Kidney Adenoma and Carcinoma	2.89 (2.00)	0.075	0.081
	M	Malignant Lymphoma	-0.739 (1.53)	0.686	0.653
	M	Lung Adenocarcinoma[2]	-2.28 (2.01)	0.872	0.985
	F	Hemangioma (any tissue)	-3.62 (5.88)	0.731	0.424
Sugimoto 1997[3], Wood 2009[13], Atkinson 1993[17], Knezevich 1983[2]	M	Hemangiosarcoma[2]	6.82 (3.72)	0.033	0.045
	M	Kidney Adenoma and Carcinoma	4.12 (1.84)	0.013	0.005
	M	Malignant Lymphoma	1.36 (1.02)	0.093	0.073
	M	Lung Adenocarcinoma[2]	0.259 (1.10)	0.407	0.937
	F	Hemangioma (any tissue)	3.01 (1.61)	0.031	0.018
	F	Harderian Gland Adenoma[2,3]	2.77 (1.62)	0.043	0.005

Entry is multiplied by 10^{-4} for ease in presentation; [1]because this tumor had a zero response in the control and low exposure groups and because the logit(0)=-infinity, the logistic regression was not appropriate in this case and a simple general linear model was used; [2]at least one of the categorical variables for experiment in the logistic regression analysis for these tumors was statistically significant ($p<0.05$); [3] this analysis excludes the study by Atkinson et al. (1993) since they did not examine Harderian gland

REBUTTAL OF DR. FOSTER

I. INTRODUCTION

Dr. Foster dismissed 18 of the 19 statistically significant findings in the animal carcinogenicity studies identified in my Expert Report. He did not comment on the increased incidence of hemangiomas in female Swiss albino mice in the study by Kumar (2001)[18]. Dr. Foster provided rationale for each of his dismissals based on the significant changes in tumor incidence failing to meet his criteria for a positive study. Table 4, illustrates the six categories of criteria that Dr. Foster uses to dismiss statistically significant ($p \leq 0.05$) positive findings from the 12 studies exposing rats and mice to glyphosate. Only certain categories were relevant to any one positive finding discussed in the Expert Report. The categories used by Dr. Foster are briefly described below:

Dose-Response: For several tumors, Dr. Foster, as one of his arguments, found there was no dose-response in the data.

Historical Control: Failure of the response to be outside the range of the historical control data or for the control response to be below the range of the historical control data was also an argument Dr. Foster used to dismiss studies.

Precursor Lesion: Some tumors can go through a progression from non-malignant lesions to cancer; failure to see increases in both non-malignant tumors and malignant tumors was another criterion Dr. Foster used.

Other Studies: If all of the studies did not give the same result, Dr. Foster used this as part of the criteria for dismissal.

Survival: In two studies, survival in the highest exposure group was different than in the controls, and Dr. Foster used this as part of the reason for dismissal.

Fisher Test: In several studies, Dr. Foster used a lack of statistically significant pairwise comparisons between the higher doses and controls as part of the reasoning to dismiss positive tumor findings.

Rather than going study-by-study and addressing these points, this rebuttal looks at each category separately and then discusses their impact in each study.

II. Dose-Response

Dr. Foster shows a lack of understanding of statistics in the use of this criteria. While Dr. Foster does not define what he means by a lack of dose-response, my interpretation of this concept is that as the dose increases, the probability of a tumor cannot decrease (this is known as a non-decreasing function in mathematics). As an example, if the responses from control to high dose

in a four-dose study were 2%, 3%, 5%, 7%, this would constitute clear dose-response whereas 2%, 1%, 4%, 7% would not. The problem with this criterion is that it has very significant impacts on false-positive and false-negative rates.

In any statistical analysis, there is a null hypothesis and an alternative hypothesis. In an animal carcinogenesis study, the null hypothesis means there is no impact of the chemical on the tumor rates; the alternative hypothesis means the chemical increases the tumor rates. A false-positive error occurs when one incorrectly rejects the null hypothesis and decides the chemical causes cancer when it really does not cause cancer. A false-negative error occurs when one does not reject the null hypothesis even though the chemical does cause cancer. The rates at which these errors occur for a specific test can be calculated.

So, what is the impact of requiring non-decreasing dose-response in addition to statistical significance? Using statistical simulations[2], it is easy to answer this question. Consider one of the examples where dose-response was part of Dr. Foster's criteria for dismissing the tumor. In the study by **Sugimoto (1997)**[3], the control response for malignant lymphomas in male CD-1 mice was 4% and the response in the high exposure group was 12%. Let's begin by estimating the probability of a false-positive error and the impact of requiring non-decreasing dose-response.

If we assume that the true background is 4% and there is no dose-response, then we can, by random sampling on the computer, generate 1,000 datasets where each group is assumed to have a true response of 4% regardless of the dose. By random chance, these groups will sometimes result in a positive response. If we reject the null hypothesis when $p_{Trend} \leq 0.05$, the exact trend test yields a false positive rate of 5%. That is, 5% of the time, by chance, the null hypothesis will be rejected. This is exactly what should happen when a test is operating correctly. What happens then if we also require that the resulting pattern of dose-response be non-decreasing? Using the exact same simulated data, the resulting false-positive error rate now drops to 2.8%, almost half of what was expected. On the surface, one might think this is a good and acceptable outcome since the error rate has dropped, but by reducing the false-positive rate, the false-negative rate increases. Let's again look at our example.

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[2] Statistical simulations are a critical tool for understanding the behavior of a statistical test in a specific setting. In this case, 1000 samples are draw from a binomial distribution where the underlying probability of a tumor and the number of animals is specified; for example, the probability of a tumor is 0.04 for all of the groups when calculating the probability of a false positive error and each dose group has 50 animals in it. For each simulated data set produced, the Armitage linear trend test is applied and if the p-value is ≤0.05, that simulation is given a value of 1 (positive tumor trend with increasing exposure) otherwise, it is given a value of zero. After 1000 simulations are completed, the number of cases with a value of 1 are counted and the estimated false-positive error rate is that number divided by 1000. Thus, for the case discussed above, fifty of the 1000 simulations were assigned a value of 1 and the underlying false-positive error rate is then 50/1000=0.05 or 5%.

Table 4: Criteria used by Dr. Foster to dismiss 19 statistically significant ($p \leq 0.05$) identified using the Armitage linear trend test in proportions to evaluate 12 studies of glyphosate exposure to rats and mice

Study	Sex	Tumor	Dose-Response	Hist. Cont.	Pre-Cursor Lesion	Other Studies	Survival	Fisher Test
Lankas (1981) SD Rat	M	Testicular Tumors	x	x	x	x	x	
	F	Thyroid C-Cell			x	x		
Stout and Ruecker (1999) SD Rat	M	Liver Adenomas	x	x	x	x		
	M	Liver Adenomas and Carcinomas	x	X	x	x		
	F	Kerato-acanthoma ($p>0.05$)		x				
	F	Thyroid C-Cell Adenomas		x				
	F	Thyroid C-Cell Adenomas and Carcinomas		x				
Brammer (2001) Wistar Rats	M	Liver Adenomas	x	x	x		x	
Wood et al. (2009) Wistar Rats	F	Mamm. Gland Adeno-carcinomas	x	x		x		
	F	Mamm. Gland Tumors	x	x		x		
	M	Kerato-acanthoma	x					x
Atkinson et al. (1993) SD Rats	M	Follicular Cell Tumors		x		x		
Enemoto (1997) SD Rats	M	Kidney Adenomas	x		x	x		x
Knezevich and Hogan (1983) CD-1 Mice	M	Kidney Tumors	x		x	x		
Atkinson (1993)	M	Hemangio-sarcoma		x		x		
Sugimoto (1997)	M	Malignant Lymphoma	x	x		x		x
	F	Hemangiomas				x		
Wood et al. (2009)	M	Malignant Lymphomas		x				
	M	Lung Adeno-carcinoma	x		x	x		x

Now, instead of assuming there is no dose-response, assume there is linear dose-response with the response in the control group is 4% and the response in the high exposure group is 12%. Since this response is linear with dose, and we use the doses for males from the **Sugimoto (1997)**[3] study, the expected response at the four dose groups are 4% at control, 4.3% at 165 mg/kg, 5.5% at 838.1 mg/kg and 12% at 4348 mg/kg. Using these as the target responses at each dose, 1,000 studies with random error can be simulated and one can count how often the null hypothesis is not rejected and an incorrect conclusion that the chemical does not cause malignant lymphomas is accepted. Using only the trend test, without the requirement of non-decreasing dose-response, yields a false-positive error rate of 29%. This is not a bad rate for this shallow dose-response. Requiring that the dose-response be non-decreasing results in a false-positive error rate of 86%. This is unacceptable and is not surprising. Just evaluating response at control and at the lowest dose, one can see that they are almost identical in response. Thus, by random chance, one would expect the lowest dose to be below the control response about 50% of the time and each time this happens, Dr. Foster's approach would reject any positive finding in a trend test. Thus, regardless of the responses in the other exposure groups, one would accept the null hypothesis and generate a false-negative error.

Dr. Foster used this argument as one of his reasons for dismissing 11 of the 19 tumors (58%) with significant dose-response trends. His use of these criteria is not methodologically sound.

III. Historical Controls

Dr. Foster begins his discussion of the interpretation of the bioassay results by stating "*I agree with Dr. Portier that it is best to compare data with contemporary controls*". Despite this statement, Dr. Foster then goes on to use historical controls as part of his reasons for dismissing 13 of the 19 tumors (68%) in Table 4. In simple terms, rejecting a significant finding observed when comparisons are made to the concurrent control because the responses fall into the range of the historical controls is akin to replacing the concurrent control with the largest control response ever seen.

During the course of an animal study, all aspects of the animal's life are controlled; the air they breathe, the food they eat, the light-dark cycle in the laboratory, handling of the animals, etc. Certain issues are very difficult to control such as noise in the laboratory, outside radiation that may seep into the laboratory, slight differences in batches of feed from one week to the next, odors drifting in from other areas of the building, etc. For these uncontrolled variables, every animal in the study is subject to the same problems, thus the controls in the study see the same uncontrolled exposures as do the treated animals. In addition, while strains of animals may be the same, there is variability in response if the animals arise from different laboratories or are even born at different times of the year. When controls are used from another study, this allows for the possibility that uncontrolled factors from that other study could have affected those controls making their response different from the concurrent control and from the animals exposed in the current experiment. Most of the guidelines developed for animal studies clearly state that the concurrent control is the best control to use for analyzing a cancer

bioassay as noted on page 21 of the Expert Report. In fact, the IARC guidelines[19] are explicit on the issue of using historical controls stating that

> *"Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability.* ***It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls****, particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals"* (emphasis added).

The scientific reasons for not using historical control ranges to reject a positive finding are clear, but there is also a statistical reason. As the number of studies in the historical control database increases, so does the range of responses. The net effect of this is that, as the historical control dataset gets larger, one is more likely to reject a positive if one insists the response be outside the range of the historical controls. Again, going back to the example of malignant lymphomas in male mice from the study by **Sugimoto (1997)**[3], the false positive rate is 5% when only the exact trend test is applied to the simulated data where there are no chemical-related effects in any of the dose groups. If there are 10 historical control groups with exactly the same background response as the controls (4%) and no extra-binomial variability (which could be caused by uncontrolled or different exposures), the false-positive error rate drops to 1.9% and if there are 26 historical control groups, as is the case for the **Sugimoto (1997)**[3] study, the false-positive error rate drops to 1.1%. This results in an increase in the false-negative error rate from 29% using just the trend test results to 38% with 10 historical control groups to 50% for 30 historical control groups.

This increase in the false-negative rate is expected since one is only rejecting positive findings, never rejecting negative findings.

Dr. Foster's discussion regarding the range of the historical control data is misleading. Again, consider the example of malignant lymphomas in male rats from the study by **Sugimoto (1997)**[3]. Dr. Foster concludes *"... the incidence of these tumors falls within the range of historical controls in the Giknis (2000) report (0-14%) cited by Dr. Portier and the range of historical controls (3-19%) from contemporaneous studies conducted at the same laboratory (BFR, 2015)".* After studying the **BfR (2015)**[20] document, I can only find one reference to

historical controls for malignant lymphomas in male Wistar rats (page 91) which references the study by **Giknis and Clifford (2000)**[5], showing a range of 1.45% to 21.7%. However, they misread the **Giknis and Clifford (2000)**[5] paper, grouping 18-month controls with 24-month controls and failing to recognize there were 13 studies with no tumors in the controls making the lower range value 0%.

Figure 1 shows a histogram of the incidence rates in the twenty-six 18-month historical control groups for malignant lymphomas in male CD-1 mice from the study by **Giknis and Clifford (2000)**[5]. It is clear from this figure that the control response from the study by **Sugimoto (1997)**[3] is easily within the usual range of control responses for malignant lymphomas in male Wistar rats. The higher end of the historical control is driven by response in a single study that is almost double the value of the next lowest response and about five times the value of the median response. This pattern is quite common in the tumors that Dr. Foster dismisses because of historical controls. This is demonstrated by the five examples presented in **Figure 2**. In all five cases, the control tumor response is in a reasonable range of the historical control response and there is good reason to use the concurrent control group in the analysis and ignore the historical controls.

Figure 1: Incidence rates in the twenty-six 18-month historical control groups for malignant lymphomas in male CD-1 mice from the study by **Giknis and Clifford (2000)**[1]

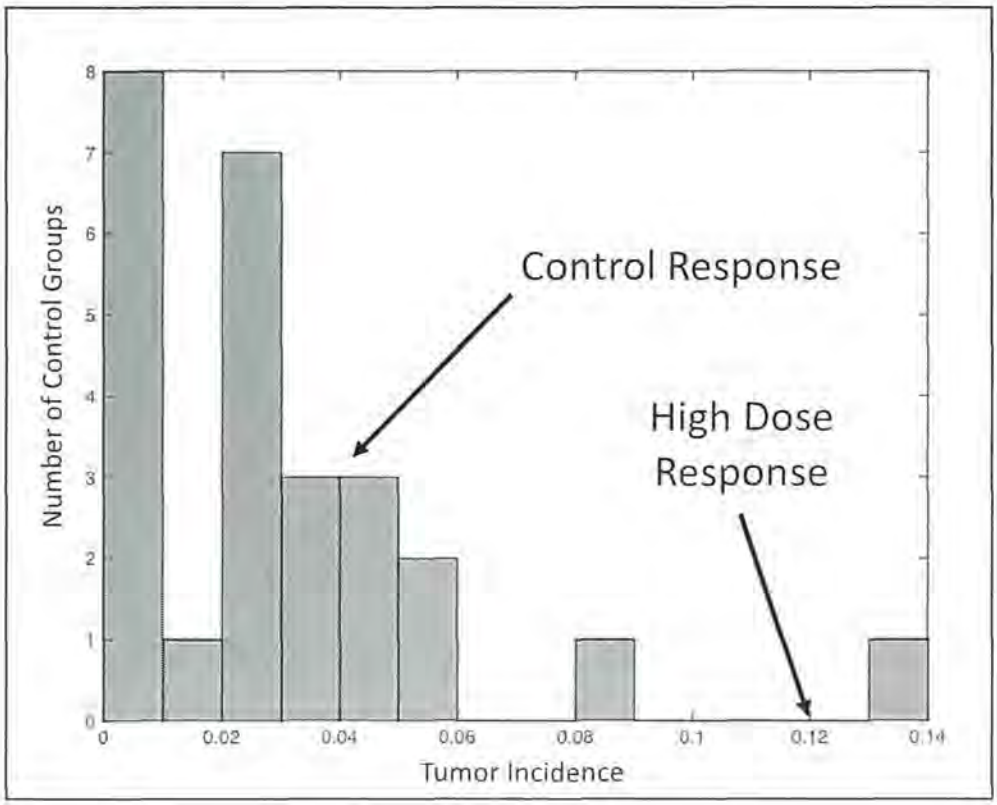
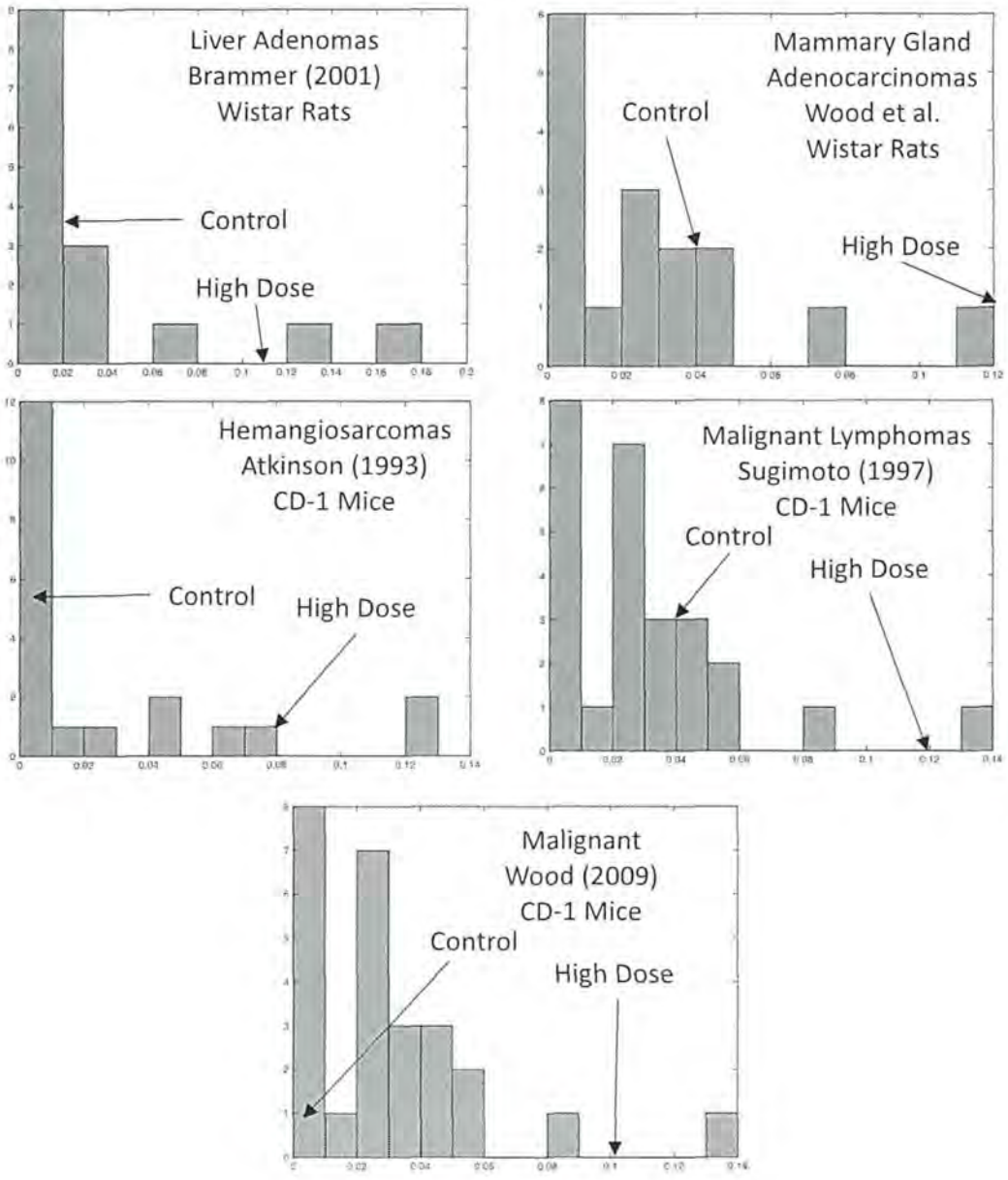


Figure 2: Incidence rates in the historical control groups for several tumors



Dr. Foster is also very selective in his presentation of the historical control data, not mentioning situations where the tumor response is well outside the range of the historical controls. Here are two examples:

Lankas (1981)[6]: Testes interstitial cell tumor – historical control range 3-7% (Monsanto), 0% to 9.3% (**Giknis and Clifford (2004)**[21]) – response at highest dose is 12%

Enemoto (1997)[11]: Kidney Adenoma – historical control range 0%-4% (**Giknis and Clifford (2011)**[22]), note 23 of 30 studies had 0% in the control group) – response at highest dose is 8%.

There were several other wrong or misleading comments in Dr. Foster's report regarding historical controls. On page 18, he mentions the average historical control rate of mammary gland tumors in female Sprague-Dawley rats (57%) and in the same sentence includes Wistar rats implying the control rate of mammary gland tumors in these animals is also large. However, according to **Giknis and Clifford (2011)**[22] the mean response for mammary gland adenomas in female Wistar rats is 2.22% and for adenocarcinomas it is 2.96%. He also states on page 24 that the historical control data from **Giknis and Clifford (2005)**[23] "*indicate it is unusual to have zero lymphomas in the control group*" of male Wistar rats. However, **Giknis and Clifford (2005)**[23] show 8 of the 26 control groups (31%) from 18-month studies have no animals with a malignant lymphoma; thus having no tumors in the control group is not unusual. The actual responses for malignant lymphomas for all of the control groups in the database provided by **Giknis and Clifford (2005)**[23] are shown in **Figure** 2.

Finally, there are four tumor sites where, used correctly, the historical control data does contribute to the interpretation of the result. These four are kidney carcinomas (p_{Trend}=0.063, p_{Hist}=0.002) and adenomas and carcinomas (p_{Trend}=0.065, p_{Hist}=0.011) in the study by **Knezevich and Hogan (1983)**[2], and kidney adenomas (p_{Trend}=0.062, p_{Hist}=0.005) and hemangiosarcomas (p_{Trend}=0.062, p_{Hist}=0.004) in the **Sugimoto (1997)**[3] study. For hemangiosarcomas, **Giknis and Clifford (2000)**[5] saw no tumors in 26 historical 18-month control studies (1,202 male CD-1 mice) making the two tumors seen in the highest dose group in the study by **Sugimoto (1997)**[3] both statistically and biologically compelling. For kidney tumors, **Giknis and Clifford (2000)**[5] only provide the mean tumor response for 46 historical control groups (twenty-six 18-month studies and twenty 24-month studies) and only 11 animals out of 2569 (0.4%) had a kidney tumor. This is broken down into seven adenomas seen in five studies and four adenocarcinomas seen in four studies; thus 41 control groups had no adenomas and 42 had no adenocarcinomas with the remaining four groups each having only one adenocarcinoma. Thus, the two adenomas seen in the study by **Sugimoto (1997)**[3] and the three carcinomas seen in the study by **Knezevich and Hogan (1983)**[2] are significant and biologically important.

Thus, Dr. Foster provides an unbalanced evaluation of the historical control data, failing to discuss it when it strengthens a significant finding and incorrectly using the range of the historical controls to reject the concurrent control group.

IV. Precursor Lesions

Dr. Foster seems to believe that virtually all tumors arise from precursor lesions like hyperplasia and adenomas and that if one does not see increases in both adenomas and carcinomas, the finding is not chemically related and can be dismissed. This is an overly simplistic view of a complicated process. For example, if one looks at human digestive tract cancers, while it is clear that many carcinomas arise from adenomas, it is also likely that some arise *de novo*[24-26].

In humans, other organs and tissues have not been as carefully studied. In animal studies, there are numerous cases in which carcinomas and adenomas combined are increased when adenomas are not increased, many cases where adenomas are increased without an increase in carcinomas and fewer cases where only carcinomas are increased. For example, in an evaluation[27] of 64 National Toxicology Program (NTP) carcinogenicity studies in rats and/or mice that produced alveolar/bronchiolar adenomas and/or carcinomas, there are multiple studies that the NTP labels as clear evidence of carcinogenicity or positive for carcinogenicity[3] where there are only adenomas, only carcinomas or both.

Cancer is a multistage process which changes cells from being normal to being malignant through a variety of steps (**Figure 3**). In general, normal cells obtain damage to their DNA. Normally, this damage can be repaired by processes in the cell that specialize in keeping the DNA sequence from changing. If the damage to the DNA is not repaired and the cell replicates, the change in the DNA sequence can become permanent in the cell and is referred to as a mutation. Most cancers require cells to undergo several mutations before the cell will completely lose growth control and begin invading the surrounding tissue. Chemicals can affect this process at many points as cells progress from a normal state to a malignant state (**Figure 3**). Precursor lesions, like hyperplastic nodules and adenomas, are generally thought to be derived from cells that are at early stages of the carcinogenic process.

Two issues are critical in understanding what is seen in the results of an animal bioassay versus the underlying biology. First, all tumors in a glyphosate study are only observed at one time in the course of the study; when the animal dies. Thus, this entire process of multistage carcinogenesis is invisible because one does not see the adenoma in the animal and then later see the carcinoma; one only sees some animals with adenomas and others with carcinomas. Second, seldom will pathologists examine the tissue surrounding a tumor and list an animal as having both a carcinoma and an adenoma. Since carcinomas generally grow faster than adenomas, the carcinoma would be the predominant pathology and that animal would be listed as having only the carcinoma. Hence, there is a likely under-reporting of the potential number of adenomas that actually occurred.

If a chemical affects mutations or cellular replication at an early stage in this process and the final stages in the process occur spontaneously (without chemical impact), one is likely to see an increase in all of the precursor lesions as well as malignancies. As an example, suppose a chemical increases the probability of having an adenoma from 10% to 30% and the probability of an adenoma becoming a carcinoma remains constant at 30%; then, with 50 animals in each group, you would expect five adenomas in controls and 15 in the treated animals. If 30% of these adenomas progress to become malignancies, one would expect one to two animals with carcinomas in controls and four to five carcinomas in the exposed animals. Now, because the carcinoma would grow within the adenoma, one is no longer likely to count an animal with a carcinoma as having an adenoma because the cancer becomes the predominant pathology. Thus, one would likely see adenomas in three to four animals (subtract one to two from the

[3] Clear evidence and positive are designations used by the National Toxicology Program for chemicals that causally induced the observed increase in tumors.

original five) in control and nine to 10 animals in the treated group (subtract five to six from the original 15).

If the tumor affects all stages of the process, then other patterns can occur. Consider the same example, but the chemical changes the rate at which adenomas become carcinomas from 20% to 60%. Now, one would expect one to two animals with carcinomas in the controls and nine animals in the treated group. The number of expected adenomas would then be three to four in controls and drop to six in the high dose group, an increase that is not likely to be significant.

If the chemical only affects the late stages (not the early stages) of cancer development, an actual decrease is seen in the adenoma counts. For example, if adenomas occur spontaneously in 30% of the animals, then with 50 animals in each group, it is expected that 15 animals in both the control and treated groups will develop adenomas. If the chemical changes the rate of conversion from adenomas to carcinomas from 20% to 60%, one would expect three tumors in the control group and nine in the treated group. Subtracting these from the adenoma counts would result in adenomas in 12 control animals and only six treated animals; a decrease.

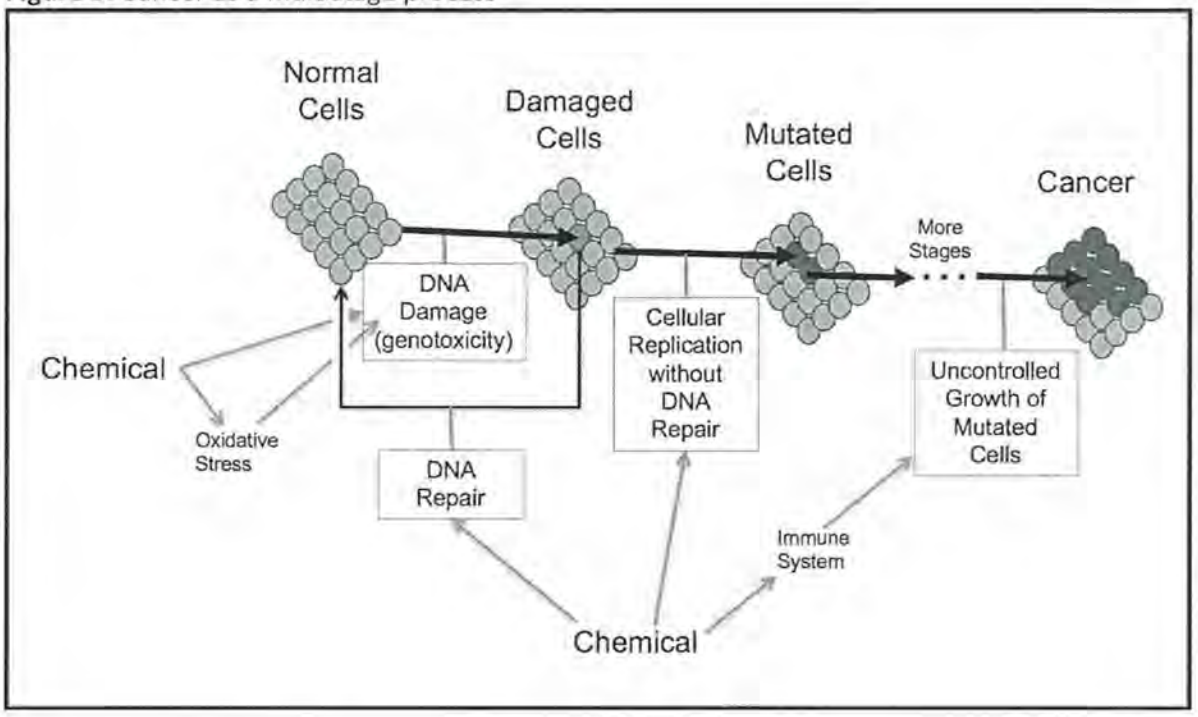
Time also plays a role in this process. Even if the chemical is affecting all stages of the process, the final stages of tumor progression may take longer than the animal lives, resulting in an increase in adenomas without a subsequent increase in carcinomas.

Finally, genotoxic carcinogens have the capability to produce carcinomas without adenomas through rapidly inducing multiple mutations. Along these same lines, some tumors have no precursor lesions (e.g. malignant lymphomas, hemangiosarcomas)

While this is a simplistic illustration of a very complicated process, it outlines the basic reasons why any pattern is possible when one is only evaluating tumors in the animals at one point in time and counting adenomas and carcinomas.

As an illustration using real data, consider the lung adenomas and adenocarcinomas seen in male mice in the study by **Wood et al. (2009)**[13]. Going from control to highest dose, adenoma counts were 9/51, 7/51, 9/51 and 4/51 while adenocarcinoma counts were 5/51, 5/51, 7/51 and 11/51. In not one case is there an animal listed with both of these pathologies in the lung. Unless Dr. Foster is arguing that the pathological diagnoses are wrong, this could clearly be a case where glyphosate is affecting the late stages of carcinogenesis resulting in a movement of tumors from adenomas to adenocarcinomas without increasing the incidence of the combined tumors. Looking at hepatocellular adenomas and carcinomas in males in that same study, the rates for adenomas are 1/51, 1/51, 4/51 and 2/51 while the counts for carcinomas are 6/51, 11/51, 7/51 and 4/51. Again, there were no animals with both adenomas and carcinomas and in every group, the carcinoma counts exceed the adenoma counts suggesting either carcinomas do not arise from adenomas or that adenomas are rapidly converted to carcinomas.

Figure 3: Cancer as a multistage process



V. Other Studies

Dr. Foster argues to dismiss 13 of the 19 tumors (68%) in Table 4 because the same tumor was not seen in other studies of the same sex and species. This is again a misinterpretation of what a statistical p-value means when applied to an animal carcinogenicity study. As an illustration of why this strategy could be very misleading, consider the case of four animal cancer studies where the p-values for an increase in malignant lymphomas are 0.01, 0.051, 0.051 and 0.051. This means that there is only a 1%, 5.1%, 5.1% and 5.1% chance that the null hypothesis (the chemical does not increase the cancer risk) is true. On the other hand, if the p-values would have been 0.01, 0.05, 0.05 and 0.05, Dr. Foster would then say they all gave the same answer. Reaching these two different opinions based on a difference of 0.1% in p-values does not properly portray the importance of the results. In the first case, converting the results from multiple bioassays into yes or no decisions and then concluding there is no cancer hazard if all the studies are not a yes ignores the fact that all of the studies are telling us there is a consistent increase with exposure in these hypothetical data. The entire purpose of the pooled analysis is to objectively address this question rather than merely counting positive versus negative studies. As an example, consider lung adenocarcinomas in females in the two 18-month studies in CD-1 mice. **Wood et al. (2009)** has a p-value of 0.028 whereas **Sugimoto (1997)** has a p-value of 0.148. Combined, the overall p-value is not significant (p=0.484) suggesting there is no effect and, in this case, I would agree with Dr. Foster. On the other hand, hemangiomas in female mice in the same two studies have p-values of 0.002 and 0.438 with the combined analysis having a p-value of 0.001; in this case, I disagree with Dr. Foster that a

positive finding and a negative finding results in a negative finding. The presumption that there is no cancer hazard whenever two or more carcinogenicity studies differ in the statistical significance of a particular tumor site is scientifically unsound and should not be used as a reason for ignoring positive findings.

VI. Survival

For two of the tumor findings, Dr. Foster argues that survival differences could allow animals in the high-dose group to live longer and could explain the significant tumor increases. The EPA disagrees with Dr. Foster regarding survival differences in the study by **Lankas (1981)**[6]. To be even more rigorous in my analysis, I used the poly-3 test adjustment for survival differences[28, 29] and reanalyzed the data. This test is similar to the Armitage linear trend test but adjusts the number of animals at risk of getting the tumor based upon duration of life and is commonly used to analyze bioassays by the US National Toxicology Program. Testicular tumors in male Sprague-Dawley rats from the **Lankas (1981)**[6] study had a p-value without survival adjustment of p_{trend}=0.009 and with survival adjustment of p_{trend}=0.015. Dr. Foster's comments regarding survival differences for hepatocellular adenomas in male rats in the study by **Brammer (2001)**[7] cannot be resolved since individual animal times of death and tumor status are not publicly available and these data were not provided by Monsanto. In essence, this is not an issue.

VI. Fisher's Test

For four tumors, Dr. Foster uses, as part of his argument for dismissal, the observation that the pairwise comparisons via Fisher's exact test were not significant even though the trend test findings were. As noted on page 20 of the Expert Report, virtually all regulatory bodies consider a positive finding in either test as sufficient evidence to reject chance as leading to the positive finding.

VIII. Summary

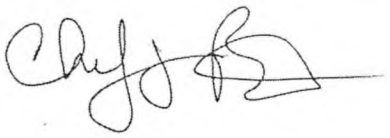
Dr. Foster's methods for evaluating and drawing conclusions from animal carcinogenicity studies suffers from a lack of understanding in and/or experience with statistics, a failure to understand the correct role of historical controls, a dogmatic view of adenomas and carcinomas that is not supported by either scientific theory or data, a failure to properly evaluate the same findings over multiple studies, and a lack of understanding of findings from pairwise versus trend analyses. Dr. Foster's comments do not impact my conclusion that the animal data provide strong evidence for the biological plausibility, biological gradient, and coherence arguments developed by **Hill (1965)**[16] supporting the conclusion that glyphosate can cause non-Hodgkin lymphoma in humans.

In this Rebuttal Report, I have not provided comments on the remaining five expert reports (Dr.s Fleming, Goodman, Mucci, Rider, and Rosol) provided by Monsanto. My lack of comments on these reports does not constitute acceptance of the arguments in these reports.

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. Nothing in the reports submitted by Monsanto, including the two reports that I respond to in this rebuttal report, changes that opinion.

Compensation

I am being compensated at $450 per hour for my expert work in this case, plus travel expenses.



Dr. Christopher J. Portier

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Appendix: Modified tables from the Expert Report

Modified Table 1: Tumors of interest in male and female Sprague-Dawley rats the 26-month feeding study of **Lankas (1981)**[6]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	3.05	10.30	31.49	
	Female	0	3.37	11.22	34.02	
Testicular interstitial cell tumors	Male	0/50	3/50	1/50	6/50**	P_{Trend}=0.009 P_{Hist}=0.006
Interstitial cell hyperplasia	Male	1/50	1/50	1/50	0/50	P_{Trend}=0.830
Thyroid C-cell Carcinomas	Female	1/47	0/49	2/50	6/47	P_{Trend}=0.003 P_{Hist}=<0.001
Thyroid C-cell Adenomas and Carcinomas	Female	6/47	3/49	8/50	9/47	P_{Trend}=0.072 P_{Hist}=0.072
Pancreas Islet Cell Tumors	Male	0/50	5/50*	2/50	3/50	P_{Trend}=0.312
lymphocytic hyperplasia, thymus and lymph nodes	Female	27/50	35/50	38/50*	35/50	P_{Trend}=0.143
Thyroid C-cell Adenomas and Carcinomas	Male	1/47	2/49	4/49	4/49	P_{Trend}=0.122
Thyroid Follicular-cell Adenoma	Male	5/47	1/49	2/49	2/49	P_{Trend}=0.748
Liver Neoplastic Nodule	Male	3/50	5/50	1/50	3/10	P_{Trend}=0.630
Kidney Adenoma	Male	1/50	5/50	0/50	0/50	P_{Trend}=0.979
Adrenal Cortical Carcinoma	Female	5/50	10/50	6/50	4/49	P_{Trend}=0.851
Skin Keratoacanthoma	Male	0/49	0/48	0/49	0/49	P_{Trend}=1
Basal Cell Tumor	Male	0/49	0/48	0/49	1/49	P_{Trend}=0.251

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Modified Table 2: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of **Stout and Ruecker (1990)**[9]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	89	362	940	
	Female	0	113	457	1183	
Pancreas Islet Cell Tumors (with interim sacrifice)	Male	1/58	8/57*	5/60	7/59*	P_{Trend}=0.147 P_{Hist}=0.140
Pancreas Islet Cell Tumors (without interim sacrifice)	Male	1/48	8/47*	5/50	7/49*	P_{Trend}=0.147 P_{Hist}=0.150
Hepatocellular adenomas (without interim sacrifice)	Male	3/50	2/50	3/50	8/50	P_{Trend}=0.015
Hepatocellular Adenomas and Carcinomas (without interim sacrifice)	Male	6/50	4/50	4/50	10/50	P_{Trend}=0.050
Thyroid C-Cell Adenomas (with interim sacrifice)	Female	2/60	2/60	6/60	6/60	P_{Trend}=0.050
Thyroid C-Cell Adenomas (without interim sacrifice)	Female	2/50	2/50	6/50	6/50	P_{Trend}=0.049
Thyroid C-Cell Adenomas and Carcinomas (with interim sacrifice)	Female	2/60	2/60	7/60	6/60	P_{Trend}=0.053
Thyroid C-Cell Adenomas and Carcinomas (without interim sacrifice)	Female	2/50	2/50	7/50	6/50	P_{Trend}=0.052
Thyroid C-Cell Adenomas (with interim sacrifice)	Male	2/60	4/60	8/60	7/60	P_{Trend}=0.063
Thyroid C-Cell Adenomas (without interim sacrifice)	Male	0/50	4/50	8/50**	5/50*	P_{Trend}=0.084
Thyroid C-Cell Adenomas and Carcinomas (with interim sacrifice)	Male	2/60	6/60	8/60*	8/60*	P_{Trend}=0.068
Thyroid C-Cell Adenomas and Carcinomas (without interim sacrifice)	Male	0/50	6/50*	8/50**	6/50*	P_{Trend}=0.091
Testis Interstitial Cell Tumors	Male	2/50	0/50	3/50	2/50	P_{Trend}=0.296
Kidney Adenomas	Males	0/50	2/50	0/50	0/50	P_{Trend}=0.813
Thyroid Follicular Adenoma/Carcinoma	Males	2/50	1/48	3/48	3/50	P_{Trend}=0.225
Adrenal Cortical Carcinoma	Female	0/50	0/50	0/50	3/50	P_{Trend}=0.015
Skin Keratoacanthoma	Male	1/50	3/50	4/50	5/50	P_{Trend}=0.078
Basal Cell Tumor	Male	0/50	0/50	0/50	1/50	P_{Trend}=0.250

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Modified Table 3: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of **Atkinson et al. (1993)**[10]

Tumor	Sex	Doses (mg/kg/day)					p-values
	Male	0	11	112	320	1147	
	Female	0	12	109	347	1134	
Thyroid Follicular Adenomas and Carcinomas	Male	0/50	0/21	0/17	2/21	2/49	$P_{Trend}=0.099$
Thyroid Follicular Adenomas and Carcinomas (adding terminal sacrifice animals to denominator)	Male	0/50	0/50	0/50	2/50	2/49	$P_{Trend}=0.034$
Thyroid C-cell Adenomas and Carcinomas	Female	8/50	1/27	1/29	1/29	7/49	$P_{Trend}=0.197$
Thyroid C-cell Adenomas and Carcinomas	Male	9/50	1/21	1/17	2/21	9/49	$P_{Trend}=0.183$
Testes Interstitial Cell Tumors	Male	3/50	1/25	0/19	0/21	2/50	$P_{Trend}=0.580$
Kidney Adenomas	Males	1/50	0/50	0/50	0/50	0/50	$p_{Trend}=1$
Hepatocellular Adenomas	Males	2/50	1/50	1/50	2/50	3/50	$P_{Trend}=0.155$
Pancreas Islet-Cell Adenoma	Male	0/50	0/50	0/50	0/50	1/50	$P_{Trend}=0.200$
Skin Epithelioma (keratoacanthoma)	Male	1/50	2/25	0/19	0/21	5/50	$P_{Trend}=0.047$
Adrenal Cortical Carcinoma	Female	0/48	0/26	0/29	1/30	0/49	$P_{Trend}=0.434$
Basal Cell Tumor	Male	1/50	0/25	0/19	0/21	0/50	$P_{Trend}=1$

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Modified Table 4: Tumors of interest in male and female Wistar rats from the 24-month feeding study of **Brammer (2001)**[7]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	121	361	1214	
	Female	0	145	437	1498	
Hepatocellular Adenoma	Male	0/52	2/52	0/52	5/52*	P_{Trend}=0.008
Hepatocellular Adenoma (from Greim et al., 2015[1])	Male	0/53	2/53	0/53	5/52*	P_{Trend}=0.008 P_{Hist}=0.006
Mammary Gland Adenomas and Adenocarcinomas	Female	3/51	2/51	0/51	2/51	P_{Trend}=0.575
Skin Keratocanthoma	Male	1/51	0/51	1/51	1/51	P_{Trend}=0.392
Pituitary Adenoma	Male	16/63	15/62	18/63	10/62	P_{Trend}=0.922
Pituitary Adenoma	Female	42/61	40/61	42/62	45/63	P_{Trend}=0.291

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Modified Table 5: Tumors of interest in male and female Wistar rats from the 24-month feeding study of **Suresh(1996)**[12]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	6.3	59.4	595.2	
	Female	0	8.6	88.5	886	
Mammary Gland Adenoma and Carcinoma	Female	5/40	3/28	8/33	2/48	P_{Trend}=0.970
Hepatocellular Adenoma	Male	24/50	22/50	10/50	21/50	P_{Trend}=0.374
Skin Keratocanthoma	Male	0/50	0/50	0/50	0/50	P_{Trend}=1
Pituitary Adenoma	Male	3/49	4/30	3/31	5/49	P_{Trend}=0.376
Pituitary Adenoma	Female	7/49	13/33	7/23	6/50	P_{Trend}=0.967

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Modified Table 6: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of **Enemoto (1997)**[11]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	104	354	1127	
	Female	0	115	393	1247	
Mammary Gland Adenoma	Female	23/50	27/50	24/50	30/50	P_{Trend}=0.106
Kidney Adenoma	Male	0/50	0/50	0/50	4/50	P_{Trend}=0.004
Thyroid C-cell Adenomas/Carcinomas	Female	4/60	7/60	8/60	4/60	P_{Trend}=0.692
Thyroid C-cell Adenomas/Carcinomas	Male	8/70	10/70	6/70	7/70	P_{Trend}=0.697
Thyroid Follicular-cell Adenomas/Carcinomas	Male	4/70	2/70	1/70	0/70	P_{Trend}=0.990
Testes Interstitial Cell Tumors	Male	3/49	2/50	0/50	2/50	P_{Trend}=0.594
Hepatocellular Adenomas	Male	1/60	0/60	2/60	1/60	P_{Trend}=0.371
Skin Keratoacanthoma[1]	Male	3/50	3/50	0/50	7/50	P_{Trend}=0.029
Pancreas Islet-Cell Adenoma	Male	4/50	1/50	2/50	1/50	P_{Trend}=0.844
Adrenal Cortical Carcinoma	Male	0/50	0/50	0/50	0/50	P_{Trend}=1
Basal Cell Tumor	Male	0/50	0/50	0/50	3/50	P_{Trend}=0.015

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$, [1] without interim sacrifices

Modified Table 7: Tumors of interest in male and female Wistar rats from the 24-month feeding study of **Wood et al. (2009)**[8]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	85.5	285.2	1077.4	
	Female	0	104.5	348.6	1381.9	
Mammary Gland Adenomas	Female	0/51	0/51	0/51	2/51	$P_{Trend}=0.062$
Mammary Gland Adenocarcinomas	Female	2/51	3/51	1/51	6/51	$P_{Trend}=0.042$
Mammary Gland Adenomas and Adenocarcinomas	Female	2/51	3/51	1/51	8/51*	$P_{Trend}=0.007$
Skin Keratocanthoma	Male	2/51	3/51	0/51	6/51	$P_{Trend}=0.030$
Hepatocellular Adenoma	Male	0/51	2/51	1/51	1/51	$P_{Trend}=0.418$
Pituitary Adenoma	Male	16/51	11/51	10/51	20/51	$P_{Trend}=0.045$
Pituitary Adenoma	Female	24/51	13/51	16/51	32/51	$P_{Trend}=0.014$

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Modified Table 9: Tumors of interest in male and female CD-1 mice from the 24-month feeding study of **Knezevich and Hogan (1983)**[2]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	157	814	4841	
	Female	0	190	955	5874	
Kidney Adenoma[1] (original pathology)	Male	0/49	0/49	1/50	3/50	P_{Trend}=0.019 P_{Hist}=0.005
Kidney Adenoma (EPA pathology)	Male	1/49	0/49	0/50	1/50	P_{Trend}=0.442 P_{Hist}=0.121
Kidney Carcinoma[2] (EPA pathology)	Male	0/49	0/49	1/50	2/50	P_{Trend}=0.063 P_{Hist}=0.002
Kidney Adenoma and Carcinoma Combined[3] (EPA pathology)	Male	1/49	0/49	1/50	3/50	P_{Trend}=0.065 P_{Hist}=0.011
Malignant Lymphoma[4]	Male	2/49	5/49	4/50	2/50	P_{Trend}=0.754 P_{Hist}=0.767
Hemangiosarcoma[5]	Male	0/50	0/49	1/50	0/50	P_{Trend}=0.503 P_{Hist}=0.591
Bilateral Chronic Interstitial Nephritis	Male	5/49	1/49	7/50	11/50	P_{Trend}=0.006
Hemangiooma[6]	Female	0/49	1/49	1/50	0/50	P_{Trend}=0.631
Lung Adenocarcinoma[7]	Male	4/48	3/50	2/50	1/50	P_{Trend}=0.918 P_{Hist}=0.899
Harderian Gland Adenoma	Female	0/49	0/49	1/50	0/50	P_{Trend}=0.505
Spleen Composite Lymphosarcoma	Female	1/49	1/49	1/50	5/50	P_{Trend}=0.015

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.27%, [2]historical rate=0.15%, [3]historical rate=0.44%, [4]historical rate=6.2%, [5]historical rate=2.5%, [6]No Historical Controls, [7]Historical rate=9.2%

Modified Table 10: Tumors of interest in male and female CD-1 mice from the 24-month feeding study of **Atkinson et al. (1993)**[17]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	98	297	988	
	Female	0	102	298	1000	
Kidney Adenoma and Carcinoma Combined[1]	Male	2/50	2/50	0/50	0/50	P_{Trend}=0.981 P_{Hist}=1
Malignant Lymphoma[2]	Male	4/50	2/50	1/50	6/50	P_{Trend}=0.087 P_{Hist}=0.085
Hemangiosarcoma[3]	Male	0/50	0/50	0/50	4/50	P_{Trend}=0.004 P_{Hist}=0.001
Hemangioma[4]	Female	0/50	0/50	0/50	0/50	P_{Trend}=1
Lung Adenocarcinoma[5]	Male	10/50	7/50	8/50	9/50	P_{Trend}=0.456 P_{Hist}=0.449
Harderian Gland Adenoma	Female	Not examined				

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=6.2%, [3]historical rate=2.5%, [4]No historical control rate, [5]Historical rate=9.2%

Modified Table 11: Tumors of interest in male and female CD-1 mice from the 18-month feeding study of **Wood et al. (2009)**[13]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	71.4	234.2	810	
	Female	0	97.9	299.5	1081.2	
Kidney Adenoma[1]	Male	0/51	0/51	0/51	0/51	$P_{Trend}=1$
Malignant Lymphoma[2]	Male	0/51	1/51	2/51	5/51*	$P_{Trend}=0.007$ $P_{Hist}=0.007$
Hemangiosarcoma	Male	0/51	0/51	0/51	0/51	$P_{Trend}=1$
Lung Adenocarcinoma[3]	Male	5/51	5/51	7/51	11/51	$p_{Trend}=0.028$ $P_{Hist}=0.031$
Hemangioma[4]	Female	0/51	2/51	0/51	1/51	$p_{Trend}=0.438$
Harderian Gland	Female	1/51	0/51	0/51	2/51	$p_{Trend}=0.155$
Animals with Malignant Neoplasms	Male	14/51	20/51	17/51	20/51	$P_{Trend}=0.203$
Animals with Malignant Neoplasms	Female	23/51	15/51	17/51	18/51	$P_{Trend}=0.628$
Animals with multiple malignant tumors	Male	1/51	2/51	3/51	5/51	$P_{Trend}=0.046$

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$, [1]historical rate=0.44%, [2]historical rate=2.6%, [3]Historical rate=2.5%, [4]No Historical Control Rate

Modified Table 12: Tumors of interest in male and female CD-1 mice from the 18-month feeding study of **Sugimoto (1997)**[3]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	165	838.1	4348	
	Female	0	153.2	786.8	4116	
Kidney Adenoma[1]	Male	0/50	0/50	0/50	2/50	P_{Trend}=0.062 P_{Hist}=0.005
Malignant Lymphoma[2]	Male	2/50	2/50	0/50	6/50	P_{Trend}=0.016 P_{Hist}=0.017
Hemangiosarcoma[3]	Male	0/50	0/50	0/50	2/50	P_{Trend}=0.062 P_{Hist}=0.004
Hemangioma[4]	Female	0/50	0/50	2/50	5/50*	P_{Trend}=0.002
Lung Adenocarcinoma[5]	Male	1/50	1/50	6/50	4/50	P_{Trend}=0.148 P_{Hist}=0.140
Harderian Gland Adenoma	Female	1/50	3/50	0/50	5/50	P_{Trend}=0.040
Number of animals with Malignant Neoplasms	Male	5/50	5/50	11/50	16/50**	P_{Trend}=0.001
Number of animals with Malignant Neoplasms	Female	9/50	13/50	16/50	13/50	P_{Trend}=0.362

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=2.6%, [3]historical rate=0/1424 (0.26% - 95% confidence limit), [4]No Historical Control Rate, [5]Historical rate=2.5%

Modified Table 15: Observed versus expected tumor sites with significant trends in the 12 acceptable rodent carcinogenicity studies using glyphosate.

Species	Strain	Sex	Total Sites[1]	Exp. <0.05	Obs. <0.05	Tumors[2] p<0.05	Exp. <0.01	Obs. <0.01	Tumors p<0.01
Rat (7 studies)	Sprague-Dawley (4 studies)	M	86	4.3	9	TICT, TFAC, KA, HA, HAC, SE, SK(2)[3], BC	0.9	2	TICT, KA
		F	80	4	3	TCCA, TCCC, AC	0.8	1	TCCC
	Wistar (3 studies)	M	64.5	3.2	3	HA, SK, PA	0.6	1	HA
		F	60	3	3	MC, MAC, PA	0.6	1	MAC
Mouse (5 studies)	CD-1 (4 studies)	M	42	2.1	8	KA, KC, KAC, HS(2), ML(2), LAC	0.4	5	KA,KC, HS(2), ML
		F	60	3	3	H, SL, HGA	0.6	1	H
	Albino (1 study)	M	10.5	0.5	0		0.1	0	
		F	15	0.8	1	H	0.2	1	H
Rats (7 studies)	All (7 studies)	M	150.5	7.5	11	TICT, TFAC, KA, HA(2), HAC, SE, SK(3), BC, PA	1.5	3	TICT, KA, HA
		F	140	7	6	TCCA, TCCC, AC, MC, MAC, PA	1.4	2	TCCC, MAC
		Both	295.5	14.5	19	TICT, TFAC, KA, HA(2), HAC, SE, SK(3), BC, PA(2), TCCA, TCCC, AC, MC, MAC	3.0	5	TICT, KA, HA, TCCC, MAC
Mice (5 studies)	All (5 studies)	M	52.5	2.6	8	KA, KC, KAC, HS(2), ML(2), LAC	0.5	5	KA,KC, HS(2), ML
		F	75	3.8	4	H(2), SL, HGA	0.7	2	H(2)
		Both	127.5	6.4	12	KA, KC, KAC, HS(2), H(2), ML(2), LAC,SL, HGA	1.3	7	KA,KC, HS(2), H(2), ML
All (12 studies)	All (12 studies)	M	203	10.1	20	TICT, TFAC, KA(2), HA(2), HAC, SE, SK(3), BC, PA, KC, KAC, HS(2), ML(2), LAC	2.0	8	TICT, HA, KA(2),KC, HS(2), ML
		F	215	10.8	10	TCCA, TCCC, MC, MAC, H(2), AC, PA, SL, HGA	2.2	4	TCCC, MAC, H(2)
		Both	418	20.9	30	TICT, TFAC, KA(2), HA(2), HAC, SE, SK(3), BC, PA(2), KC, KAC, HS(2), ML(2), LAC, TCCA, TCCC, MC, MAC, H(2), AC, SL, HGA	4.2	12	TICT, HA, KA(2), KC, HS(2), H(2), ML, TCCC, MAC

[1] Number of sites examined is based upon suggestions by Dr. J. Haseman in his written testimony to the EPA with female rats modified for fewer sites with 3 or more tumors; male mice – 10.5 sites; female mice – 15 sites; male rats – 21.5 sites; female rats – 20 sites

[2] Tumor abbreviations are: KA – kidney adenoma; KC – kidney carcinoma; KAC – kidney adenoma or carcinoma; HS – hemangiosarcoma; H – hemangioma; HA – hepatocellular adenoma; LAC – lung adenoma or adenocarcinoma; ML – malignant lymphoma; MC – mammary gland carcinoma; MAC – mammary gland adenoma or carcinoma; TCCA – thyroid C-cell adenoma; TCCC – thyroid C-cell carcinoma; TFAC – thyroid follicular cell adenoma or carcinoma; TICT – testes interstitial cell tumor; SK – skin keratoacanthoma; SE – skin epithelioma; AC – adrenal cortical carcinoma; BC – basal cell tumor; PA – pituitary adenoma; SL – skin lymphoma; HGA – Harderian gland adenoma

[3] (x): x studies with this result