EXHIBIT 122

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 CASES	)	

CONFIDENTIAL - PURSUANT TO PROTECTIVE ORDER

Videotaped Deposition of WARREN G. FOSTER, Ph.D., taken in the above-captioned matter, before and by Janis L. Ferguson, RPR, CRR, Court Reporter, on Friday, September 15th, 2017, commencing at 9:08 a.m., at the Sheraton Gateway Hotel, Terminal 3, Toronto AMF, Toronto, ON L5P 1C4.

Reported by Janis L. Ferguson
Registered Professional Reporter
Certified Realtime Reporter

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Also Present:
Peter Goodale
Videographer

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MR. GOODALE: We are now on the record. My name is Peter Goodale, certified legal videographer for Golkow Technologies.

Today's date is September 15, 2017, and the time on the video monitor is 9:08 a.m.

This video deposition is being held in Toronto, Ontario, Canada, in the matter of In Re: Roundup Products Liability Litigation, for the United States District Court for the Northern District of California, MDL No. 2741.

The deponent is Dr. Warren G. Foster, Ph.D.

Counsel, please identify yourselves and state who you represent for the record.

MS. ROBERTSON: Pearl Robertson, Plaintiffs.

MS. GREENWALD: Robin Greenwald, Plaintiffs.

MR. DHINDSA: Ranjit Singh Dhindsa on behalf of Monsanto.

MR. KALAS: John Kalas on behalf of Monsanto.

MS. TABATABAIE: Tara Tabatabaie for Plaintiff.

MR. GOODALE: The court reporter is Janis Ferguson, and who will now swear in or affirm the witness.

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W A R R E N G. F O S T E R, Ph.D., first having been duly sworn, testified as follows:

MR. GOODALE: Please begin.

EXAMINATION

BY MS. ROBERTSON:

Q. Good morning, Dr. Foster. Have you ever given a deposition before?
A. Yes.
Q. And when did you give a -- what -- how many prior depositions have you given?
A. One.
Q. When was that?
A. 2011, 2012, somewhere thereabouts.
Q. And did you give this deposition as an expert?
A. Yes.
Q. And what was the litigation?
A. The litigation was Merck. Marderosian v. Merck.
Q. And what was your expert opinion about?
A. The trial or the case was about health effects of hexavalent chromium, and I provided an

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expert opinion on whether or not hexavalent chromium caused adverse reproductive effects in people exposed.
Q. And which party were you an expert for?
A. Plaintiffs.
Q. Did you write an expert report for that --
A. I --
Q. -- case?
A. I did.
Q. Have you ever written any other expert reports?
A. No, I have not.
Q. Have you ever been previously retained, aside from the case we just talked about and aside from the case today, as an expert in litigation?
A. As an expert in litigation?
Q. Correct.
A. Not to my knowledge, no.
Q. Have you ever been hired for litigation to serve as a consultant?
A. I have provided opinions to different -- different firms at different points in time.
Q. Were any of these opinions related to chemicals and health effects in humans?
MR. DHINDSA: I object, to the extent it calls for attorney confidential

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communications between Dr. Foster and whoever may have retained him.
Q. You can answer.
A. In one case, I was asked by an attorney whether or not pesticide might be involved in a person's -- child's neurodevelopmental effects. And after a brief telephone conversation and discussion of issues, it didn't go any further.
(Discussion held off the record.)
Q. And what was the name of the pesticide?
MR. DHINDSA: Same objection.
A. I believe the pesticide's name was Dursban.
Q. Prior to being retained by Hollingsworth, have you ever looked at the carcinogenic effects of glyphosate?
A. No.
Q. Prior to being retained by Hollingsworth, did you have any opinion as to whether glyphosate could cause cancer in humans?
A. I hadn't looked at it, so, no, I had no opinion on it.
Q. And your expertise is toxicology, with a special focus on reproductive toxicology. Isn't that correct?
A. I trained in reproductive biology and pursued

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further training we had through Health Canada in toxicology.
Q. Aside from reproductive toxicology, do you focus on any other subareas of toxicology?
A. I'm not sure I understand your question. Do I focus on anything outside? Does my work touch on anything outside of reproductive toxicology? Is that what you're getting at?
Q. No, sir. You make a distinction on your CV that you're -- you have a subspecialty in reproductive toxicology. Correct?
A. Correct.
Q. I'm just wondering if you have any other subspecialties.
A. No.
Q. Do you conduct any toxicologic studies in animals as part of your reproductive toxicology work?
A. I have, over the past 25, 30 years, used numerous animal studies in toxicology.
Q. Have you conducted any?
A. Yes. Designed, conducted, collected the data, collected the tissues, done the analysis, interpreted the results.
Q. And were these studies that you conducted and designed related to carcinogenicity effects?

A. Some, yes.
Q. What is your understanding of a human health risk assessment?
A. Human health risk assessment is a complex process that involves collection of data from animal studies where hazards may have been identified. The risk assessor would then take the -- the information, including human biomonitoring studies, human epidemiological studies, animal studies, mechanistic studies, and carry out a very thorough assessment of the literature to determine whether or not there was a risk or not.
Q. Now, did you just describe for us a human health risk assessment or a human health hazard assessment?
A. That would be a risk -- human health risk assessment.
Q. And what do you appreciate as a human hazard health assessment?
A. I have no idea what that means in the general lexicon of what we do.
A health -- a hazard is where somebody would conduct an animal experiment and determine whether or not a hazard was present.
Q. And a hazard assessment only occurs in an

animal study, animal experiment?
A. Hazards, in my understanding of how risk assessment is conducted, are determined through animal studies.
Q. Does your expert report apply a human risk assessment to the animal carcinogenicity analysis?
MR. DHINDSA: Objection.
A. I want to make sure I understand your question correctly. You're asking me did I do a risk assessment of glyphosate's potential carcinogenicity? Is that correct?
Q. For the animal carcinogenicity analysis you offer in your report.
A. I reviewed the animal literature to determine whether or not there were compound-related effects.
Q. So is your answer that you did not conduct a risk assessment on the animal carcinogenicity data?
A. A risk assessment would be a much more thorough analysis requiring assessment of biomonitoring data, the epidemiological data, and the animal data together. And in -- as well as the mechanistic information. And I was retained to look at the animal studies and determine whether or not there was a compound-related effect, and that's what I focused my attention on.

Q. Are you a statistician?
A. No, I'm not, but I use statistics routinely on everything I do.
Q. Are you offering an opinion today as a statistician?
A. I'm not offering an opinion, although I use it routinely in what I do.
Q. Does your report evaluate the data using statistics?
A. I did not use statistics in calculating any statistics in the review of the literature. I reviewed this -- the animal data.
Q. Is it your opinion that a finding of a risk between a chemical and a disease, based on animal bioassays, is not sufficient to establish a causal relationship between exposure and human health?
MR. DHINDSA: Objection.
A. I want to make sure I understand. It's a long question.
Q. I can ask it again, if you'd like.
A. Please. Go ahead.
Q. Okay. Is it your opinion that a finding of a risk between a chemical and a disease, based on animal bioassays, is not sufficient to establish a causal relationship between exposure and human health?

MR. DHINDSA: Objection.
A. So if I understand the question correctly, if a risk assessment has been conducted, and in the conduct of the risk assessment there -- a risk is identified, is that sufficient to establish a causal relationship in humans? And the answer to that question would be no.
Q. Is it probative, in your opinion?
MR. DHINDSA: Objection.
A. What do you mean by "probative"?
Q. Does it offer any probative value to the overall analysis of a risk assessment?
MR. DHINDSA: Objection.
A. I'm not -- I'm not a lawyer, so what do you mean by "probative"? That's a legal term, as far as I'm aware, and I don't use it in -- normally in what I do.
So are you -- are you suggesting that if I were to see evidence of a -- a risk assessment's conducted, and at the end of that risk assessment, the risk assessor says there is a risk -- Compound X has a risk for behavioral abnormalities. Does that then provide me with an interest in conducting further studies to determine whether or not there's a causal relationship?

Q. Correct.
A. If it was an area that I was interested in in pursuing as a scientist, then I might look at that and say, you know, this is -- this would justify further studies.
Q. Have you ever worked with any corporations to assist them in gaining registration with a regulatory body over a product?
A. Okay. The way I'm understanding your question is have I worked with any company to assist them in getting a product registered.
Q. Correct.
A. No, I have not.
Q. What about any sort of drug or device, pharmaceuticals?
A. No, I have not.
Q. Have you ever had any past involvement working with EPA?
A. Yes, I've worked with EPA on numerous occasions.
Q. And have you worked with EPA as a paid employee of EPA?
A. No.
Q. Did you work with them as a consultant?
A. Yes. They've covered my expenses.

Q. And was this related to serving on a scientific advisory panel?
A. Over the course of my career, I've interacted with them in -- in different capacities; reviewer on grant programs, advisory panels, meetings, contributions to meetings.
Q. Have you had any involvement with EPA during these meetings related to EPA guidelines?
A. Sorry. Have I had any interaction with EPA in the past year or two on EPA guidelines?
Q. When you've -- when you've been -- when EPA has sought your opinion related to meetings or grant programs and the like, have any of -- has any of this work been related to EPA guidelines?
A. I would say so, yes, in the respect of developing endocrine-disrupting testing guidelines.
Q. What about carcinogenicity guidelines?
A. No, I have not participated in that area.
Q. You state in your expert report that regulatory studies favor the detection of false positives -- false positive adverse outcomes in preference to false negatives. Do you recall that?
A. Do you have a copy of my report?
Q. I do.
(Foster Deposition Exhibit 18-1 - Expert

Witness Report of Warren G. Foster, Ph.D. - marked for identification.)
Q. I'm going to mark the expert report of Dr. Warren Foster as Exhibit 18-1.
A. Thank you.
MR. DHINDSA: I just want to note for the record that the exhibit that you marked doesn't have his attached CV that was entered with it.
MS. ROBERTSON: That's correct. It's going to be entered a separate exhibit. If you'd like me to enter it all at once, by all means, I'd be happy to.
MR. DHINDSA: Whatever you prefer.
BY MS. ROBERTSON:
Q. So, Dr. Foster, this is the -- this is your expert report, correct?
A. It appears to be, yes. I have not reviewed it from cover to cover, but it looks like it.
Q. Understood. And so what approach do you take in looking at the animal data related to the detection of false positives, as compared to false negatives?
MR. DHINDSA: Objection.
A. Can you restate that, please?
Q. Sure. What approach do you take in looking

at the animal data related to the detection of false positives, as compared to false negatives?
MR. DHINDSA: Objection.
A. The approach that I use is one that I've used throughout my career; is to look at the conduct of the study, details of the methodology, as well as the interpretation of the data that's been generated, and to explore all the -- all the data that's available in relation to the outcomes of interest.
So I would look where -- where I have the data, body weight, behavior of animals, if there's any adverse affects, atypical behaviors that might be present, and then take a look at the -- the -- the -- the outcomes that we see.
Q. Dr. Foster, does the quality of the study or observed effects during a study relate to whether a false negative is observed?
A. Does the quality of the study relate to whether or not a false negative is detected?
Q. Yes. I asked -- my previous question, some two questions ago, was about false positives and false negatives.
A. Right.
Q. And your answer informed that you look at the conduct of the study, details of the methodology, et

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cetera.
So I'm wondering if that's responsive to my question regarding -- related to false negatives and false positives.
A. It would be responsive to both.
Q. So the quality --
A. Because you're looking at the quality of the study and how reliable the results are, regardless of the direction in which they go.
Q. So does your report approach the studies with an eye toward finding a false negative or a false positive?
A. I don't approach the study a priori with the goal of finding false positives or false negatives. My approach is to -- is to take an objective assessment of the study and determine whether or not the outcomes that were presented in the data are compound-related or not.
Q. Dr. Foster --
A. So --
Q. Oh, sorry. Please finish.
A. -- you know, I might look at a study and -- so I'm reviewing a paper, and in reviewing a paper, I am going to be asking the -- the author of that paper whether or not they have interpreted their results

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fully, just as well as I might look at the paper and say, well, you've overinterpreted your data as well. So I'm looking at -- in both directions.
Q. What would an overinterpretation of data be?
A. An overinterpretation in a -- in a study that's been submitted for publication might be where they're making conclusions that are not supported by the data that's presented in the paper.
Q. What about for a study that is not submitted for publication?
A. Can you give me an example of what you mean here. There could be many things like that.
Q. Well, what I'm trying to understand is what an example of an overinterpretation of data would be. And your answer relates to submitted publications. So is there overinterpretation of data from original study authors? Is that possible?
A. Original study authors may overinterpret their data, yes.
Q. In what way?
A. They may make conclusions that are not supported by the data that they -- that they present in their report.
So that -- I'm trying to think of an example that I've seen recently. But somebody might make the

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claim that they saw -- the chemical that they're -- that they're interested in was associated with an adverse health effect, when in the study they had not actually measured any health effects.
So an example of this is a recent thesis I just examined, where the student examined exposure to -- to Bisphenol A in the study, and in their conclusions, they were commenting on health effects that were not -- not examined in their -- anywhere in their thesis.
Q. Is the inverse also true? Can study authors underinterpret their original data when conducting an experiment in animal bioassays?
A. That can also happen, yes. So somebody may -- the example here might be somebody may not fully appreciate the complexity of the assays they're looking at and may not understand -- say they're measuring a thyroid-stimulating hormone, and they've also noted that as thyroid-stimulating hormone fell, they saw a corresponding rise in thyroxine, and they've -- they've not interpreted that as showing that there's -- they've got internal consistency in corroborating evidence from two different assays.
Q. And, Dr. Foster, when you looked at the animal carcinogenicity in this case, did you consider

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what the study authors submitted as in relation to overinterpretation or underinterpretation of their data results?
A. Did I interpret the studies to determine whether or not they were over- or underinterpreted? Is that your question?
Q. Yes.
A. That was something that I would consider, yes.
Q. And how did you go about this consideration?
MR. DHINDSA: Objection.
Q. Did you have access to all of the studies?
A. I had access to study data in three studies, and I also had a review paper in which I had the data. But I don't typically rely upon reviewed data -- review studies. I might read them from the perspective of giving me a place to start. But in this particular case, they actually had the study data appended that I was able to -- to review.
Q. And so for the appended study data, did that study data include the original authors of the animal carcinogenicity study's overinterpretation or underinterpretation of results?
MR. DHINDSA: Objection.
A. To my knowledge, I only had the -- the

tabulated data. In the text of the paper, on occasion, there was some text discussion of the conduct of the study.

Q. And which review paper are you referring to, Dr. Foster?

A. I'm referring to the Greim, et al. study.

Q. In your expertise, and listed on your CV, what do you mean by "environmental carcinogenesis"?

A. I'm looking at chemicals that are commercial -- commercial chemicals that have been shown to be environmental contaminants. So --

Q. And is this -- I'm sorry.

A. So they're -- they're in the environment, and there's potential for human exposure.

Q. And is this in the context as it relates to reproductive toxicology?

A. Not always, no. In occasion -- for instance, in Dieldrin, we were interested in looking at the carcinogenicity of that pesticide outside the reproductive tract.

Q. And that was the Merck case; is that right? Did I get the name right?

A. No. That was -- the Merck -- the trial, you mean?

Q. I can -- let me rephrase. And when you say

"when we were looking at Dieldrin," what do you mean?

A. I mean that my students and I had written a grant for which we had obtained funding to examine the impact of Dieldrin as a carcinogen.

Q. What is Dieldrin?

A. Dieldrin is a pesticide.

Q. Do you know who manufactures Dieldrin?

A. I do -- I do not know. My understanding is it's banned from production, and so I don't know who manufactured it historically.

Q. Okay. Let's take a look --

(Discussion held off the record.)

Q. Dr. Foster, what is an animal bioassay?

A. An animal bioassay is a study involving animals in which you would dose the animals with known concentrations of your test substance, vehicle control, plus at least three additional dose groups, and assess outcomes of interest decided before the initiation of the study.

Q. What is a null hypothesis?

A. A null hypothesis would be -- Chemical X will not cause an increase in body weight would be a null hypothesis. It's a -- it's stated in a way that you can -- the outcome of your study will either support or disprove that -- that hypothesis.

Q. What type of rodents are used for rodent carcinogenicity studies as it relates to this case?

A. Mice and rats.

Q. Does it matter which type of rodent is used in an animal bioassay?

A. The -- the decision to use mice and rats has been something that has been arrived at through international harmonization of test guidelines through the OECD, as well as other test guideline groups.

So these are guidelines that have been thoroughly vetted, they've been reviewed by each participating country's expert delegate, as well as peer-reviewed by experts within each country.

So, in essence, the guideline is a peer-reviewed guideline that advises which -- what is the most appropriate animal model to use, and mice and rats have been chosen.

Q. And you applied these OECD guidelines in your analysis to -- as to whether these -- as -- your analysis related to the quality of these studies, correct, in your expert report?

A. My knowledge is limited to the guidelines? Is that what you're asking me?

Q. I'm asking if you applied the guidelines in -- in reviewing whether these reports were of

sufficient quality for you to include in your expert opinion.

A. Well, I wouldn't have applied the guidelines -- if I understand you correctly, the studies were conducted in other labs, according to the guidelines that were established at that point in time. I would have reviewed the studies that were conducted to see, to the extent possible, that they followed the guidelines and that the data was of good quality.

Q. All right. And you found that these studies all followed the guidelines. Correct?

MR. DHINDSA: Objection.

A. I think that in looking at the individual studies, that largely they followed the guidelines -- in general, they did.

So, for example, a study -- the OECD guidelines advises that you -- your top dose is 1,000 milligrams per kilogram or thereabouts, the maximum tolerated dose. And some studies approached it and got near it, but didn't quite achieve it.

Q. Yes. And that's the Lankas study you're referring to.

A. The Lankas study is one that did not achieve it.

Q. All right. So I'd like to direct your

attention to Page 27 of your expert report, if we could.

A. (Witness complies.)

Q. It's a rather lengthy paragraph carried over from Page 26. I'll give you a moment to find it.

But in the middle of that paragraph, you state, "Therefore, as designed, the regulatory studies favor the detection of false positive adverse outcomes, finding non-treatment-related tumors in preference to false negatives, missing detection of treatment-induced tumors."

Do you see where I'm reading?

A. Yes, I see where you're reading.

Q. And as you sit here today, do you agree with that statement?

A. Yes, I do.

Q. And is your -- is your expert opinion following this notion to detect false positive adverse outcomes?

A. Can you say that again, please?

Q. Sure.

THE WITNESS: Sorry, Ran.

Q. Is your expert analysis, as described in your expert report following the statement, meaning are you likewise -- are you likewise favoring the detection of

false positive adverse outcomes as compared to false negative adverse outcomes?

MR. DHINDSA: Objection.

A. I would say no to that question [sic]. My goal in reviewing the -- the individual studies was to try and determine what, if any, outcomes were compound-related.

Q. Dr. Foster, do you know what the precautionary principle is?

A. I've heard of it. It's been used widely in the lay press and elsewhere. I'm not sure I really understand it.

Q. Do you know whether EPA follows the precautionary principle?

A. Well, since I really don't understand what it is and how it would be put into practice, I can't answer that question. I don't know whether they do or don't.

Q. Let's look at Page 11 of your expert report.

A. (Witness complies.)

Q. You state here that, "The goal of a bioassay is to identify adverse outcomes for hazard identification."

Do you still agree with that statement today?

A. I don't know, because I don't know where

you're reading. I'm on Page 11. But where are you?

Q. If you go into the first -- the main paragraph, the one that stands alone on this page, and it's in your discussion of -- and the paragraph begins with, "In assessing rodent bioassay data..."

A. Yes. I'm in that paragraph.

Q. Okay. If you read down maybe six lines, "Finally, bioassays are carried out with the goal of identifying adverse outcomes for hazard identification."

A. Yes.

Q. As you sit here today, do you agree with that statement?

A. I agree with that statement, yes.

Q. Can you explain for us what you mean by this statement, "Outcomes for hazard identification."

A. The bioassay is conducted because you don't really have any idea what the toxicological profile of your chemical is. So you're administering a vehicle, plus at least three additional doses, one up to the maximal tolerated dose, in assessing a broad range of outcomes, in the effort to determine whether or not there are adverse outcomes.

So an adverse outcome in this particular case would be to see whether or not there are statistically

significant differences in treatments versus controls.

(Discussion held the record.)

MR. GOODALE: Off the record at 9:45 a.m.)

(Recess held.)

MR. GOODALE: We're back on the record at 9:57 a.m.

BY MS. ROBERTSON:

Q. All right, Dr. Foster, I'd like to show you an exhibit we'll mark as 18-2.

(Foster Deposition Exhibit 18-2 - Notice to take Oral and Videotaped Deposition of Dr. Warren G. Foster - marked for identification.)

Q. This is a Notice of Deposition of Dr. Warren Foster.

Dr. Foster, have you seen this document before?

A. I've seen an email version of it, yes.

Q. And if you could please go back to the fourth page. It's titled Schedule A.

A. I'm sorry.

Q. It's got a -- it's a number 1. It's 4 on the document, but it should be -- my apologies. I'm double-sided.

A. Yes. I'm on Page 4. Or the last page.

Q. The last page. And it says Request No. 7?
A. Yes.
Q. And, Dr. Foster, were you asked to provide any of these communications in response to this request?
A. I was. And I didn't have any to provide.
Q. Okay. Thank you, Dr. Foster.
I'm going to go ahead and hand you what we're going to call Exhibit 18-3.
(Foster Deposition Exhibit 18-3 - USEPA Lacayo Memorandum - marked for identification.)
Q. Dr. Foster, for the record, if we could please just consult your expert report quickly and look at Citation 47. I would ask, please, whether you can confirm the document I handed you as Exhibit 18-3 is your referenced Exhibit 47 -- or, sorry, Citation 47.
A. I believe it is.
Q. Thank you. So, Dr. Foster, it's fair to say that you've reviewed this memo before, correct?
A. Yes, I believe I've reviewed this document before.
Q. And this document is an EPA memorandum, correct?
A. Yes.

Q. And this document relates to the glyphosate feeding study, which is EPA Registration No. 524-308. Correct?
A. Correct.
Q. And what do you appreciate this -- which study do you appreciate this document as discussing?
A. I believe this would be referring to the Knezevich and Hogan study.
Q. And who sponsored that study? Do you know?
A. The Knezevich and Hogan study?
Q. Yes.
A. I would have to look at my expert report to see if I noted that.
In my expert report, I indicate that this study was conducted by Monsanto.
Q. And, Dr. Foster, was this one of the three studies you mentioned earlier that you reviewed the full data for?
A. I believe that is the -- correct.
Q. So, Dr. Foster, if we can go to the last full page of content of Exhibit 18-3, the page right before References.
A. I'm sorry; which document do you want me to go to?
Q. Document 18-3.

A. Yep. Last page before References.
Q. So the last page of the memo.
A. Yes.
Q. And here the EPA is articulating that they disagree with the registrant's position. The registrant in this context would be Monsanto, correct?
A. The registrant would be Monsanto, yes.
Q. And the last -- the last two sentences of the first paragraph on Exhibit 18-3 read, "The registrant wishes to avoid false positives while those concerned with public health wish to avoid false negatives. Hence, for this reason alone, Monsanto's argument is unacceptable."
Do you see where I'm reading?
A. I see where you're reading, yes.
Q. So, Dr. Foster, you would agree that at least at the time of this memo, that the regulatory studies should favor the detection of false negatives. Correct?
MR. DHINDSA: Objection.
A. Regulatory -- as I understand your question, regulatory studies should favor the detection of false negatives?
Q. Correct.
A. I think that the more appropriate way of

stating that is that regulatory studies should favor the detection of effects over not seeing something.
In other words, what you're trying to do is screen, and you want to make sure that the -- you're using a sensitive assay so that if there is something worth looking at, you're not missing it by being too conservative.
Q. So, Dr. Foster, do you agree or disagree that regulatory studies should favor the detection of false negatives?
MR. DHINDSA: Objection.
A. I can't --
MR. DHINDSA: Objection.
A. I can't speak to the author of this report and what's in their mind at the time, what's happening before this email or this memo exchange is taking place.
But the point that I'm making -- and I think it's the valid point -- is that when you're a government agency, you're trying to protect the health of the -- of the overall population. You want to design an assay, a screening assay that's sensitive enough in order to detect an effect over missing things that may -- may be there. So you don't want your assay to be too conservative.

Q. Dr. Foster, I think potentially you misspoke there. You were talking about if you're a government agency and you're trying to protect the health of overall population, you want to design an assay or a screening assay that's sensitive enough. You don't mean the government agency wants to design an assay, correct?

A. The reason I stated it that way is that the governments globally have come together and developed the guidelines that companies then follow. So the company didn't develop the guideline. The company had no say in it.

Q. Um-hum.

A. So you're -- yeah, they're following a prescribed guideline for -- for regulatory purposes.

Q. And one of the goals of a government agency in this context is to protect human health. Correct?

A. Governments in the United States and Canada and elsewhere have participated in the development of these guidelines in an effort to develop data that would be useful in protecting the health of their populations.

Q. But, Dr. Foster, the government isn't developing the data. Aren't the study authors developing the data? Knezevich and Hogan in this

instance?

A. Knezevich and Hogan conducted the study that generated data using a guideline that was approved by governments. So in this case, an OECD-style-type guideline.

Q. Understood. And in evaluating the data that Knezevich and Hogan gathered when they conducted the study, the EPA, from a public health perspective, has a concern with protecting against false negatives. Isn't that correct?

MR. DHINDSA: Objection. Asked and answered.

A. The public health agency is interested in order -- is interested in the results of studies that would provide them information on whether or not a compound has any potential hazard to health that they could then investigate further.

Q. And would it be fair to say that investigating further is the result of finding study results that have some sort of suspicious finding? Meaning that it appears there is a dose relationship within the animal bioassay?

MR. DHINDSA: Objection.

A. Can you -- can you rephrase or say that again, please.

Q. We'll just go ahead and look at Exhibit 18-3,

and we'll do the second-to-last paragraph that begins with, "Viewpoint is a key issue," and continues with, "Our viewpoint is one of protecting the public health when we see suspicious data. It is not our job to protect registrants from false positives. We sympathize with the registrant's problem, but they will have to demonstrate that this positive result is false."

Do you see where I'm reading?

A. I see where you've read that, yes.

Q. And so would you agree, Dr. Foster, that it is, in fact, true that the EPA is concerned with seeing -- with a false negative, as compared to a false positive?

MR. DHINDSA: Objection. Asked and answered.

A. I can see that the author of this is stating that as his view -- his/her viewpoint.

Q. Dr. Foster, let's look at the first page of substance of Exhibit 18-3. And we'll see here that the author is Mr. Herbert Lacayo, statistician.

A. Yes.

Q. Tox/HED/OPP.

A. Correct.

Q. And would you agree that Dr. Herbert Lacayo is an employee of the EPA?

A. Correct.

Q. So this is an EPA memo, and it is the EPA's position that there is a concern with false negatives. Isn't that correct?

MR. DHINDSA: Objection. Asked and answered.

A. I can't -- I can't say what the EPA position is. I see that an EPA employee, writing to another EPA employee, is stating this as their opinion. But I don't know that this person, a statistician, speaks for the entire EPA and states EPA policy.

Q. Dr. Foster, you listed this document in your Materials Consulted of your expert report, but you don't cite to it anywhere in your expert report. Does that mean you didn't rely on it to form your expert opinion?

A. I read the report as information that was provided to me. I did not cite it, because I did not see it as being relevant in my expert report.

Q. Well, if we look at Page 21 and 22 of your expert report with respect to the Knezevich and Hogan study, the only citation I see is Greim, et al., 2015.

So my question, Dr. Foster, is what you relied on in forming this analysis.

A. You're asking what -- what information I used in order to conduct my review of the Knezevich and

Hogan study. So I looked at the Greim table. I also looked at the memo that you had shared. I also looked at the information from the Pathology Working Group and additional memos going back and forth between the group.

Q. Can you identify me -- for me in your materials consulted which citation relates to the (PWG), which I assume is your citation to the Pathology Working Group?

A. Can I identify the reference that refers to that?

Q. Yes, please.

A. I believe Reference No. 49 might be one that refers to that.

Q. Okay, well, let's go ahead and look at Reference No. 49, then, Dr. Foster.

I'm going to hand you what we'll go ahead and mark as Exhibit 18-4.

(Foster Deposition Exhibit 18-4 - USEPA Kasza Memorandum - marked for identification.)

Q. Can you identify this document for the record, Dr. Foster.

A. This is a memo to William Dykstra, Reviewer, Toxicology Branch, from Lou Kasza, D.V.M., Ph.D., pathologist of the toxicology branch.

Q. So this is not the PWG?

A. No. This is relating to that issue, but no.

Q. And did you consider this document when analyzing Knezevich and Hogan?

A. I did review this article, yes.

Q. This document states that the purpose was to identify whether there was a tumor in the control animal. Correct?

A. That's correct.

Q. And your report states that there -- you believe there is a tumor in the control animal. Is that correct?

A. I believe that the Pathology Working Group unanimously came to the conclusion that there was a tumor there, yes. I did not individually personally review the slides.

Q. All right. Do you recall when the Pathology Working Group made this determination?

A. I don't know the date, no.

Q. Was there a control tumor found by the initial study authors, Knezevich and Hogan?

A. My recollection is, no, they did not see the initial -- the initial tumor.

Q. You described for us that there was a request to reanalyze tissue blocks identified -- tissue blocks

within the Knezevich and Hogan study.

A. Yes, there was.

Q. What do you mean by "tissue blocks"?

A. Okay. At the end of a study -- in this case, since we're talking about kidneys, we'll focus on kidneys. The kidneys would be embedded into paraffin, and the paraffin is referred to as a tissue block. And that tissue then would be used to -- that paraffin tissue block would be cut on a microtome, and thin paraffin sections would be added to a glass slide which would then be stained with routine hematoxylin and eosin, mounted with a cover slip for analysis by the pathologist.

Typically, in these studies, because you're dealing with large numbers of animals, one section is -- is prepared per animal.

Q. And so a tissue block is different from a slide. Is that correct; my understanding?

A. A tissue block is different from a slide, yes.

Q. Do you know who made the decision to reanalyze the kidney sections of the Knezevich and Hogan study?

A. I do not know who made that decision, no.

Q. Do you know why the decision was made?

A. I believe the decision -- well, no, I don't -- I don't know why the decision was made. I wasn't part of the process.

Q. Is it -- after a -- after study authors provide final pathology reports of the study conducted, is it typical that two, three years after that study report is submitted, that slides are recut?

A. It's not unusual, no. If you see something in the conduct of your study that's -- that might be interesting or worthy of -- of reinvestigation, you might go back and cut additional slides, yes.

Q. Do you know whether there was anything interesting or worthy of investigation with the Knezevich and Hogan study that would warrant such a recut of slides?

A. I think in this particular case, the kidney adenomas were rare, and so they wished to determine whether or not any additional tumors might be present.

So in cutting the additional sections, the -- Monsanto is now at risk of -- of finding additional tumors in their treated group.

Q. Um-hum. Do you know whether --

A. They did not.

Q. Oh, sorry.

A. They did not find any additional tumors in

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the treated animals --
Q. Um-hum.
A. -- but the one in the control did appear.
Q. Did you review any of the notes related to Dr. Kuschner in the Knezevich and Hogan study?
A. Did I review any of the notes between who?
Q. Dr. -- any of the memorandum, I should say, between Dr. Kuschner and Monsanto related to the Knezevich and Hogan studies.
A. I don't believe so, no.
Q. Do you understand that a pathologist named Dr. Kuschner reviewed the kidney slides of the Knezevich and Hogan study?
A. Yes. Sorry, I do. Yes.
Q. Okay. And do you know when he conducted this review?
A. No, I don't.
Q. Do you know whether he conducted the review after the kidney slides were recut?
A. I believe it was after, but I can't state for certain.
Q. So as you sit here today, you don't have any reason to know necessarily why the slides were recut, do you?
A. No, I don't. My -- again, I'm looking at the

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animal data and assessing the quality of the data and what the data is telling me. What the -- the decisions behind why studies were conducted, who conducted them, it's not something that I looked at.
Q. I understand. I don't want you to speculate.
So on Page 22, you note that additional tissue sections were taken from all four dose groups.
A. I note that on Page 22?
Q. Correct.
A. Where are you?
Q. We're in that same paragraph that we were just referring to.
A. (No response.)
Q. If you look at the first sentence, it's rather lengthy, but it ends with, "Examination of additional tissue sections in all four dose groups..."
A. Yes, I see that.
Q. What do you mean by "all four dose groups"?
A. Control, low, medium, and high.
Q. Do you also mean in both males and females?
A. I don't recall at the time.
Q. When one conducts a reanalysis of tissue blocks because there is a -- a need, wouldn't it be important to resection all of the tissues in a particular study in order to give the best quality of

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assessment of that study?
MR. DHINDSA: Objection.
A. I can't speak to what the rationale was of the individuals that made the decision.
Q. But in your expert opinion, wouldn't it be important to gather all of the data from all of the animals in the study?
MR. DHINDSA: Objection.
A. Not necessarily. I think in this particular case -- or, in general -- I can't really speak to this case, because I don't recall. But, in general, if I was doing a study, and I saw something that was interesting in the males, then I would go back and look at the males.
Q. Dr. Foster, is there equality in having blinded review of animal data?
A. What do you mean by "having blinded review"?
Q. When a pathologist gets the study results, is it important that that pathologist does not know which dose group the animal is he's reviewing? Blinded.
A. I think that would be a benefit.
Q. Is there any harm to conducting an unblinded review?
MR. DHINDSA: Objection.
A. I'm not a pathologist, so I really can't

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speak to that.
Q. I understand.
A. In conducting a study, we do it with the animals coded, so that we were unbiased in the interpretation of the general results.
Pathology, as I understand it, is a little bit different, and you would have to speak to the pathologist about that.
Q. Okay, Dr. Foster, you -- part of your opinion related to the Knezevich and Hogan study and the determination that there is a tumor in control animal is based on the PWG report. Correct?
A. That's correct.
Q. Did you look at the individual animal data for -- from the PWG report?
A. To my recollection, no. I saw the -- the -- the correspondence.
Q. How did you get the correspondence?
A. I believe this is information that was provided to me by Monsanto lawyers.
Q. Did Monsanto lawyers also provide to you the original study results conducted by Knezevich and Hogan?
A. Yes, I believe they did.
Q. And did the Monsanto lawyers also provide you

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the addendum to the Bio/Dynamics, Knezevich and Hogan study?
A. If you have a copy of it, could I look at it, and then I'll be able to answer that?
Q. I might -- I might be able to, so we'll start on this. Don't want you to answer any further. I don't know if I brought it.
Do you know if the Pathco PWG report is publicly available?
A. I don't know.
Q. Do you know whether the original pathology conducted by Knezevich and Hogan is publicly available?
A. That, again, I would not know.
Q. Your materials consulted cite to a number of EPA documents, most of which deal with the Knezevich and Hogan study. Is there a reason you chose to focus your research on EPA documents for this particular study analysis?
A. Those were documents that were provided to me by the Monsanto lawyers.
Q. Did you conduct any independent research on the Knezevich and Hogan study?
A. I did my own independent PubMed electronic search. I did not find anything additional related to it. In my recollection.

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Q. Let's go ahead and look at Page 6 of your expert report, Dr. Foster.
A. Page?
Q. 6.
A. 6.
Q. Sorry. In the Literature Reviewed section.
A. Yes.
Q. It starts with, "A critical review of the literature was carried out in which I reviewed all of the available case materials."
Who carried this review out?
A. I carried the review out.
Q. So what do you mean --
A. So --
Q. -- by "available case materials"?
A. So the variable case materials as they were provided to me by Monsanto lawyers. And then I go on and -- and talk about the -- the literature cited in the literature as well.
Q. Right. I understand that. I'm just trying to understand what you mean by "case materials" and what materials that would include.
A. Again, that would be the materials that were provided to me for review.
Q. Oh, okay. So you did a critical review of

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the materials provided to you by Monsanto's attorneys.
A. Correct.
Q. Did you have any assistance in writing your expert report?
A. Sadly, no. It was all mine.
Q. No research assistant helping you pull documents?
A. My -- my wife helped with photocopying and things like that.
Q. Did you list all of these case materials you conducted a critical review over in your Materials Considered list?
A. I believe it is complete, yes.
Q. Dr. Foster, you have a lot of experience with peer-reviewed journals; is that correct?
A. Define "a lot of experience".
Q. You're a journal referee, you've sat on editorial boards, you've been published over 150 times. You're very familiar with peer-reviewed journals.
A. Yes.
Q. Can you explain to me what a journal referee is. It's listed in your CV.
A. It's a person that is identified by journal editors as having expertise in the field, that would be able to give a critical assessment of the quality and

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scientific merit of the submitted article.
Q. So does this mean you receive a submitted draft manuscript prior to publication?
A. Prior to publication, authors submit their articles to the journal through an electronic portal, and the editor anonymously -- the editor selects reviewers who are anonymous to the authors.
Q. And where does the journal referee come in?
A. Please help me. What are you asking?
Q. I'm trying to figure out what your role is in the process as a journal referee to the peer-reviewed literature process.
A. Okay. The peer reviewer would read the submitted manuscript and would look at the manuscript from title through to the last page, asking questions about does the title accurately reflect the -- the subject of the paper.
We would look at the introduction to determine whether or not that the rationale for the paper has been adequately described, has it been thorough, has it -- has it omitted information that could be important to include, have they provided an adequate justification for the study and the doses that are going to be used.
You would look at the materials and methods

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to determine whether or not they're complete. You might also look at the methods that have been employed to determine whether or not they're the state of the art and whether they're comprehensive.

You would look at the statistical methods that have been applied and determine whether or not they've been adequately described and they're complete.

You would review the results and determine whether or not the results have been accurately presented. Are they presented in the best format possible. Are they publication quality.

So, I mean, there's many, many issues that, as a reviewer, you're looking at. And what you're trying to do is provide the editor with feedback on terms of whether or not the paper makes a substantial contribution to the scientific literature that's worthy of publication. You try and give them some context in terms of priority for publishing; whether it's appropriate for that journal. And if there are issues that might be useful in guiding the authors to improve the quality of the paper.

Q. So is journal referee just another name for peer reviewer?

A. If you would have asked that earlier, we could have got there quicker, but, yes.

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Q. And the process for peer review takes significant time, correct?

A. Yes.

Q. And in the process of peer review, after you've engaged in the first submitted draft, are critiques or comments ever sent back to the study author articulating we can't publish this; please look at these concerns we have?

A. Every submitted -- every submitted article, the peer reviewer submits their comments back to the editor. The editor then reviews them to determine whether or not they've been -- they're fair.

Sometimes you might get a reviewer that takes advantage of the anonymity of the process and provides comments that are not appropriate.

Q. Um-hum.

A. In any case, all of the comments are sent back to the -- to the submitting author, the corresponding author.

Q. And then the submitting author likely makes the determination as to whether they are going to revise and resubmit, or maybe they need to go back to the drawing board. Correct?

A. It would be up to the submitting author to make a decision what they're going to do at that point.

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Q. In your experience as a peer reviewer, how long does the revision process normally take?

A. I can't answer that. It's --

Q. More than a day?

A. The -- the revision process?

Q. Correct.

A. You know, I've had papers come back and say "accept as is".

Q. Um-hum.

A. So no revision needed. Lovely to receive a letter like that.

Q. Okay.

A. Extremely rare.

Q. Okay.

A. Most often you get something that requires comment and revision. And the revision process is something that could be done quickly, depending upon what are the things the submitting author has on their desk at the time. It might take a couple months.

So I think -- you know, I think outside sometimes it might be three months, and editors might give more time, depending upon the issues.

Q. Okay. So let's go ahead and look back at Exhibit 18-4.

A. (Witness complies.) Yes.

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Q. And it's the EPA memo we discussed earlier that you have on your Materials Consulted list as Citation 49.

This is a representation of the review of the kidney section slides of the Knezevich and Hogan by Dr. Kasza, branch pathologist at EPA. Correct?

A. That's correct.

Q. And the interpretation in the Results section states that, "The lesion may be a proliferative change, having the potential to lead to the development of a frank tumor. But as the tissue can be seen under the microscope as a small, well-demarcated focal cell aggregate morphologically different --"

(Attorney Robertson interrupted by the reporter.)

Q. "-- tissue can be seen under the microscope as a small, well-demarcated focal cell aggregate morphologically different from the healthy-looking surrounding kidney tissue. The morphological alteration does not represent a pathophysiological significant change."

Do you see what I'm reading?

A. (No response.)

Q. That's what it says, right, Dr. Foster?

A. That is what it says, yes.

Q. And do you know whether EPA's analysis of the kidney tissue slides occurred before or after the PWG working group's review of the kidney slides?

A. I can't state with certainty, but I believe it happened before the Pathology Working Group.

Q. Is this the type of incidence that you noted earlier that would have encouraged a full tissue block reanalysis of slides?

MR. DHINDSA: Objection.

A. I'm sorry; I got lost there. Is this the type of finding?

Q. Earlier you had described that sometimes years after a study is completed, tissue slides may be recut. Is -- given the language in this EPA memo, is this one of those instances that would support recutting kidney tissue slides?

MR. DHINDSA: Objection.

A. I can't say what were the driving factors there. I do know from my interaction with pathologists, that it is not uncommon for them to see something and for them to seek the input of other pathologists and to cut additional slides.

Q. But in this EPA memo, there's no indication that EPA is asking for recut slides. Correct?

A. There's no indication in this memo that that

took place or that this pathologist consulted with any other pathologist at EPA.

Q. Okay. And on Page 22, same paragraph, you note, "As Dr. Portier notes, with the tumor in the control mouse included, there are no statistically significant differences."

A. This is Page 22; is that correct?

Q. Correct.

A. In that same paragraph?

Q. First full paragraph, right after your citation to PWG.

A. Yes.

Q. And is it your opinion today that Dr. Portier also did not find a statistically significant difference when adding a -- the supposed tumor in the control group?

A. Well, let's take a step back there. The Pathology Working Group, I think, was composed of five different pathologists who all looked at -- looked at the slides and unanimously came to the conclusion that that was a real tumor; it wasn't a supposed tumor.

Q. Okay. Do you stand by the --

A. So I don't think you've accurately characterized --

Q. -- position that Dr. Portier notes that the

tumor in the control group included there are no statistically significant differences?

A. That's what I interpreted from his report, yes.

Q. Okay. Well, let's look at his report.

(Discussion held off the record.)

Q. I'm sorry, Dr. Foster, I need that real quick to mark it as Exhibit 18-5. Apologies.

A. I was going to ask.

(Foster Deposition Exhibit 18-5 - Christopher J. Portier, Ph.D. Expert Report - marked for identification.)

Q. So Dr. Portier discusses the Knezevich and Hogan study on Page 36. I guess that's not really -- he starts on Page 36, and he goes through 39.

Now, Dr. Foster, on Page 37, within the first paragraph carried over, Dr. Portier explains that, "Adenomas no longer have a significant trend, but carcinomas have a marginally significant trend against concurrent controls and clearly significant trend using historic controls."

Do you see where I'm reading?

A. Yes.

Q. So, in fact, on Page 22 of your expert report, it's not true that Dr. Portier included in his

expert report a finding that stated no statistically significant differences even with the tumor in the control animal?

MR. DHINDSA: Objection.

A. Marginally significant cite. Marginally significant is non-significant. You start out at the beginning of your study, and you state a priori that your cutoff value is .05.

In my experience as a peer reviewer, nobody's going to publish anything as marginally significant.

Q. Let's then take a look at Exhibit -- oh, wait. Before we take a look at Exhibit -- before we take a look at the next exhibit, you stand by your statement on Page 22 that Dr. Portier stated there are no statistically significant differences. Is that correct?

A. I do.

Q. Now I will hand you what we'll mark as Exhibit 18-6.

(Foster Deposition Exhibit 18-6 - Joseph Haseman article in the Toxicology Pathology Journal - marked for identification.)

A. Yes.

Q. And this is a journal article from Dr. Joseph Haseman, published by the Toxicologic Pathology Journal

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in 1984.
A. Um-hum.
Q. And, Dr. Foster, this is also listed on your materials consulted as Citation 90. So you've reviewed this article previously, correct?
A. I have looked at it, yes.
Q. Now, in the Abstract, the last sentence of the first paragraph, Dr. Haseman uses "marginally significant" here. Do you see where I'm reading?
A. No, I do not.
Q. In the Abstract, first --
A. I'm in the Abstract.
Q. First paragraph, last sentence.
A. Oh, first paragraph, last sentence. Yes, I see that.
Q. And would you agree that Toxicologic Pathology is a peer-reviewed publication?
A. It is a peer-reviewed publication, yes.
Q. And can you -- what is the Society of Toxicologic Pathologists?
A. It is an organization to which pathologists belong to share information, ideas.
Q. And you're a member of the Society of Toxicology, correct?
A. I am.

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Q. Are the two related?
A. Don't know that they are.
Q. Okay. I'm going to go ahead and hand you now what is going to be marked as Exhibit 18-7.
(Foster Deposition Exhibit 18-7 - Article in Biometrics Journal - marked for identification.)
Q. And, Dr. Foster, this is an article that's written by two department heads in biostatistical science. Would you agree?
A. Correct. Well, it's written by four people. I don't know that they're department heads. They are from the department of biostats.
Q. At the Harvard School of Public Health and at the Dana-Farber Cancer Institute in Boston. Correct?
A. That is correct.
Q. And if we can flip to Page 220 of this article.
A. (Witness complies.)
Q. In the paragraph above No. 7, Discussion. The fourth and -- well, I guess the first sentence on -- in that column, second line down, through the fifth line, we see, again, the use of "marginally significant trend", don't we, Dr. Foster?
A. I see that sentence, yes.

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Q. And you'd agree that on the first page of this article, this article is discussing the trends with respect to neurotoxicity of substances in animal bioassays. Correct?
A. I do.
Q. Okay.
A. And I would also note that in the section that you just asked me to read, they conclude with, "In that regard, chemicals showing marginally significant P trends based on our method may warrant further investigation." May. It's a qualifier.
Q. Okay. But, Dr. Foster, you represented on the record that no peer-reviewed article would ever publish or use the phrase "marginally significant".
MR. DHINDSA: Objection. Misstates his testimony.
A. What I am stating is that no peer-reviewed journal is going to look at data that's presented as marginally significant in which the data -- the conclusions of the report are based on that. I'm not saying that the words won't appear in a paper.
Q. So you disagree with Dr. Haseman that you can have a marginally significant trend in historical controlled databases?
MR. DHINDSA: Objection.

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A. I'm not saying that. I'm saying that you can do statistics and people can assign those words to them, but they don't carry a lot of weight in the interpretation of the analysis.
Q. Dr. Foster, do you know whether statisticians use the phrase "marginally significant"?
A. I have seen it used, yes.
Q. And you're not a statistician yourself. Correct?
A. No, I am not.
Q. Let's talk about your ultimate conclusion in the Knezevich and Hogan study. You state that there is no evidence of tumor progression in the Knezevich and Hogan study. Isn't that correct?
MR. DHINDSA: Objection.
A. There are several reasons in this study why I determine that the results are not compound-related.
Q. Can you, please, direct me in your citation -- Materials Consulted as to which citation you rely upon to make those decisions and conclusions.
A. In the final paragraph of my report, I lay out the reasons why I've made that decision.
Q. And which -- what do you cite to, Dr. Foster?
A. I'm not citing to anything in my report. I'm citing to my experience of almost 30 years as a

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toxicologist in reviewing animal literature from these types of studies. These are the types of analysis we would come to.

Q. And in your experience with animal studies, you rely on historical controls in some instances; isn't that right?

A. They are one factor that we might look at, yes.

Q. Right.

A. But not the only factor.

Q. Agreed. And on Page 6 of your expert report, you give us a list of statements and opinions and rationale. And No. 6, in fact, discusses historical controls.

A. What page is that?

Q. Page 6.

A. Page 6, No. 6?

Q. Right.

A. Yes, that is there.

Q. Okay. And, in fact, you rank in order of priority the appropriateness of the application of historical controls to animal bioassays. Isn't that correct?

A. Yes, I do.

Q. And in the Knezevich and Hogan study, did you

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use the concurrent control or historic controls?

A. I believe in my analysis, in looking at the Knezevich and Hogan study, I looked at the concurrent controls, in addition to looking at the additional analyses that were conducted, together with the other outcomes that were seen in the study.

Q. What do you mean by "additional analyses conducted"?

A. I'm referring to the Pathology Working Group there.

Q. And did the Pathology Working Group at all address historical controls?

A. No, they did not.

Q. All right. And so you looked at the concurrent controls as --

A. I believe that's correct.

Q. So if we looked at Dr. Portier's expert report on Page 38, Table 9, he offers the data for tumor incidences observed in the Knezevich and Hogan study. Do you see where I'm at?

A. I see that, yes.

Q. And we can agree that on Table 8 [sic] that the column that lists under Doses, zero is going to be the concurrent control group. Correct?

MR. DHINDSA: Table 8?

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MS. ROBERTSON: Table 9.

A. I believe that would be the concurrent control, yes.

Q. All right. So we have concurrent control, low dose, mid dose, and high dose. Is that right?

A. That would be correct.

Q. Okay. So if we look at the concurrent controls for the Knezevich and Hogan study, and we look at the -- for the purposes of your expert analysis, the incidence of adenomas and carcinomas with one tumor in the control group, no tumors in the low group, one tumor in the mid dose group, and three tumors in the high dose group. Correct?

A. So first -- first row?

Q. It would be the fourth row, Dr. Foster, to match the numbers --

A. Fourth row, 1013?

Q. Correct. To match the numbers on the top of Page 22 in your expert report.

A. Yes.

Q. Okay. And in this instance of applying the concurrent controls, you establish that there is no dose response relationship, even though we have one tumor in the concurrent control, one tumor in the mid dose, and three in the high dose.

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A. I see that, yes.

Q. Yet, Dr. Foster, you conclude that there is no dose response relationship shown in the Knezevich and Hogan study.

A. Again, I think you have to look at the study in its totality. So when we looked at the -- well, when I looked at the Knezevich and Hogan study, in the high dose group, we're looking at an 11 percent loss in body weight in the highest dose group. This is a concern to me. That's suggesting that there's something going on in this study at that high dose group that's potentially confounding the data.

Q. Dr. Foster, where did you find the 11 percent loss in body weight? Where did you find that information?

A. This would have been found during the conduct of my reading. Whether this was reported in the -- the -- either the -- the -- I'm trying to come up with the word -- the text of the Greim study or in the EPA reports.

Q. But you don't know, sitting here today, where you got this number of 11 percent loss in body weight in the highest dose group.

A. No, I cannot tell you exactly where I found that. However, it is something I came across in my

review.
Q. Is it not important to cite to statistical information that you get from your review?
A. Can you rephrase the question?
Q. Is it not important to cite to where you get statistical information from your review?
A. It's important to reference where you get information. In this particular case, I'm referring to the Knezevich and Hogan. And so in my review of that material, it was from the material relating to that study.
It was either in the material I reviewed directly relating to the data from the study or the Greim, but it was in direct relationship to that study.
Q. In your experience as a peer reviewer, would you note that a citation is needed in this instance?
MR. DHINDSA: Objection.
A. In -- were I reviewing a paper like this, I might suggest that they should put in a reference.
Q. But it wouldn't always be necessary to put in a reference that -- when you're citing 11 percent loss in body weight?
MR. DHINDSA: Objection.
A. Again, I'm talking about the study that was conducted, and I'm assuming that in my read of the

material that was provided with this study, that is where that information came from.
So in a report, in a published paper that is referenced above, I would assume that's where that information is coming from.
Q. Dr. Foster, on Page 21, you note that there was no statistically significant effect on survival. Correct?
A. I do make that statement, yes.
Q. And if there's no statistically significant effect on survival, wouldn't that mean that the dose level is appropriate?
A. Not on its own, no.
Q. Well, isn't the purpose of achieving a maximum tolerated dose is to administer as much as possible without affecting the survival rates within the study?
A. OECD guidelines state that you're to use up to 1,000 mg's. per kg. of your test substance or 5 percent of the maximal tolerated dose.
Now, in this study, they're using in their highest dose group 4,945 mg's. per kg. in males, and in the females, 6,000.
In conducting the study, didn't affect survival. However, in the high dose group, there was

an 11 percent loss in body weight in the male animals.
Now, that body weight, I don't know why they lost the weight. Is it because the test substance is affecting the palatability of the -- of the -- of the food and they're not eating? Is it because it's having an effect upon the central nervous system and affecting their desire to eat? Is it because it's having a systemic toxic effect that's affecting food absorption? Is it giving them diarrhea? Is it having an effect upon the liver? There are many reason why you might be seeing a loss in body weight.
But if I see a 10 percent loss in a body weight, my pathologists -- the veterinary pathologist at our institution is going to tell me I need to look at my animals and consider sacrificing the animals; they're being adversely affected.
Q. And was that done here? Did they sacrifice the animals?
A. At the conclusion of the study, they sacrificed the animals.
Q. Well, you always sacrifice the animals at the conclusion of a study, don't you, Dr. Foster?
A. Correct. This was done in 1993 under the -- sorry. Done in 1983 at the conclusion, following their guidelines.

Q. Right. And --
A. Whatever was standard at that time, they followed that.
Q. Right. And so we don't know today why the animals in the study lost the weight. That's right, correct?
A. As I've just stated, what I know is they lost 11 percent of their body weight.
Q. Okay.
A. Which, to me, confounds the data in the highest dose group.
Q. But you're not a pathologist. That's correct?
A. I'm an expert in animal toxicology. I'm not a pathologist. I work with pathologists, but I am not a pathologist.
Q. What training do you have in animal toxicology?
A. I don't even know how to answer that.
Q. Do you have any formal education in animal toxicology?
A. I trained at the -- at McMaster University as a reproductive biologist and toxicologist. And then --
Q. In animals?
A. In animals. And then 10 --

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Q. What's a reproductive biologist?
A. Someone that studies the -- the physiology of the reproductive system.
Q. Is it when the animal is alive?
A. Can be when the animal is alive. It might be in tissue. So I've done tissue culture. I've done human studies.
And then 10 years at Health Canada, to finish answering your question, where I carried out animal toxicology studies, from design through to publication of study results. And as the associate director, the acting director of the environmental toxicology program, I oversaw approximately 50 scientists and technicians --
Q. So it's --
A. -- affecting animal toxicologies.
Q. Apologies. So it's your experience at Health Canada and McMaster University that makes you an expert in animal toxicology. Am I understanding?
A. I think what makes me an expert in toxicology is not my decision, but that of the -- my colleagues that call upon me for my opinion and for insight into issues in toxicology.
So being invited to be an editor of the Journal of Applied Toxicology, serving on the editorial

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boards for -- for different journals establishes me as an expert. Not my decision.
Q. Um-hum. Dr. Foster, your answer there said an expert in toxicology. I want to make a clear distinction, because semantics are important.
Are you an expert in animal toxicology?
A. I --
Q. You stated that earlier. I just want to make the record clear.
A. I'm sorry; I got lost.
Q. I just want to make the record clear that as you sit here today, you are offering an opinion as an animal toxicologist -- expert in animal toxicology.
A. Okay. To be full in my answer, I am a -- have expertise as a toxicologist, and I've been asked to provide my expert opinion on the animal literature in this -- in this litigation.
Q. Okay.
MR. DHINDSA: Is now a good time for a break?
MS. ROBERTSON: Yes. I understand we only have a little bit of time left on the tape, so we can go ahead and take a break, Dr. Foster.
MR. GOODALE: This marks the end of Media 1 in the deposition of Dr. Warren G. Foster,

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Ph.D. Going off the record at 11:07 a.m.
(Recess held.)
MR. GOODALE: Here begins Media No. 2 in the deposition of Dr. Warren G. Foster, Ph.D.
We're back on the record at 11:24 a.m.
BY MS. ROBERTSON:
Q. Okay, Dr. Foster, I'm going to hand you Exhibit 18-8.
(Foster Deposition Exhibit 18-8 - USEPA Zendzian Memorandum - marked for identification.)
Q. Dr. Foster, if you could please look at your Materials Consulted and identify whether this citation matches -- or this Exhibit, 18-8, matches Citation No. 57, please.
A. (Witness complies.) As best as I can tell, this is the document, yes.
Q. And this document is another EPA memo. Correct?
A. This is a memo from William Dykstra, who I believe is at EPA, passed through Dr. Zendzian at EPA to Robert Taylor. I don't know where Robert Taylor is.
Q. Well, it says product manager, registration division.
A. Right. But I don't know if that's

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registration division within EPA or elsewhere. But I'm going to assume it's in EPA.
Q. Okay. So, again, this memo is still talking about the Knezevich and Hogan study, as indicated by, "Review pathology report on additional kidney sections." Correct?
A. Okay. I've read the article -- the memo.
Q. And we see on Page 2 in the conclusion that the EPA determined that additional tumor in the control group which had been re -- diagnosed from the re-evaluation of the original slides was not present in the recut kidney sections. Correct?
A. So in additional sections, no, there were no additional tumors.
Q. Well, it actually says "was not present".
A. I see that sentence, and this is -- I don't know the training of the individual, so they're reporting the EPA pathologist Dr. Kasza's statement.
Q. Do you know the training of the individuals who made up the Pathology Working Group?
A. I believe all of the five members were Board-certified pathologists.
Q. But you don't have any knowledge as to whether EPA employed Board-certified pathologists to review these kidney slides? Is that your testimony

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today?
A. That's not what I said. I said, looking at the front page of this document, I do not know the training of these people; Robert Taylor, Robert Zendzian, William Dykstra. I don't know if any of those three are pathologists.
When I read the sentence, it's not stating that they have examined them. They're stating -- they're restating Dr. Kasza's statement. That's the way I'm interpreting this.
Q. So do you disagree with the EPA that the EPA did not find a -- do you disagree with the statement that the EPA concluded that an additional tumor in the control group was not present in the recut slides?
MR. DHINDSA: Objection. Objection.
A. What I'm saying is that this -- the way I read this memo is that they're restating Dr. Kasza's statement, the EPA pathologist.
Q. And so the restatement of Dr. Kasza's statement is that an additional tumor in the control group was not present in the recut kidney slides. Is that correct?
A. Again, I'm state -- what I'm saying is I stand by my original statement. They are parroting the statement that was made by Dr. Kasza. We've already

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said what Dr. Kasza said.
Q. Dr. Foster, I'd like you to look at Citation -- your Materials Consulted, No. 153. That is a study that appears to be authored by Sawyer, and Pathology Working Group report on glyphosate in CD-1 mice.
A. I see that.
Q. And would that citation be referring to your PWG citation on Page 22?
A. I believe that's correct.
Q. And the date of that report is October 10, 1985. Is that correct?
A. The date on this report, yes.
Q. And the date on this EPA memo is December 12, 1985. Is that correct?
A. Correct.
Q. So, in fact, the EPA did review the recut slides after the Pathology Working Group and concluded that there was no renal tumor in the control animal. Isn't that correct?
MR. DHINDSA: Objection.
A. Again, I come back to what I had said before; that this memo is stating Dr. Kasza's -- they're reporting what Dr. Kasza said.
Q. And Dr. Kasza reviewed the slides after the

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Pathology Working Group. Isn't that correct?
A. I don't know when Dr. Kasza reviewed the slides.
Q. I direct your attention to Exhibit 18-4. Is this the memo you've been referred to, Dr. Foster, that is Dr. Kasza's opinion?
A. December 4 of 1985, yes.
Q. And so it's true that Dr. Kasza reviewed the recut kidney slides and did not find a tumor after the Pathology Working Group had stated there was a tumor. Is that correct?
A. What I have here is a memo dated December 4 of 1985. The memo was written December of 19 -- December 4th of 1985. That does not tell me that he did the analysis on December 3rd. I have no idea when the analysis was done.
Q. Okay. Well, let's look at the last page in this exhibit and the test for significances of differences between proportions dated 11/13/1985.
Dr. Foster, does this look like some study results from a pathologist?
A. This looks like statistics done December 11, 1985.
Q. And is December -- no. It is dated 11/13/1985.

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A. The last page?
Q. Correct.
A. The top of my page says 12/11/85.
Q. 11/13/85. Are you on Exhibit 18-4?
A. (Witness indicates.)
MS. ROBERTSON: Counsel, what does your say?
MR. KALAS: 11/13/85.
MS. ROBERTSON: Apologies. To make the record clear, I'm going to have to confirm whatever was printed off of EPA's FOIA website. My apologies.
MR. KALAS: Let the record reflect there's just -- at least two versions of this document. We don't know which one's right or which one's wrong. Or whether both are right.
BY MS. ROBERTSON:
Q. Dr. Foster, do you know which version you used when you cited to Citation 49?
A. Sitting here today, I could not tell you the date that was on the document.
Q. Dr. Foster, when you reviewed these memos supplied to you by Monsanto's counsel, did these memos bear a MONGLY Bates stamp along the bottom? During your review, Dr. Foster, not the one handed to you.

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A. I -- I cannot answer that. I don't know.
Q. Do you know whether --
A. I have no recollection.
Q. Do you know whether these documents had "USEPA Archive Document" cover page that these exhibits have? Do you recall?
A. Yes, the -- I'm pretty sure that what I looked at looks like this (indicating).
Q. And they had the USEPA Archive Document cover page that you see on the front of 18-8, 18-4, and 18-7?
A. Yes.
Q. Dr. Foster, why didn't you apply concurrent controls in your analysis of Knezevich and Hogan?
A. I looked at all the data, not just the concurrent controls.
Q. What other historic controls did you look at?
A. If we go to my report, I state in my report that I looked at the information provided from the Knezevich and Hogan, the recut, the Pathology Working Group, and then I also looked at the results from other endpoints, including the body weight.
Q. Okay.
A. So it wasn't just control groups and how control groups -- I'm looking at all the data.
Q. Dr. Foster, you do agree that in order to

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analyze a dose response, you need to look at the treatment groups compared to the control group, correct?
A. I do.
Q. And in this study, you chose the concurrent control. Isn't that correct?
A. I believe that is correct. But, again, I looked at all the data. I may have relied on the concurrent controls in this case, but I looked at all the data.
Q. Dr. Foster, do you know whether the regulatory bodies of EPA and ESLA looked at the current controls or the historic controls?
A. I cannot comment on what other regulatory bodies did or didn't do.
Q. Dr. Foster, would you agree that a renal tubule adenoma is a rare tumor?
A. I can agree that renal adenomas in mice are rare, yes.
Q. And in the instances of rare tumors, is it appropriate to look at the historical controls?
A. It would not be out of the question to look at historical controls.
Q. Isn't it --
A. And, again, I looked at the concurrent

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controls, the historical controls, and the whole body of data, not just whether or not there was statistics involved or not.
Q. Not talking about the concurrent controls, not talking about the whole of the data, which set of historical controls did you apply to your analysis of Knezevich and Hogan?
A. I believe I relied upon the concurrent controls.
Q. Dr. Foster, you just stated that you relied on concurrent controls, historical controls, and whole body data. Did you not rely on historical controls for your analysis?
A. What I am stating is that I had looked at them, but I relied upon the concurrent controls.
Q. Which historic controls did you look at?
A. Sitting here, I can't tell you which ones I looked at.
Q. So even in the instance of a rare tumor, such as a renal tubule adenoma seen in the Knezevich and Hogan study, you applied concurrent controls. Is that correct?
A. I gave them more weight in this review.
Q. Let's look at the article that you cited to by Joseph Haseman. It was handed to you earlier.

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A. (Witness complies.)
Q. I think it's 18 -- Exhibit 18-6.
A. It is.
Q. Okay. And that first paragraph in the abstract agrees that concurrent controls are an appropriate control group for interpretive purposes, just as you state on Page 6 of your report. Correct?
A. That's correct.
Q. And, again, the last sentence in that paragraph applies to the discussion of the use of historical controls when you have a rare tumor. Correct?
A. Sorry. Can you state your question again. I was reading.
Q. Sure. The last sentence in the paragraph -- the last sentence of the first paragraph in the abstract applies to the discussion of the use of historical controls when you have a rare tumor. Correct?
A. Correct.
Q. Okay. What methodology did you use to omit the evaluation of historical controls in arriving at your conclusion that there was no dose response relationship with the renal tubule adenomas in the Knezevich and Hogan study with glyphosate?

MR. DHINDSA: Objection.
A. Again, coming back to my point, I looked at the entire data set that was available to me. And when I see that we've got an increase -- or, sorry, a decrease in body weight in the highest dose group, that leads me to concern that there's something happening in that group of animals that calls into the question the interpretation of the data.
Q. And so because you saw a loss in body weight, you made the expert opinion to use concurrent controls as compared to historical data controls, even though --
A. It wasn't --
Q. -- it was a rare tumor.
A. I wasn't making the decision based on that to which control group to look at; whether it was concurrent controls or historical. At this point, I'm looking at the quality of the study and interpretation of the overall information; what this study is telling me, as is standard practice within the field.
Q. Isn't it also standard practice in the field to apply historical control data sets to rare tumors?
A. Again, I didn't say that I did not look at them. What I am saying is that in looking at the data, when I saw an 11 percent loss in body weight in my high dose group, I became concerned that interpreting the

results from the study was going to be difficult. So at that point, that became more important.
Q. Your conclusion is that there's an absence of dose response together with lack of evidence of tumor progression, supporting your conclusion that the tumors are spontaneously occurring and unrelated to treatment. It's the second full paragraph on Page 22 of your expert report.
A. I see that. I'm just going to read it again. (Witness read.) So in the body of that paragraph, I lay out my reasons for determining that these were not compound-related effects.
I come back to my point that in the high dose group, you're almost five times the maximum dose recommended by OECD, and you've got an effect on body weight that leads me to question the -- the relevance of the effects seen in those animals. You take that out, there is no dose response. One, zero, one.
Then you add in that that there were step sectionals done. No additional tumors on any dose group were found.
Q. Dr. Foster, do you know what the mathematical equivalent is to 1,000 ppm?
A. Not off the top of my head, no.
Q. In administering high doses in animal

carcinogenicity studies, isn't one of the purpose to administer a high dose so you can show the potential toxic effect in humans?
A. The purposes of going up to the high dose is to have a dose that's sufficiently high that you don't miss an effect if one is present.
Q. And don't we use these animal bioassays and gauging whether there is a present effect to apply to whether a chemical can be a human carcinogen?
A. Again, I come back to the point I've made previously, is that in your high dose group, if you see adverse outcomes on different endpoints that calls in question and makes it difficult to interpret the -- whether or not those results are compound-related, then you assign less weight to them.
Q. Dr. Foster, did you assign less weight to this study?
A. I don't know what you mean by "did I assign less weight to this study".
Q. In your introduction of your expert report and in your recent testimony, you talk about the weight of studies, and you would assign less weight to studies that have high doses in the high dose group. Did you assign less weight to this study?
A. In this particular study, I did not find

evidence of compound-related effects.
Q. That's not the question.
A. I think that's the bottom line.
Q. That's not the question. Did you assign less weight to this study because of the high dose administered to the high dose animal group?
MR. DHINDSA: Objection. Asked and answered.
A. I looked at the study and asked the question, did -- in this study, were there compound-related effects. I did not see compound-related effects, so there was no need to assign a weight to it.
Q. So you only assign a weight to a study that shows a compound-related effect.
A. No. What I'm saying here is that this -- in looking at compound-related effects, I found it to be a negative study.
Q. Isn't loss in body weight the result of a dose response?
A. Sorry. Say that again. Isn't loss of body weight --
Q. Isn't loss in body weight the result of a dose response?
A. In this particular case, I don't know what's causing the loss in body weight.
Q. But it contributes to your overall conclusion

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that this is a negative study, even though you don't know what caused the lower body weight.
A. I'm saying that the loss in body weight, 11 percent loss in body weight, leads me to question the relevance of the findings.
Q. So if there's --
A. It's not reliable.
Q. -- no loss in body weight, the results of these findings would be relevant?
A. Again, I come back to my point. When I see a loss in body weight, it causes me to question the relevance of the findings. There -- and whether or not they're reliable. I don't believe they're reliable, and I don't believe they're reliable, because, again, if you look at cross-studies now, I don't see this tumor being recapitulated, re -- replicated in any other study.
Q. And as you sit here today, you don't know where you got the information that there was a loss of body weight of 11 percent. Isn't that correct?
MR. DHINDSA: Objection. Asked and answered.
A. In reading the material that was provided to me from the Knezevich study, in that -- in my review, there was a citation or an indication that there was an 11 percent loss in body weight.

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Q. But as you sit here today, you don't know which document that is.
A. I do not -- I cannot tell you which document that was, sitting here right now.
Q. And do you recall, sitting here right now, which set of historical controls you considered or looked at or read when looking at the Knezevich and Hogan study?
A. Again, coming back to what I've said previously, as I look primarily at concurrent controls and the overall information I had on the study.
Q. Right. And as you sit here today, when you looked at the overall information, do you recall the data set name of the historical control data set that you read when considering the Knezevich and Hogan study?
A. No, I do not know the name.
Q. Okay. Dr. Foster, we talked a little bit earlier this morning about your experience, and we mentioned your CV. So I'd like to enter that into the record at this time as an exhibit.
MS. ROBERTSON: And, Counsel, for the record, this is the continuation of Dr. Foster's expert report submitted on July 31, 2017, and that's why it begins on Page 47.

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This will be Foster Exhibit 18-9.
(Foster Deposition Exhibit 18-9 - Curriculum Vitae of Warren G. Foster, Ph.D. - marked for identification.)
Q. Dr. Foster, your CV mentions that you've done work for other industry. Isn't that correct?
A. Can you tell me where you're referring to.
Q. Well, do you recall, as you sit here today, as to whether you've done any industry work?
A. Can you tell me what you mean by "industry work".
Q. Have you ever done any work for the a company Exponent?
A. I have participated with Exponent in the authorship of an article.
Q. And do you still correspond with Exponent?
A. I don't know what you mean; do --
Q. Do you have any emails with Exponent?
A. I don't even know how to answer that. I mean, Exponent -- I -- I corresponded during the writing of the article with several people, but I don't know who all works at Exponent.
Q. What about after the article?
A. Not to my knowledge, no.
Q. Do you know Mr. James Lamb?

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A. I know the name, yes.
Q. Do you know that James Lamb works at Exponent?
A. I don't know whether he does or doesn't.
Q. Have you ever --
A. He may.
Q. Have you ever worked with James Lamb?
A. I think we have worked together in the past.
Q. What about Dr. Keith Solomon? Do you know Dr. Keith Solomon?
A. I know who Dr. Solomon is.
Q. Did you correspond with Dr. Solomon at all related to glyphosate?
A. No, I have not.
Q. Did you do any research at the University of Glelph [sic]?
A. Who?
Q. Did you do any research in preparation for your export report at the University of Glelph [sic]?
A. University of Guelph.
Q. Please correct me.
A. Guelph.
Q. Pardon?
A. Guelph.
Q. Guelph.

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A. I have no idea where Glelph is.
Q. My apologies.
A. That's okay. I don't think I've ever heard it pronounced that way. That's pretty good.
Q. I'm horrible. My husband makes fun of me all the time.
A. Well, that's okay.
Yes, I -- I did my undergrad at Guelph, I did a Master's Degree at Guelph. Guelph's just down the road. So, yes.
Q. Did you work at Guelph at all while engaging in expert research for the report you submitted in this lawsuit?
A. I've been to the library there, yes.
Q. When did you go to the library there?
A. It's been over a year of working on this. I couldn't tell you exactly when.
Q. Six months ago?
A. Possibly.
Q. Three months ago?
A. I don't believe so, no.
Q. And while you were at the University of Guelph, is that where you conducted your PubMed searches?
A. No. I did the PubMed searches from my home

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office.
Q. Okay. Why did you go to the University of Guelph?
A. Potentially, because I was in the area already for other reasons.
Q. Did you do any research at the -- at your University, McMaster's University's library?
A. Yes.
Q. Do you have any notes from the research that you conducted at these libraries?
MR. DHINDSA: Objection, to the extent it calls for drafts of his expert report.
A. Sorry?
Q. Do you have any notes from the research you did at these universities?
MR. DHINDSA: Same objection.
A. I would assume, yes. I don't know exactly what you're getting at. It's --
Q. Did you check out any books at either of these universities to take home and conduct your critical literature review?
A. I don't believe I've checked out books in probably the last 15 years.
Q. Did you make any copies of any books or articles while you were at the library?

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A. I believe what I normally do is I read in the library, make notes, insert into my reference manager information that I might need.
Q. Have you ever done any work with a company called Gradient?
A. I believe I have had a contract with Gradient at some point.
Q. What was the subject matter for the contract with Gradient?
MR. DHINDSA: Objection, to the extent it calls for confidential information. Go ahead and answer.
A. I can't say right off the top of my head what that was about.
Q. Do you know a Dr. Larry Kier, K-I-E-R?
A. K -- sorry, K --
Q. -- I-E-R.
A. I don't think so, no.
Q. Do you recall when you entered into an agreement with the Hollingsworth firm related to this case?
A. Do I remember the date?
Q. Or the approximate time.
A. It's been a little more than a year. I would think.

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Q. Do you recall who first contacted you to work on this case?
A. I believe that was Ran Dhindsa.
Q. And you knew that at the time that you were retained, the IARC had classified glyphosate as a 2A carcinogen. Correct?
A. I don't know what I did or didn't know at that time with -- with regard to glyphosate.
I think when I was initially approached, I was asked if I would be able to provide an expert opinion, and I provided Mr. Dhindsa with my CV to ask whether or not it would -- they would be interested in having my opinion.
Q. Um-hum. And was this CV similar to same as the one we've entered here today as Exhibit --
A. The CV that I sent to --
Q. -- 18-9?
A. Yes. It would be very -- I mean, this has been updated with the recent publications, but very similar.
Q. And so that CV would not include any articles on glyphosate. Isn't that correct?
A. I have not published anything on glyphosate specifically. I've not carried out any -- any experimental studies looking at glyphosate.

Q. You are aware that IARC classified glyphosate as a 2A, right?
A. I am aware of that, yes.
Q. Were you aware at the time Monsanto approached you to serve as an expert in this case?
A. I may have been aware of it. I -- I can't say one way or the other.
Q. We have a letter here from your counsel dated August 18, 2016. That's the initial correspondence between you and the attorney. And I'll show it to you, just to refresh your recollection, and we'll mark this as Exhibit 18-10.
(Foster Deposition Exhibit 18-10 - Dhindsa Letter Dated August 18, 2016 to Dr. Foster - marked for identification.)
Q. Does this letter look familiar to you?
A. So far. Yes.
Q. Okay. So, Dr. Foster, this letter shows that you entered into an agreement to provide expert consulting services with Hollingsworth, LLP on behalf of Monsanto Company on August 18, 2016. Isn't that correct?
A. That's correct.
Q. And on August 18, 2016, sitting here today, you can't recall whether you knew IARC had classified

glyphosate as a 2A?
A. I can't say that I know one way or the other. I may have known that.
Q. Did you review the IARC monograph for your -- for this case?
A. I have, yes.
Q. And to be clear, I'm talking about IARC Monograph 112.
A. Sorry. Yes, to be clear --
Q. Sorry.
A. -- I have read IARC Monograph 112 --
Q. And did you --
A. -- subsequent to being retained, not before.
Q. So you read it after you were retained.
A. Yes.
Q. And were you asked to read the monograph as part of your expert consulting services by Monsanto lawyers?
A. Yes.
Q. Prior to Monsanto lawyers asking you to read the IARC Monograph 112, you did know that glyphosate had been categorized as a 2A carcinogen, correct?
MR. DHINDSA: Objection. Asked and answered.
A. As I already answered, I can't state with certainty what I did or didn't know. I may have known

that.
Q. Well, prior to receiving IARC Monograph 112, you don't know today whether you knew if the classification was a 2A?
MR. DHINDSA: Objection. Asked and answered.
A. Again, I don't recall one way or the other what I did or didn't know at that time.
Q. So Monograph 112 could have been the first time that you learned that glyphosate was a 2A. Is that correct?
A. Again, at the time, I -- I can't say what I knew on August 18th. I may have known that.
Q. When you entered into the expert consulting agreement with Hollingsworth on behalf of Monsanto, you were aware that Monsanto did not agree with IARC's assessment. Correct?
A. Sorry, but I -- at the time I entered into the agreement with Hollingsworth, I may have been able to assume that, but I had no idea what Monsanto did or didn't agree with.
Q. Well, your expert consulting -- expert consulting letter marked as Exhibit 18-10 describes that you are to provide expert consulting services for the purpose of assisting Hollingsworth in representing Monsanto in connection with potential or actual

litigation against Monsanto involving injuries allegedly caused by Roundup and/or glyphosate. That's correct, right?
A. That's what it says in the letter, yes.
Q. And at the time you signed this letter, you did understand that Hollingsworth was retaining you on behalf of Monsanto --
A. Yes.
Q. -- to write an expert opinion related to glyphosate. Correct?
A. That's correct.
Q. You are aware today that Monsanto disagrees with IARC's conclusion that glyphosate is a 2A carcinogen, correct?
A. I can deduce that, yes. I haven't had any direct conversation with anyone from Monsanto, that I am aware of, but, yeah, I can -- I can figure that out.
Q. You haven't read any documents that -- you haven't read any news where Monsanto actively criticizes IARC's 2A classification? Is that correct?
A. I can't say one way or another if I've seen things like that. I mean, it's quite likely that over the past year I may have seen a news article or something on CNN or -- or someplace.
Q. How did you first begin researching

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glyphosate and/or Roundup, as manufactured by Monsanto, in connection with providing an expert opinion in this case?

A. How did I begin to conduct my research?

Q. Correct. What was the first thing you did?

A. I don't recall what -- the first thing I did, but I can imagine what the first thing I would have done would be to have gone and done a PubMed search.

Q. You didn't do any basic Internet searches to figure out what glyphosate was, seeing as how you've never written on glyphosate before?

A. Internet searches, you mean go on Google?

Q. Yes.

A. I don't believe so, no. I would have gone to the published literature.

Q. Have you done any research on IARC related to the Monograph 112 and the classification of glyphosate as a 2A carcinogen?

A. Your question is not very clear to me.

Q. I can rephrase. In preparing to write your expert report --

A. Yes.

Q. -- did you do any research on IARC as it relates to Monograph 112 and the classification of glyphosate as a 2A carcinogen?

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A. Again, I have trouble understanding exactly what you're asking me. Did I -- did I investigate who sat on the panel for IARC at 112? Did I investigate how IARC operated in 112? Did I investigate what IARC is? No, I did not do those things.

Q. Did you research Monsanto at all after being retained by Hollingsworth, LLP?

A. Again, the question is very vague, and I don't know exactly what you're asking me. Did I -- did I seek to find out what chemicals Monsanto makes, where -- you know, who works for Monsanto, any of those things? No, I did not.

Q. Prior to being retained by Hollingsworth, LLP, did you know that Monsanto manufactured glyphosate?

A. I can't state with certainly whether I knew that or not, but I think I may have known that as just part of general knowledge.

Q. Prior to being retained by Hollingsworth, LLP, did you know whether or not Monsanto manufactured Roundup?

A. I believe prior to being retained, I may have known that glyphosate was the active ingredient in Roundup.

Q. But you didn't know whether manufactured --

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whether it was manufactured by Monsanto.

A. I can't state with a hundred percent certainty that it -- that I knew that it was or wasn't manufactured by Monsanto. But as part of general knowledge, I think probably.

Q. That's fair. I understand.

Is it your understanding that by entering into this expert consulting services agreement with Hollingsworth, LLP on behalf of Monsanto Company, that you would be advocating for Monsanto's position on glyphosate?

A. No, I don't believe that's the -- the situation, in my understanding. My understanding is the same level of objectivity I bring to everything that I do, and that is I'm advocating for the data; what does the data say.

Q. And by "data," you mean the three studies that you reviewed and the Greim article. Correct?

A. I'm stating that for the studies that I reviewed and for the data tables that were presented in Greim.

Q. Okay. Are you aware that Monsanto posts comments about IARC on its website?

A. I don't know that. I don't know -- I'm sure they have a website, but I've never been to it.

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Q. Now, Dr. Foster, you served on Monograph 117; isn't that correct?

A. I have served on that -- that panel, yes.

Q. When was that IARC meeting in Lyon?

A. If memory serves, it was in the fall of -- was it last fall?

Q. Perhaps October 2016?

A. Yeah.

Q. And do you recall what Monograph 117 was asked to assess; which chemical?

A. We looked at Dieldrin, pentachlorophenol, Aldrin, and T-cab.

Q. And pentachlorophenol, or PCP, is an insecticide and herbicide, isn't it?

A. It was. I don't believe it's manufactured anymore.

Q. Did you tell anyone in the administration of IARC that you were working for Monsanto relating to Roundup and glyphosate?

A. I do not recall the details of my conflict of interest statement that I submitted to IARC. I believe I informed them of everything that I felt was relevant and was aboveboard.

Q. Dr. Foster, you are aware that IARC's conflict of interest requires disclosure of employment

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and consulting activities; isn't that correct?
A. I believe it requires that, yes.
Q. And did you disclosure your consulting agreement with Hollingsworth, LLP, on behalf of Monsanto, with IARC in advance of Monograph 117?
A. I can't say at this time whether I did or did not.
Q. Did you identify your work with Monsanto when you filled out your declaration of interest?
A. I have not done any work with Monsanto. I didn't --
Q. Did you identify your work with Monsanto when you filled out the declaration of interest with IARC?
A. Again, I have not been employed by Monsanto, I have not worked for Monsanto.
Q. Dr. --
A. I was obtained by Hollingsworth.
Q. Yeah, but, Dr. Foster, this resulting agreement [sic] says "on behalf of Monsanto Company". You don't appreciate that to mean that Monsanto is paying your bills?
A. I believe that I filled out the conflict of interest statement, to the best of my knowledge, as honestly as I could.
Q. Okay. My question, though, actually was:

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The -- this exhibit, Exhibit 18-10, does, in fact, state that you are doing consulting services on behalf of Monsanto Company, does it not?
A. It states that I am consulting to Hollingsworth on behalf of Monsanto.
Q. And doesn't that mean that you are employed by Monsanto Company?
A. I don't interpret it that way, no.
Q. So you believe you're employed by Hollingsworth, LLP?
A. I don't believe I'm employed by Hollingsworth either. I believe I'm being compensated for my time.
Q. Dr. Foster, what are the checks made out to -- what are the checks payable to, to pay for your time in this case?
A. They're paid to my consulting company, Tech Tox Consulting.
Q. Does your consulting company pay taxes?
A. It does, yes.
Q. And so you pay taxes because you received compensation for your services; is that correct?
A. Compensation for the time put in on the product, yes.
Q. And as you sit here today, you don't believe that is employment; is that correct?

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A. Again, I come back to the point that I'm being compensated for the time I put in to provide an expert opinion as a scientist.
Q. And you don't consider that employment; is that correct?
MR. DHINDSA: Objection. Asked and answered.
A. I don't believe to be -- myself to be employed by Hollingsworth or by Monsanto.
Q. So you believe --
A. I'm being compensated for my time.
Q. Do you believe Tech Tox Consulting to be employed by Monsanto or Hollingsworth?
A. No, I do not. I think we are being compensated for our time.
Q. Did you disclose whether Tech Tox Consulting -- did you disclose to IARC on your declaration of interest that Tech Tox Consulting was being paid by Monsanto in advance of Monograph 117?
A. I cannot state today what I did or did not put on my confidential -- my conflict of interest statement to IARC.
Q. Well, did you disclose to IARC that you were being compensated for your time by Monsanto?
MR. DHINDSA: Objection. Asked and answered.
A. Again, I don't recall what I did or did not

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put on.
I would point out, however, that in our review, we -- including my writeup for IARC, that we concluded that Dieldrin, Aldrin, and pentachlorophenol, the compounds that I was charged with looking at, were all rated as carcinogenic.
Q. And as you have pointed out for the record, they're all banned and not sold in the United States. Isn't that true?
MR. DHINDSA: Objection. Misstates testimony.
A. I -- my knowledge is, is that they're no longer produced.
Q. So it follows logic that because they've been banned for several years, they would be a carcinogen. Isn't that correct?
MR. DHINDSA: Objection.
A. Not necessarily, no. They may have been banned for other reasons.
Q. But in this instance, they were banned because they were carcinogenic; isn't that correct?
MR. DHINDSA: Objection.
A. I don't know that to be the case.
Q. So you agree that if you did not disclose Tech Tox Consulting being paid for its time or you

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individually being paid for your time from Monsanto or Hollingsworth, that IARC had no way to know that you were working for Monsanto at the time you sat on Monograph 117.

MR. DHINDSA: Objection.

Q. Isn't that right?

MR. DHINDSA: Objection.

A. Again, I think that mischaracterizes the point. I'm being compensated for the time that I put in. And, again, in all three compounds that I was charged to look at, we all came to the conclusion that they were carcinogenic.

Q. Okay. And the question was: You agree that if you did not disclose your consulting arrangement with Hollingsworth on behalf of Monsanto, IARC had no way of knowing in October of 2016, when you sat on Monograph 117, that you were, in fact, doing work for Monsanto.

MR. DHINDSA: Objection.

Q. Isn't that right?

MR. DHINDSA: Objection. Asked and answered. Repeatedly.

A. Prior to my signing this agreement on October 18th, my review for IARC and the information had already been written well in advance and submitted

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to IARC. The panel meeting took place in October.

Q. So you don't have any obligation in advance of a meeting to disclose any -- any new conflicts of interests, real or perceived, that appear in advance of you sitting on a monograph panel?

MR. DHINDSA: Objection.

Q. Is that your testimony?

A. Had I come to a conclusion that these compounds were not carcinogenic, I -- I may have thought to bring it up at that point. But because we arrived at the conclusion, I did not see it being relevant.

Q. But, Dr. Foster, you were engaged by Hollingsworth, LLP months in advance of October 2016. So it's only relevant if you would come to an adverse decision? Is that what your testimony is?

MR. DHINDSA: Objection.

A. No. Again, I am saying that when I was first consulted by IARC, I was not retained by Hollingsworth. My review of the chemicals Aldrin, Dieldrin, and and -- pentachlorophenol was conducted, submitted to IARC prior to that time.

Q. When did you submit your review to IARC prior to October 4th through 11th of 2016 for Monograph 117?

MR. DHINDSA: Objection.

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A. I can't say with certainty when it was submitted. There was back-and-forth.

Q. And had you concluded that these three chemicals that were subject of Monograph 117 were not carcinogens, then you would have disclosed your consultancy arrangement with Monsanto and Hollingsworth? Is that correct?

MR. DHINDSA: Objection.

A. Your -- your question is if I had -- if I felt in my mind they were not carcinogens, I would have disclosed?

Q. I thought that's what your testimony was, Dr. Foster.

A. Is that what you're asking me?

Q. I thought that was what your testimony was, Dr. Foster.

A. I believe if there was question in my mind and uncertainty, then I would have disclosed.

Q. So you knew there was a duty to disclose a conflict of interest to IARC in advance of sitting on Monograph 117. Isn't that correct?

MR. DHINDSA: Objection.

A. Again, in -- in participating with IARC, I believe I had conducted myself properly and had informed them, to the best of my knowledge, what my

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consulting agreements were and weren't at that time.

Q. Isn't it true that the IARC standard is to update your declaration of interest in advance of sitting on a monograph panel, Dr. Foster?

MR. DHINDSA: Objection.

A. I don't know what it is, to be honest.

Q. You didn't read the IARC preamble?

A. I have read the IARC preamble. I don't recall what it states on this issue right now.

Q. But, in any event, you did not update your declaration of interest and submit it to IARC after you signed this agreement with Hollingsworth and Monsanto on August 18, 2016; is that correct?

MR. DHINDSA: Objection. Asked and answered.

A. I stand by the question I've asked -- answered. Or the answer I --

Q. You can't stand by his objection, Dr. Foster.

A. No, I stand by the answer I have given.

Q. That you did not disclose the conflict of interest to IARC after you signed this agreement with Hollingsworth and Monsanto on August 18, 2016.

MR. DHINDSA: Same objection.

A. And as I've stated, I informed them, to the best of my ability, of what I thought was relevant.

Q. Okay. My question isn't what you thought was

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relevant. My question is what you did.
MR. DHINDSA: Same objection.
A. And I answered to the best of my ability.
Q. And you did not disclose your relationship with Hollingsworth and Monsanto after you entered into the agreement on August 18, 2016 to IARC. Isn't that correct?
MR. DHINDSA: Objection. Asked and answered.
A. As I stated, I provided all the information that I felt could represent a real or perceived conflict of interest. I did not see this as a real or perceived conflict of interest.
Q. Is that your determination to make, or is it IARC's?
A. They asked me to fill out the conflict of interest, and I filled it out to the best of my understanding and ability at the time.
Q. And that you did not resubmit the conflict of interest after you entered into this agreement with Monsanto and Hollingsworth. Is that correct?
MR. DHINDSA: Objection.
A. I did not resubmit another conflict of interest statement. I believed what I had already submitted was adequate.
Q. Did you tell any of your fellow working group

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participants that you were working for Monsanto relating to Roundup and glyphosate while you were at Monograph 117?
A. The issue never came up, to my knowledge.
Q. Do you think the IARC administrators had a right to know you were working for Monsanto in connection with Roundup and glyphosate?
MR. DHINDSA: Objection.
A. I didn't consider it to be relevant, in view of the position that I held on these chemicals.
Q. Do you consider it relevant today?
MR. DHINDSA: Objection.
A. No, I do not.
Q. Are you aware, Dr. Foster, that Monsanto is engaged in a campaign to defund IARC?
MR. DHINDSA: Objection.
A. I have no knowledge of that.
Q. Would you find it relevant to disclose your consulting arrangement had you known that?
MR. DHINDSA: Objection.
A. That's asking me to speculate. I have no idea, A, that it's happening, or, B, what the rationale, if any, there is.
Q. Okay, Dr. Foster, let's look at your billing records.

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MS. ROBERTSON: Counsel, I'll represent for the record that these were sent as three separate PDF's. We put them all in one exhibit, rather than doing single pages. This is Foster Exhibit 18-11.
(Foster Deposition Exhibit 18-11 - Billing records for Tech Tox Consulting - marked for identification.)
Q. Okay. So on August 2nd, 2016, you billed 1.5 hours for review of IARC document, General plus mice, Pages 1 through 35.
A. I see that, yes.
Q. All right. And that's your third entry in your relationship with Hollingsworth and Monsanto. Correct?
A. Correct.
Q. On August 16, you billed two hours for review of IARC document general, plus rat, Pages 35 to 92. Right?
A. Yes.
Q. And this review was conducted just months before the IARC meeting of Monograph 117. Right?
A. That's correct.
Q. Then if we go to the second page, on October 15, 2016, you've billed two hours for IARC

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guidelines for conducting a review. Do you see that?
A. Yes.
Q. And that was only four days after the end of the IARC meeting in Lyon, France, which you sat on for Monograph 117. Isn't that correct?
A. That's correct.
Q. So immediately upon return from Lyon, France in your service on IARC 117, you returned to work on behalf of Monsanto. Isn't that correct?
A. I returned to work and reviewed materials for Hollingsworth.
Q. And Hollingsworth and you entered into an agreement on behalf of Monsanto. Isn't that correct?
A. That's correct.
Q. Then if we look at the third page, the first entry, October 19, 2016, you again billed three hours for IARC guidelines for conducting your review.
A. Yes.
Q. And, again, that's just days after you served on an IARC monograph; isn't that correct?
A. That would be correct.
Q. Did you use info you gained at Meeting 117 in your review for the IARC guidelines?
A. Sorry; what was the question? I missed the first part.

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Q. I'm sorry. Did you use any of the knowledge you gained from serving on Monograph 117 for reviewing the IARC guidelines in connection with your work for Hollingsworth on behalf of Monsanto?
MR. DHINDSA: Objection.
A. I don't know how to answer that.
Q. Did Monograph 117 include review of guidelines for conducting an IARC review?
A. Did -- did the 117 panel meeting involve looking at the --
Q. Apologies. I'll rephrase.
When you worked on the IARC Monograph 117, did you review IARC guidelines for conducting review?
A. On the first day, I believe it was something that would have been presented.
Q. But you didn't do it before. Is that correct?
A. Before going to the meeting?
Q. Correct.
A. I may have read them before going to the meeting.
Q. Okay. And as part of these guidelines, doesn't IARC ask invited panelists to honestly disclose any conflict or perceived conflict of interest, so that IARC can decide whether its panelists should serve in

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the subgroups?
MR. DHINDSA: Objection.
A. I believe that's in the guidelines, yes.
Q. But you didn't give IARC the opportunity to make the decision, because you failed to disclose your work on behalf of Monsanto. Isn't that correct?
MR. DHINDSA: Objection.
A. Again, coming back to the issue of looking at Aldrin, Dieldrin, and pentachlorophenol, I did not see a conflict of interest.
(Discussion held off the record.)
Q. Hypothetically, had you known that Monsanto was engaged in a campaign to defund IARC before the Lyon meeting for Monograph 117, do you think you would have been obligated to inform IARC that you were retained by Hollingsworth on behalf of Monsanto related to Roundup and glyphosate litigation?
MR. DHINDSA: Objection.
A. Hypothetically speaking, if I knew that Hollingsworth -- or, sorry, that Monsanto was involved in a campaign to defund --
Q. Correct.
A. -- would I then have disclosed a conflict of interest?
Q. Would you have felt you would have been

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obligated to inform IARC that you had been retained by Hollingsworth on behalf of Monsanto for Roundup and glyphosate litigation?
MR. DHINDSA: Objection.
A. I have no knowledge that Monsanto is involved in such activity. But hypothetically speaking, if I was involved in a meeting with IARC, and Company X is acting in a manner to defund or -- I would have to understand and know what the reasons were, to re-evaluate my position in either direction.
Q. And what if your research showed that the Company X sought to defund IARC for an adverse opinion, in their respect, to a chemical classified as a 2A?
MR. DHINDSA: Objection.
A. If the Company X is taking a position because they had an opinion that was contrary to what they wanted, what would I do? I think, again, that I would need a lot more information around the situation of why they've adopted that position.
Q. So Company X -- IARC reviewed a chemical that's manufactured by Company X. IARC determines the chemical manufactured by Company X is a carcinogen. You subsequently sit on an IARC panel unrelated to Company X, but in your unrelated work, you are retained as an expert for Company X. When Company X engages in

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a campaign to defund IARC, should you not tell IARC, even if your work with IARC is unrelated to Company X?
MR. DHINDSA: Objection.
A. I think I need a lot more information on that. The -- the situation -- you know, there -- there might by many reasons why. There -- there might be legitimate reasons why they might adopt that position that I -- that I have no knowledge of.
Q. So as you sit here today, just association between consulting work with -- as you sit here today, your interpretation of what you must disclose on a declaration of interest is subjective, in your view.
MR. DHINDSA: Objection.
A. No, I'm saying that there's -- it's a complex issue. And you're asking me to -- to adopt a hypothetical situation where I have very limited information, that I can't make a decision about.
I would need to know what the -- why Company X has adopted the position, what the issues are. Are they -- are they meritus, are they not meritus. I would need to know what the IARC process was and what their -- their conclusions and what they were -- why they came to their conclusion. And I would also have to take a look at what I was consulting the company for. It might be minimal. Trivial.

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Q. Okay. So you filled out the declaration of interest to the best of your ability and to the best of your knowledge, and you feel like you did that accurately, as you sit here today.

MR. DHINDSA: Objection.

A. Again, I believe that I did it accurately.

MS. ROBERTSON: Okay, thank you. Let's break for lunch.

MR. GOODALE: This marks the end of Media No. 2 in the deposition of Dr. Warren G. Foster, Ph.D. Going off the record at 12:35 p.m.

(Recess held.)

MR. GOODALE: Here begins Media No. 3 in the deposition of Dr. Warren G. Foster, Ph.D. We're back on the record at 1:26 p.m.

BY MS. ROBERTSON:

Q. Okay. Dr. Foster, earlier you testified that you've done several animal studies; conducted, directed, overseeing, et cetera. Correct?

A. Yes.

Q. And is it true that all of those studies relate to reproductive health issues?

A. As I stated previously, no. Some of those studies were also involving cancer.

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Q. Have you done any studies that relate to pesticides in association with cancer?

A. Yes.

Q. And can you please look at your CV for us and identify which of those studies relate to animal studies.

A. No. 43 is one.

Q. And what page are you looking on in your CV?

A. That is Page 75.

Q. And what -- does this deal with a pesticide?

A. No. Sorry. Let me just check. That one did not, no.

Q. And with your research here on the mammary gland differentiation, was that related to a reproductive health issue?

A. I'm sorry; where are you?

Q. I'm still on 43.

A. That was on mammary gland differentiation, yes.

Q. And does that relate to reproductive health issues?

A. It relates to cancer. It's -- mammary gland is hormonally dependent, but it's not part of the reproductive tract.

Q. Okay. So women's health issues?

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A. Yeah.

Q. Okay.

A. 64, 65.

Q. Do either 64 or 65 deal with a pesticide or a chemical?

A. 64 is dealing with dieldrin, which is a pesticide. 65 is dealing with a dietary supplement.

Q. And so with 64 and 65, the research is related to transgenic mice?

A. It's involving transgenic mice, yes.

Q. And are transgenic mice used in the data set that you reviewed for glyphosate?

A. Transgenic mice were not used in the data set that I'm looking at.

Q. And were the transgenic mice used in your Study 64 and 65 because you were looking for a specific observed effect that could be induced by the transgenic mice?

A. Sorry; I don't understand the question.

Q. Why did you choose transgenic mice for these two studies?

A. Because we were looking at mechanism.

Q. And these transgenic mice were known to be good study subjects for the mechanism. Correct?

A. Correct.

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78.

Q. And that's the Dieldrin again?

A. Yes.

Q. And what was the purpose behind this study?

A. We were looking again at mechanism.

Q. And for the -- how mechanism -- or how breast cancer may be caused by Dieldrin, correct?

A. We were looking, at this case, of how Dieldrin is involved in a process that may be important in cancer.

Q. In breast cancer.

A. And in this case, it applies to breast cancer, but the process is not limited to breast cancer. It's in -- it's in development, it's in many different kinds of cancers.

Q. Was this study on 78 limited to breast cancer?

A. The focus was breast cancer.

99.

Q. Did 99 look at a pesticide?

A. 99 was a study that looked at a number of different chemicals, if I remember correctly. Pesticides, if I remember correctly, were included.

Q. Herbicides?

A. I couldn't tell you for sure if they were or

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were not included at that time.
Nos. 121 and 122 involve complex mixtures of which there were pesticides, and there were tumors that were looked at in those as well.
Q. And the purpose was to not look at cancer, though. It was to look at systemic, immune, and reproductive effects. Correct?
A. Correct.
138 is a tissue culture assay with my colleague, Diane Desaulniers, from Health Canada, where we were looking at a breast cancer cell line, and we were looking at pesticides and other chemicals there as well.
So on a quick review of the literature, those are the ones that jump out at me.
Q. So it's fair to say, Dr. Foster, that the majority, if not most of your studies related to animals deal with reproductive health and not the chemical and potential association with cancer. Is that correct?
A. I think it's fair to say that my work has focused on chemical exposure and its impact upon animal reproductive health.
Q. But the majority of your articles aren't looking at chemical exposure. Or studies, rather.

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Isn't that correct?
A. Sorry. Say that again. The majority --
Q. Of these articles are not looking at the chemical effect and the potential to cause cancer. Is that correct?
A. The majority of these studies are looking at -- are conducted in animal studies using environmental contaminants to look at effects on target organs, mostly of which are in the reproductive tract.
Q. Okay. Dr. Foster, if we could look at Page 59 of your CV. And you offer Areas of Research Interest.
A. Yes.
Q. Okay. And is this still -- are these three categories -- No. 1, reproductive epidemiology in biomonitoring; No. 2, reproductive and development toxicity and carcinogenicity of environmental and dietary chemicals; and, No. 3, the cellular and molecular mechanisms of endometriosis -- still your top three research interests, as you sit here today?
A. Yes.
Q. Dr. Foster, if we could go to Page 22 of your expert report, which focus on the Atkinson study, please.
A. (Witness complies.) Page 22, you said?

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Q. Yes, please.
A. I'm there.
Q. Okay. And for the Atkinson study, do you recall whether you reviewed the raw study data in assess -- in evaluating the study for your expert opinion?
A. I don't -- I can't say one way or another. I believe what I was using in this case were the Greim tables.
Q. Okay. And so in this instance, again, you offer the low, mid, and high dose groups using milligrams per kilogram per day. Correct?
A. Those were the dose levels used, yes. In milligrams per kilogram.
Q. Right. And you do agree that there was a significant trend in hemangiosarcomas seen in high dose group males. Correct?
A. I note that there was a significant trend for hemangiosarcomas in the high dose group males.
Q. And yet you discount that trend. Correct?
A. When you say I "discount", what do you mean?
Q. You found a -- you determined that the trend was not significant, based on other literature review. Correct?
A. "Significant" refers to a statistical

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determination. Do you mean important?
Q. The significant trend seen that's noted in your expert report, does that factor into your conclusion that the tumors are not treatment-related?
A. What I see is there was a statistically significant trend for hemangiosarcomas. That's not the end of the interpretation of the study, but, rather, the beginning. So I looked at that.
Q. Okay. But for your analysis on the Atkinson study, it does begin with a discussion of hemangiosarcomas only. Correct?
A. I don't know what you mean by "only".
Q. You start with -- you're right. You start with hemangiosarcomas in looking at the Atkinson data, correct?
A. I start by describing the study, and then I -- one of the tumors here that I discuss is hemangiosarcomas, where I note that a significant trend was found.
Q. Okay. And do you recall, as you sit here today, what the numbers are that support that significant trend? You note that there are four of 45 -- that four hemangiosarcomas in 45 are found in the high dose group males only. Do you have the numbers for the control, low, or mid dose groups?

A. Sorry, I do not have the numbers before me.
Q. Okay. Well, let's take a -- a compare here and look at Dr. Portier's report on Page 39, Table 10. Do you see Dr. Portier's table, Dr. Foster?
A. I see his table, yes.
Q. Do you have any reason to dispute the accuracy of the numbers in Table 10 of Dr. Portier's report?
A. I have no reason to either agree, nor disagree with them.
Q. Your expert report is consistent to show four of 45 lesions in the high dose group.
A. Sorry, I see four of 50. On Page 10?
Q. Yes.
A. Or, sorry, Page 39, Table 10.
Q. Yes.
A. Hemangiosarcomas in the high dose group?
Q. Yes.
A. Males only.
Q. Yes.
A. He's got it reported as four of 50, not 45.
Q. And where does your number 45 come from?
A. I thought that's what you just finished saying.
Q. It's on Page 22 of your expert report. You

observe a significant trend of hemangiosarcomas with four of 45 lesions found in the high dose group of males.
A. Okay. If that's there, I most likely obtained that from the Greim summary table.
Q. But you do acknowledge that at the beginning of the -- your analysis here in Atkinson, when you describe the study, there were 50 animals in each dose group. Correct?
A. I -- as I reported, yes.
Q. Okay. So why have you used only 45 as the denominator for the high dose group?
A. I would have to see the Greim table in order to be able to -- to answer that question properly.
Q. Is it fair to say that you think you got the information from the Greim table?
A. As I've just finished stating previously, I believe I relied upon the Greim table for that information.
Q. Okay. Do you know whether there were any hemangiosarcomas found in the male control group for the Atkinson study?
A. Hemangiosarcomas in the control group. I see zero.
Q. Do you have any reason to dispute the number

reported by Dr. Portier on Page 39?
A. I see no reason to agree, nor disagree with it.
Q. Dr. Foster, your report is unclear as to whether there were any hemangiosarcomas reported in the male control group. So in explaining your analysis, isn't it important to report on the hemangiosarcomas in the control group?
A. I'm not sure what it is you're asking there.
Q. Isn't it true that the hemangiosarcomas seen in the Atkinson study in the male mice should be controlled -- compared against the concurrent controls; thus it should be included in your report?
A. By citing the paper, I'm citing what they found. I didn't -- did I write out zero of 50, zero of 50, zero of 50, four of 50 -- four of 50 or four of 45? No, I did not write that out.
Q. When you conducted your analysis, did you consider the control group?
A. Yes.
Q. And you explain on Page 23 that the tumors were not detected in a statistically significant trend in male mice and other appropriately conducted bioassays.
So what I'm trying to understand here is what

your statistically significant trend is and whether you've used the concurrent controls to calculate a significant trend to compare against other studies.
A. So you're reading the top sentence on Page 23?
Q. I'm actually trying to figure out as a whole, Dr. Foster, how -- what your conclusion was, related to the significant trend you noted in the Atkinson study.
A. Sorry. I don't understand your question.
Q. Are the hemangiosarcomas seen in the male mice in the Atkinson study dose-related?
A. I am saying that according to the analysis conducted, whether it was -- the four of 45 or four of 50, there was a statistically significant trend.
Q. And is that the result of a dose relationship?
A. It's the result of the high -- the number in the high dose group only. But is that a dose-related trend?
Q. Correct.
A. Yeah, I guess you could call that a dose-related trend. It's a -- a significant effect at a high dose.
Is it a trend to -- a significant trend, dose-related trend, zero, zero, zero, four, I don't see

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it as a trend, because you're not getting an increasing line, but you're getting dose-significant effect.
Q. Okay. So you call it a dose-significant effect, but because we can't apply a linear model, it -- it isn't a positive linear trend? Is that what you're saying?
A. I stand by my report, where I say there was a significant trend in hemangiosarcomas.
Q. But you also --
A. That was only found in the high dose group.
Q. But you ultimately find that this is a negative study. So I'm trying to under --
A. Ultimately, yes.
Q. I'm trying to understand how you dismiss or how you go about dismissing the significant trend you noted in the hemangiosarcomas in the male mice.
A. I don't dismiss. I look at the entire study, and I evaluate the overall study. And in this particular case, you've got tumors that are -- hemangiosarcomas in mice.
Now, I know that these are rare in humans. They're also relatively rare in rats. But in mice these are not an uncommon tumor.
Q. And you cite to the Elwell 2004 article for that?

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A. I do.
Q. And when did you review the Elwell 2004 article?
A. During the conduct of my background reading for this report.
Q. And did you -- have you reviewed the -- have you reviewed the Elwell 2004 article recently in preparation for your deposition?
A. I have not reviewed any -- I have not reviewed most of the papers that are on my Materials Cited list recently.
Q. Do you have a copy of the Elwell article?
A. I'm sure I have a copy somewhere in my records, yes.
Q. Did your lawyers ask you to provide a copy of that article?
A. Yes, they did.
Q. And did you provide a copy of that article?
A. When I got asked for the article, I had already left the office and was on my way here.
Now, I have prepared my expert report, reviewed the literature in my home office here, in my university office, as well as my -- my residence in Florida, as well, as well as going into libraries and so forth. I know I have accessed the paper. I don't

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know where that paper is at present. And given the short time frame that I had, I did not have the opportunity to scour all my -- my file -- files to provide that.
Q. And so you don't have a copy of the article electronically.
A. I did not have access to one electronically.
Q. Did you make a copy of the article for your own personal use?
A. I cannot recall whether I made a copy or just made notes.
Q. So you actually don't know if you have the article. Is that what you're saying?
A. What I'm saying is this is a publicly available article that has been published. I don't -- I can't say with a hundred percent certainty that I have a copy of the article. I may have read the article and simply made notes from it.
Q. Okay. So, previously, you misspoke when you said you had a copy, but you had left the office on your way here, and so you couldn't give it to your lawyers. You actually don't know if you have a copy; is that right?
MR. DHINDSA: Objection. Mischaracterizes.
A. With a hundred percent certainty, without

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going through my files and sitting down, I can't say, a hundred percent certainty, I do or don't. I know I have read the paper.
(Discussion held off the record.)
Q. Okay. So, yeah, you did, Dr. Foster, identify that this paper is publicly available. So did you access it through PubMed?
A. It's listed in PubMed.
Q. Um-hum.
A. But did -- what do you mean by "did I access it in PubMed"?
Q. Did you obtain it from having a subscription to PubMed and being able to pull the article electronically after you ran your search on the computer?
A. No, I did not.
Q. So you had to go and find the article. Is that correct?
A. That's correct.
Q. Okay. So it's publicly available in published form; hard copy only. Is that correct?
A. I don't know if that's true or not. I know that I didn't get it off the net.
Q. Okay. So in your instance, your PubMed search led you to the article, and you then sought to

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find the hard copy, because you couldn't find it online. Is that right?
A. I believe that's correct.
Q. And do you remember where you found the hard copy of this article?
A. The hard copy? The textbook is available at the University of Guelph in the main library.
Q. Okay. So is it a textbook or is it an article?
A. It's a book chapter, I believe.
Q. Do you remember how long the article was?
A. Not off the top of my head, no. I don't remember how long any of the articles were.
Q. Do you --
(Discussion held off the record.)
Q. Do you recall the mice that were the subject of the Elwell article?
A. Not right off the top of my head, but I think they were the CD-1, but I'm not sure.
Q. Well, it would be pretty important that they're CD-1, wouldn't it be, Dr. Foster?
A. Probably, yeah.
Q. The Atkinson study was done with CD-1 mice, correct?
A. Yes, I believe that is correct

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Q. And it's true that common neoplasms in mice different -- or differ based on strain. Isn't that correct?
A. They can, yes.
Q. So Elwell, in order to be an appropriate cite here, needs to be discussing CD-1 mice. Isn't that correct?
A. The Elwell paper would. However, it's not the only paper that I -- I have on my Materials Cited list that goes to this point.
Q. That goes to the hemangiosarcomas -- or sarcomas are common neoplasms in mice?
A. In mice, yes.
Q. Okay. If you can direct me to additional support. See if those are CD-1 mice.
A. I believe it's the Cohen reference. No. 29.
Q. And you believe that the Cohen reference includes CD-1 mice?
A. I believe it does, yes.
Q. The title says "Hemangiosarcoma in Rodents".
A. Correct.
Q. For your discussion on the hemangiosarcomas, you note that the hemangiosarcoma of four and 45 at an incidence of 8.9 percent in the high dose group males falls within the historical ranges reported by Giknis

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and Clifford 2000. Correct?
A. I note that, yes.
Q. Why did you choose to apply historical control data when you had current controls you could have discussed?
A. Because when I'm looking at the concurrent controls, I see zero out of 50, and I have data here that says that hemangiosarcomas in the CD-1 mice are not uncommon. They're not rare. And so I'm asking the question, is not finding them at all in the -- in the low dose -- or the control group, I'm asking whether or not the study is a reliable study.
Q. But isn't it true, Dr. Foster, that the concurrent control group is the first choice when comparing studies?
A. I agree. It's one that I would weigh -- or look at in my assessment.
Q. But you don't assess the concurrent controls in this study.
A. I didn't say that. I look at concurrent controls, I look at historical controls.
Again, it's not where you'd look at just one thing. You look at it in balance.
Q. Okay. You don't evaluate the hemangiosarcomas in the male mice against the

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concurrent controls in the Atkinson study, at least within the Pages 22 and 23 of your expert report. Isn't that correct?
A. I don't know what you mean by I didn't -- I don't evaluate or I don't consider it.
Q. Dr. Foster, do you discuss the concurrent controls related to hemangiosarcomas in Pages 22 and 23 in your expert report related to Atkinson?
A. I don't explicitly state that the concurrent controls were zero of 50. That doesn't mean I didn't consider it in coming to my conclusions.
Q. But your conclusion is that the hemangiosarcomas reported in the Atkinson study fall within the historical ranges reported by Giknis and Clifford 2000.
A. I do state that, yes.
Q. And because the incidence is well within the range of historical controls, this makes these hemangiosarcomas not treatment-related.
A. I suggest that is one reason why it calls that into question.
Q. Now, you have a footnote, Footnote 3 on Page 23, that cites to Dr. Portier's expert report for the premise that he's confused of the historical control data related to whole body hemangiosarcomas,

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capturing all hemangiosarcomas.
A. I see that, yes.
Q. And is that still your opinion today?
A. Yes.
Q. All right. Now, Dr. Foster, did you look at the Giknis and Clifford data to make the determination related to your criticism of Dr. Portier and the whole body hemangiosarcomas, or did you just take the range point?
A. Sorry. Did I refer to the Giknis --
Q. Did you look at it? Did you look at it to see that Dr. Portier, as you state, is confused related to the reporting of the hemangiosarcomas as whole body?
A. I looked at the report, yes.
MS. ROBERTSON: This will be Foster Exhibit 18-12.
(Foster Deposition Exhibit 18-12 - Giknis and Clifford 2000 Report - marked for identification.)
Q. So if we look at Page 9, Table 3 of the Giknis and Clifford control data set --
MR. KALAS: Counsel, can I note that the copy you gave us appears to be missing the even-numbered pages.
MS. ROBERTSON: It's not double-sided?

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MR. KALAS: It is double-sided, but it's missing the even-numbered pages.
Q. Dr. Foster, do you have all the pages?
A. No, I do not.
MS. ROBERTSON: This was an exhibit that was entered into by the deposition of Dr. Portier by the Hollingsworth firm, and this is the complete exhibit entered into in that deposition.
MR. KALAS: I understand you're making that representation. I don't have those exhibits in front of me. But this does not appear to be the complete Giknis and Clifford data set.
So we object to questions based on this document based on that.
BY MS. ROBERTSON:
Q. Dr. Foster, can you answer questions related to the data listed on Table 3?
A. I don't know how to answer that question, because I -- if there's questions that are from Table 3 that might contain information from other pages, I'm not going to be able to answer them.
Q. Would you agree that Table 3 on Page -- beginning on Page 9 lists neoplasms in males and appears to be the beginning of the table?

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A. The title is Neoplasm in Male [sic]. And what was your other point?
Q. And that it appears to be the beginning of Table 3; hence Table, comma -- colon -- 3.
A. I can't tell if it is the beginning or not.
Q. The beginning of the table identifies columns by location and tumor, number of studies total, number of studies. Do you see that, Dr. Foster?
A. I do.
Q. And you can see that location and tumor included in that column is liver?
A. I see it.
Q. And hemangiosarcoma is listed within the liver category, correct?
A. I see it.
Q. And in the columns, reading across the line, we see that there's data entry observed from 29 lesions in 15 studies. Correct?
A. Yes.
Q. For an overall incident range of 1.11 through 5 percent. Correct?
A. Yes.
Q. And your expert report on Page 22 reports an incident range for hemangiosarcomas of 12 percent. Correct?

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MR. DHINDSA: Objection.
A. Yes. I see that in the citation to Giknis 2000 --
Q. Yes.
A. -- that reports hemangioma -- hemangiosarcoma incident rate reported in historical controls up to 12 percent. That would be whole body hemangiosarcomas, I believe.
Q. Okay. So do you know whether the Atkinson study looked at the whole body hemangiosarcomas in reporting on hemangiosarcomas?
A. My recollection is that was whole body hemangiosarcomas.
Q. Isn't it true, Dr. Foster, that the Atkinson study in CD-1 mice identifies hemangiosarcomas under the identifying name, quote/unquote, Vascular System?
A. Yes.
Q. And is --
A. I believe that's accurate.
Q. Isn't it true that the liver is within the vascular system and not whole body?
A. Sorry. That you're -- you're asking me if the liver is part of the vascular system?
Q. Correct.
A. I would not normally consider it part of the

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vascular system.
Q. Would you agree that hemangiosarcomas are vascular tumors?
A. I believe that hemangiosarcomas are vascular tumors that occur throughout the body.
Q. So the data you cited to in Giknis and Hogan [sic] is looking at the body, multiple organ. Is that correct? The 12 percent range.
A. I believe that's accurate.
Q. Are you aware, Dr. Foster, that EPA cites to the hemangiosarcoma range, as Dr. Portier does in his expert report, with 1.1 to 11 percent? Citing also to the Giknis and Clifford paper.
A. I don't recall that.
Q. Do you know what rates EFSA used in their recent reevaluation of the animal carcinogenicity data for the range of hemangiosarcomas from Giknis and Clifford 2000?
A. No, I don't.
Q. You do agree, Dr. Foster, that the tumor trend in CD-1 mice is different in other strains of mice for that same tumor, correct?
MR. DHINDSA: Objection.
A. Can be, yes.
Q. So it's entirely practical that the dose

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response among rodent strains will differ, correct?
MR. DHINDSA: Objection.
A. You're asking me to speculate on whether or not it might -- a dose response may differ by different strains? I would need to see more information on it, but I think it's possible.
Q. Okay. And on Page 23, Dr. Foster, you -- you note that you didn't see any hemangiosarcomas and other bioassays. Is that correct? Apologies. Let me correct. That's not right.
You note that hemangiosarcomas did not show statistically significant trends in male mice and other cancer bioassays, correct?
A. Yes, I note that. In other well-conducted cancer bioassays in mice -- in male mice, there was no statistically significant trend noted.
Q. So if we look at Page 42 of Dr. Portier's expert report, Table 12 in the Sugimoto study.
A. What page?
Q. 42. Are you there, Dr. Foster?
A. I'm on Page 42.
Q. And you see in Table 12 that hemangiosarcomas in male mice, there were two hemangiosarcomas noted in the Sugimoto study in the high dose group. Correct?
A. Hemangiosarcomas in male was zero of 50, zero

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of 50, zero of 50, 2 of 50, for a P trend of 0.062.
Q. And that would be a significant statistically trend, correct?
A. No, that would not be a statistically significant trend. That is greater than .05.
Q. Is it important to look at the fact that the hemangiosarcomas are seen in the high dose group and no other groups related to the Sugimoto study in the male high dose group?
A. Sorry. Say that again.
Q. Is it important to look at the fact that the hemangiosarcomas are in the high dose group and no other groups in the Sugimoto study?
MR. DHINDSA: Objection.
A. In the high dose group -- first off, there's no statistically significant difference here. However, for completeness, we see two of 50 in the high dose group, in the Sugimoto study.
And then if you look at the Sugimoto study, we note that this is a study that in the high dose group, where they're being dosed in males with 4,348 mg's per kilogram per day, that these animals were noted to have liquid stool. Liquid stool in an animal is also considered to be sign of a potential systemic toxic effect.

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So although I see something going on, two of 50, that's not statistically significant. I would again begin to question this study.
Q. Did this study report any body weight loss in the high dose groups?
A. I don't recall whether it reported body weight loss. Let me look at my report, please.
So they reported it as retarded growth and reduced food consumption.
Q. Who reported?
A. In this case, it was in the Greim text.
Q. So the Greim review article report of this finding.
A. In the Greim review article, again, I reviewed -- I relied primarily on the data that was provided. However, I note that there was also some text that was provided in terms of how the study was conducted and what was seen. And that was useful.
Q. Okay. Now, in the paragraph above in the Sugimoto study, we have a discussion here on malignant lymphomas. Correct?
A. Sorry; I don't know where you're referring.
Q. The first paragraph of Sugimoto.
A. First paragraph? Okay. Yes.
Q. And, here, you provide the control, low, mid,

and high dose numbers reported as two of 50, two of 50, zero of 50, six of 50. Correct?
A. That's what's written here, yes.
Q. Okay. And if you look on Dr. Portier's expert report, Table 12, Page 42, that gives us a statistically significant trend. Correct?
A. Yes, that gives a statistically significant trend.
Q. However, your conclusion for this study is that it's strongly negative. How do you reach that conclusion?
A. In the -- sorry. In the Sugimoto?
Q. Correct.
A. In looking at this, again, I come back to the point that these animals in the high dose group were noted to have liquid stool, retarded growth, reduced food consumption, calling into question the effects in the high dose group.
If we look at that, that would then go two, two, zero, suggesting that somehow or another glyphosate is potentially protective.
Q. How would glyphosate be potentially protective when you have an incidence of six out of 50 in the Sugimoto study in the high dose group?
A. As I just indicated, when you've got retarded

growth, reduced food consumption, liquid stool in the high dose group, that calls into question the relevance of findings in that dose group.
Q. So do you not include the high dose group -- oh. So the high dose group, then, is not included in your analysis of whether this is a statistically significant trend for malignant lymphomas. Correct?
A. No. What I am saying is that in this study, where we see evidence of potential systemic toxic effects as shown by liquid stool, retarded growth, decreased food consumption, that's -- the interpretation of the -- of findings in the high dose group is difficult, if not impossible, to relate to a compound-related effect.
Q. Did EPA accept the Sugimoto study as -- as acceptable study?
A. They -- I didn't say it was an unacceptable study, and I don't know what EPA -- EPA did or didn't do. I'm conducting my own assessment of the literature.
Q. Dr. Foster, isn't it important to ward against false negatives? And by excluding the high dose group, based on your analysis, you are, in fact, encouraging false negatives?
A. I don't agree with that. I think it's

important when you're interpreting the study results that you evaluate all the information that you have before you.
Q. And in this --
A. I'm trying to determine whether or not we have a compound-related effect. And when I see evidence that there is systemic toxicity, that makes it very difficult for me, if not impossible, to conclude that that's a compound-related effect.
Q. Do you know whether there was a survival difference between the controls in the high dose group in the study?
A. Sitting here at this moment, without having the information before me, I can't say one way or another whether there was a difference in survival.
Q. Do you have any reason to think that the other observed effects led to a higher tumor rate?
A. The other observed effects. What are you referring to?
Q. Do you have any reason to believe that the liquid stool, retarded growth, and reduced food consumption led to the tumors seen in the highest dose group?
A. It's possible that the same mechanisms that are leading to these metabolic effects. Or liquid

stool, retarded growth, reduced food consumption could be the consequence of something in these animals or in that the -- the feed or in the dosing material that is creating systemic toxicity, irritation of the gut lining, or something like that, that could, indeed, contribute to the -- the tumors.
Q. And you saw those potential contributions to tumors in -- in the Sugimoto study when you did your literature review?
MR. DHINDSA: Objection.
A. I -- I stand by what I've said, in that when I see evidence of systemic toxicity, it makes it very difficult to evaluate the quality or the compound-related effect of -- of the test chemical. This -- and this is not my decision. This is something that is routinely done in evaluating toxicological data.
Q. So when I have a high dose group that shows tumors, I don't consider the cause of those tumors. I first consider the quantity of the dose given to see whether the tumor should even be evaluated?
A. What I'm saying is that -- let's forget the outcome measure, whether it's tumors, whether it's decreased follicle loss, whether it's behavioral effects. You have animals in which you're getting

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systemic toxicity. That now makes it very difficult to determine whether the outcome you're looking at, regardless of what it is, is being driven by the test substance you're looking at.

Q. And this is an analysis that you engage in to ensure that you don't have a false negative.

MR. DHINDSA: Objection.

A. It's an analysis that I engage in, in order to determine whether or not the outcome that I am looking at is compound-related.

Q. As you sit here today, do you know whether the liquid stool, retarded growth, and reduced food consumption are compound-related effects?

A. In the conduct of this study, I see an -- I see report that the animals experienced retarded growth, reduced food consumption, and liquid stool.

Q. And is is that a compound --

A. Suggesting that that's systemic toxicity.

Q. And is that a compound-related effect?

A. At this point I don't know what's driving it.

Q. But you conclude that the animals with malignant lymphomas seen in the high dose group, because there may be a systemic toxicity, this high dose group is not a compound-related effect. Am I understanding correctly?

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MR. DHINDSA: Objection.

A. I'm saying because these effects were seen in the high dose group, I cannot state with certainty that these are compound-related effects. The tumors, that is.

Q. Do you have any indication from this study or the literature you reviewed that there's evidence that anything other than glyphosate caused these malignant lymphomas in the CD-1 mice in Sugimoto?

A. Again, I stand by my report and what I've already testified; that at the high dose group, we've got liquid stool, retarded growth, and reduced food consumption.

Q. And --

A. The consequence of that is I cannot conclude that there's a compound-related effect there.

Q. Do you know when these observations were made?

A. What do you mean, when they were made?

Q. In the study. At what point in time in this 18-month study were these observations made?

A. At this point in time, I believe they were reported towards the end of the study.

Q. Is it not possible that cancer started to develop before these events were seen?

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A. It's also possible that these events started before, too. I don't know.

Q. So you don't know whether the malignant lymphomas existed prior to your confounders you've identified here. Is that -- is that correct?

A. No. What I'm saying is that with the high dose group, because I've got evidence of systemic toxicity, that might have gone on for long periods of time as well. I cannot conclude that the malignant lymphomas here are a consequence of the compound.

Q. And the inverse is also true.

MR. DHINDSA: Objection.

A. I'm looking at the data here and looking at what I've seen. Because I have systemic toxicity, I can't say that what it has -- what didn't appear, I can't comment on, because I don't know what all didn't appear.

Q. But we do know that malignant lymphomas appeared.

A. We do know that there was -- six out of 50 animals had malignant lymphomas.

Q. And how does cancer --

A. When they --

Q. -- develop?

A. Cancer is a -- a multi-step process that

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involves initiation and promotion --

Q. So cancer doesn't develop, does it, Doctor --

MR. DHINDSA: Were you finished with your answer?

THE WITNESS: Sorry?

MR. DHINDSA: Were you finished with that answer?

THE WITNESS: No, I was going to go on, but --

A. It's -- it's a multi-step process involving initiation, mutation in the -- in the -- in the DNA, and promotion, proliferation. There's also repair mechanisms that might take place to prevent tumors from -- from developing. Tumors may be present spontaneously in the animal and only show up later when a promotional event happens.

Q. As you sit here today, do you believe glyphosate's a promoter?

A. No, I do not believe it's a promoter.

Q. So in this instance, the malignant lymphomas would need to develop over time, not upon some spontaneous event such as glyphosate-administered dose. Correct?

A. For tumors to have appeared, you're suggesting that glyphosate would -- has to induced

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[sic] a mutation earlier in the lifetime of the animals that would result in tumors being seen at some point.
Q. But we don't know that here, correct?
A. We do not know that here.
Q. And that's because these animal cancer bioassays look at the animal one time, and that is at death. Isn't that correct?
MR. DHINDSA: Objection.
A. I don't believe that's true. In the conduct of our animal studies, we're looking at the animals on a daily basis. So the animal health technicians are in examining the animals and looking for any signs, any outward signs of issues.
So you might be looking for stereotypical behaviors; circling, abnormal grooming, porphyria. Multiple of things. You would monitor the animals over the course of the study.
Q. And when over the course of a study, aside from at death, do we look at animals to see if they have developed malignant lymphomas?
A. If -- if an animal dies during the course of the study, it would be examined at that time --
Q. At his death. Yes, I agree.
A. And if you saw something in animals where they might be losing body weight or whatever, you might

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sacrifice -- do interim sacrifices to see if something's going on there.
Q. But, otherwise, it's only at death that terminal sacrifice --
A. Otherwise, it's at terminal sacrifice, yes.
Q. And these malignant lymphomas were observed at terminal sacrifice, correct?
A. That's my understanding, yes.
Q. So the malignancies found were only looked at one time. Correct?
A. That's my understanding in this case, yes.
Q. Is there any other method for assessing carcinogenicity besides initiation and promotion?
A. Can you help me out with that question? I don't know what you're asking. It's -- it's too broad.
Q. Initiation promotion is not the only methodology to use -- that can be used to assess carcinogenicity.
MR. DHINDSA: Objection.
A. They're not methods.
Q. Approaches?
A. Nor are they approaches.
Q. Is there -- can I have an agent that causes cancer without it being an initiator or a promoter?
A. If an agent -- if a chemical does not act as

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a -- as a -- as an initiator or a promoter, then I do not see how you're going to get a tumor.
Q. Because for initiation and promotion, the DNA needs to be reactive to the chemical agent that's causing the cancer. Correct?
A. I might state that differently; that the chemical needs to be reactive. It needs to induce a mutation. It needs to be genotoxic, induce a mutation, or it needs to act as a -- as a promoter.
Q. Right.
A. The DNA is not going to go find the chemical and interact with it.
Q. Yeah. So meaning the carcinogen or their metabolites react directly with the DNA.
A. Correct.
Q. As you sit here today, is it your opinion that there are no other carcinogens -- there are no carcinogens that are not also genotoxic?
MR. DHINDSA: Objection. Beyond the scope.
Q. Did I understand that right?
A. Can you state it again?
Q. Yeah. I'm just trying to make sure that I clearly understand your earlier answer. Is it true that there -- a carcinogen must be genotoxic?
MR. DHINDSA: Objection. Beyond the scope.

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Q. My -- so I was asked to provide an assessment of the animal literature, which I've done. My -- although I've looked at cancer carcinogenesis and I've looked at different mechanisms in cancer development, my understanding is that a chemical must be an initiator or must act through tumor promotion in order to produce carcinogenicity.
Q. I understand that. And I understand you're not a pathologist. Correct?
A. No, I am not.
Q. Do you have knowledge on epigenetics effects on tumor suppressor genes?
MR. DHINDSA: Objection.
(Attorney Robertson asked for clarification by the reporter.)
Q. Any knowledge on epigenetic effects on tumor suppressor genes.
A. Okay. So epigenetic modification of the DNA is something that's becoming increasingly important in transgenerational effects. It's something that I have studied in our work, although I'm not a -- a molecular biologist or -- and certainly not focused entirely on epigenetics.
Q. But we can agree that epigenetic effects on tumor suppressor genes is different than initiation,

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promotion in the realm of carcinogenesis. Correct?
MR. DHINDSA: Objection.
A. It would act in the ballpark of promotion.
Q. But it's not promotion. Is that correct?
MR. DHINDSA: Objection.
A. It could be seen as being in that ballpark.
Q. But it's not always.
A. I don't think that's -- I don't think that's been resolved in the literature.
MR. DHINDSA: May I just make a statement for the record?
Looking at what's been marked as Deposition Exhibit 18-12 -- this is the CD-1 mouse data from Giknis and Clifford -- I'm just objecting to any questions on this document because the even-numbered pages are missing, and moving to strike any such questions and answers. This was Deposition Exhibit 15-33 in the Portier deposition, where the exhibit was a complete exhibit, with all pages contained therein.
MS. ROBERTSON: Counsel, are you objecting to the content's accuracies on Table 3?
MR. DHINDSA: It's just not -- it's not complete. He's not able -- he's not able to

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properly answer the question you asked without a complete document. That specifically omits whole body data.
(Discussion held off the record.)
MR. GOODALE: This marks the end of Media 3 in the deposition of Dr. Warren G. Foster, Ph.D. Going off the record at 2:32 p.m.
(Recess held.)
MR. GOODALE: Here begins Media No. 4 in the deposition of Dr. Warren G. Foster, Ph.D. We're back on the record at 3:03 p.m.
BY MS. ROBERTSON:
Q. Dr. Foster, have you ever done any work, expert or otherwise, for CropLife Canada?
A. To my knowledge, I have never done anything directly for them.
Q. And what about for CropLife America?
A. Same answer. To my knowledge, I have never done anything directly for them.
Q. Isn't it true that CropLife Canada and CropLife America are lobby groups for the industry?
A. They may be, they may not be. I don't know.
Q. Isn't it true that CropLife America is a trade organization that represents developers and manufacturers of herbicides and pesticides?

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A. Again, I don't really know.
Q. Dr. Foster, have you ever, in connection with expert consulting, communicated via email, telephone, or in person with Clare Thorp?
A. With whom?
Q. Clare Thorp.
A. To my knowledge, no. Where is Clare Thorp?
Q. CropLife America.
A. Not -- not to my knowledge. I don't believe I've ever met with or spoken to that person.
Q. Okay. We can look at Page 112 of your CV, please.
A. Of my CV? 112. Yes.
Q. And, specifically, the entry from 2013 to 2014 related to Exponent, Inc. in Alexandria, Virginia.
A. I see that, yes.
Q. And here you describe provided expert technical advise for inclusion, government submissions, on the relevance of exposure to hormonally active chemicals and adverse human health outcomes. Correct?
A. Correct.
Q. And was there any work product that was the result of this advice you gave to Exponent in 2013?
A. Was there any -- sorry. Was there any work --

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Q. Work product. An article. A paper.
A. No. I -- this was not -- I did not provide a published paper or anything like that, no.
Q. And did you provide an internal expert report to Exponent?
A. (No response.)
Q. Non-published.
A. I believe what I did is I provided a letter in which I -- I provided my opinion on assessing hormonally active chemicals; how -- how to do it, what it means.
Q. Were you paid for this work?
A. I believe I had a small contract for this, yes.
Q. Was it hourly?
A. No. It was a flat rate.
Q. Do you recall what the flat rate was?
A. I do not recall what the actual number was. But if I had to guess, I would say it was between 3- and $4,000.
Q. And was this your only work that you've done with Exponent?
A. As far as I'm aware, yes.
Q. Who approached you to do this work? Do you recall that person's name?

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MR. DHINDSA: Objection to the extent it calls for anything confidential.

A. I can't say with certainty who it was that actually approach -- approached me. It might have been Lorenz Rhomberg.

Q. Is that somebody who works at Exponent?

A. I believe it is.

Q. How much time would you say you spent on drafting this letter for Exponent?

A. I really couldn't say.

Q. Do you know what Exponent did with your letter?

A. No, I don't.

Q. Dr. Foster, I'm going to hand you an article that was published in Regulatory Toxicology and Pharmacology. We'll mark that as 18-13.

(Foster Deposition Exhibit 18-13 - Regulatory Toxicology and Pharmacology Article - marked for identification.)

Q. Dr. Foster, have you ever seen this article before?

A. Yes, I have.

Q. And you're listed on this article. Isn't that correct?

A. That's correct.

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Q. As a corresponding author. Is that correct?

A. That's correct.

Q. And this is an article that was sponsored by Exponent. Correct?

A. Exponent is listed on the author page, yes. And then in the Conflict of Interest as well.

Q. And is this article sponsored by Exponent the same one that's referred to here on Page 112 of your CV?

A. Sorry; 112 of my CV?

Q. Correct.

A. Is this referring to this contract?

Q. Correct.

A. I believe that's probably accurate, yes.

Q. Okay. And, Dr. Foster, what participation did you have in the drafting and publishing of these critical comments, as published in Regulatory Toxicology and Pharmacology?

A. I drafted a section, I read and edited the section providing critical comments and intellectual contribution to the overall document. I also spoke on the telephone with the -- the co-authors.

Q. So you did more than just write a letter for Exponent, as you previously testified. Is that correct?

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A. Correct.

Q. Now that you have seen this article, how much time did you spend in total on this project, would you estimate?

A. Again, I couldn't say with certainty.

Q. Okay. And which section did you draft?

A. It was contents of different sections. Let me take a look. So right off the bat, I had read the updated 2012 assessment, so I read that over. Provided my own notes and critical comments on what I thought were strengths, weaknesses of the -- the 2012 update, which I shared with my co-authors. I certainly provided comment in the written sections of the state of the science. And then the majority of my work related to the human health issues. So sperm, semen quality would be one area in which I drafted sections. Endometriosis would have been another.

Q. And when you say "drafted sections", you -- you started from scratch and then submitted your sections to the various other co-authors for review. Is that correct?

A. Correct.

Q. And what was your criticism to WHO-UNEP State of the Science of Endocrine Disrupting Chemicals following the assessment?

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A. Following -- following what assessment? Where -- where are we in the process? What are you --

Q. You initially said that you started by reading the assessment.

A. So the WHO-UNEP State of the Science 2012 report came out. I read that and formed my own opinions on that and held my own opinions for a while, and then I was contacted by somebody from Exponent -- it might have been Lorenz Rhomberg -- and asked if I would be interested in working with the group in formulating this -- this document.

Q. And what was the purpose of this document?

A. Glen Van Der Kraak and I were both members of the 2002 Assessment of Endocrine Disrupting Chemicals, and both Glen and I felt that the 2012 assessment was not a fulsome analysis and not a real update of the state of the science. It was a selective review, as opposed to a critical review of all of the available literature.

Q. And a draft of -- or the first submission of this article was received by the Journal of Regulatory Toxicology and Pharmacology on December 4, 2013, as indicated in the article info. Do you see that?

A. No. I will look for it, though.

Q. Front page.

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A. Yeah.
Q. Article --
A. I see, yeah.
Q. So does that mean that these critical comments underwent peer review?
A. My understanding is that, yes, this paper underwent peer review.
Q. Do you recall whether -- or were you part of the process after the peer reviewers revised or had comments or any notations? Did you, again, then look at this article prior to it being resubmitted for publication?
A. If I remember correctly -- I mean, this is going back some time, so I've published quite a few papers since that time. But if I remember correctly, we got reviewers' comments, and that there was a teleconference amongst us and emails about how we should respond to the comments.
Q. Had you ever previously worked with any of your other co-authors on this report, aside from Mr. Glen Van Der Kraak, who we already identified?
A. I believe it's Dr. Van Der Kraak.
Q. Yes. I'm so sorry. You're right; Doctor. Apologies
A. I hold him in very high regard.

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Jim Lamb, I've met at SOT; a highly regarded toxicologist. Julie Goodman is somebody I know. And Lorenz Rhomberg I met. I don't -- I can't state with a hundred percent certainty that we have not communicated or done something together in the past, but.
Q. Okay. Did you ever have an in-person meeting in order to work with your co-authors on this critical comment article?
A. Meeting? Meeting --
Q. Face-to-face.
A. -- face-to-face?
Q. Yes, correct.
A. I didn't feel that was necessary in this case.
Q. And you're listed as the third author on this article. Was there any -- was there any dispute as to the order of author articles -- article authors. Sorry. Dyslexic.
A. I don't recall any dispute. And I believe, outside of James Lamb, we're all listed alphabetically.
Q. And James Lamb here is likely listed as the first author because he would be the corresponding author. Is that correct?
A. That would be correct.
Q. Now, Dr. Foster, I'm going to hand you know a

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document that was produced in this litigation by Monsanto. This document is going to be Exhibit 18-14, and it begins with the Bates number MONGLY01947702, and it ends with 7704.
(Foster Deposition Exhibit 18-14 - Monsanto Document - MONGLY01947720 through 7704 - marked for identification.)
Q. I'd give you a moment to review, Dr. Foster, unless you can tell me that you've seen this before.
A. I don't recall seeing it before, so I'd like to read it over.
Q. Please.
A. (Witness reads.) Okay.
Q. Okay, Dr. Foster. On the second page of this exhibit, MONGLY01947703, we see that part of Phase 2 is that Exponent and Gradient staff will draft a detailed critical review in response to the WHO-UNEP endocrine report. Correct?
A. I see that that's what they're proposing, yes.
Q. And we see that after this draft is completed, select experts will review and comment as co-authors on the draft document. Correct?
A. I see this. This reads a response to a request for application and a proposal for work to be

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done. So it's -- it's what they're proposing to do.
Q. Okay. Now --
A. Not necessarily what was done.
Q. Okay. And they're proposing that the draft be completed by Exponent and Gradient staff, and the draft will then be shared with select experts who will become co-authors after they review and comment on the draft document. Correct?
A. That's what this says, yes.
Q. And you are listed as being considered for inclusion in this critical review. Correct?
A. That is correct.
Q. And the very next paragraph, there's the preliminary cost estimates for the labor by Exponent and Gradient, as well as a 4- to $5,000 honorarium or fee which will be appropriate for each of the experts. Correct?
A. That's correct.
Q. Dr. Foster, isn't it true that this critical review article was in part funded by the American Chemical Council?
A. Based on the information that's put forward before me, I don't see that that's where the money came from.
Q. Isn't it true that the American Chemical

Council collaborated with CropLife America to fund this article?
A. I don't know that to be the case. I can't -- I can't comment one way or another. I don't have that information.
Q. Let's go back to your expert report on Page 24.
A. (Witness complies.)
Q. And Page 24 talks about the Wood study, which is listed as Study 14 in Greim. Correct?
A. Yes.
Q. And this is, again, a CD-1 mouse study. Correct?
A. That is what I have written here, yes.
Q. And do you recall, as you sit here today, whether this was 18-month or 100 -- or a 24-month study?
A. This was an 80-week study.
Q. It's close to 18 months. Correct?
A. That's correct.
Q. And you have a -- a criticism here of Dr. Portier with regard to biological development of lymphomas in rodents and humans, and you cite to the Morse 2003 article. Correct?
A. Yes.

Q. Is that your position, as you sit here today; that there are clear differences in the biological development of lymphomas in rodents and humans, as described by Morse?
A. It's my testimony that Morse has made this point that there are clear differences, and I cite that here.
Q. Are you familiar with the data from Jackson Laboratory Mouse Tumor Biology Database?
A. What do you mean by am I familiar with it?
Q. Do you know it exists?
A. Do I know that Jackson Laboratory has such data?
Q. Correct.
A. I believe I do know that.
Q. And isn't it true that Morse 2003 and Morse 2010, both listed on your Materials Consulted, use information from the Jackson Laboratory Mouse Tumor Biology database in writing their articles on lymphomas? Isn't that correct?
A. I can't state with certainly one way or the other.
Q. Isn't it true that B cell lymphomas in mice has been compared to human immunohistochemical staining, and many feel that this exhibits a parallel

to the same disease in humans?
A. I can't comment on what many others state or don't state. I'm referring in -- I'm citing the -- the Morse study that has reviewed in the peer-reviewed literature.
Q. Okay. So Morse 2003 represents that B cell lymphomas in mice are not consistent with the same cells seen in humans.
A. Morse is saying that there are clear differences and in the biological development of lymphomas in rodents and humans. The immune system in mice and humans are well-known to be different.
Q. Do you know whether Morse offers an opinion on B cell lymphoma?
A. I believe Morse does, yes.
Q. And is it your testimony today that Morse states that B cell lymphoma seen in mice is not similar to that seen in humans?
MR. DHINDSA: Objection.
A. I go back to the -- what I've already testified to; that Morse points out that there are clear differences in the biological development of lymphomas in rodents and humans, and, thus, he's questioning and leading me to question whether there's a connection between lymphomas in mice and humans.

Q. And does he do this specifically for B cell lymphomas in mice?
MR. DHINDSA: You're asking him that question without showing him the article?
MS. ROBERTSON: He cited to it. He relied on it. It's his expert opinion. He should be able to testify what he relied on to make his expert opinion.
A. And I'm relying upon the point made by Morse that there are clear differences in the development of lymphomas in rodents and humans and that the immune systems in mice and humans are -- are different in important ways.
Q. Did Morse 2003 report on whether there were any similarities between lymphomas found in mice and those found in humans, or did he only describe the differences?
A. To my knowledge, he was emphasizing the differences.
Q. When you say "emphasizing", does that mean to say that he didn't discuss the similarities?
A. I don't recall one way or the other.
Q. Is it your testimony today that some -- that it is not possible for some mouse lymphomas to have strong histologic similarities to the human NHL

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subsets?
A. Say that again, please.
Q. Is it your testimony today that based on your literature review, mouse lymphomas do not have strong histo -- histologic similarities to human NHL subsets?
A. Histologic similarities is a point in time. It's a snapshot. It doesn't give me any insight into the development of the tumor. And so although there may be histologic similarities, it doesn't get to the point of whether or not they have similarities in development between mice and humans. They have same cellular components. They both contain ribosomes, they both both contain nuclei.
Q. Do you have whether mice and humans have the same -- have similar histologic -- have histologic similarities for B cell lymphoblastic cells?
A. Okay. I think where you're going with this information is really outside my scope of expertise. You're now starting to enter into the realm of a pathologist. And the expert opinion that I was asked to provide was on the conduct of the animal studies, not to histopathology.
So for the purposes of looking at this information, I can't comment as an expert on the histopathology.

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Q. Okay. But as an expert, you do comment on the idea that your -- well, your opinion holds that it's not biologically plausible for glyphosate to cause NHL in humans. Isn't that correct?
A. My opinion is that glyphosate in the Wood study did not induce a compound-related increase.
Q. What about your overall conclusion for the entirety of your expert report? Don't you conclude that it's not biologically plausible for glyphosate to cause NHL in humans?
A. My overall conclusion from the seven rat studies and the five mouse studies is that glyphosate did not induce compound-related effects that would lead me to conclude that there is no evidence of glyphosate acting as a human carcinogen.
Q. So you don't offer an opinion as to biological plausibility?
MR. DHINDSA: Objection.
A. In my report, would you like to point to my report where we're talking about that?
Q. I'm just asking you if you reached a conclusion, based on your review, as it relates to biological plausibility.
MR. DHINDSA: Objection.
A. Again, I'm going to come back to what I've

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testified and what my expert report states, is that in looking at the individual studies and then looking at the studies in aggregate, I saw no evidence of a compound-related effect.
Q. And that's different of biological plausibility. Is that what you're telling me?
A. Biological plausibility becomes an issue once one has seen a compound-related effect in a bioassay.
Now, I've looked at each of the individual studies, and I've looked across the studies in aggregate to reach the conclusion there was no compound-related effect.
Q. Still didn't answer the question.
A. Yes, it does --
MR. DHINDSA: Objection.
A. -- answer the question. It states quite clearly that I did not see evidence of compound-related effects.
So I'm -- you're asking me on biological plausibility to explain something that didn't occur. I can't do that.
Q. Well, in this section of the Wood, you have talked about clear differences in the biological development. You cite to Morse. And you then question whether a connection between NHL in mice and humans can

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be definitively established.
A. I see that section of my report, yes.
Q. And that's what you cite to -- Morse to. To the best of your ability, as you sit here today, you believe that's what that Morse citation stands for, correct?
A. To the best of my knowledge, Morse is pointing out that there are clear differences between the development of lymphomas in rodents and humans and that there are important differences in the immune system. Only one issue that I looked at.
Q. All right. So for the data for the Wood study, is this another one of the reports that you relied on the Greim summary tables in forming your expert opinion, or did you have the raw data?
A. This report was in -- cited in Greim, so it was in the Greim data tables. And I looked at the Giknis and Clifford data for historical controls as well. And there -- if I remember correctly in this study, there was also concurrent controls from the same lab -- concurrent controls. Historic controls in the same time frame, conducted in the same lab.
Q. There were historic controls, not concurrent controls. You corrected yourself there, right?
A. Concurrent controls would be from the same

study. There were historical controls from other studies in the same lab at the same time frame.
Q. How did you get that data?
A. It's in the Tier 2 summary data.
Q. What's the Tier 2 summary data?
A. Tier 2 summary data is the data from the -- the lab.
Q. Is the Tier 2 summary data from the lab publicly available?
A. I don't believe that's publicly available.
Q. So who gave it to you?
A. That would have been provided to me by the attorneys.
Q. Okay. And then can you point to me in your Materials Consulted where you cite to Safepharm?
A. Where I cite to Safepharm?
Q. Right. You have it in parentheses here, so I assume it's listed in your Materials Consulted?
A. I believe it's No. 185.
Q. Okay. Wood, et al., 185?
A. I believe that's the one, yes.
Q. Does that citation say Safepharm in there anywhere?
A. No, it does not.
Q. Okay. So how is a reader intended to follow

to your citation here with Safepharm to Citation 185? It would be a little confusing, wouldn't it?
A. It would be a little confusing, yes.
MS. ROBERTSON: I'd like to mark Exhibit Foster 18-15.
(Foster Deposition Exhibit 18-15 - Eric Wood Document, MONGLY07070096 through 0099 - marked for identification.)
Q. I'll represent for the record this was produced by Monsanto, and it starts with Bates number MONGLY07070096 and ends with 0099.
Dr. Foster, have you seen this document before?
A. Yes, I believe. I believe -- just let me look through it, please. Yes.
Q. And is this document what you refer to in your materials consulted as 185?
A. I believe that's correct.
Q. Okay. And so your expert report identifies a historical background incidence of 12 percent in the 18-month study from Safepharm. And that's what -- this document, Exhibit 18-15, is what you're citing to there, correct?
A. I believe that to be correct.
Q. Okay. And why did you choose to use the

Safepharm data here, when this is just one study, not a historical control data set?
A. When I looked at the historical control data cited in Giknis and Clifford, it indicated that it's unusual to have zero lymphomas in a control group.
I then looked at this group, as well, to see in another study conducted at the same lab what their rates were.
Q. And is that appropriate methodology to follow?
A. In trying to evaluate the overall value of the study and the quality of the data, yes, it wouldn't be inappropriate to do that.
Q. Why not use a historical-controlled data set, as compared to one study to compare? Isn't there a fear of skewing numbers?
A. Again, I'm looking at historical controls -- I'm sorry -- controls that were conducted by the same investigators, at the same lab and the same time, and by same pathologists, I assume. Same lab, so I would assume the same pathologists.
Q. And so the Safepharm data set is used in your expert report as the better data set, as compared to the concurrent controls? Is that correct?
A. No. It's -- it is another piece of

information that I can look at and help me in arriving at my conclusion as to whether or not this study performed as one would expect. Are the differences there compound -- or potentially compound-related or not.
Q. Can you identify another instance in where it would be appropriate to apply a control group set from one study, as compared to a historical-controlled database study? Have you ever done this before?
A. Have I ever done --
Q. Have you ever chose to use one historical control study, as compared to a data set of historical controls in analyzing data?
A. Well, the way -- the way you're phrasing your question is -- is difficult for me, because it sounds like I do something at the exclusion of something else; that I just ignore it, and I -- and I don't. It's -- I weigh all the information before me and evaluate it.
Have I had the opportunity to do this previously? I don't recall having the opportunity to do it, because it's rare that you have control data from another lab that's done contemporaneously by the same investigators in the same lab and the same time with the same pathologists.
Q. Okay. And on the second page of this

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exhibit, in fact, the author is Brooks. Is that correct?
A. Sorry. The second page?
Q. Wood is listed as the third author, but the -- the first author there is Brooks. Correct?
A. I see that, yes.
Q. Okay. And this article is titled CD-1 -- in part, CD-1, in parens, (ICR) BR Strain Mice, correct?
A. It is, yes.
Q. And your expert report indicates CR strain mice. Is that a typo in your expert report, or is there another data set we should be concerned with? I'm looking at Document -- I'm looking at No. 185 on your Materials Consulted list.
A. It's possibly that that's a typo.
Q. And Citation 185, right? That's what we're talking about? Not the study?
A. Well, it's possibly a typo somewhere.
Q. Okay.
A. I can't state where the typo came from.
Q. Well, if you can't state where the typo came from, is there some other data you relied on here that would match this title for the CR strain of mice?
A. No, I don't -- no, I do not believe so.
Q. So it is this document that is 185?

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A. That's -- I would agree with that.
Q. Would it have made a difference in your analysis if you were aware that the animals in the Safepharm data set, which is Exhibit 18-15, were fed a different diet than those in the Wood 2009 study?
A. So in 18-15, they were fed a different diet?
Q. Would it make a difference of your analysis if 18-15 animals were fed a different diet than those in the Wood 2009 study that you compare?
A. It would be something that I would want to look at and I would want to know about. I did not note that as a difference in my analysis.
Q. Sitting here today, do you know whether the Wood animals were fed the same as the Safepharm animals?
A. I cannot state one way or another without that information. However, again, coming back to the comment that I made, that this was work that was conducted by the same group, the same lab, at the same time, with the same pathologist, I would anticipate that they would most likely have been fed the same diet and housed under similar conditions.
Q. Okay. And we note here that there's a certified diet fed to the Safepharm animals identified as Rodent 5LF2. Correct?

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A. I see that, yes.
Q. And do you know whether Greim identifies what the animals are fed?
A. Greim provided me with the data tables and summary of the studies. I don't believe that they stated the diet.
Q. Okay. So you're not aware today whether or not Wood was fed the same as Safepharm. Is that correct?
A. I cannot state whether they were or were not.
Q. Doctor, you testified that this Safepharm data came from a Tier 2 summary. Can you explain that a little further, for what you mean by Tier 2 summary.
A. Tier 2 summary, in my mind, is a second look at the overall data; the pooling of the data.
Q. And who conducted the Tier 2 summary that you're talking about?
A. Well, I believe this is Brooks.
Q. When you received this document, was it received as produced and used as an exhibit here today?
A. I don't understand.
Q. Did it have any accompanying pages, or is this the complete document you used when you referenced Safepharm in cite to 185?
A. My recollection is that this is how I

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received the information.
Q. And on the second page of the exhibit, you do see that it says "internal publication", correct, underneath the title and the author name?
A. I see that, yes.
Q. Okay. So what do you take "internal publication" to mean?
MR. DHINDSA: Objection.
Q. In this context with this document.
MR. DHINDSA: Objection.
A. In the context of this document, I believe this is a report that was prepared by these authors for internal use.
Q. And these authors also conducted the Wood 2009 study. Do you know who sponsored the Wood 2009 study?
A. I do not know that for sure at this point in time.
MS. ROBERTSON: I'd go ahead and enter into -- as an exhibit 18-16 the Greim article that we've talked so much about.
(Foster Deposition Exhibit 18-16 - Greim Review Article - marked for identification.)
(Discussion held off the record.)
MR. KALAS: Just note this is the article

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without the supplementary material.
BY MS. ROBERTSON:
Q. Dr. Foster, this is the review article that we've been discussing today, correct?
A. (No response.)
Q. Is this what you appreciate to be the review article that you --
A. This is -- yes, that -- this is the -- what I appreciate to be the review article that I've used the summary tables from.
Q. Okay. And Greim doesn't use the study authors. They number the studies and then put in parens the sponsor of those studies. Correct? On Table 1, first page.
A. Yes, they do.
Q. Okay. And so if we look for -- your expert report has Wood 2009b. We see that that's Study No. 8 sponsored by Nufarm. Correct?
A. Sorry? Say that again.
Q. So your expert report identifies Wood 2009b.
A. Yes.
Q. And Greim identifies Nufarm 2009b as Study 8. Your report says 14. I just want to make sure that we can be accurate here on the record as to whether this discussion here in your report is a or b.

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A. I'm going to have to check to be sure. It could be a typo.
Study -- Study 8. Sorry. This was -- Study 8 was a study conducted in rats, whereas Wood, et al., 2009 is Study 14, which is one that is conducted in CD-1 mice. So we're referring to Study 14 --
Q. Okay. So I can change that to 2009a.
MR. DHINDSA: Well, I'm not sure about that. Counsel, if this -- if it helps at all, the top of Table 19, it's actually listed as 2009a, and then on the first line it's listed as 2009b.
MS. ROBERTSON: I'm just looking at the table of contents.
MR. DHINDSA: Okay.
MS. ROBERTSON: I'm with you. I agree with the confusion here. I'm just trying to make sure that we're all on the -- on the same page of what we're talking about.
A. Yeah, we're all confused.
Q. In any event, we're going to agree that Wood 2009 in your report is discussing Cd-1 mice and that that study was sponsored by Nufarm. Correct?
A. What do you mean by "sponsored by Nufarm"?
Q. Nufarm paid for the study to be conducted?

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A. I don't know who Nufarm is, so they either paid for it or they are the ones that conducted it themselves. I don't know -- I'm not in the industry, so I don't know if this is a contract lab or -- or what they are.
Q. Okay. Well, we can look at the Table of Contents here in Greim, and we see that Greim identifies Monsanto, Cheminova, Feinchemie Schwebda --
MS. ROBERTSON: I'm sorry, Court Reporter.
A. -- Excel, Arysta Life Sciences, Syngenta, Nufarm.
A. Yes.
Q. And these appear to be industry-sponsored studies and -- that's listed here, not the lab. Correct?
A. Sure. I can go with that.
Q. Okay. And so the Safepharm data that you used that was for internal use only must be a Nufarm document. Correct?
A. Sorry. You're asking me in this Safepharm document here is a Nufarm document?
Q. Correct.
A. I would say that's possible, yes.
Q. Okay. And if it's for internal publication only, how did you come to receive Nufarm unpublished

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documents?
MR. DHINDSA: Objection.
A. In the materials that I was provided to review, this is a document that was included.
Q. Dr. Foster, would you call this Safepharm document a historical control database? Would that be an accurate representation of it?
A. Would I refer to it as a historical control database? I would refer to it as contemporaneous control database.
Q. Dr. Foster, are you aware of the concept of dual controls?
A. Yes.
Q. And as you sit here today, do you know whether dual controls were applied to any of the studies here in your expert report?
A. Well, I think we need to define what is being meant by "dual controls". What -- what are you asking me here?
Q. What do you appreciate a dual control to mean?
A. A dual control might be a control group that is through -- so you've got one control group that's getting just the diet, and you've got another control group that's just getting the vehicle.

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Q. And did you see that in any of these studies?
A. I don't recall seeing that in any of these studies.
Q. One of your criticisms of Dr. Portier is his use of pooling data. Isn't that correct?
A. I'm not sure that I agree with the characterization of criticizing him. I'm saying that the use of pooling is an interesting concept that has not been validated in the overall literature.
Q. And you came to this conclusion by doing a PubMed search. Well, several of them. Correct?
A. Correct.
Q. And when you engaged in your analysis of these carcinogenicity studies, did you consider comparison of similarly structured studies, meaning same rodent, same duration, same number of rodents? Did you look at those studies together, or did you look at all the studies as a whole?
A. I think I looked at it both ways. I think in looking at the literature, I evaluated studies that were conducted -- so most studies that were conducted in 18 month -- and conducted according to OECD guideline carcinogenicity bioassays, I compared them, yes.
Q. And your -- your evaluation of the studies

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certainly took into account comparing CD-1 mouse, 24 month with other CD-1 mouse, 24 month, in part.
A. In part, yes.
Q. And you identify on Page 11 that Dr. Portier employs a novel statistical approach, as you already stated, that is not generally accepted by regulatory toxicology. Isn't that correct?
A. What I'm stating there is that in my knowledge, that it's an interesting proposal that has not stood the test of time. It hasn't been evaluated in the literature. And as a consequence, I'm not sure that it's appropriate to use in this context. I think it's an interesting research proposal.
Q. Has science developed over time?
A. Science continues to develop over time.
Q. And do methodologies change over time?
A. Methodologies always are changing, yes.
Q. Is it your expert opinion that scientific analysis that is ahead of the curve should be discounted or dismissed?
A. Sorry. My --
MR. DHINDSA: Objection.
A. Is it my opinion --
Q. Your expert opinion, yeah. You have a lot of experience in science.

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A. That novel, innovative methods should be discounted and dismissed?
Q. Correct.
A. It depends on the context. I -- I would need to know more about what it is you're implying there.
I think we move forward by developing novel, innovative techniques that we put out to our colleagues to debate, critique, evaluate, and help us to improve and strengthen. Highlight where the weaknesses are and develop a better product.
Q. Let's look at Page 15 of your expert report.
A. (Witness complies.)
Q. Now we're -- now, this -- it begins on Page 14, and you're discussing the Lankas 1981 study. Correct?
A. On Page 14, beginning at -- near the top, it is the start of a discussion on the Lankas study.
Q. Correct, yeah. All right. I'd like to direct your attention to Page 15.
Now, page 15, in the last paragraph, you state, "Dr. Portier speculates that the 26-month duration of the study offers unique insights that may be missed in a study lasting only 24 months."
Do you see where I'm reading?
A. I do.

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Q. And then you offer a counter to that, saying that you're not aware of any data that demonstrates a 26-month study would detect tumors at any different rate. Correct?
A. No, that's not what I said. I said that I'm not aware -- sorry. I'm not -- "However, no evidence is offered that I am -- and I am not aware of any evidence demonstrating that a 26-month study would detect interstitial tumors at any different rate than a 24-month study."
Q. Okay. Well, let's look at what I believe is responsive to your criticism here of Dr. Portier, which would be Page 34 of Dr. Portier's report.
A. Okay. Page 34?
Q. Um-hum. I am trying to understand, Dr. Foster, if this matches your criticism to Dr. Portier that you identify on Page 15 of your expert report.
So if you could please look at the first full paragraph after the third Lankas 1981, which is in bold, that begins with "however".
A. Okay.
Q. After the second Lankas bold. Sorry?
A. I'm going to want to look at the entire paragraph here to see what --

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Q. Okay. Understood.
A. -- to get my context here. Okay.
Q. And is this what you're -- is this paragraph what you're referring to on Page 15 of your expert report, when you say, "Dr. Portier speculates..."?
A. Yes, I believe that's what I'm referring to.
Q. And as you sit here today, do you still believe that this portion from Dr. Portier's report is speculation?
MR. DHINDSA: Objection. I don't know which portion you're referring to.
A. What he's saying is that thyroid C cell carcinomas could be a result of the longer exposure period, even though the dose is substantially lower in the study compared to the other two. So he's saying "could". He's qualifying it as well. So it's -- it's speculative.
Q. I'm just asking if you're -- if as you sit here today, you still agree that Dr. Portier speculated there.
A. I believe he speculated there, yes.
Q. It's important to consider study length and the incidence of any adverse effect, isn't it, Dr. Foster?
A. It's important to evaluate the entire study,

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not just the study length.
Q. You're right. In part, study length is important to consider when evaluating the entirety of a study. Correct?
A. It would be one thing that I would look at, yes.
Q. And if tumors are observed in animals that live for 26 months, but not in animals that live for only 24 months, wouldn't it be a prudent observation that perhaps those extra two months need to be considered when looking at the study results for the 26 months showing tumors?
MR. DHINDSA: Objection.
A. Again, I would come back to the argument that I would be looking at making comparisons of compound-related tumors. If there was a compound-related tumor, then I would, indeed, look at that. But I did not see compound-related tumors here.
Q. When you say "compound-related tumor", how do you identify a compound-related tumor in advance of looking at the study quality such as length, final results, survival rates, et cetera?
A. I don't do it in advance. I do it in -- by evaluating the entire study.
Q. So the duration of the study does, in fact,

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go into whether there is a dose response.
A. It's something that goes into my overall assessment of the study and whether or not the compound -- there are compound-related effects or not.
Q. Okay. And on Page 14, you give us, again, some percentages for historical control data in the second paragraph. I'll give you a moment to locate it.
A. Yes.
Q. Why not use the concurrent controls?
A. In this particular study, if I remember correctly, there were a number of things that were at issue.
In particular, the survival rate in the control group was lower than in the higher dose group. And for some reason in this study, the higher dose group survived longer and did better.
Q. And that's why you used historic controls instead of the concurrent controls?
A. It is one of the things that I considered, yes.
Q. And where did you find information related to the survival rates of the animals? It's uncited in your report here.
A. Again, this is one in which I believe, because I didn't have the original data, I would have

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relied upon the Greim study, summary tables, and the write-up in the -- in the Greim paper, if I remember correctly.
Q. So maybe we should have cited to Greim there, correct?
A. I'm sorry?
Q. So Greim could be cited there. Correct?
A. Greim could be cited there in that case, if that was it.
Q. Would there be any other material you relied upon that would give you such information?
A. Such as?
Q. It's your report, Dr. Foster. I don't know everything you reviewed.
So was there anything in addition to Greim that could have told you that the number of animals surviving to the end -- end of the study was higher in the dose groups than the controls?
A. Everything that I consulted is on my Materials Consulted list. And in my review of this study, if I remember correctly, I looked at the Greim summary tables and the text.
Q. Which historical controls did you look at for the study?
A. In this particular case -- let me see if I

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can figure it out here.
If I remember correctly in this particular case, I may be referring to the Greim paper.
Q. The Greim paper is a review summary, correct, not a historical control database.
A. No, it's not a -- a historical control database.
MR. DHINDSA: Is this an appropriate time for a break?
MS. ROBERTSON: The question is pending. He's looking.
MR. DHINDSA: Okay.
A. Okay. This is Study 1 under the Greim, so this would have been material that I had from -- it's a Monsanto-funded study, so I believe I actually had the original data to look at.
Q. Right. But we're talking about historical controls, and Monsanto doesn't have historical-controlled data sets, do they?
A. I don't know what Monsanto does or doesn't have.
Q. Well, in this instance, you said that you had the original Monsanto study, but we're talking about historical controls. So I just want to make sure that we're not -- we're not crossing hairs here.

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A. No, I get that. So as I read the Greim paper, investigators noted that a terminal sacrifice in the interest -- "The range of control animals, five contemporary studies, historical controls was..." The incident with the highest dose was 12 percent, compared to contemporary historical controls. So this is where I believe I'm getting that information from.
Q. And you're talking about testicular tumors there?
A. Interstitial cell -- yes, I believe I am.
MS. ROBERTSON: Okay. We can take a break.
MR. GOODALE: This marks the end of Media 4 in the deposition of Dr. Warren G. Foster, Ph.D. Going off the record at 4:14 p.m.
(Recess held.)
MR. GOODALE: Here begins Media No. 5 in the deposition of Dr. Warren G. Foster, Ph.D. We're back on the record at 4:33 p.m.
BY MS. ROBERTSON:
Q. Okay, Dr. Foster, we're -- we were on the Lankas study before the break and your analysis of the Lankas study.
Now, still talking about the interstitial tumors of the testis, as stated in your expert report on Page 14, the incidence is reported as zero, three,

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one, and six. Correct?
A. Correct.
Q. And because of the 16 in the high dose group, that's why you include as the last sentence in the second paragraph, "The neoplastic changes in the testis of the high dose group were evaluated to better elucidate their importance," is that your analysis you were talking about or Greim's?
A. No, this is my evaluation.
Q. Okay. And so here you note that it's important to look at the high dose group survival rate, compared to the controlled group survival rate, because these neoplasms may develop spontaneously. Correct?
A. I think it's well-documented that neoplastic changes can occur spontaneously. And in this particular study, we had a much higher survival rate in the -- the higher dose group than in the control group.
Q. And as a result, you conclude that this can't be -- the six interstitial testicular tumors are not compound-related tumors. Correct?
A. Not solely on that basis.
Q. Okay. What's the other basis?
A. So I'm looking at this. I see the pathology -- pathologist in their evaluation notes that there was absence of compound-related hyperplasia.

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Hyperplastic changes would be expected to be present. In -- if these were compound-related changes. I looked at the control. And then the -- I looked at the issue of the higher survival rates in the high dose group, versus the controls. And then I also went and looked at other animal studies that also looked at exposures that covered the same dose range, as well as much higher levels. And I note that this was not reported in any other rodent study.
Q. Interstitial testicular --
A. Testicular tumors.
Q. -- tumors are not in any other rodent study.
A. I noted that there was no evidence in my review of any compound-related replication of the testicular tumors.
Q. And for the Lankas study, the dose administered to the high dose group is below OECD current guidelines, correct?
A. It was, yes.
Q. And, in fact, you note that it's 300 ppm of glyphosates for the high dose group. Correct?
A. Yes, I noted that that was the case, yes.
Q. And do you know what 300 ppm correlates to for milligrams per kilogram per day?
A. I believe in the high dose group in the

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males, that equivalent -- the equivalent of that is 34, roughly, mg's per kg per day.
Q. And 31, almost 31 and a half for the males.
A. That -- I'm sorry. I thought that -- 31.5 -- let me be clear -- is for the males. Sorry. 34 for the females.
Q. And we can agree that that's a relatively, if not greatly, low dose for the high dose group. Correct?
A. That would be a low dose, yes.
Q. And it was such a low dose -- did that come into your consideration with result to six tumors seen in the high dose group?
A. What do you mean, did it come into my consideration?
Q. With six tumors in the high dose group, higher than any other group, doesn't this suggest that the tumors are compound-related, as compared to the controls, because the doses are so low?
A. No. I mean, it -- in your control group, you don't have them surviving. And we know that the longer the animal lives, that spontaneous tumors occur, and that the longer the animals live, the greater the chance you're going to see tumors.
Q. And so --

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A. Spontaneously occurring.
Q. Sorry. Are you finished? I don't want to cut you off. I'm sorry.
A. You can cut me off now.
Q. Okay. Sorry. So -- so, yeah, we can agree that the longer the animal lives, the more likelihood there is for a spontaneous tumor to occur. Correct?
A. Correct. So in this particular study, even though the doses are lower, I've got a problem with the study on the basis that the low dose, survival bias, the histopathology report, and the lack of replication of the diet -- of the outcome in other well-conducted studies that use this dose and much higher doses.
Q. Can you identify a study that uses a dose that's even within 500 ppm of the Lankas study?
A. Atkinson used a dose of 11 mg's per kilogram, so that would be in the same ballpark.
Q. For the high dose group?
A. Sorry. You asked me if they used any -- any dose that was in that range, not the high dose. Any dose.
Q. Well, would you compare a high dose group result to a low dose group result?
A. I would compare on the equivalent dose.
Q. But an equivalent dose is based on milligrams

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per kilograms per day. So you're going to take a study from 1981 in males, that from a high dose group observation, and compare that to a study that has a low dose group administration, that has a similar to same milligram per kilogram per day? Am I understanding correct?
MR. DHINDSA: Objection.
A. What I stated was that there was no replication of the testicular tumors in other studies that used similars doses through to much higher doses. You asked me was there another study that used any dose that was similar.
Q. Um-hum.
A. I gave you a study in which they used one of their doses that was similar and consistent with what I had testified.
Q. And that's the Atkinson study.
A. I believe that was the Atkinson study, yes.
Q. And which dose group are you referring to --
A. Sorry. Sorry. Let me --
Q. Sorry.
A. Let's just make sure we're talking the right one here. Atkinson, et al., 1993. This is Greim, et al., Study No. 3, Page 19 of my report.
Q. And which dose group are you referring to

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that's similar --
A. So they have one dose group that's using 11 mg's per kilogram.
Q. And that's the low dose group, correct?
A. That's the low dose in that group.
Q. And you didn't see a replication with the -- with tumor incidents in the Atkinson low dose group for these testis interstitial cell tumors --
A. That's correct.
Q. -- or testicular tumors.
A. That's correct. And if you look at Suresh, Greim study, they use the males a dose of 6.3 mg's.
So it's a little bit lower, covering the same range, going 6.3 for 59.4 to 592.
(Witness asked for clarification by the reporter.)
A. 59.4 to 595.5 mg's per kilogram per day. So they're overlapping that dose range.
Q. Now, Dr. Foster, did the Atkinson study authors report on all 50 animals in the low dose group when they did their final analysis, as it relates to testicular tumors?
A. The Atkinson study is the study in which they looked at the control in the high dose group and made their comments there, if I remember correctly.

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Q. So, Dr. Foster, how did you compare the Lankas study high dose group with the Atkinson study low dose group for testicular tumors?
A. If you're seeing something that's compound-related, you would expect to see a dose response with higher -- as you got higher. They did not see that in that study.
In the high dose group, there was no report of a testicular tumor.
Then you look at the Suresh, another study covering the same dose range. They don't see it either.
Q. Okay. But my question wasn't that. My question was whether Atkinson looked at the 50 animals in the low dose group receiving the like -- the similar dose that Lankas high dose group received. Did the study authors look for testicular tumors?
A. Not in the low dose group, because they didn't see them in the high dose.
Q. So how did you compare the Atkinson low dose group to the Lankas study?
A. I didn't say I did. The way I -- I stated my testimony was that in studies that looked at similar doses through to higher, they did not see a replication in testicular tumors.

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Atkinson -- you asked me which studies covered similar doses. Atkinson is one that did. They only looked at the high dose versus the control.
If one is seeing a compound-related effect, one would expect to see that if there were compound-related effects, as you increase dose, you would see an increase in the number of tumors. That wasn't seen in control versus the high dose group.
Then you go on to Suresh, that did look at the animals from all the dose groups, and they don't see an increase in testicular tumors.
Q. Is it --
A. So it's not just looking one -- one off at one end point.
Q. As you sit here today, do you know how many testicular tumors appeared in the low dose group in Atkinson?
A. No, I do not.
Q. As you sit here today, do you know how many testicular tumors appeared in the low dose group of Suresh?
A. In the Suresh study -- This is Study 4. In this study was a negative study. They did not find evidence of compound-related tumors. They would have evaluated the testis as -- in a thorough study. They

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did not find them. So they were not reported.
Q. And is your testimony today that Suresh conducted a different analysis than Atkinson 1993? Is that my -- is that correct?
A. What do you mean by a "different analysis"?
Q. Well, Atkinson did not report on tumors -- all the tumor incidences seen, unless it showed positive -- unless there was a positive finding or compound-related finding between the control group and the high dose group. Correct?
A. They -- the way I understand the Atkinson study to have been conducted is they looked at the control versus the high dose group and -- to determine whether or not there were tumors being seen there that were different than the control, to decide whether or not they were going to invest the money to go back and look at the intermediate doses.
Q. Okay.
A. That would be my interpretation of their thinking in that study.
Q. And is that the same or different from the study analysis of Suresh?
A. That is different -- different than what Suresh did.
Q. So when you conclude that the interstitial

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testicular tumors have not been replicated, that's by looking at the Suresh report. Is that correct?
A. Looking across all the studies, I see no replication of testicular tumors in any study.
Q. Now, your first full paragraph on Page 15, still talking about the Lankas study, observes that the statistical significant disappears once thyroid C cell adenomas and carcinomas are combined. Do you see where I'm at?
A. I'm reading that paragraph now. Yes.
Q. Okay. And so once you combine the carcinoma with the adenoma and the thyroid C cell for female animals only, there's no statistical significance.
A. Correct.
Q. Do you know what animals McConnell 1986 used when they published this article that you cite?
A. I cannot recall at this point in time which animals they were looking at.
Q. Would it make a difference to combining adenomas or carcinomas as to what animals McConnell is talking about?
A. It depends on the context in which this is being written. If he's talking as a pathologist and stating that this is the appropriate thing to do in evaluating rodent carcinogenicity assays, then, no, I

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don't think it does.
Q. Let's take a glance at Stout and Ruecker 1990 test on Page 16 and 17 of your expert report.
A. Yes.
Q. Stout and Ruecker is a Monsanto study, correct?
A. This was a study conducted by Monsanto in Sprague-Dawley rats.
Q. And is this one of the studies that you received the full data set for?
A. Yes.
Q. And here you discuss the results of the Stout and Ruecker using 60 animals in each group. Is that correct?
A. Those are the numbers that they had, yes.
Q. Okay. If I could direct you to the Greim paper, Study 2, that you have in front of you.
A. Sure. Somewhere.
Q. Exhibit 18-16. Isn't it true, Dr. Foster, that Greim uses 50 animals when discussing the Stout and Ruecker study?
A. This is Table No. 5? Where are we looking?
Q. I'm looking at --
A. I'm sorry. In the text?
Q. Yeah, 191 of the Greim article, Study 2,

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Monsanto 1990.
A. He's reporting 50 animals per dose group.
Q. As you sit here today, do you recall where you got the number 60?
A. I'm just reading through my report now. If I remember correctly, they used 10 animals in this study as an interim sacrifice, leaving the 50 animals to go through to the study conclusion.
So I believe Greim is talking about the study conclusion. I think at the start here, I'm talking about the 60 that entered per each dose group, from which ten were used for intermin sacrifice.
Q. Okay. In the second paragraph of your expert report on Page 16, under the Stout and Ruecker study, when you provide the numbers for pancreatic islet cell adenomas, you do use the denominator using presumably the number 60. Correct?
A. I have here, yes.
Q. And why did you include the ten interim sacrificed animals in your overall -- in your identification of the pancreatic islet cell -- islet cell adenomas?
A. I believe that the reason that it was 60 was looking at the overall study.
Q. Isn't it true, Dr. Foster, that interim kills

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pursuant to OECD guidelines should not be part of the final statistical analysis from a main study?
A. They would be -- normally would be omitted.
Q. Now, in this same discussion, you again note historical controls and a range of zero to 17 percent for these pancreatic islet carcinomas. Correct?
A. I don't see where you are.
Q. The third paragraph. I apologize. Please take your time.
And here in Footnote 2, you give -- you offer your methodology behind using the range of historical controls, as -- as opposed to the mean. Correct?
A. This is where I'm talking about that issue, yes.
Q. Okay. And sitting here today, you believe it's most appropriate to use the range of historical controls as compared to the mean? Is that correct?
A. I do.
Q. And for support of this, you cite to Baldrick 2005 and Baldrick 2007.
A. That's correct.
(Discussion held off the record.)
Q. Dr. Foster, we -- we'll mark both Baldrick 2005 and Baldrick 2007 -- Baldrick 2005 will be Foster Exhibit 18-17.

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(Foster Deposition Exhibit 18-17 - Baldrick 2005 Study - marked for identification.)
Q. And Baldrick 2007 will be Foster 18-18.
(Foster Deposition Exhibit 18-18 - Baldrick 2007 Study - marked for identification.)
Q. Here is 18-18.
(Discussion held off the record.)
Q. And these are the articles you refer to. Correct, Dr. Foster? I pulled the correct articles? I'd like your confirmation, please.
A. I believe these are the articles, yes.
Q. Okay. And we see that 18-17 deals with Sprague-Dawley rats, and 18-18 is CD-1 mice. Right?
A. Correct.
Q. Now, this -- the subject of this article is for comparison of tumor data with dual control groups. Correct?
A. Yes.
Q. Okay. And so in the context of your methodology used for the use of range of historical controls, you choose to cite to two articles related to dual control groups. Correct?
A. They are talking about dual control groups, yes.
Q. And dual control groups are different from

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historical control groups. Correct?
A. Yes. I believe that to be true.
Q. So Baldrick 2005 and Baldrick 2007 don't necessarily support your position that the use -- that the range of historical controls, as opposed to the mean, is the most appropriate and common standard practice for interpreting toxicologic data, does it?
A. I'm going to take a few minutes to review the paper.
Q. Dr. Foster, sitting here today, if you can't tell me whether Baldrick 2005 and 2007 support your Footnote 2, we can just move on.
MR. DHINDSA: Objection.
Q. I won't ask any more questions on these documents.
MR. DHINDSA: Objection. He's still reviewing these documents.
Q. I have no further questions on these documents.
Dr. Foster, as part of your review of the literature related to forming your expert opinion, you looked at the OECD guidelines. Correct?
A. Correct. I used OECD guidelines. I looked at them.
Q. I'm going to mark Foster Exhibit 19.

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(Foster Deposition Exhibit 18-19 - OECD Guidelines, Guidance Document 116 - marked for identification.)
Q. Dr. Foster, I just handed you Guidance Document 116. And -- and you consulted this document in preparation to author your expert report. Correct? Report. Citation 144. I just want to make sure this matches and I pulled the correct version.
A. I've looked at these documents, yes.
Q. I'd like to direct your attention to Page 135, which discusses Historical Control Considerations, Section 4.22. And, Dr. Foster, these are the guidelines that you've referenced throughout the day with your use of the historical controls and the evaluation of forming your expert opinion. Correct?
MR. DHINDSA: Objection.
A. I have familiarity with OECD and their guidelines, and I have referred to them.
Q. And Paragraph 400, referring to Elmore and Peddada 2009, discusses the incorporation of historical control data and statistical analysis of carcinogenicity studies, correct?
A. Yes.
Q. Okay. Did you review Elmore and Peddada, as

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referenced here in OECD guidelines?
A. I may have looked at it at some point during my time as the Canadian national coordinator for OECD. I did not look at it in the context of this study, that I recall.
Q. And Elmore and Peddada, as cited here in the OECD guidelines, discuss how historical controls need to consider rogue outliers. Correct?
A. That's what they are saying, yes.
Q. And when you use a range of historical controls, as compared to the mean, are you not more likely to have a rogue outlier when you use the range?
A. It is possible that you could. However, I did not rely on historic controls or concurrent controls in reaching my opinion. They are but one factor.
Q. And when you looked at the historical controls of Chandra in 1992 that reported a historical control range of zero to 17 percent, did you look at the historical control data to consider whether there was an outlier making the range so large?
A. I'm sorry; where are we?
Q. Page 16 at the bottom.
A. Okay.
Q. Accompanying Footnote 2, the range is zero to

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17 percent. And you, I believe, are referencing Chandra, et al., 1992.
A. Correct.
Q. And did you look at Chandra, et al., 1992, to determine whether there was an outlier with respect to this range of historical controls?
A. Well, they're looking at the range, whereas what you're referring to is this -- let's go back to -- what page was it? 134?
Q. It was Section 4.22, if that helps out. And I will confirm 135.
A. They are saying the mean and the standard deviation can be affected by a rogue outlier, while the mean and interquartile range is not. Here I'm talking about range. I'm not talking about the mean, the standard deviation.
Q. You're talking about the interquartile range?
A. I'm talking simply about the range, not the interquartile range. The range, period.
Q. Okay. So historical control considerations as outlined by OECD don't talk about using the range, do they?
A. They don't exclude using it, no.
Q. So what are you basing your methodology on for using the range in your expert report?

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A. Almost 30 years' experience working in the field. And, again, it wasn't the only thing that I relied upon.
Q. What else did you rely upon?
A. I looked at whether or not these were compound-related effects based on the conduct of the study.
So my methodology throughout all was assessing survival of the animals. Was there systemic toxicity -- signs of systemic toxicity seen. Were there histopathological evidence of tumor progression. Things like that.
Q. Okay, yeah, I didn't ask a proper question.
I thought you were saying that you relied on other things beyond your experience to use the range of historical controls, and I was asking what else you relied on that supports your use of ranges.
A. Again, this is common throughout toxicology.
Q. Do you find the range to be more relevant than the mean when applying historical control data to rare tumors?
MR. DHINDSA: Objection.
A. Again, I don't rely upon it to the exclusion of other factors. It's something that I look at.
Q. So you can't answer that question because you

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don't isolate that particular analysis when deciding whether to use historical controls. Is that correct?
MR. DHINDSA: Objection.
A. I look at the data, I look at what's -- the controls are doing. If there's reason for me to look at historical controls, then I will do so. But I'd look at it in the context of the overall study.
Q. And what was your purpose in using historical controls in the Stout and Ruecker analysis?
A. In this particular study, we see differences in survival with higher survival in the high dose groups. So 29, 38, 34, 34.
In males, you're look -- sorry. That was males.
Now, in this study, I also note that there was a number of issues going on as well. There's no change in food consumption, but there's also a change in increased liver weight found in the males. Seeing a sign of increased liver weight tells me that I've got liver induction, and that is potentially confounding effects at higher dose.
Q. But, Dr. Foster, you state on Page 16 that the data taken together suggests that the dose selection was considered adequate for females. Are you speaking only to the males?

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A. In this particular case, that's in reference just to the males.
Sorry. Are we --
Q. I was trying to figure out why you choose to use historical controls as opposed to concurrent controls here.
A. Okay. I'm -- again, I'm looking at the overall conduct of the study. I'm seeing differences in survival rate. And then I go on and I also note that the USEPA requested that additional data on historical controls be looked at as well.
So it was not just me. USEPA is asking that they look at historical controls as well.
And this is in the context of the thyroid C cell adenomas and hyperplasia. The hepatocellular --
(Witness interrupted by the reporter.)
A. Thyroid C cell adenomas, carcinomas, and hyperplasia; hepatocellular adenomas, carcinomas, and hyperplasia; and, three, the keratoacanthomas.
Q. Okay. But the EPA didn't ask for historical control data related to the pancreatic islet cell adenomas. Isn't that correct?
A. Not in this case, no.
Q. But you consulted historical control data sets.

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A. In order to conduct a fulsome analysis of the study, yes, I did look at historical controls.
Q. Was this use of historical controls based on using the study results from the 60 total animals, as reported in your report, including the interim sacrificed?
A. I believe that's correct.
Q. Let's take a look at the Brammer study, which is the very next page in your expert report on Page 17.
A. Yes.
Q. And, here again, we're -- we have a discussion on historical control data, this time using Giknis and Clifford 2011. Correct?
A. Correct.
Q. And in your analysis, what did you -- what led you to use the Giknis and Clifford 2011 historical control data set?
A. In my analysis of the data, I believe that I looked at Dr. Portier's report and noted that he used it, so I went and looked at it as well.
Q. And did you find it sufficient for the purposes of this study?
A. Did I find what sufficient for the purposes of this study?
Q. A sufficient historical control database to

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apply to the Brammer results.
A. I believe it was appropriate to apply in this study.
Q. Do you know the years of the Giknis and Clifford data set?
A. Do we have a copy here that we can refer to?
Q. I'm just asking if you know it off the top of your head.
A. Off the top of my head, I don't know.
Q. Okay. Did you look at each of the studies in this historical controlled data set to determine whether there was an outlier causing such a large range?
A. (No response.)
Q. In liver adenomas in Wistar rats.
A. How would you look at an outlier in an individual study, when it only reports the total number?
Q. The historical control data set, is what I asked about.
Did you look at each of the studies in the historical control data set taken as a whole and determine whether there was an outlier at any of that historical control data, such that the range of zero to 17.5 percent for liver adenomas in Wistar rats is not a

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wholly correct number?
A. It's a correct number for the range for all of the studies that they looked at.
In order to determine whether or not there's a statistical outlier, one would be required to do a Grubbs test. I did not do a Grubbs test here.
Q. Dr. Foster, are you aware that 13 of the 16 studies in the historical control data set, Giknis and Clifford 2011, show a response of less than or equal to 2 percent?
A. I don't have recollection of that at this point in time.
Q. Would it change your application of the Giknis and Clifford data set to -- to note liver adenomas with a range of zero to 17 1/2 percent?
MR. DHINDSA: Objection.
A. It wouldn't cause me to change my view. I would still look at the range. They -- we have studies that have had high response. One might want to look at that and say, well, we've got a study here that's a high response; how do I interpret it.
So as -- looking at it as one factor in my overall assessment.
Q. Dr. Foster, 81 percent of the studies in the historical control database for Giknis and Clifford

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report equal or less than 2 percent incidence of liver adenomas in Wistar rats.
Given that knowledge, isn't the range of zero to 17.5 percent an example of how using ranges for historical controls may skew results?
MR. DHINDSA: Objection.
A. It's an example of where you have a wide range. And if you take an average or look at the percentage of below a certain value, you can get a different number.
(Discussion held off the record.)
MR. GOODALE: Off the record at 5:17 p.m.
(Recess held.)
MR. GOODALE: We're back on the record at 5:31 p.m.
BY MS. ROBERTSON:
Q. I'm marking as Exhibit Foster 18-20 an article entitled "Proliferative and Non-proliferative Lesions in the Heart and Vasculature in Mice", as authored by Elwell, et al.
(Foster Deposition Exhibit 18-20 - Elwell Article - marked for identification.)
Q. Dr. Foster, is this the article that we talked about earlier that is your Citation 39 in your Materials Considered -- Consulted list at the end of

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your expert report?
A. Yes, this is the article.
Q. We were handed this article by Monsanto counsel around 2:00 p.m. today after the lunch break. Did you give this report to the attorneys at the break?
A. Yes.
Q. How did you locate this article today?
A. What do you mean, how did I locate it today?
Q. How is it that you were able to give it to your attorneys today?
A. When it was requested that I obtain --
MR. DHINDSA: I'm going to object to that line of inquiry.
MS. ROBERTSON: How did he get the document?
MR. DHINDSA: Yeah, I think it's -- conversations between counsel and the deponent are privileged.
Q. Dr. Foster, did Monsanto's counsel give you this document?
A. No, they did not.
Q. How did you come about obtaining this document?
A. I found this document through my PubMed search, and I reviewed the document. And then when I was informed that you wanted a copy of it, as I

mentioned earlier today, I had already left my office and was not able to locate it in my home office, and so I asked one of my colleagues if they could look for it for me.

Q. And that's how you located the document today.

A. They were able to provide me with the photocopy, yes.

Q. Not had time to study the document or review the document, given the density, but you have reviewed this document in connection with forming your expert opinion. Correct?

A. I have reviewed this document, yes.

Q. I'd like to direct your attention to Page 5, which is shown in the upper right-hand corner.

A. The number 5 is, yes.

Q. Yes. And, also, on that page in the right-hand column we see hemangiosarcomas. Correct?

A. Correct.

Q. Is it not -- it's true, isn't it, that this is the only place that mentions hemangiosarcomas with discussion?

A. What do you mean, "with discussion"?

Q. Let me ask it another way, Dr. Foster.

Does Page 5, the paragraph on

hemangiosarcomas, support your statement in your expert report wherein you cite to Elwell for the premise that hemangiosarcomas are common in CD-1 mice?

A. This is one area in the report in which they talk about it.

Q. And is this the area that supports your statement on Page 22 that tumors are rare in human, but they are common neoplasms of mice, citing to Elwell 2004?

A. This is one area where I saw it. And then the other, I note in the introduction they also point out. The -- given the relatively common occurrence of spontaneous background lesions and the potential for treatment of disk lesions in the cardiovascular system --

(Witness asked for clarification by the reporter.)

A. Sorry. So in the introduction, they point out, "Proliferative and non-proliferative lesions of the blood vessels are not uncommon in mice. Given the relatively common occurrences in spontaneous and background lesions --" so this -- they're giving this as the rationale for why they're doing this study.

Q. Okay. And so is their rationale what caused you to cite to Elwell 2004 on Page 22 of your expert

report?

A. Part of the reason. And then I also cited -- or I didn't cite in the text, but I also have Cohen in my Materials Considered list, which also looked at the same issue.

Q. And in the Elwell article, can you please point me to where Elwell is stating that in CD-1 mice hemangiosarcomas are common neoplasms?

A. So in the introduction, they talk about it. And then when you go to Page 5, they are talking about Figures 2 -- 22 to 23, where they talk about it.

Q. Okay. And in the introduction, can you please direct me -- because I must be missing it -- where they are talking about CD-1 mice.

A. They are talking about mice in general.

Q. Isn't it true that tumor incidences in mice occurred differently among different strains?

MR. DHINDSA: Objection. Vague.

A. Yes. Do you have a -- are you -- are you suggesting that CD-1 mice might be different than other mice?

Q. Well, isn't it true that CD-1 mice are different than other mice?

A. I'm not sure that the -- the information that's providing [sic] in this report is suggesting

that it's different for CD-1 mice. They are talking about mice in general. These people, I believe, are pathologists, so I'm going to rely upon them.

Q. Okay. And in the section from this article on Page 2, first column, Amyloidosis, we get a specific reference to B6C3F1 strains and CD-1 strains. Correct?

A. Yes.

Q. But we don't get any specific such reference in the hemangiosarcoma section, correct?

A. To a specific strain being different? No.

Q. Okay. Doctor, if I could direct your attention to Page 18 of your expert report.

A. (Witness complies.)

Q. We talked a lot today about comparing studies, quality of studies, considering studies. Correct?

A. Yes.

Q. And as part of your consideration for the studies and the material, you note the publication year as relevant to study publications, for example, in the context of applying historic controls. Correct?

A. I've -- I'm sorry. Are you referring to when I cite -- say Wood 2009a?

Q. Just generally throughout your report, you do have a mind toward citing to data and literature that

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matches or is within the similar time frame as the study you're discussing. Correct?
A. I'm trying to do that, yes.
Q. Okay.
A. And, also, just trying to make it possible so that we can refer to the right study. This is a -- a voluminous amount of -- of literature to look at. And as we've both noted, looking at the individual studies and looking at Greim, there is some difficulty in matching them up, so.
Q. Right. And just so the record's clear, we're talking this time about Wood and the Wistar rat study. Not the mouse. We previously talked about the mouse.
A. This is -- excuse me -- Greim Study 8, and it's in the Wistar rats, that's correct.
Q. Okay. And you have a reference here related to mammary gland tumors and that they are common in rats with a prevalence of 57 percent in female Sprague-Dawley rats that are allowed to live out their naturally lifespan. Correct?
A. Correct.
Q. Are animals -- were animals in the Wood 2009 rat study allowed to live out their natural lifespan?
A. No. They were -- this was a rat study, so it was a two-year carcinogenicity study.

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Q. Is it true that mammary gland tumor incidence is likely to increase the longer the rat lives?
A. Yes.
Q. And isn't it true that the Wood 2009 rat study was only an 18-month study?
A. I believe it was a two-year cancer bioassay.
Q. Doctor, does your review in Greim just now refresh your recollection that this is a 18-month study in rats?
A. I'm just looking for the right place. So there is the Nufarm 2009b. This is Wood Study No. 8.
Q. Yes.
A. And this is a duration of two years.
Q. And you relied on Greim to get this data, not the actual study report. Correct? The study data. Sorry.
A. In this case, I believe I looked at Greim for the data tables, and then I also -- if I remember correctly, I also looked at Dr. Portier's report.
Q. Okay. Dr. Foster, are you familiar with the journal Environmental Health Perspectives?
A. Sorry. The Journal of Environmental Health Perspectives.
Q. Perhaps I got the name wrong. I better check.

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(Discussion held off the record.)
Q. Yeah, Environmental Health Perspectives.
A. I --
Q. Are you familiar with that journal?
A. I -- I am familiar with that journal. I've published it in the past, and I have reviewed for them.
Q. And you find it to be a reputable journal?
A. I don't know what you mean by "reputable".
Q. Well-respected?
A. It is one of many scientific journals that we publish in.
Q. Yeah. Standing alone. But it's not, for example, a journal that's supported by lobbyists or anything like that. It's a scientific journal.
A. Environmental Health Perspectives is a journal that is published by the Environmental Health -- sorry -- Environmental Protection Agency. I believe they own and operate it.
Q. Okay. By chance, have you read the articles by Lauren Zeise, Z-E-I-S-E, et al., on dose response relationships for carcinogens?
A. It's not ringing a bell for me at the moment.
Q. Dr. Portier -- I'm sorry. My apologies.
Dr. Foster, isn't it true that animal bioassays can be looked at using non-linearity and

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linear trends?
A. I would have to look at the paper in order to get some context about where this is being referred to.
Q. Dr. Foster, do you use linear trends when analyzing the data for your expert report?
A. I have as one -- one factor looked at that.
Q. And when you see a dose response that doesn't offer a linear trend, isn't it true that you determined the dose response is not compound-related?
A. Not based solely on that issue, no.
Q. But in part.
A. It is a factor that I look at, yes.
Q. Isn't it true that a rare tumor will likely result in a sublinear trend?
A. It is possible, yes.
Q. And under your analysis, rare tumors would be dismissed or speculated, at least, because further evaluation would need -- be needed, even though a dose response is shown.
MR. DHINDSA: Objection.
A. I don't understand the question. Can you restate that, please.
Q. If you observe a sublinear trend in the data, you don't determine that that sublinear trend is a positive study. Correct?

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MR. DHINDSA: Objection.
A. I don't determine that it is a positive or negative study based on that factor alone.
Q. Now, you see the list. Many publications -- or -- yeah, publications, journals where you're a journal referee. We discussed that a little bit earlier this morning. Correct?
A. Yes, we did.
Q. And can I use journal referee to be synonymous with peer reviewer in this context? Is that fair?
A. That would be fair.
Q. And on your CV you list that you're a peer reviewer for the journal article Critical Reviews in Toxicology. Correct?
A. I have reviewed on occasion, ad hoc basis, for Critical Reviews in Toxicology, yes.
Q. So you're not a permanent peer reviewer for Critical Reviews in Toxicology. Is that what you're telling me?
A. To my knowledge, there is no journal that has such a thing as a permanent reviewer.
Q. So it's more that you are contacted by the journal when they think that your expertise could be utilized as a peer reviewer because a paper is going to

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be submitted. Is that correct?
A. Not because a paper is going to be submitted, but because a paper has been submitted.
Q. Apologies.
A. That they think I might --
Q. Right.
A. -- be able to provide them with a timely review for.
Q. Okay. So I'll clear that up. So you get contacted by the journal after a paper has been submitted, and that journal determines that perhaps your expertise would make you a valuable peer reviewer, and you're given the opportunity as to whether you want to accept that -- accept the offer from the journal to become a peer reviewer for a submitted article.
A. For that article, yes.
Q. Okay. We talked about when the -- after an article is peer-reviewed, it often has revisions sent back to the article author. Do you recall that testimony?
A. Yes.
Q. Okay. And in -- you stated that the return time for resubmission to the journal varies. Correct?
A. Yes, I did.
Q. Are there any factors that play into the

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variance, as to when a resubmission may be reviewed again and published?
MR. DHINDSA: Objection.
Q. Like, is there a -- such a thing as a rush review?
A. (No response.)
Q. On a resubmitted paper.
A. I am not familiar with that.
Q. Okay. Have you ever, in your experience as a peer reviewer for any journal, experienced a situation where peer reviewers have sent substantive edits back to the study author, and the study author resubmits the paper in less than a day, and the paper is published the very next day?
A. In my experience, I have -- as a journal editor, I have been on occasion surprised by how quick some authors have turned around their -- their revisions. And I have seen quick -- within a day or -- a day or two.
Q. And what about within a day or two and then the journal accepts it? Have you seen that as well?
A. I think I've done it.
Q. You've accepted same day?
A. If I'm in the office, and I'm getting -- I get an email from the -- the journal that says, one of

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the papers that has been assigned to you as by an editor is in your dashboard to look at, I try and look at them as quickly as I can in order to keep my email from getting plugged up. And, so, yeah, I try and deal with them quickly.
Q. And so you deal with them as a peer reviewer, and the other peer reviewers assigned to this article are, likewise, reviewing the resubmission by the author, correct? You're not the only person that's looking at a resubmission.
A. No. If -- if there has been two or three expert peer reviewers assigned to it, then when it is -- comes back into the journal, it's automatically sent to the two or three peer reviewers to reassess.
Q. And do each of the peer reviewers need to accept the changes from the resubmitted article before it's published?
A. They need to respond one way or the other.
Q. How important is it to you in your practice, your many years of experience, to have access to data when you're completing a scientific article for publication?
MR. DHINDSA: Objection.
Q. You do a lot of the data yourself for -- in those instances where you're not conducting your own

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study and then publishing on it. How important is it to you -- is it to you to have the underlying data before you publish an article?

MR. DHINDSA: Objection.

A. I don't -- I'm not following your question. I -- in my typical practice, I am reviewing -- I -- I run the -- the study in my lab or together with my collaborators. We generate the data, we review it, and write the paper. So I have the data.

Q. So the data is all your own. You don't have -- you don't ever publish or author anything on someone else's data. You use your own data.

Q. If I'm doing a systematic or critical review of the literature, then I would do a computerized data search in order to obtain all the published literature in both the peer-reviewed press and the gray literature, to the extent possible, for my review.

Q. And that would be a review article, though. Correct?

A. That would be a review article.

Q. Okay. When you were reviewing the Greim review article and the supplemental tables, did -- did it ever cross your mind as to whether Greim might underreport any tumor incidences seen in the data sets?

A. Did it cross my mind that he would

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underreport it?

Q. That underreporting could happen?

A. That's not something that crossed my mind. I don't have any reason to believe that did or did not occur.

Q. Okay. Well, let's look at --

(Discussion held off the record.)

Q. So if we look at Greim, the review article, Exhibit 18-16 --

A. I have the paper.

(Discussion held off the record.)

Q. And under my interpretation, the --

(Discussion held off the record.)

Q. -- the Atkinson studies were conducted by Cheminova. I have in my notes the Atkinson studies are No. 3 and 11 in the Greim paper.

A. Okay.

Q. I'll give you a moment to review, and if you could confirm that Cheminova 1993a and b are Atkinson, we can move on.

(Discussion held off the record.)

Q. Dr. Foster, can we agree that the Cheminova studies refer to the Atkinson studies?

A. It appears that they do.

Q. Okay. Great. And in the review article by

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Greim on Page 199, Study 11, Cheminova 1 -- 1993b.

A. Sorry. P age 199.

Q. Yep, the Cheminova study.

A. Table 15. I'm sorry?

Q. No, just the Cheminova study. I just want to get your attention there. That's where -- that's where I want to look at.

Now, Table 16 on the next page relates to the Atkinson findings as reported by Greim in the summary article. Correct?

A. This refers to Cheminova study, yes; 1993b.

Q. Okay. And in Table 16, Study 11, do we see any reporting of hemangiosarcomas?

A. They are not listing them here as being included in this table.

Q. Okay. Yet you discuss hemangiosarcomas on Page 22 -- Pages 22 and 23 of your expert report. Correct?

A. Yes.

Q. Okay. So in the -- in the context of reviewing data to form an expert opinion or even to publish an article, there is a true value in receiving underlying data. Correct?

MR. DHINDSA: Objection.

Q. A review article would not be enough.

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MR. DHINDSA: Objection.

A. In this case, I'm responding to Dr. Portier, and I would have gone back to Dr. Portier's report to look at that information.

Q. Okay. So the hemangiosarcoma discussion in your report is using some of Dr. Portier's data that he reports on.

A. Correct.

(Discussion held off the record.)

MS. ROBERTSON: Can we take a five-minute break, please.

MR. GOODALE: Off the record at 6:00 p.m.

(Recess held.)

MR. GOODALE: We're back on the record at 6:07 p.m.

MS. ROBERTSON: Dr. Foster, I appreciate your time today. I pass the witness.

THE WITNESS: Sorry?

MS. ROBERTSON: I pass the witness.

MR. DHINDSA: Can we have a few minutes, please, off the record?

MR. GOODALE: Off the record at 6:07 p.m.

(Recess held.)

MR. GOODALE: We're back on the record at 6:18 p.m.

EXAMINATION

BY MR. DHINDSA:

Q. Dr. Foster, do you recall earlier today answering some questions relating to an article and data tables by Greim?

A. Yes, I do.

Q. How did you use the Greim paper and data tables in drafting your expert report?

A. In drafting my expert report, I used the original data to the extent that it was available to me. And in the events that I didn't have original data, then I referred to the Greim summary tables. And, if necessary, for additional context, I may have gone to the Greim paper to look at some of the text.

Q. When you say "Greim summary tables", are you referring to data tables?

A. Sorry. The data tables?

Q. When you -- when you --

A. The data tables, yes. Not the tables in the text, but the data tables.

Q. I'm going to hand to you what's been previously marked as Deposition Exhibits Foster 18-17 and 18-18. These are two articles authored by Dr. Baldrick.

Do you recall testifying about those earlier?

A. I recall looking at these papers earlier today, yes.

Q. And you cited those papers in your expert report; is that right?

A. I did, yes.

Q. For what purpose?

A. Well, there's a -- as you know, there's a ton of literature in this litigation. And had I had the chance to get to Table 6, you can see that looking at two control groups that have been conducted presumably at the same time, in the same lab, the same housing conditions, with the same diet, that there's a range that you -- you see that -- even between the two groups. So, presumably, the same pathologists -- everything else held the same. And, therefore, I believe it's important to look at the historical controls as well and look at the range. I think the range is the more appropriate thing to examine.

MR. DHINDSA: No further questions.

MS. ROBERTSON: I have one follow-up question, Dr. Foster.

EXAMINATION

BY MS. ROBERTSON:

Q. We can stick with Exhibits 18-17 and 18-18. We're correct that even at the table you cite at Table 6, that the range is used there in the context of dual controls. Correct?

A. This is in the context of dual controls, yes.

MS. ROBERTSON: Thank you, Dr. Foster. No further questions.

MR. DHINDSA: Nothing further.

MR. GOODALE: This marks the end of Media 5 in today's proceedings in the deposition of Dr. Warren G. Foster. Going off the record at 6:20 p.m.

* * * * *

STATE OF NEW YORK)
) SUPREME COURT
COUNTY OF NEW YORK)

I, Janis L. Ferguson, RPR, CRR, a Notary Public in and for the State of New York, do hereby certify:

That the witness whose testimony appears herein before was, before the commencement of his/her testimony, duly sworn to testify the truth, the whole truth, and nothing but the truth; that the testimony was taken pursuant to notice at the time and place herein set forth; that said testimony was taken down in shorthand by me and after, under my supervision, transcribed into the English language, and I hereby certify the foregoing testimony is a full, true, and correct transcription of the shorthand notes so taken.

I further certify that I am neither counsel for, nor related to any parties to said action, nor in any way interested in the outcome thereof.

IN WITNESS WHEREOF, I have hereunto subscribed my name this the 16th day of September, 2017.

Janis L. Ferguson, RPR, CRR
Notary Public in and for the State of New York
My Commission expires: 5/28/2021
Registration No. 01FE6282686

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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 WITNESS REPORT

of

Warren G. Foster, Ph.D., FCAHS
Professor
McMaster University
Hamilton, Ontario, Canada

Table of Contents

1.0 Introduction:

Glyphosate (N-(phosphonomethyl)glycine) is a broad spectrum post emergent herbicide that has been registered for use globally. Though it has been confused with organophosphate pesticides, glyphosate is not an organophosphate but rather an aminophosphonic analogue of the natural amino acid glycine (Greim et al. 2015). Briefly, glyphosate is a highly water soluble (hydrophilic) chemical that is poorly absorbed from the skin (Wester et al., 1991). Oral exposure to glyphosate is considered to be the primary route of exposure (EPA, 2016). Absorption from the gut is estimated to be less than 30% of the oral exposure with negligible tissue accumulation and the majority excreted unchanged in the urine. Inhalation exposure is minimal and dermal penetration is low. The glyphosate that is absorbed from the skin is rapidly excreted mainly via the urine within 24 hrs. (Wester et al., 1991; Chan, 1992). Maximal human exposures of 0.47 mg/kg/day were estimated for children (1-2 years) and up to 0.03-7 mg/kg/day for mixer/loaders assuming that personal protective equipment was not employed (EPA, 2016). Regulatory agencies worldwide have independently assessed the ***human health risk*** for glyphosate, consistently reaching the conclusion that glyphosate is not a carcinogen. In contrast, in March 2015 the International Agency for Research on Cancer (IARC) finalized its ***health hazard*** assessment of glyphosate, a less stringent process than risk assessment, concluding that glyphosate is a probable carcinogen (classification 2A).

I have been retained as an expert to render opinions concerning the experimental rodent carcinogenicity bioassay literature including, but not limited to, those described by IARC and plaintiffs' experts purporting to link glyphosate exposure in rodents and carcinogenicity. Following a review of the available data I have concluded that glyphosate is not a rodent carcinogen. If glyphosate were carcinogenic in rodents, one would expect to see replication of carcinogenic findings of a particular tumor type across multiple studies. Such evidence is absent from this comprehensive and rich data set.

The following sections outline my background and expertise, approach taken in conducting my objective review of the data, assessment of the evidence, and my scientific opinions of the data. The opinions I plan to offer in this matter will include opinions set forth in this report, opinions that may be elicited from me in discussing or elaborating on those areas and/or responding to the testimony of plaintiffs' experts and any opinions formed based upon further literature review and review of any additional materials. My opinions are based on my review of the relevant scientific literature; materials specifically related to this case and related proceedings; and my education, training, research, and experience. A list of materials I have considered in forming my opinions is included in Section 6.0 below.

2.0 Background and Qualifications:

My expertise is in toxicology with a special focus on reproductive toxicology and environmental carcinogenesis. I have continuously carried out research in the field since 1991 conducting primarily animal studies according to established internationally accepted test guidelines

designed to provide data for government regulatory needs. I have also carried out numerous studies designed to assess human exposure and define mechanistic pathways to explain toxic phenomena including cancer. Over the course of my career, my expertise in the field has been recognized as shown by numerous invitations to provide expert technical advice to non-government organizations, government, and industry since 1991. Further detail of my background and expertise are summarized below:

(i) I obtained my undergraduate training (Hon. B.Sc.) in Human Biology from the University of Guelph, Guelph, Ontario, Canada (1979) and a M.Sc. from the University of Guelph in medical sciences (1986). I completed my doctoral training in medical sciences in 1991 at McMaster University.

(ii) I joined the staff of the Environmental Health Directorate at Health Canada in 1990 where I worked as a reproductive toxicologist. I was promoted to Head, Reproductive Toxicology Section and subsequently served as the Acting Division Chief, Environmental Health Directorate. As a Health Canada scientist, I oversaw an active research program consisting of four Sections focused on general, inhalation, reproductive/developmental toxicology and mutagenicity. During my career, I have designed and carried out animal studies to provide data necessary for regulatory assessment of chemicals under the Canadian Environmental Protection Act. Specifically, I designed, executed, and performed relevant data analyses, interpreted the study findings, and published the results of numerous animal studies for the assessment of the general, endocrine, reproductive and developmental toxicity as well as carcinogenesis of a broad range of chemicals including pesticides. I have also designed and executed numerous animal and tissue culture studies designed to elucidate mechanisms underlying the pathophysiology of observed adverse outcomes. I also participated in several epidemiological studies designed to assess human exposure to metals and persistent organic compounds to evaluate the potential impact of these exposures on human health. I have continuously carried out research and am recognized for my expertise in animal models and working at the intersection between animal research and clinical research (translational science). My productivity in the field and impact of my work has led to numerous invitations to present my findings at major international medical and scientific conferences and provide expert advice to government, non-government organizations, and industry since 1991 as detailed in my attached CV.

(iii) I am currently a Professor in the Department of Obstetrics and Gynecology at McMaster University where I lead a productive and well-funded research program designed to assess human exposure and the effect of environmental chemicals on adverse outcome pathways including oxidative stress, inflammation, autophagy, apoptosis, and cell proliferation; all of which are normal physiological processes that have also been associated with the pathogenesis of human disease including cancer. A separate line of inquiry in my laboratory is focused on the identification of clinical markers of endometriosis and novel therapeutic interventions. I am also a voluntary clinical professor in the Department of Reproductive Medicine at the University of California, San Diego where I conduct collaborative research in women's health.

(iv) McMaster University is a leading Canadian research intensive university that trains medical, undergraduate and graduate students in the medical sciences. I am involved in the teaching of undergraduate Bachelor of Health Sciences and Medical Students (Ovarian regulation and physiology of selective estrogen receptor modulators and selective progesterone receptor modulators). I teach several graduate courses (Reproductive Endocrinology and Environmental Toxicology) and directly supervise the training of graduate students and postdoctoral fellows. I mentor residents on their research projects and have served as the resident research coordinator and a member of the resident postgraduate education program as well as the postgraduate evaluation committee. I am also a member of the animal advisory committee and the animal research ethics board in the Faculty of Health Sciences at McMaster University.

(v) I have been continuously supported by the Canadian Institutes of Health Research (CIHR) since 2001. My research has also been supported by grants and contracts from the Natural Sciences and Engineering Research Council, The New York Community Trust, the American Chemistry Council, and Health Canada. I have published greater than 180 total career peer reviewed scientific publications. In addition, I have been invited to give over 92 invited scientific presentations and more than 137 presentations at scientific and medical conferences over the course of my career. My work is frequently cited with over 5,820 citations and an H-Index=45 (Measure of impact on the field).

(vi) I have served on numerous local, national and international expert panels including: National coordinator for the Organization for Economic Cooperation and Development (OECD) Test Chemical Guideline Program (bioassays for toxicology and carcinogenesis); WHO/IPCS Steering Group on Endocrine Disruptors, and Member, Council of Canadian Academies Panel, Integrating Emerging Technologies into Chemical Safety Assessment, and Expert Panel on the Integrated Testing of Pesticides. Recently, I also served as a member of an IARC expert monograph working group. I have also served on numerous, Local, National, and International grant review committees (e.g. Canadian Cancer Society, CIHR, NIH, and EPA-STAR), editorial boards, and have been elected by my peers to serve on the board of several prestigious scientific societies (e.g. Society of Toxicology Canada and the Canadian Fertility and Andrology Society) and recently was elected as a Fellow of the Canadian Academy of Health Sciences (CAHS).

(vii) I am currently an editor of the Journal of Applied Toxicology and a member of the editorial boards of the Journal of Toxicology and Environmental Health: B Critical Reviews, Reproductive Toxicology, Immunology, Endocrine & Metabolic Agents in Medicinal Chemistry, and the Faculty of 1000. Further details of my training and contributions to science are provided in my curriculum vitae included in section 7.0 of this report.

3.0 Statement of Opinions and rationale:

Unless otherwise stated, all the opinions expressed in this report are to a reasonable degree of scientific certainty including my opinion that glyphosate is not a rodent carcinogen. My opinion is based on my interpretation of the experimental animal studies and the following points:

(1) The animal studies have been conducted in accordance with recognized animal test protocols for carcinogenicity;
(2) Appropriate routes of test agent administration and dose ranges were used in these studies;
(3) The dose ranges used cover low concentrations through, and in some studies, well above the limit dose of 1,000 mg/kg/day;
(4) The methods of tissue analysis and data interpretation were appropriate;
(5) There is insufficient reliable scientific evidence of a dose-response relationship;
(6) Tumor incidences are generally within historical control ranges with the order of priority as follows:
    a. concurrent controls;
    b. historical controls from the same lab within 2-3 years; and
    c. historical controls from other labs or the same lab beyond 2-3 years.
(7) In all studies reviewed the data fails to show evidence of tumor progression;
(8) There is a lack of consistency of findings of tumor types across the animal studies (mice and rat) including within the same strain of rodent model; and
(9) Additional factors that further call into question the biological plausibility of putative compound-related changes.

Thus, taken together, these data demonstrate that tumors identified in the animal studies are most likely spontaneously occurring and unrelated to glyphosate exposure. Therefore, there is no scientifically reliable basis to justify a conclusion that glyphosate is a rodent carcinogen. Furthermore, I am not aware of any reliable scientific evidence available that Roundup formulations are a rodent carcinogen. I will use the following paragraphs to provide a detailed description of the literature reviewed, the methods of analysis employed to arrive at my conclusions, and highlight in each case how the study contributed to the above conclusions.

Literature reviewed: A critical review of the literature was carried out in which I reviewed all available case materials, which are summarized in the literature-cited section of this report. I reviewed detailed data reports arising from industry sponsored animal carcinogenicity studies, the IARC report on Glyphosate (IARC 2015), EPA evaluations and correspondence, and other regulatory documents (e.g. EFSA, BFR, and the Science Advisory Panel report). In addition, I also carried out an independent literature search using PubMed on August 18th, 2016 and updated on October 3rd, 2016, May 17th, 2017, and July 7th, 2017 to ensure that all relevant literature was included in my assessment. Bibliographies of each paper were also searched for additional relevant papers. To assess the literature, I assigned greater weight to studies conducted according to internationally accepted test guidelines for carcinogenicity for the following reasons:

(1) Greater weight was assigned to studies using at least three dose levels (low, medium, and high) allowing for assessment of dose-response characteristics. Dose levels that covered broad ranges of concentrations including a high dose that approached or included the limit dose (1,000 mg/Kg/day) were also given greater weight. Studies that exceeded the limit dose with concentrations that fell below 5% of the overall diet were also highly valued in my assessment. It is essential to include in the study a high dose group represented by the limit dose or 5% diet concentration to assure that animals have been exposed to a concentration of the test agent that will markedly exceed human exposure. If the dose is in the 5% range it should be below the maximally tolerated dose (MTD) to mitigate potential frank toxicity that would confound the results. Thus, evidence of adverse health effects was also considered in my assessment in reaching my final conclusions.
(2) It is essential that cancer studies use an adequate number of animals in each treatment group to detect statistically significant increases in neoplastic lesions. For this reason, studies that used at least 50 animals/treatment group were viewed as compliant with regulatory test guidelines. Studies that failed to use an adequate number of animals/groups were assigned lower weight in my analysis.
(3) Study duration for cancer studies typically should be at least two years in length (24 months) in rats or 18 months for certain strains of mice. This is done to capture the majority of life expectancy of the animals. Unless justified by evidence of increased mortality or neoplastic lesions of sufficient size or number to induce unreasonable pain or suffering, experimental animal studies of shorter duration were given less weight.
(4) Tumor progression was considered important in my assessment owing to current understanding of the mechanisms of chemical carcinogenesis. Consequently, if present, I would assign greater weight to studies in which evidence of chemical-induced tumor promotion was demonstrable. Additionally, factors contributing to biological plausibility were evaluated.

4.0 Assessment of Carcinogenicity:

Introduction and definitions - To understand how exposure to a chemical can lead to cancer, it is necessary to introduce some definitions and briefly discuss how cancer bioassays are conducted. Cancer refers to a malignant neoplasm (an abnormal growth of tissue that forms a swelling or mass), a lesion resulting from the new or autonomous growth of a tissue. Neoplastic lesions may be either benign (non-cancerous growth of cell mass that does not possess the ability to invade neighboring tissues) or malignant (cell growth that tends to worsen and has the properties of cells that have reverted to a less differentiated form, uncontrolled cell growth, invasiveness, and metastasis). Benign lesions are characterized by slow growth of the tissue that fails to invade surrounding tissues. Examples of benign growths include moles, fibroids in the uterus and endometriosis. In contrast, a malignant neoplasm is characterized by rapid growth,

invasions of surrounding tissue, and metastases (growth of cancer cells in distant tissues). When cancer develops it typically follows the progression from benign to malignant growth.

A chemical carcinogen is any chemical or its metabolite that can induce neoplasia (abnormal growth). Throughout the animal literature I reviewed and the studies cited by plaintiffs' experts (Drs. Jameson, Portier, Neugut, Weisenburger, and Nabhan), reference is made to several different types of tumors. Plaintiffs' experts have noted the different tumors in relevant studies but have failed to carry out a critical appraisal of these studies and the data generated. The evaluation and interpretation of data from such rodent studies is paramount in determining their significance. Plaintiffs' experts merely count several tumors and generate statistical comparisons, often novel and untested, absent further analysis. Critical analyses largely absent from plaintiffs' expert reports include, but are not limited to, biological relevance (e.g. dose response, mechanism, relevant human exposure, and translation from rodents to humans), neoplastic continuum or progression, expected tumor incidences, and replication of tumor types across multiple studies. Therefore, I will describe the different types of tumors here and provide a detailed assessment of each study considered in rebutting the plaintiffs' experts and arriving at my conclusions.

Several different tumor types are discussed in the literature reviewed and therefore definitions are provided. Adenomas are benign tumors in which epithelial cells cluster together and form recognizable glandular structures. Also discussed in one study is an interstitial tumor of the testes. These tumors are also known as Leydig cell tumors (the cells that produce testosterone) a type of tumor that is typically benign although some may progress to malignancy. Another tumor type mentioned in the reports that I reviewed was a hemangioma. A hemangioma is a congenital malformation consisting of a benign tumor made up of newly formed blood vessels. The cause of these benign tumors is unknown and they can appear throughout the body, including the skin, liver, and bones. In contrast, a hemangiosarcoma is a malignant tumor of the blood vessels that has its origin in the vascular endothelium (the cells that line the blood vessel). Finally, also discussed in the animal studies are lymphomas. Lymphoma refers to a group of over a dozen tumors that arise from lymphocytes which are a type of white blood cell.

Multistep pathway to cancer - Cancerous growths are thought to arise through activation of the carcinogenic cascade that involves initiation, promotion, and ultimately neoplastic progression (Cohen and Ellwein 1991). A carcinogen is a physical (e.g. radiation) or chemical agent (or one or more of its metabolites) whose interaction with DNA typically induces a mutation in the genetic code and thus acts as an initiator of cancer. Mutations do not always lead to cancer since cells possess DNA repair mechanisms or the damage occurs in a non-coding region of the DNA. In contrast, clonal expansion of the mutated cell can occur if repair of the damaged DNA is unsuccessful.

Tumor growth occurs through the influence of growth factors or hormones that induce cell proliferation and thus tumor promotion. Substances that are only tumor promoters are typically not mutagenic and are unable to induce neoplastic lesions on their own.

Cancer progression refers to the irreversible conversion of a benign pre-neoplastic lesion to a neoplastic lesion. Chemicals that induce tumor progression are usually genotoxic. Tumor progression can occur spontaneously from the accumulation of chromosomal aberrations or instability of the chromosomes.

Hallmarks of carcinogens - The impact of chemical agents on gene expression, cell signaling pathways, receptor binding and signaling, inflammation, immune surveillance, cell proliferation and nutrient supply has been recognized and are potentially important in the pathogenesis of cancer (Hanahan and Weinberg 2011). Ten key characteristics of chemical carcinogens have been described and summarized (Smith et al. 2016) and cited by Dr. Portier in his expert report. Although chemical carcinogens are reported to induce one or more of the 10 key characteristics, use of these hallmarks as a "rule in" test for carcinogenicity is unfounded. The concentrations and the experimental conditions needed to induce changes in any of the hallmark pathways must be carefully evaluated for their relevance to human health. Indeed, numerous chemicals have one or more hallmarks of carcinogens but the effects can only be produced at concentrations that far exceed potential human exposure.

While rodent carcinogenicity assays are used for identification of potential hazards, it is important to note that not all chemicals that have been shown to be rodent carcinogens have been found to be human carcinogens. Potential reasons for this lack of relationship include: different mechanisms of action in rodents compared to humans; differences in absorption, distribution, metabolism, and excretion; and the concentration of test chemical needed to induce cancer in rodents exceeds concentrations that can effectively be achieved in humans. The assessment of carcinogenic potential and health risk is a complex task involving more than simply counting lesion types and assigning a label. Critical to the process is assessment of the biological relevance of all adverse outcomes enumerated in a study and ultimately evaluation of human exposure relative to doses needed to induce an adverse outcome in the most sensitive animal model accounting for uncertainties in translation of results from animals to humans.

Overview of cancer bioassays - In recognition of the long-term serious health consequences represented by chemical carcinogens, chemicals are routinely screened for their potential to induce cancer. Beginning in the early 1960's the National Cancer Institute began to develop animal test methods for the assessment of potential chemical carcinogenicity. Within a decade the two rodent species, two sex, and two year cancer bioassay was in wide use. Regulatory agencies from multiple countries subsequently standardized, validated, and harmonized rodent carcinogenicity test protocols. Standardized cancer bioassays are regulatory requirements for chemical registration. The World Health Organization (WHO) under the leadership of the Organization for Economic Cooperation and Development (OECD) oversees the International Program on Chemical Safety that is mandated with the development and validation of test guidelines for the assessment of chemical hazards. The OECD Test Guideline Program is responsible for a collection of the most relevant internationally agreed upon testing methods used by governments, industry and independent laboratories to assess the safety of chemical products. Test Guidelines are updated on a regular basis to keep pace with progress in science and countries' regulatory needs. The objectives of OECD carcinogenicity studies (OECD-TG-

451/452) and the combined chronic toxicity and carcinogenicity study (OECD-TG-453) are designed to observe test animals for a major portion of their life span for the development of neoplastic lesions with exposure to at least three doses of a test substance and a vehicle control using an appropriate route of administration (typically oral). Carcinogenicity bioassays are conducted over a period of 24 months for rodents; however, for specific strains of mice a duration of 18 months may be more appropriate, to account for the shorter life-span for these strains (e.g. CD-1 mice). A tumor incidence of 57% was found in Sprague Dawley (SD) rats allowed to live out their entire life-span (Davis et al. 1956). The average life-span of SD rats in this laboratory was approximately 760 ± 21 days and 87% of all tumors appeared after the animals were 540 days of age. Consequently, the study duration of 24 months (730 days) in cancer bioassays has been selected to account for the recognized long latency between initiation of cancer and the detection of tumors that follows tumor promotion and progression. This study design also accounts for compensatory mechanisms (e.g. DNA repair) as well as tissue repair providing an adequate time for tumors to appear. Note that a study may be terminated early should the number of survivors in the lower dose groups or the control group fall below 25 per cent. The study may also be terminated early if the tumor volume attains a size or number of tumors that seriously compromises the health of the animals. It is important to note that two-species, two-sex, rodent cancer bioassays conducted according to test guidelines usually generate reproducible results (Gold et al. 1987; Gold et al. 1989; Haseman and Huff 1987) that are valuable for human risk assessment. It is expected that studies adhering to standard operating procedures and following regulatory study guidelines would produce reproducible findings. Failure of studies to generate replicable data causes concern and calls into question the relevance of the data because of the probability the finding might be due to random chance, normal variation of the outcome, or methodological issues. Scientists faced with divergent results are compelled to explore the reasons for the lack of consistency in the data. Common reasons for lack of reproducible findings include: differences in study methodology; animal model used; duration or amount of test chemical exposure; analytical methods employed; time frame of the study; and normal variation in the outcome being observed.

Interpretation of bioassay results – Evaluation of bioassay results and determination of their importance involves several steps, including assessment of adherence to study protocol, statistical methods, data analysis, and interpretation. When reviewing any study, the first step involves understanding the question being addressed and the appropriateness of the animal model employed. For cancer bioassays, the main points to be addressed are the use of an appropriate rat or mouse strain, randomization to treatment groups, appropriate route of test chemical administration, dose levels that cover a broad range up to and including the limit dose, duration of study that allows for development of tumors, assessment of systemic toxicity, and accepted histopathological methods. In reviewing study reports it is important to consider the statistical methods employed to ensure that prescribed methods have been followed or if alternative methods have been employed, their use has been adequately justified.

Detection of statistically significant differences among and between treatment groups is important to note but their biological relevance must also be determined. Specifically, it is

possible to have statistical significance in the absence of biological relevance and thus the investigator must evaluate whether the changes detected are internally consistent based on the totality of the animal data collected and current understanding of underlying biological mechanism(s). This may involve consideration of the normal range for a given outcome. To do this it is best to make comparisons with concurrent controls or alternatively appropriate historical controls. I agree with Dr. Portier that it is best to compare data with contemporary controls. However, historical controls generated in the same lab within 2-3 years of the study may also provide useful information. If such historical control data is not available then it may be necessary to compare with data outside the preferred time period. However, that data should be used with extreme caution for quantitative analysis due to differences in the genetic makeup of animals of the same species/sex/strain over time and between laboratories.

In assessing rodent bioassay data, evidence that could indicate systemic toxic effects as shown by changes in body weight, stereotypical behaviors, abnormal vocalizations, porphyria, lacrimation, ruffled coat, barbering of the hair or changes in clinical chemistry and hematology should also be considered. The interpretation of bioassay outcome is based on the integration of what is known of study conduct, data produced, statistical analysis, and understanding of the underlying biology for each outcome. Finally, bioassays are carried out with the goal of identifying adverse outcomes for hazard identification. A properly conducted hazard identification, taking into account all of the available relevant evidence, is but one step in the process of determining risk. Risk assessment is a protective process used in regulatory toxicology that is the product of hazard, human exposure, and recognition of translational differences between rodents and humans. Furthermore, the determination of a risk does not necessarily mean causation has been established. Evidence of scientific causation involves the integration of additional issues such as demonstration that human relevant concentrations of the test chemical can reproducibly induce the adverse effects, evidence of human exposure, knowledge of internal dose, target tissue exposure, understanding of mechanism of action, and its applicability to humans. Consequently, these rodent bioassays on their own do not generate data that can establish causal relationships between external exposure and human health. However, these bioassays may generate data that suggests a compound is unlikely to be carcinogenic in humans.

The case of glyphosate is unusual in that there are multiple rodent (mouse and rat) study results from cancer bioassays. As a result, there are individual study results to evaluate. Additionally, results of the data generated can be assessed across studies. Dr. Portier uses a novel statistical approach for generating a test statistic for comparing current results with those of historical controls. I have not seen this approach applied elsewhere in the toxicology literature or in my profession, and thus I am not aware that this is a validated method that has been assessed by scientific peers or achieved general acceptance by the scientific community. In addition, Dr. Portier employs pooling of data across studies which again is a novel statistical approach that has not been peer reviewed, validated, and to my knowledge has not been tested to reach the level of a generally accepted approach in regulatory toxicology. Indeed, Dr. Portier admits that his methodology utilized in his report is novel and untested (Portier report, pg. 21). While pooling

such data has not yet been evaluated, validated, and thus is not generally accepted in the scientific community or ever even done to my knowledge, comparing data from rodent studies is a standard practice and paramount in assessing carcinogenicity.

Further, Dr. Portier acknowledges that "simple evaluation of the positive versus negative findings fails to resolve the issue of which findings are driving the overall responses in these data." (Portier report, p.47). A central concept of science is reproducibility of data both within a laboratory, across laboratories, and over time. The lack of reproducible effects, as revealed by the glyphosate data set, indicates that these effects are not compound-related.

Where statistically significant results are lacking, Dr. Portier repeatedly relies upon so-called "marginal trends" to ascribe significance to statistically insignificant data. In my field of expertise, typical research activity outcomes are either statistically significant at the $p<0.05$ level or they are not. The concept of "marginally significant trends" is not typically used in the biomedical literature.

In contrast to the approach of Dr. Portier I, like other scientists in the field, compare the results from multiple studies mindful of differences in animal strain, doses of test chemical employed, experimental conditions, analytical methods employed, data analysis, and interpretation of the study results. This comparison is undertaken utilizing a qualitative evaluation, with statistical significance forming just one piece of the overall evaluation. The generally accepted scientific methodology, which I employed, involves careful consideration of study design, conduct, analytical methodology, data analysis and interpretation to ensure that the results are not over or under interpreted. Moreover, to fully appreciate the data, a critical and qualitative appraisal of the data is necessary and this cannot be achieved through statistical analysis alone.

5.0 Assessment of experimental animal literature:

Animal studies are essential in regulatory toxicology, particularly in the absence of evidence of human exposure and epidemiological data. Animal studies allow scientists to address important questions that are either unethical or cannot be carried out in human studies. For example, in human studies, exposure to test chemicals and developmental life-stage of exposure are often unknown. Moreover, many target tissues (e.g. brain, liver, and kidney) are not easily accessible and thus cannot be examined in human studies. Thus, surrogate markers are frequently used to detect effects in these tissues. In contrast, experimental animal studies allow for the administration of known quantities of a test chemical of known purity under carefully controlled environmental conditions (temperature, humidity, time of day, lighting conditions, and unlimited access to water and food of controlled nutritional composition) in genetically similar animals of known age, developmental stage and health. Experimental animals are monitored over the course of the study for changes in biochemistry and hematology, allowing for the early detection of changes in health status. At study conclusion, a full necropsy is performed and all organ and

tissue samples undergo careful gross and histopathological assessment by board certified veterinary pathologists. Thus, these studies provide robust data for the detection of potential adverse outcomes for regulatory purposes that cannot be achieved through alternative means. Of additional importance, the concept of multiple comparisons increases the probability of finding differences through chance alone (Squire 1989). Dr. Portier also recognizes the problems multiple comparisons pose with a data set of this magnitude (Portier report, p. 40), though we disagree on the remedy for that problem (see pp. 21 and 47). Dr. Portier further acknowledges that one expects a certain number of positive findings due to chance alone (Portier report, p. 50). Thus, the finding of a statistically significant difference cannot be interpreted by itself to indicate a compound-related effect. Therefore, results of animal studies may elucidate statistically significant effects of treatments that must be evaluated further for their biological relevance.

Glyphosate has been assessed using regulatory toxicology studies in mice and rats. Sufficiently high doses of glyphosate were used in most studies, approaching or exceeding the limit dose as described in regulatory cancer test guidelines (e.g. OECD TG 451). Results from over a dozen regulatory studies revealed spontaneous tumors in several different tissues but all unrelated to glyphosate treatment. In view of the relatively large number of studies that have been carried out, it is remarkable that although incidental tumors unrelated to glyphosate exposure were found in individual studies, there is a consistent absence of evidence via replicated results for carcinogenicity across studies. The lack of reproducible tumor findings in animal studies designed specifically to produce reliable and reproducible results is compelling evidence for a lack of association between glyphosate and carcinogenicity. One should be mindful that rodent bioassays are not hypothesis driven, and require both gross and histopathological evaluation of all tissues thus increasing the probability of false positive results. Indeed, these studies are designed to maximize the potential of detecting compound-related effects at the expense of detecting false positive results. Detection of a statistically significant positive result is not the end of the study analysis but rather only the beginning of the scientific assessment as it is necessary to determine if the findings are spurious or represent biologically important findings. Consequently, I will describe each study in detail in the following sections.

Rat studies

Studies judged as inadequate

In combination, Drs. Neugut, Portier, and Jameson excluded six studies (Reyna, Chruscieleska, Excel, Seralini, Burnett; Pavkov and Wyland), all of which were reported to be negative studies with the exception of one (Seralini et al. 2014). While in total, plaintiffs' experts excluded six studies, they were not in complete agreement. However, given the methodological concerns and the lack of reliance of plaintiffs' experts, I give the six studies referenced above and the plaintiffs' expert opinions based on those same studies minimal weight in my causation analysis and will not discuss these studies further.

Studies judged as adequate

Of the studies judged as adequate, Dr. Portier provides a statistical assessment of the data only whereas Dr. Jameson provides a summary of the results analogous to the listing of data in the IARC report for glyphosate. The entirety of Dr. Neugut's discussion of the animal data is comprised of two paragraphs and an accompanying table. Similarly, Dr. Weisenburger, though acknowledging the existence of numerous negative glyphosate rodent studies, concludes without engaging in generally accepted toxicological analysis that "positive studies listed above cannot be dismissed, and provide sufficient evidence for the carcinogenicity of glyphosate in experimental animals … ." (Weisenburger Report at p. 8). Plaintiffs' experts fail to provide a critical appraisal of the studies or interpretation of the data. Further they fail to discuss potential explanations for lack of consistency of study findings. Hence, the rationale for their conclusions is in my view unsupported. The results of each study and its' biological relevance are described in detail below.

Bio/Dynamics Inc. 1981 Study BDN-77-2062 (Lankas et al., 1981 discussed in Greim et al., 2015 - Study 1): In 1981 Bio/Dynamics Inc. conducted a combined chronic toxicity and carcinogenicity study of glyphosate for the sponsor. Sprague-Dawley rats were exposed to 30, 100 and 300 ppm glyphosate in the diet over the course of their lifetime (26 months). The dose was adjusted according to changes in body weight such that the rats were exposed to 3.05, 10.30, and 31.49 mg/Kg/day for males and 3.37, 11.22, and 34.02 mg/kg/day for females. Body weight, food consumption and clinical laboratory studies were conducted over the course of the study.

Neoplastic lesions were documented in the pituitary and pheochromocytomas in males and females and mammary tumors in females; however, the incidence was similar across all treatment groups and thus is not considered to be treatment related. Interstitial tumors of the testis (Leydig cell tumors) were detected in this study with an incidence of 0, 3, 1, and 6 in the controls, low, medium, and high dose groups, respectively. While the incidence of testicular tumors in the low and medium dose groups was within the highest incidence found for historical control (7%), the incidence of these tumors in the highest dose group (12%) was greater than that for the historical control group examined for this research laboratory. Consequently, neoplastic changes in the testis of the high dose group were evaluated to better elucidate their importance.

The testes received thorough histopathological evaluation. The study pathologists did not report any evidence of any dose related changes but did report a notable absence of compound-related hyperplasia. Hyperplastic changes would be expected to be present in the case of compound-related tumors and indeed to be coincident with the development of lesions. Moreover, there are several additional issues noted in the conduct of the study that impact the relevance of the testicular tumors. Specifically, the number of animals surviving to the end of the study was greater in the highest dose group compared to the control group. This is an important point because it creates the scenario where there were more animals in this group that had the opportunity to develop spontaneous neoplasms and thus could artificially increase the likelihood

of detecting a neoplastic change in this group compared to the control group. Had animals in the control group lived for the same length of time as those in the highest dose group (this is referred to as survival bias), it is possible that no effect may have been found. Furthermore, the absence of testicular tumors in the control group is below the historical range noted for this strain of rat and studies conducted by this laboratory. A lower response rate than expected in the control group could therefore increase the likelihood of detecting a false positive increase in testicular neoplasms.[1] Finally, interstitial testicular tumors have not been replicated in any other study including those in which much higher doses of glyphosate were employed. Moreover, it is relevant to note that, in the studies considered acceptable by plaintiffs' experts, doses similar to Lankas et al., along with much higher doses were employed, and no relationship between glyphosate and interstitial testicular tumors was found.

This study also revealed the presence of spontaneous occurrence of thyroid C cell tumors in females. A statistically significant trend for thyroid C cell carcinomas in the female animals only was observed (1/47, 0/49, 2/50, and 6/47). However, after combining thyroid C cell adenomas and carcinomas, which is appropriate (McConnell 1986), the statistical significance disappears. Although Dr. Portier agrees that combining these tumors is appropriate, he raises concern about these tumors in female rats even though none of the other studies revealed a statistically significant increased incidence of these tumors. I therefore conclude that the presence of thyroid C cell tumors in female rats in this study is not compound-related.

Although pairwise comparisons revealed a statistically significant increase in the number of pancreatic islet cell tumors for the lowest dose group (3.05 mg/kg/day) in male animals only, there was no evidence of a dose response (0/50, 5/50, 2/50, and 3/50). The low incidence of tumors, lack of evidence for tumor progression, absence of a dose response, and consistency with historical controls all support the conclusion that these tumors are not compound-related.

In summary, both the decreased survival in the control group compared to the highest dose group of rats together with the lower incidence of testicular tumors in the control group compared to historical controls increases the likelihood of finding a statistically significant increase in tumors amongst the other dose groups whose biological relevance is questionable. Dr. Portier speculates that the 26-month duration of the study offers unique insights that may be missed in a study lasting only 24 months. However, no evidence is offered and I am not aware of any data demonstrating that a 26-month study would detect interstitial tumors at any different rate than in a 24-month study in dose groups compared to control groups. I therefore conclude that the absence of a dose related increase in incidence of interstitial tumors, the absence of changes that

[1] An example might be illustrative here. If one expects a background rate of 6% for a given tumor in a study with four arms of 50 rats each, one would expect 3 out of 50 rats in each group to have that tumor (or 12 out of 200 overall). However, if the control group has 0% by chance, then one would expect 4 out of 50 rats in the remaining groups to have that tumor by chance because one would still expect 12 rats out of 200 to have that tumor.

would be indicative of tumor progression, and statistical limitations suggests that these tumors are incidental findings unrelated to glyphosate exposure.

Strengths of this study include an appropriate study design, adequate number of animals/dose group, use of three dose groups plus a negative control, appropriate methodology for tissue assessment and statistical analyses of the data. The study was conducted prior to the introduction of standardized and internationally accepted OECD test guidelines for carcinogenicity although much of the methodology is consistent with those guidelines. However, the use of a high dose that was substantially below the limit dose is a weakness of the present study.

MSL-10495 (Stout and Ruecker, 1990; discussed in Greim et al., 2015 - Study 2): This was a chronic study conducted by Monsanto in albino Sprague-Dawley rats (n=60/group) following a two-year cancer bioassay (consistent with the current OECD carcinogenicity TG-453). Rats were fed glyphosate (96.5% pure) in the diet for 24 months. Target doses were 2,000, 8,000, and 20,000 ppm. Using food consumption data, the authors calculated that the rats were exposed to 89, 362, 940 mg/Kg/day for the males and 113, 457, and 1,183 mg/Kg/day for the females of the low, medium, and high dose groups.

There was a treatment-related significant decrease in body weight among the female rats in the highest dose group in the absence of any change in food consumption. Significantly increased liver weight was also found for males in the highest dose group. The number of animals surviving to the conclusion of the study was 29, 38, 34, and 34 for males and 44, 44, 34, and 36 for females. Taken together, these data suggest that the dose selection was considered adequate for a carcinogenicity study. However, signs of toxicity in the highest dose group could confound interpretation of neoplastic changes. Regardless, non-statistically significant neoplastic changes were noted in pancreatic islet cells. Specifically, pancreatic islet cell adenomas (benign lesion) were found in 1/58 (2%), 8/57 (14%), 5/60 (8%), and 7/59 (12%) in the control, low, medium, and high dose group males. In females the incidence was 5/60 (8.33%), 1/60 (1.67%), 4/60 (6.67%), and 0/59 in the control, low, medium and high dose group females, respectively.

I conclude that the pancreatic islet cell adenomas are not treatment-related for several reasons. First, a dose related increase in the incidence of these lesions was not demonstrated in the males and the incidence of these tumors was higher in the control females compared to those treated with glyphosate. Furthermore, while pancreatic islet cell tumors are more common in male than female rats (Majeed 1997), these tumors are known to occur spontaneously in aged Sprague-Dawley rats (Chandra et al. 1992) and the incidence of these lesions in the current study was within the range of historical controls (0-17%)[2]. Moreover, there was no evidence of neoplastic

[2] I have used the range of historical controls as opposed to the mean, which is the common and standard practice in interpreting toxicological data. The range is more relevant compared to the mean because it provides the reviewer with a better appreciation for the spread of the data, which can be variable for many tumors and is thus important to take into consideration (Baldrick 2005; 2007).

progression noted in any of the pancreatic specimens examined and the only carcinoma that was found occurred in a male animal from the control group. Hence, the neoplastic changes documented in this study are in my opinion spontaneously occurring pancreatic islet cell tumors and unrelated to glyphosate treatment.

To complete its review, the United States Environmental Protection Agency (US-EPA) requested additional data on the historical controls for the following lesions: (1) thyroid C-cell adenomas, carcinomas, and hyperplasia; (2) hepatocellular adenomas, carcinomas, and hyperplasia; and (3) keratoacanthomas. A review of the data submitted on incidence of historical controls led to a conclusion that, for all three neoplasms, the incidences for all lesions fell within the range of historical controls and therefore, I conclude that these lesions were spontaneously occurring and unrelated to glyphosate treatment. Dr. Portier reports that there was a statistically significant trend for liver adenomas; however, this disappears when these lesions are combined with hepatocellular adenocarcinomas. I further noted that there was no compound-related replication of these tumors across multiple studies, there was no progression to carcinoma, no evidence of a dose response, and finally no significance when combining adenomas/carcinomas. Accordingly, I conclude within a reasonable degree of scientific certainty that glyphosate was not carcinogenic in this study.

Strengths of this study include use of an appropriate study design, number of animals/dose group, three dose groups and a negative control, appropriate route of exposure, use of a high dose that reached the limit dose, and adequate study duration.

MRID (Brammer, 2001 – discussed in Greim et al., 2015 - Study 7): This study was conducted by Syngenta and included Wistar rats of both sexes (52/group) treated with vehicle or glyphosate (121, 361, and 1214 mg/kg/day for males and 145, 437, 1498 mg/kg/day for females) in the diet for 24 months in a standard cancer bioassay. Strengths of this study include use of an appropriate study design, number of animals/dose group, three dose groups and a negative control, appropriate route of exposure, use of a high dose that exceeded the limit dose, and adequate study duration.

Results of this study revealed the presence of liver adenomas with an incidence of 0/52, 2/52, 0/52, and 5/52 in the control, low, medium, and high dose animals, respectively. It is important to note that in this study, males of the highest dose group were more robust as reflected in a better survival compared to the control group (26/52 vs. 16/52, respectively). Increased survival to the end of the study is relevant because it allows the animals longer exposure time for tumors to spontaneously emerge and thus increases the likelihood of detecting tumors in the high dose group compared to the control group. Furthermore, according to the historical control data cited by Dr. Portier, it is relevant to note that the range of liver adenomas in Wistar rats is 0 to 17.5% (Giknis and Clifford, 2011). Results of the present study are within the range of these historical controls. Thus, the findings of a 10% incidence in adenomas in rats of the highest dose group in

the present study are not in my opinion treatment related. Beyond just a statistical comparison of the numbers, there was no evidence of a dose response and evidence of progression from adenomas to adenocarcinomas was also lacking. Hence, for multiple reasons this is considered a negative carcinogenicity study.

MRID 49987401 (Wood et al., 2009a – discussed in Greim et al., 2015 - Study 8): Adult male and female Wistar rats were treated with vehicle of 95.7% pure glyphosate (95, 317, and 1230 mg/kg/day) in the diet. This was a combined chronic toxicity and carcinogenicity study and conducted according to regulatory guidelines. Strengths of this study include use of an appropriate number of animals/dose group, three dose groups and a negative control, appropriate route of exposure, use of a high dose that exceeded the limit dose, and adequate study duration. Combining a chronic toxicity study with a two-year cancer bioassay is seen as an additional strength of the study owing to the incorporation of additional outcome measures of general toxicity.

Results of this study failed to reveal a statistically significant increase in the incidence of mammary gland adenomas whilst there was a significant trend for increased incidence of mammary gland adenocarcinomas (2/51, 3/51, 1/51, and 6/51). Combination of adenomas and adenocarcinomas was significant using a pair wise test for the highest dose group only (2/51, 3/51, 1/51, and 8/51) and trend analysis was also significant. However, it is noted that there was no evidence of a dose response. Moreover, I note that in the Brammer study discussed above there was no evidence of a statistically significant trend for an increase in the number of mammary gland adenomas and adenocarcinomas. Furthermore, the incidence of adenomas and adenocarcinomas was higher in the controls of the Brammer study than in the treated animals. The same results were found in the Suresh study discussed in detail below.

Taken together these considerations lead me to conclude that mammary gland tumors in this study were not compound-related. In the summary of the study, there was no mention of proliferative changes. Dr. Portier asserts without reference that mammary adenocarcinomas can arise without the presence of adenomas. It is unclear where this comment derives from and it is inconsistent with the generally accepted view of cancer pathobiology. Mammary gland tumors are common in rats with a prevalence of 57% in female Sprague-Dawley rats allowed to live out their natural life-span (Davis et al. 1956) and within the historical control range for these tumors in Wistar rats (Giknis and Clifford, 2011). I note that there were no statistically significant mammary tumors detected in other well conducted studies in Wistar (Brammer, 2001; and Suresh, 1996) or any Sprague Dawley (Lankas, 1981; Enemoto, 1997; Atkinson et al., 1993; Stout and Ruecker, 1990) rats as summarized in Table 8 from Dr. Portier's report (p. 33).

A non-significant increase in skin keratoacanthomas (2/51/ 3/51/ 0/51, and 6/51) was noted but trend analysis was significant in the males. The dose response was not detected and the lack of pair-wise statistical significance suggests that this pattern of tumors is not compound-related. Furthermore, the lack of reproducibility of these findings - in other well conducted studies - further indicates that these findings were not compound-related.

In summary, this was a well-designed carcinogenicity bioassay that employed an appropriate route of exposure, number of animals, dose groups, and study duration. The maximal dose exceeded the regulatory requirement for a limit dose. Absence of evidence of a significant dose response for the mammary tumors, a common spontaneously occurring tumor, and lack of findings of tumor progression lead me to conclude that the mammary tumors were unrelated to glyphosate treatment. Therefore, it is my assessment that this is a well-conducted negative study.

Atkinson et al. 1993 (discussed in Greim et al., 2015 - Study 3): A combined chronic toxicity and carcinogenicity study was carried out using dietary exposure of glyphosate (98.9% pure) administered to 50 Sprague Dawley rats of both sexes/dose group. Five dose groups including a vehicle control were used. The males received 0, 11, 112, 320, and 1,147 mg/Kg BW/day while the females received 0, 12, 109, 347, and 1,134 mg/Kg BW/day for 104 weeks. Interim sacrifices were carried out at one-year in an additional 35 rats from each sex and dose group.

There were no adverse effects of treatments and histopathological assessment of tissues failed to reveal any morphological abnormalities in this study. Furthermore, there was no increase in the incidence of neoplasia in any tissue studied. Although there were no significant glyphosate effects on thyroid tumor incidence, Dr. Portier notes a statistically significant trend for follicular thyroid tumors based on the assumption that the unexamined mid-dose groups would not have any tumors. Thyroid follicular tumors are relatively common in rats with an average incidence of 3.79% and a range of 0-14% in control animals studied over 24 months (Giknis and Clifford, 2004). Thus, the high dose tumor incidence falls within the range of historical controls suggesting that these tumors are not compound-related. Moreover, the lack of reproducibility of these tumors in other studies further suggests that these are incidental findings that are not related to glyphosate exposure.

This study has a number of strengths including the study design employed, use of an appropriate route of administration, inclusion of four dose groups in addition to a vehicle control, use of an appropriate high dose, appropriate number of animals/dose group, two-year duration of the study, and inclusion of interim analysis of animals for signs of toxicity. No weaknesses were detected with the study design, execution or interpretation of the study results. Dr. Portier considers this a weak study because it failed to examine the pathology of all animals in mid dose groups. However, Dr. Portier's own report (p. 27) showed that adding in additional animals to the mid-dose groups did not produce a meaningful change in the p-trend unless one assumes that all animals in the mid dose groups would not have had tumors. However, as noted above, these are common tumors and thus this maybe an unreasonable assumption. Therefore, I assign little

weight to Dr. Portier's criticism especially because this study was consistent with the state of the art of the time that it was conducted. Accordingly, this study was considered a strong negative study that lends strength to the view that glyphosate is not a carcinogen.

Suresh, 1996 (discussed by Greim et al., 2015 – Study 4): In this study, 50 Sprague Dawley rats of each sex were assigned to one of three dose groups or a control. The animals were administered glyphosate (96-96.8% pure) at doses of 0, 6.3, 59.4, and 595.2 mg/Kg BW/day (males) and 0, 8.6, 88.5, and 886 mg/Kg BW/day (females) in the diet for 24 months. Results of this study did not elicit any evidence of adverse health effects and no morphological abnormalities were demonstrated in the histopathological assessment of the animal tissues studied. Furthermore, there was no evidence of a statistically significant increase the trend in tumor incidence in any of the tissues studied.

Overall, this is a well-designed study with numerous strengths including an appropriate study design for the assessment of carcinogenicity, use of three dose groups plus a control, route of glyphosate administration, and appropriate study length. A weakness of this study is the highest dose group falls below the limit dose.

Enemoto, 1997 (discussed in Greim et al., 2015 – Study 6): This was a combined chronic toxicity and carcinogenicity study carried out by Arysta Life Sciences in 50 Sprague Dawley rats for each sex and dose group. Rats were administered glyphosate in the diet at dose levels of 0, 104, 354, and 1127 mg/kg BW/day (males) and 0, 115, 393, and 1247 mg/kg BW/day (females) for two-years. Interim sacrifices were carried out at 26, 52, and 78 weeks in 10 rats of each sex/dose group. This study did not reveal any signs of adverse effects and histopathological assessment of the tissues did not demonstrate any evidence of any morphological abnormalities. However, although pair wise comparisons failed to reveal a statistically significant effect of treatments, Dr. Portier reports that there was a statistically significant trend for kidney adenomas (p. 30). Histopathological assessment of the tissues failed to reveal any evidence of hyperplasia and thus there was no evidence of tumor progression. The lack of evidence of morphological abnormalities (hyperplasia), absence of significant differences by pair wise comparisons, absence of dose response, and failure to replicate these findings in other well-conducted studies leads me to conclude that this observed trend is not glyphosate related.

This study has a number of strengths including the study design employed, use of an appropriate route of administration, inclusion of three dose groups in addition to a vehicle control, use of an appropriate high dose, appropriate number of animals/dose group, two-year duration of the study, and inclusion of interim analysis of animals for signs of toxicity. No weaknesses were detected with the study design, execution or interpretation of the study results. Accordingly, this negative study lends strength to the view that glyphosate is not a carcinogen.

Synthesis of rat studies

In summary, while potential neoplastic changes were documented in these studies, the totality of the evidence leads me to conclude that these tumors were not glyphosate related. This is especially because, as Dr. Portier readily admits, statistically significant results are to be expected given the high number of tests performed across these studies. These studies all failed to demonstrate any evidence of statistically significant compound-related increased incidence of tumors. These studies are highly relevant and were generally conducted according to well-established and internationally harmonized regulatory carcinogenicity test guidelines. The conclusions in the current report diverge from those of Dr. Portier. Reasons for our divergent conclusions can in part be explained by differences in the methodology and analyses carried out. Specifically, in the current assessment of the data, I have assessed the overall scientific quality of the studies in addition to evaluating neoplastic changes in the context of the totality of scientific knowledge rather than limiting discussion to just a statistical analysis of the data. The absence of compound-related tumor findings in each of these individual negative studies indicates that in total glyphosate is not carcinogenic in rats. Therefore, I conclude that there is no scientifically reliable evidence of glyphosate carcinogenicity in rats.

Mouse studies

Studies judged as inadequate

The doses of glyphosate used in the Reyna and Gordon (1974) and Pavkov and Turner (1987) studies were inadequate and thus were excluded from my analysis. Dr. Portier similarly considered these studies and excluded them from his analysis. These studies were all negative; however, in view of their limitations and consistency of opinions on these studies they will not be discussed further here.

Studies judged as adequate

Knezevich and Hogan, 1983 (discussed by Greim et al., 2015 - Study 10): The results of this mouse study conducted by Monsanto have received considerable attention owing to the pattern of kidney tubule lesions. Briefly, CD-1 mice (50/dose group for both sexes) were administered 99.8% pure glyphosate (161, 835, and 4,945 mg/Kg/day for male mice and 195, 968, and 6,069 mg/Kg/day for female mice) in the diet for 24 months. Results of this study revealed an 11% loss in body weight of the male animals in the highest dose group compared to controls. In addition, this study revealed that glyphosate treatment had no statistically significant effect on survival; however, kidney adenomas were found in 0/49, 0/49, 1/50, and 3/50 male mice. A reanalysis of

the tissue blocks identified one additional adenoma in the control group changing the dose response to 1/49, 0/49, 1/50 and 3/50.

Since it is typical of large cancer bioassays to only grossly examine the whole organ and to cut a single paraffin section for histopathological analysis, it is possible that even more tumors could be identified and further insight gained from examination of additional tissue sections in all four dose groups. Therefore, additional sections were cut for histopathological assessment and further insight was sought. Subsequently, a Pathology Working Group (PWG) met to review the kidney adenoma and carcinoma data. It is noteworthy that the PWG unanimously agreed that the control mouse tumor was present and should be considered. As Dr. Portier notes, with the tumor in the control mouse included there are no statistically significant differences. Moreover, I note Dr. Portier's statistical analysis indicated that none of the other mouse cancer bioassays to assess the carcinogenicity of glyphosate generated statistically significant incidences of compound-related kidney tumors using the guideline Fisher test or Cochran-Armitage trend analysis. The high dose of glyphosate used gives me confidence that that the absence of significant changes in kidney tumors is a genuine negative finding.

From my review of the data and subsequent analyses together with a review of the relevant correspondence, I conclude that the absence of a dose response together with lack of evidence of tumor progression supports the conclusion that these tumors are spontaneously occurring and unrelated to treatment. Drs. Neugut and Jameson use the *p* trend from the IARC assessment to justify their conclusions of a statistically significant trend yet Dr. Portier disagrees with this conclusion. Moreover, the dose levels employed were at or near the limit dose for the medium dose group whereas in the highest dose group they are 5 times above the limit dose for the male high dose group. While an 11% loss in body weight in the highest dose group of males was detected no compound-related tumors were demonstrated. Finally, the step sectioning employed makes it even more unlikely that the tumors were a compound-related effect, as extra sections failed to identify any new tumors in any dose group.

Atkinson, 1993b – (discussed in Greim et al., 2015 - Study 11): In this carcinogenicity study, 50 mice/dose group of each sex were administered 97% pure glyphosate (98, 297, and 988 mg/Kg/day for males and 102, 298, and 1,000 mg/Kg/day for females) in the diet for 24 months. No pre-neoplastic or related neoplastic lesions were detected. Incidental pituitary adenomas were noted and there was a non-significant increase in bronchioalveolar adenomas of the males only. Dr. Portier suggests that some of these tumors are marginally significant. However, as previously noted in my report, the concept of marginal significance would not typically be accepted in any credible scientific publication. There was a significant trend in hemangiosarcomas with 4/45 (8.9%) lesions found in the high dose group of males only. While these tumors are rare in humans (Weiss 2008) they are common neoplasms of mice (Elwell 2004), suggesting a potential different underlying mechanism for their development in mice compared to humans. Also note that the two-year hemangiosarcoma incidence data reported for historical controls in CD-1 mice ranges up to 12% (Giknis 2000). This incidence is well within the range of the historical controls

cited by Dr. Portier[3]. Moreover, since these tumors were not detected in a statistically significant trend in male mice in other appropriately conducted cancer bioassays, the lack of replication weighs against considering these tumors to be treatment related. Finally, I note that kidney adenomas in this study were found in a dose pattern of 2, 2, 0, and 0. This pattern contrasts with that reported previously in mice (Knezevich and Hogan, 1983) with a pattern of 1, 0, 1, and 3. These conflicting data further illustrate the lack of consistency of data across studies and further indicate the lack of compound-related effects. This is a strong study owing to the study design, and the dose levels used, including a dose representative of the limit dose, and absence of confounding systemic toxicity. Hence, this study is considered a negative study.

Sugimoto, 1997 (discussed by Greim et al., 2015 - Study 12): A chronic study in ICR-CD-1 mice (50/dose group) treated with 97.6% pure Glyphosate (165, 838, and 4,438 in mg/kg/day in males and 153, 787, and 4,116 mg/Kg/day for female animals) in the diet for 18 months was performed consistent with an OECD carcinogenicity TG. In this study, malignant lymphomas were reported 2/50, 2/50, 0/50, and 6/50. The absence of a dose response, lack of statistical significance by Fisher pair wise comparison, and absence of compound-related effects on lymphomas in other well conducted mouse cancer bioassays lead me to conclude that these tumors are not compound-related. Furthermore, 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).

A statistically significant increased incidence of hemangiomas (a non-malignant tumor) was found in the female mice only with a pattern of 0/50, 0/50, 2/50, and 5/50. However, effects seen at the high dose are potentially confounded by signs of systemic toxicity as revealed by liquid stool, retarded growth, and reduced food consumption (Greim et al. 2015). These are non-malignant lesions of unknown cause that generally appear early in life. The absence of evidence of tumor progression in an 18-month study is reassuring that glyphosate is not carcinogenic. In addition, I note that there were no compound-related hemangiomas found in other well designed carcinogenicity bioassays. Thus, potential compound-related effects in the high dose group of this study are considered less reliable.

In summary, this study has numerous strengths including study design including multiple dose groups, dose range and duration of the study and is therefore regarded as a strongly negative study.

[3]Dr. Portier appears to confuse historical control data for "whole body" hemangiosarcomas as capturing all hemangiosarcomas. Thus, he does not count hemangiosarcomas reported in the Giknis data at other sites, like the liver. In fact, hemangiosarcomas are a vascular tumor that appears throughout the body and thus it may be best to report these tumors as the number of mice with these tumors regardless of site.

Wood et al., 2009b – (discussed in Greim et al., 2015 - Study 14): In this chronic toxicity study, CD-1 mice (50/sex/treatment group) were given free access to food containing 95.7% pure glyphosate (71, 234, and 810 mg/Kg/day for male mice and 97.9, 300, and 1,081 mg/kg/day for female mice) for 80 weeks. Lung tumors and malignant lymphomas were detected in the male mice. While Dr. Portier argues that rodent and human NHLs are similar, it is unclear what he means. Specifically, are they similar in the biological processes of their origin, their pathobiology, incidence, progression, or ultimate impact on health? Contrary to Dr. Portier's suggestion, clear differences in the biological development of lymphomas in rodents and humans have been described (Morse, 2003) leading me to question whether the connection between lymphoma in mice and NHL in humans can be definitively established. Consequently, the published evidence, along with the known difficulty of directly extrapolating animal findings to humans, suggests that these tumors cannot be considered similar as suggested by Dr. Portier.

In this study, there was a statistically significant increase in the trend for the incidence of malignant lymphomas in the male mice. Historical controls from the same lab were available. The historical background incidence was 12% in an 18-month study (SafePharm) and thus the incidence in the high dose group in the current study is consistent with historical controls. Furthermore, lymphomas are common tumors in mice (Haseman et al. 1998; Ward 2006). The historical control data cited by Dr. Portier (Giknis and Clifford, 2005) indicate that it is unusual to have zero lymphomas in a control group. This observation, together with the absence of malignant lymphomas reported for the control group of the current study and considering the historical control rate of 12% in the same laboratory, suggests that the finding of statistically significant differences is most likely a statistical artifact. Therefore, I conclude that there were no treatment-related tumors in this study.

Treatment had no effect on lung adenomas but a trend towards an increase in lung adenocarcinomas was detected although statistical significance could not be demonstrated for the high dose group. The lack of agreement between the Fisher's comparison test and assessment of a trend is less convincing than if both are significant and prompts further analysis. Furthermore, the combined incidence of lung tumors (14/51, 12/51, 16/51, and 15/51) in this study lacks any evidence of a dose response and statistically significant changes could not be demonstrated. Moreover, absence of evidence of preneoplastic changes and tumor progression was noted indicating lack of compound-related effects. Dr. Portier speculates that tumors could arise by alternative mechanisms that do not involve pre-neoplastic lesions but fails to provide any citation to support his opinion. This notion runs contrary to widely accepted understanding of tumor pathobiology and thus is speculative at best. Therefore, I conclude that these are spontaneously occurring lesions unrelated to treatment.

This study has numerous strengths including study design including multiple dose groups, dose range, and number of animals/dose group. The 80-week duration of the study is shorter than the 24 months used for rat studies but is consistent with regulatory requirements for this strain of mice. Consequently, this study is regarded as a negative study.

Kumar et al., 2001 – (discussed in Greim et al., 2015 - Study 13): This study was conducted in Swiss Albino mice and failed to show evidence of morphological abnormalities although there was a statistically significant pairwise increase in the number of malignant lymphomas seen in the highest dose group; however, a statistically significant trend was not detected.

This study was noted to be of questionable value in a prior review (Greim et al., 2015) owing to a possible viral infection amongst the study animals. I note that this study was excluded from consideration by EPA and Dr. Jameson but that Dr. Portier considered this study. Furthermore, in Dr. Portier's revised report (p. 43), he cites a recent memo from Martens (2017) asserting that the incidences for malignant lymphomas and kidney adenomas described in Greim et al., (2015) and BFR (2013) are incorrect. I am troubled by the potential existence of multiple data sets for the same study and the lack of explanation or evidence of data verification. Consequently, the existence of two different data sets and lack of data validation together with the questionable value of this study owing to the potential viral infection leads me to conclude that this study is unreliable and thus was excluded from my analysis.

Synthesis of mouse studies

In summary, a statistically significant trend towards an increase in incidental tumors in varying tissues was reported in four studies (Knezevich and Hogan, 1983; Atkinson, 1993b; Wood et al., 2009b; and Sugimoto, 1997). However, looking beyond a simple statistical analysis of the data to include a comparison of incidence with concurrent controls, historical controls or the relevant literature suggests that these tumors did not depart from normal variation for the individual tumor types. The lack of consistent evidence of dose response further indicates that glyphosate is not carcinogenic. Furthermore, the lack of evidence for tumor progression and absence of statistically significant effects when benign and malignant tumors were combined adds further strength to the conclusion that any effects were not compound-related. I also found that there was no replication of potential compound-related effects across these studies.

I note that these studies are highly relevant and were conducted consistent with well-established test guidelines. The conclusions in the current report diverge from those of Dr. Portier. Reasons for our divergent conclusions can in part be explained by differences in the methodology and analyses carried out. Specifically, in the current assessment of the data, I assessed the overall scientific quality of the study in addition to evaluating neoplastic changes in the context of the totality of scientific knowledge. My analysis extends beyond that of Dr. Portier who limits discussion to a statistical analysis of the data only, utilizing novel statistical procedures without

scientific validation supported only by unreferenced speculation about potential causes. The absence of compound-related tumor findings in each of these individual negative studies indicates that in total glyphosate is not carcinogenic. Therefore, I conclude that there is no scientifically reliable evidence of glyphosate carcinogenicity in mice.

Synthesis of animal data

My review of the animal literature on the potential carcinogenicity of glyphosate revealed a robust data set. These studies were conducted over a wide span of time including introduction of regulatory test guidelines for carcinogenicity testing. I note that the majority of the studies reviewed followed regulatory guidelines for or were consistent with carcinogenicity testing guideline requirements.

Dr. Portier in his report argues (p. 52) that you cannot compare data across animal studies if you also argue that the data cannot be combined in a pooled analysis of the kind he carries out. However, it is a very different thing to look at results across studies you know are similar but have some important differences as opposed to treating them as if they are one big study suitable for combining in an unvalidated pooled analysis. Specifically, important differences between studies include a) different time periods, b) different labs, c) different doses, d) different rodent stocks, and e) known genetic drift. Animal studies are designed to control for or minimize the effect of other sources of variation that would confound the detection of a compound-related effect within the study. However, if you combine the data from multiple animal studies then you cannot exclude the influence of the above noted variables on the outcomes of interest (e.g. tumors). If you have a bias in time going one way (i.e. an increase in stomach tumors in that particular strain from 1970 – 2000), then that might produce significance when in fact there is no compound-related effect. Similarly, if there is a trend towards a decrease in incidence for a particular tumor over time, then combining data would increase the odds of not detecting tumors when they were in fact present. It is routine for toxicologists to compare the results of studies whereas combining studies in a single statistical analysis is not the current scientific standard. Although all studies detected tumors and some detected statistically significant increases of tumors, it is my opinion that the occurrences of these tumors were, within a reasonable degree of scientific certainty, incidental findings unrelated to glyphosate treatment. Glyphosate does not induce rodent tumors and thus, animal carcinogenicity experiments do not support the hypothesis that glyphosate poses a ***health risk to humans***. The basis for my conclusions arise from multiple lines of consideration including the lack of consistency of the data across studies, weakness of the reported associations, lack of dose response characteristics, and absence of biological plausibility. Details of my considerations are described in the following paragraphs.

The animal studies reviewed were conducted according to or consistent with standardized and internationally recognized carcinogenicity test guidelines. Test guidelines are designed to produce robust and reproducible data. However, in the studies that I reviewed, I found no

consistency of tumor findings across the studies and tumors identified in the individual studies are, in my opinion, nothing more than statistical anomalies arising from multiple comparisons, unusually low prevalence of tumors in the control groups for common tumor types, decreased survival of control animals relative to treated animals, or evidence of systemic toxicity in the high dose group. Thus, there is a lack of consistency for any association of glyphosate exposure and tumor development. It was noted that a statistically significant trend was detected for hemangiosarcomas, a relatively common neoplasm in mice (Elwell 2004), in one mouse study (Atkinson, 1993) and was not replicated in other mouse studies. If glyphosate was acting as a carcinogen then I would expect the data to be reproducible with neoplastic changes in one study being replicated by other carefully conducted studies as previously described (Gold et al. 1987; Gold et al. 1989). Although there may be small variations between animals and studies, the mechanism of compound action is expected to remain constant and thus tumors in a given target tissue should be reproducible across animal studies. Indeed, I agree with Dr. Portier when he states that replication of studies "is critical in most scientific debates." (p. 5). Furthermore, I note that these regulatory studies typically assessed a broad spectrum of outcome measures including histopathological assessment of major organs. Therefore, as designed the regulatory studies favor the detection of false positive adverse outcomes (finding non-treatment related tumors) in preference to false negatives (missing detection of a treatment-induced tumor). In view of the lack of reproducibility of the tumor data between studies I conclude that these tumors are not compound-related. This view is further supported by similarity of incidence with concurrent and historical controls. While I appreciate that it is best to compare results with contemporaneous historical controls, this is not always possible especially with retrospective data. However, I note that the incidence of the tumors is generally in agreement with the published literature on tumor incidence in rats and mice (Chandra et al., 1992; Davis et al., 1956; Haseman et al., 1998; Majeed 1997; Prejean et al., 1973; Ward 2006; Giknis 2000; and Giknis and Clifford, 2011) providing further assurance that the observed tumor findings are spontaneously occurring and not attributable to glyphosate treatment. Thus, I conclude that the observed tumors are false positives and cannot be attributed to glyphosate treatment.

In addition to the lack of consistency across the studies, I further note that there is a general lack of a dose response for the tumor data. The dose response patterns reported in the reviewed studies can be characterized as inconsistent and in most cases statistically non-significant. Thus, the statistically significant dose-response curves when observed were of questionable biological relevance. It is important to acknowledge that, in almost all the cases, when tumor incidence became an observation of interest, it was almost exclusively a result of increased incidence in the highest dose group. Several studies used doses that were slightly to well above the limit dose (Brammer, 2001; Wood et al., 2009a; Knezevich and Hogan, 1983; Sugimoto, 1997). While this is acceptable when dosing through the diet, it remains important to ensure that the dose used is not inducing systemic toxicity that could confound interpretation of the study results. Moreover, the translational importance of potential adverse findings in these studies to humans is questionable. Therefore, I conclude that there is no scientifically reliable evidence from the studies reviewed that glyphosate treatment, under the conditions of these animal studies, can be considered carcinogenic.

In the context of assessing the animal carcinogenicity of glyphosate, I also assessed the biological plausibility that glyphosate is carcinogenic. Specifically, carcinogenesis is widely acknowledged to be a multistep process involving tumor initiation, promotion, and progression. Central to the process of carcinogenesis is the process of tumor initiation and tumor progression arising from genotoxic effects of a test chemical or its metabolites. While my task was to assess the animal literature, I note that the genotoxicity studies with glyphosate were both numerous and almost all (98%) were negative (Greim et al., 2015).

I further searched the literature for any evidence that glyphosate could act as a tumor promoter. One study suggested that glyphosate could act as a tumor promoter in a skin carcinogenicity test (George et al. 2010); however, any such mechanism remains elusive. While plaintiffs' expert Dr. Portier cites the preceding study as evidence of glyphosate's potential to act as a tumor promoter, this study has numerous shortcomings including but not limited to: no positive vehicle control, no defined source of substances or purity, low numbers of animals, and lack of pathological analysis. Therefore, I conclude that this poorly defined study does not provide convincing (or reliable) support for the notion that glyphosate acts as a tumor promoter.

From my review of the literature, I conclude that the carcinogenicity of glyphosate has been thoroughly evaluated according to validated and internationally recognized carcinogenicity test guidelines. Dr. Portier is correct when he notes, "it is clear that not every tumor shows a positive trend with glyphosate exposure." (pg. 46). In fact, the vast majority do not. Multiple well designed and executed studies conducted in rats and mice reveal that tumors are not more common in glyphosate treated animals than in the concurrent control groups. When perceived differences in tumor incidence were detected, careful evaluation of animal survival, body weight, historical control incidence, dose-response, and assessment for signs of tumor progression showed that tumors did not occur with higher incidence in the treatment groups compared to controls and thus glyphosate was not carcinogenic. Assessment of animal survival and body weight, as well as comparison with historical controls and histopathological assessment of proliferation and tumor progression are standard and expected procedures carried out routinely by scientists in regulatory, government, and academic laboratories worldwide. Thus, as an end-point, carcinogenesis does not meet the standard required for the establishment of a no effect level in the hazard identification step of the risk assessment process. Moreover, the lack of consistency of effects across well designed regulatory carcinogenicity studies, weakness of the evidence for any association in the animal studies, flat or non-linear dose-response, and absence of credible or reproducible evidence for biological plausibility further add confidence to the conclusion that glyphosate is not a carcinogen, a conclusion that is consistent with independent reviews from multiple expert government regulatory panels from around the globe (EFSA, US-EPA, BFR etc.).

In summary, I conclude that, on the basis of multiple carcinogenicity studies conducted in rats and mice, there is no scientifically reliable evidence of glyphosate-induced increased tumor incidence. I disagree with the conclusions of Drs. Portier, Jameson, Weisenburger, Neugut, and Nabhan that any of the individual glyphosate rodent studies discussed in their reports demonstrates that glyphosate is a rodent carcinogen, let alone that there are any replicated findings of tumor-related effects. Accordingly, I disagree with Dr. Portier's statement that in the rodent carcinogenicity studies "there is clear evidence of a biological gradient" (Portier report at p. 75). Moreover, any extrapolation of the incidental tumors found (all of which are unrelated to glyphosate) to humans is scientifically implausible given the differences in relevant dosing, as well as the translational challenges in extrapolating from animals to humans. Additionally, pooling of these studies is an unproven approach that makes no toxicological sense. The hallmark signs of carcinogenicity are absent from the robust glyphosate data set. The glyphosate data does not demonstrate: a dose-response relationship between glyphosate exposure and tumors; tumor progression (neoplastic continuum); or a biologically plausible mechanism of action. Moreover tumor incidences are generally what one would expect when considering pairwise and historical controls, and the expected number of positive findings due to chance alone. The absence of glyphosate-induced tumor incidence in any one study, given the large number of studies, is compelling evidence that glyphosate is not carcinogenic. With such a robust data set, if glyphosate were carcinogenic, one would expect to see evidence of carcinogenicity not only in an individual study, but replication of carcinogenic findings in a particular tumor type across multiple studies. Accordingly, I conclude that, within a reasonable degree of scientific certainty, glyphosate is not a rodent carcinogen.

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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	**PLAINTIFFS' NOTICE TO TAKE ORAL AND VIDEOTAPED DEPOSITION OF DR. WARREN G. FOSTER**

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. Warren G. Foster on September 15, 2017** before a person duly authorized to administer oaths. The deposition shall commence at **9:00 a.m. ET at Sheraton Gateway Hotel, Terminal 3, Toronto AMF, Toronto, ON, L5P 1C4, Canada.** 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 5, 2017

Respectfully submitted,

/s/ Robin Greenwald
Robin Greenwald
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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. Warren G. Foster

(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	09/12/2017 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: 09/05/2017

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. Christopher Corcoran, Dr. William Fleming, Dr. Jay Goodman, Dr. Lorelei Mucci, Dr. Jennifer Rider, and Dr. Thomas Rosol.

Dated: September 5, 2017

Respectfully submitted,

/s/ Robin Greenwald

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 26 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Use of historical data in determining the weight of evidence from kidney tumor incidence in the Glyphosate two-year feeding study; and some remarks on false positives

TO: Reto Engler, Chief
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

FROM: Herbert Lacayo, Statistician
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

Herbert Lacayo! Feb 26, 1985

THRU: Bertram Litt, Statistics Team Leader
Scientific Mission Support Staff
TOX/HED/OPP (TS-769C)

3/24/85

BACKGROUND

The Glyphosate feeding study (EPA Reg. #: 524-308, Caswell #: 661A, Accession #: 251007-014) on Charles River CD-1 mice generated renal tubular adenomas in male mice at the 5000 and 30000 ppm dose levels. The registrant (Monsanto) claims that such tumors are "unrelated to treatment." (ref.1). In support of that they provide historical data from Bio/dynamics and two other laboratories (ref.2).

With respect to historical data we note the large number and variety of factors which influence the life history of rodents in chronic studies. Hence, it is generally agreed that the most relevant historical controls are experiments from the subject laboratory studied within a 3 to 4 year "window" (ref.3).

SUMMARY

The main purpose of this memo is to show one way historical data may be used to evaluate the significance of tumors in the glyphosate feeding study. When these data are so used we can conclude that Glyphosate dosing has a statistically significant effect (at the p ≈ .006 level) in the production of kidney tumors in male mice. The appropriate procedure is outlined in the next section entitled Use of Historical Data. The last Section, Remarks on False Positives, addresses some comments by Monsanto (Ref.1) on this subject. That section outlines some of the weaknesses in Monsanto's position.

USE OF HISTORICAL DATA

The following information was derived from Reference 2.

Data Source*	p (est.of tumor rate)	Sigma (est.of standard deviation)
Bio/dynamics	.00368	.00212
IRD Corp.	.00437	.00109
Combined	.00399	.00094

The value p = .00368, derived from Bio/dynamics data is a reasonable choice to use as a historical control. The data are from the same laboratory that performed the Glyphosate study and are within the appropriate 3-4 year time "window" (ref.3). Further, the standard deviation of the estimate is reasonably small.

We will now examine the Monsanto contention that the kidney tumors are unrelated to treatment. (i.e. Glyphosate has no effect on kidney tumors). First, consider the tumor rate in the Glyphosate Study: 4/198 = .0202 ---

In contrast, Bio/dynamics has the lower historical rate:

3/815 = .00368

The relevant question is: What is the probability that the 198 CD-1 mice in the Glyphosate study will produce by pure chance 4 or more mice with kidney tumors? Another way of stating this is - How likely are we to have a tumor rate of .0202 --- for the Glyphosate study given that the historical rata is .00368?

Questions of this type may be answered from manipulation of the relevant distribution which, in this case is the Binomial:

$$P(r \text{ out of } n \text{ mice have tumors}) = \binom{n}{r} p^r q^{n-r}$$

Where: n = the # of male mice in the study

r = the # of male mice with kidney tumors

p = .00368, the historical probability that an individual male mouse will develop kidney tumors.

q = 1 - p

*This does not include Hazleton Laboratories America, Inc. due to the small sample size of that data set

Using the above distribution and elementary but tedious calculations, we generate the following table:

# of mice with tumor	Probability that r or more mice will have tumors in a study with 198 male mice
r = 0	1.
1	.518177
2	.165711
3	.037443
4	.006481

This last table indicates that based on a historical rate of p= .00368 that the probability of seeing 3 or more mice with kidney tumors is about .037; and the probability of seeing 4 or more such mice (i.e. seeing what in fact happened) is about .0064. We note that even considering data from I.R.D., the p value is about .01.

Under such circumstances a prudent person would reject the Monsanto assumption that Glyphosate dosing has no effect on kidney tumor production. Another way of saying this is that if Glyphosate were truly unrelated to kidney production we would expect to see 4 or more tumors in less than 1 out of 100 experiments of the type sponsored by Monsanto. Thus, Glyphosate is suspect.

REMARKS ON FALSE POSITIVES

In ref. 1 Monsanto notes that "...if 20 types of lesions were evaluated at a probability level of .05, the number expected to be positive would not be one in 20, but rather the probability would be 64 in 100, an unacceptably high value..." Monsanto is referring to the well-known fact that by examining enough data it is likely that one will find an excess of some tumor type by chance alone; thus generating a false positive.

The Monsanto argument required the following assumptions:

1. A mouse may develop 20 distinct and independent (in the statistical sense) types of tumors.
2. The probability of each tumor type in a typical mouse is .05.

It follows from the above that:

$$P(\text{a mouse has at least one tumor}) = 1 - .95^{20} = .6415$$

Hence in 100 mice one would on the average see 64 with tumors. Monsanto proposes to avoid this "problem" of false positives by analyzing the study" ...at the .01 probability level."

We disagree with the Registrants position. First, even if one did analyze the study at the .01 level as they suggest it would still result (using the same mathematics as before) in seeing 18 mice out of 100 with tumors. And hence one still has the problem of false positives from the registrant's viewpoint. But this causes something worse from a regulatory viewpoint. We have decreased the false positive rate (i.e., the probability of saying that a chemical causes tumors when in fact it does not) at the cost of increasing the false negative rate (i.e., the probability of saying that a chemical doesn't cause tumors when in fact it does). The Registrant wishes to avoid false positives while those concerned with the public health wish to avoid false negatives. Hence, for this reason alone Monsanto's argument is unacceptable.

We further disagree as follows:

1. The two assumptions needed to support the Monsanto argument are themselves in need of support (especially the requirement for statistical independence).
2. False positive results are less likely to occur with rare tumors (ref. 5). And the tumors in question are rare.

Viewpoint is a key issue. Our viewpoint is one of protecting the public health when we see suspicious data. it is not our job to protect registrants from false positives. We sympathyze with the Registrants problem; but they will have to demonstrate that this positive result is false.

Finally, we mention that none of the tumors occurred in the control or low dose groups. Instead there was one at 5000 ppm and 3 at the 30000 ppm dose level. This together with the previous comments make it likely that there is a dose-tumor relationship for Glyphosate.

REFERENCES

1. Letter from Monsanto (signed by Frank. S. Serdy) to EPA (Attn: Robert J. Taylor) dated Feb. 5, 1985.

2. Letter from Monsanto (signed by Robert W. Street) to EPA (Attn: Robert J. Taylor) dated March 20, 1984.

3. J.K. Haseman, et al: Use of Historical Control Data in Carcinogenicity Studies in Rodents - Toxicologic Pathology - 12:126-134. 1984.

4. TOX Branch Memo from William Dykstra to Robert Taylor dated 9/4/84.

5. T.R. Fears et al: False-Positive and False-Negative Rates for Carcinogenicity. Cancer Research. 271:1941-1945. July 1977.

CFR 180.364 Glyphosate Roundup 3/12/85

File last updated 3/12/85

ACCEPTABLE DAILY INTAKE DATA **DRAFT**

RAC,Liver NOEL mg/kg	ppm	S.F.	ADI mg/kg/day	MPI mg/day(60kg)
10.000	200.00	100	0.1000	6.0000

Published Tolerances

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Grain Crops(64)	0.100	13.79	0.02069
Avocados(6)	0.200	0.03	0.00005
Citrus Fruits(33)	0.200	3.81	0.01144
Coffee(36)	1.000	0.75	0.01119
Grapes, inc raisins(50)	0.100	0.49	0.00074
Leafy Vegetables(80)	0.200	2.76	0.00828
Nuts(101)	0.200	0.10	0.00031
Pome Fruits(120)	0.200	2.79	0.00837
Root Crop Veg(138)	0.100	11.00	0.03299
Seed&Pod Veg(143)	0.200	3.36	0.01098
Palm Oil(202)	0.100	0.03	0.00005
Pistachio nuts(210)	0.200	0.03	0.00009
Asparagus(5)	0.200	0.14	0.00043
Bananas(7)	0.200	1.42	0.00426
Olives(104)	0.100	0.06	0.00009
Stone Fruits(151)	0.200	1.25	0.00374
Sugar,cane&beet(154)	2.000	3.64	0.10915
Molasses(96)	20.000	0.03	0.00920
Cranberries(44)	0.200	0.03	0.00009
Cottonseed (oil)(41)	15.000	0.15	0.03375
Kidney(203)	0.500	0.03	0.00023
Liver(211)	0.500	0.03	0.00023
Peanuts(115)	0.100	0.36	0.00054
Guava(184)	0.200	0.03	0.00009
Papayas(109)	0.200	0.03	0.00009
Mangoes(83)	0.200	0.03	0.00009
Soybeans (oil)(148)	6.000	0.92	0.08263
Pineapple(123)	0.100	0.30	0.00044
Fish,shellfish(59)	0.250	1.08	0.00406
Cucurbits(49)	0.100	2.84	0.00426
Fruiting Vegetables(60)	0.100	2.99	0.00449
Small Fruit,berries(146)	0.100	0.83	0.00124
Hops(73)	0.100	0.03	0.00005
Potable Water(198)	0.500	133.33	1.00000
Tea(162)	4.000	0.07	0.00429

MPI	TMRC	% ADI
6.0000 mg/day(60kg)	1.3686 mg/day(1.5kg)	22.81

****

Unpublished,Tox Approved 2F2680,2G2686

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Soybeans (oil)(148)	4.000	0.92	0.05509
Coconut(35)	0.100	0.03	0.00005

[illegible]	[illegible]	[illegible]
[illegible] mg/day(60kg)	1.4238 mg/day(1.5kg)	23.73

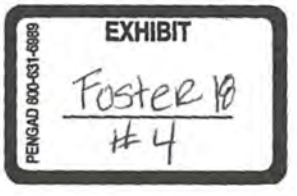
****

Current Action [illegible]

Crop	Tolerance	Food Factor	mg/day(1.5kg)
Fish,Shellfish(5%)	0.000	1.00	0.00000

ADI	PAD	% ADI
5.0000 mg/day(60kg)	1.4238 mg/day(1.5kg)	23.73

****



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

December 4, 1985

004855

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: William Dykstra, Ph.D.
Reviewer, Toxicology Branch, TS-769

FROM: Louis Kasza, D.V.M., Ph.D. L K
Pathologist, Toxicology Branch, TS-769

SUBJECT: Glyphosphate -- Evaluation of Kidney Tumors in Male Mice.
Chronic Feeding Study.

INTRODUCTION:

Tumors (0 (1)*; 0; 1; 3) were found in the kidneys of male mice at different dose levels. There were differences in the pathologists' opinions as to whether the small localized change in one kidney of the control group (#1028) represented a tumor or not. In order to provide more information, the Agency recommended the preparation of three (3) additional sections from each kidney in the male groups. "The lesion was not present in the recut specimens from that animal" in the control group (#1028). In the final re-evaluation of the questionable control kidney slides (#1028), the conclusion was formulated that "The pathology staff at Bio/dynamics and I (Dr. McConnell) reviewed the lesion and concur that it may be representative of a developing tumor".

MATERIALS AND METHODS:

I (Dr. Kasza, Branch Pathologist) requested all kidney sections from male mice. After selection of slides from all animals in which kidney tumors were diagnosed, I studied them under the microscope.

RESULTS:

There was no difference in diagnoses between my and other pathologists' diagnoses with respect to kidney tumors in mid- (#3023) and high dose (#4029, 4023, 4041) groups. With regard to the questionable male control kidney (#1028), it is my opinion that the presence of a tumor can not definitely be established. My interpretation is similar to the conclusion of Bio/dynamics' pathology staff and Dr. McConnell, that the lesion "may be" a proliferative change having the potential to lead to the development of a frank tumor. But as the tissue can be seen under the microscope as a small well-demarcated focal cell aggregate morphologically different from the healthy looking surrounding kidney tissue, this morphological alteration does not represent a pathophysiologically significant change.

*In parentheses is the review pathologist's findings.

cc: T. Farber
W. Burnam
R. Engler
R. Zendzian

Test for Significance of Differences Between Proportions 11/13/85

renal tubule adenoma mice

004855

ppm	# RESP	Total	%	+/-2(S.D.)	One Tail P Fisher's Statistic
0.000	1	49	2.04	+/-(4.98)	
1000.000	0	49	0.00	+/-(1.02)	$$$$$
5000.000	1	50	2.00	+/-(4.88)	$$$$$
30000.000	3	50	6.00	+/-(7.58)	0.316

This linear trend test often gives incorrect results

Test for a linear trend is not significant

Test for Significance of Differences Between Proportions 12/11/85

renal tublule adenoma ,male mice

004855

ppm	# RESP	Total	%	+/-2(S.D.)	One Tail P Statistic Fisher's
0.000	0	49	0.00	+/-(1.02)	
1000.000	0	49	0.00	+/-(1.02)	$$$$$
5000.000	1	50	2.00	+/-(4.88)	0.505
30000.000	3	50	6.00	+/-(7.58)	0.125

This linear trend test often gives incorrect results

Test for Linear Trend in Proportions P = 0.016

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.

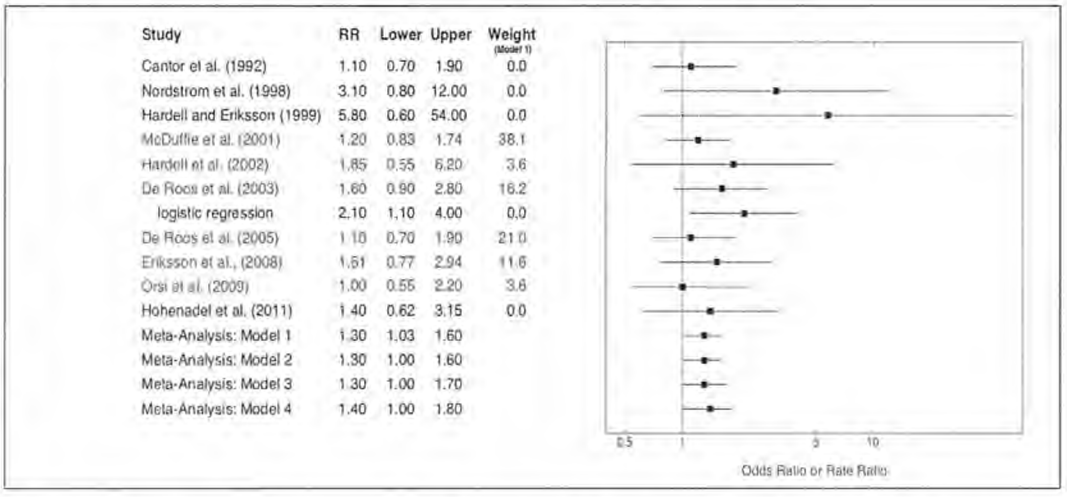
The first obvious conclusion to be drawn from Figure 1 is that all of the mean OR/RR estimates (black squares) are consistently ≥1. This implies that all of the studies are pointing in the same direction toward a positive effect. In their meta-analyses, **Schinasi and Leon (2014)**[57], **IARC (2015)**[56] 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.

<u>There was a significant increase in hemangiomas (any tissue) in female mice (p_{Trend}=0.004).</u>

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.

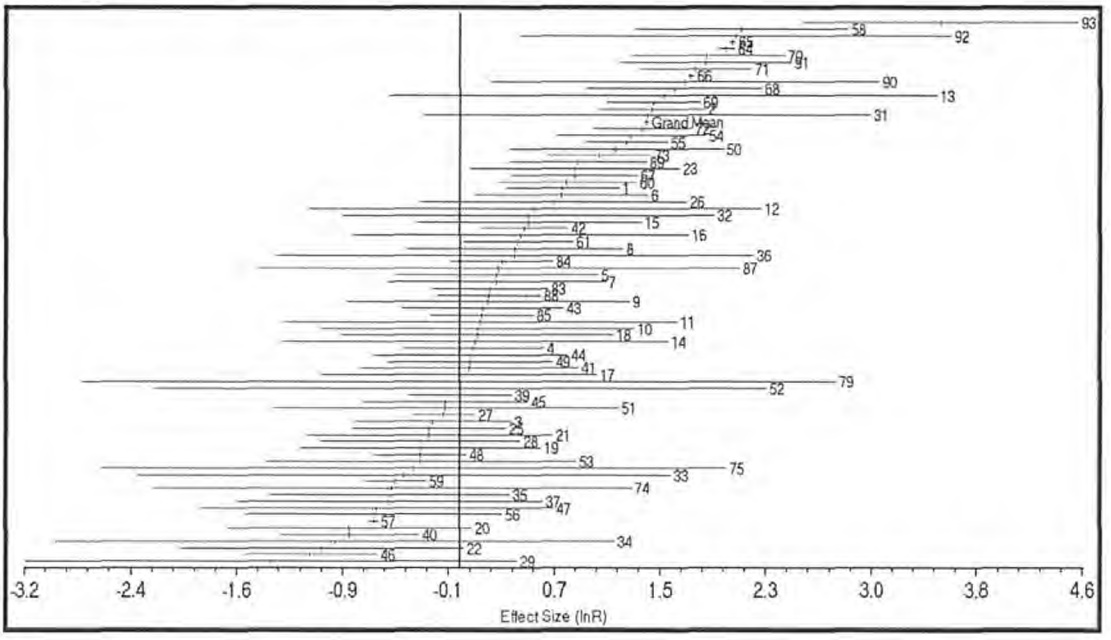
In this case, a pooled analysis of the data is not possible because in almost every case, no one study is a clear replicate of another. Instead, the appropriate approach would be to do a meta-analysis and evaluate which aspects of the experimental designs are important to producing positive findings 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 ($p<0.0\text{-}5$) 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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Use of Historical Control Data in Carcinogenicity Studies in Rodents*

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Abstract

This paper considers the use of historical control data in the evaluation of tumor incidences from carcinogenicity studies in rodents. Although the most appropriate control group for interpretative purposes is always the concurrent control, there are instances in which the use of historical control information can aid an investigator in the overall evaluation of tumor incidence data. One example is rare tumors; another is a tumor that shows a marginally significant result relative to concurrent controls.

However, before historical control data can be used in a formal testing framework, a number of important issues must first be considered. The nomenclature conventions and diagnostic criteria for each study should be identical to insure unambiguous identification of all relevant tumors in the historical control database. Criteria should be established that will aid in determining whether a particular study should be included in the database. This will assure a homogeneous set of studies upon which to base statistical comparisons. Since study-to-study variability in tumor rates may exceed what would be expected by chance alone, these sources of variability should be identified and controlled. Finally, statistical procedures should be employed that adjust for extra-binomial variability.

This paper also summarizes tumor incidence data from untreated Fischer 344 rats and B6C3F$_1$ mice in the National Toxicology Program (NTP) historical control database. All studies in the database are of two years duration, and all neoplasms occurring with a frequency of 0.5% or more are reported.

Introduction

The National Cancer Institute (NCI) Carcinogenesis Testing Program began in the 1960's. In 1978, the National Toxicology Program (NTP) was established, and in July 1981, the responsibility for the NCI carcinogenicity studies was transferred formally to NTP. To date, NCI and NTP have generated nearly 300 Technical Reports summarizing the results of laboratory animal carcinogenicity studies for a wide variety of chemicals [1, 2]. The majority of these investigations are two-year feeding or gavage studies involving male and female Fischer 344 rats and B6C3F$_1$ mice. For each of these studies detailed histopathology data—information on neoplastic and non-neoplastic lesions for individual animals—have been computerized and stored on the Carcinogenesis Bioassay Data System (CBDS).

Although the concurrent control group is always the first and most appropriate control group used for decision making [3, 4], there are certain instances in which the use of historical control information can aid an investigator in the overall evaluation of tumor incidence data. One example is rare tumors (which may require somewhat less stringent statistical evidence in a given study if the low spontaneous rate of the tumor can be demonstrated from historical control data); another is a tumor which shows a borderline

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increase relative to concurrent controls (which may be discounted or considered to be biologically meaningful when historical control data are considered). Historical control data are also useful for quality control aspects of the study to determine if concurrent control tumor incidences are consistent with previously reported tumor rates [5].

There is currently no consensus regarding how and when historical control data should be used in the decision making process. The National Cancer Institute made limited use of historical control data to supplement the statistical analyses in certain Technical Reports [6]. In these instances the tumor incidences in chemically-exposed animals were often compared with the historical control range. If this tumor rate was within the historical control range, the effect was frequently regarded as being unrelated to chemical administration. Conversely, a tumor incidence outside the historical control range was often regarded as a chemically-induced effect.

Statistical issues related to the use of historical control data have been considered by a number of investigators [3, 4, 7, 8]. One goal of the National Toxicology Program is to investigate further the use of historical control information in the evaluation of tumor incidence data. This paper describes that research effort.

Methods

A systematic examination of historical control tumor incidence data from NCI/NTP carcinogenicity studies was carried out. These data were taken primarily from two year experiments involving Fischer 344 rats and B6C3F$_1$ mice. Modification of existing CBDS programs were made to facilitate detailed comparisons of tumor incidences within and among contract laboratories. One objective of this investigation was to define an NTP historical control database and to compare tumor incidences in this database with previously reported rates from earlier NCI studies [9, 10]. This new database could then be utilized as a reference point in the evaluation of tumor incidence from current NTP studies. A second objective was to identify major sources of study-to-study variability in tumor rates, using an approach similar to that employed by Tarone, Chu and Ward [4].

Within each laboratory the binomial variance test for homogeneity [11] was employed to assess the presence or absence of extra-binomial study-to-study variability. Analysis of variance procedures [12] were employed to quantify the potential sources of variability in tumor incidence (e.g., laboratory; pathologist within laboratory; animal supplier). The variance stabilizing arc sine transformation was employed in these analyses.

Results and Discussion

As the historical control tumor incidence data from NCI/NTP studies were reviewed, four issues became evident: (1) Different nomenclatures were used to describe the same lesion, (2) standardized criteria had not been defined for the inclusion of a study in the historical control database, (3) extra-binomial variability (i.e., variability among studies in excess of what would be expected by chance alone) was evident for certain tumors, and (4) appropriate statistical methodology for taking extrabinomial variability into account had not been adequately studied. These issues must all be addressed before historical control data can be used in a formal testing framework.

Resolving Nomenclature Differences. An examination of NCI/NTP historical data revealed that different terminologies were often being employed to describe the same tumor even for studies at the same laboratory carried out at approximately the same time. As an illustration, consider the data in Table I. If historical control data from this laboratory on pituitary chromophobe adenoma were to be used in a formal testing framework, one must be aware that the Adenoma NOS (NOS = not otherwise specified) diagnosis is almost certainly chromophobe adenoma, notwithstanding the different nomenclature. Thus, in this instance a statistical analysis should be based on the combined incidence of all pituitary adenomas including chromophobe adenomas.

TABLE I—Example of Differences in Pathology Nomenclature: Pituitary Tumors in Female F344 Rats

Study[a]	Adenoma, NOS	Chromophobe Adenoma	Combined
A	22/49	0/49	22/49
B	25/48	0/48	25/48
C	1/50	21/50	22/50
D	21/48	0/48	21/48
E	1/50	20/50	21/50

[a] Studies A–E are all recently completed studies from the same laboratory. NOS: not otherwise specified

TABLE II—Incidences of Primary Tumors in Untreated Control F344 Rats and B6C3F$_1$ Mice[a]

	MALE RATS		FEMALE RATS		MALE MICE		FEMALE MICE	
	Number of Tumors (%)	SD (%)	Number of Tumors (%)	SD (%)	Number of Tumors (%)	SD (%)	Number of Tumors (%)	SD (%)
Circulatory System	2320[b]		2370[b]		2343[b]		2486[b]	
Hemangioma	4 (0.2)	0.6	2 (0.1)	0.4	34 (1.5)	3.3	39 (1.6)	1.9
Hemangiosarcoma	12 (0.5)	1.1	3 (0.1)	0.5	64 (2.7)	2.6	48 (1.9)	2.3
Digestive system								
Liver	2306		2356		2334		2469	
Neoplastic nodule or adenoma	78 (3.4)	3.5	71 (3.0)	3.0	240 (10.3)	5.5	98 (4.0)	3.9
Carcinoma	18 (0.8)	1.1	4 (0.2)	0.7	498 (21.3)	6.9	101 (4.1)	3.0
Nodule or adenoma or carcinoma	96 (4.2)	3.9	74 (3.1)	3.2	725 (31.1)	7.5	196 (7.9)	4.6
Forestomach	2276		2329		2252		2336	
Squamous cell papilloma	5 (0.2)	0.6	5 (0.2)	0.8	6 (0.3)	0.7	12 (0.5)	1.5
Squamous cell carcinoma	1 (<0.1)	0.3	2 (0.1)	0.4	0 (0.0)	0.0	2 (0.1)	0.4
Small intestine	2212		2284		2148		2234	
Adenocarcinoma	9 (0.4)	0.9	1 (<0.1)	0.3	14 (0.7)	1.2	2 (0.1)	0.4
Endocrine System								
Pituitary	2158		2262		1903		2051	
Adenoma	468 (21.7)	11.7	995 (44.0)	11.4	11 (0.6)	1.5	163 (7.9)	0.5
Carcinoma	51 (2.4)	3.0	80 (3.5)	4.7	1 (0.1)	0.3	8 (0.4)	0.9
Adrenal	2280		2338		2240		2306	
Cortical adenoma	27 (1.2)	1.3	74 (3.2)	4.0	53 (2.4)	3.0	7 (0.3)	1.1
Cortical carcinoma	5 (0.2)	0.6	7 (0.3)	0.7	3 (0.1)	0.6	1 (<0.1)	0.3
Pheochromocytoma	388 (17.0)	9.2	81 (3.5)	3.0	28 (1.2)	1.9	16 (0.7)	1.2
Pheochromocytoma, malignant	23 (1.0)	1.4	11 (0.5)	1.0	2 (0.1)	0.4	0 (0.0)	0.0
Thyroid	2230		2265		2178		2203	
C-cell adenoma	114 (5.1)	4.4	111 (4.9)	4.1	0 (0.0)	0.0	2 (0.1)	0.4
C-cell carcinoma	84 (3.8)	3.3	81 (3.6)	3.0	0 (0.0)	0.0	0 (0.0)	0.0
Follicular cell adenoma	22 (1.0)	1.4	10 (0.4)	1.0	22 (1.0)	1.6	40 (1.8)	2.1
Follicular cell carcinoma	17 (0.8)	1.4	10 (0.4)	0.9	5 (0.2)	0.6	6 (0.3)	1.5
Pancreatic islets	2226		2303		2237		2280	
Adenoma	84 (3.8)	3.6	18 (0.8)	1.5	8 (0.4)	0.9	9 (0.4)	0.8
Carcinoma	46 (2.1)	2.3	6 (0.3)	0.8	0 (0.0)	0.0	2 (0.1)	0.4
Hematopoietic System	2320		2370		2343		2486	
Leukemia	648 (27.9)	10.2	414 (17.5)	7.4	17 (0.7)	1.7	52 (2.1)	4.6
Lymphoma	51 (2.2)	3.4	36 (1.5)	2.2	280 (12.0)	7.2	625 (25.1)	10.0
Leukemia/lymphoma[c]	699 (30.1)	10.5	448 (18.9)	7.0	297 (12.7)	7.3	677 (27.2)	9.9
Integumentary System	2320		2370		2343		2486	
(Neuro)fibroma	107 (4.6)	3.2	34 (1.4)	1.5	28 (1.2)	2.7	1 (<0.1)	0.6
(Neuro)fibrosarcoma	27 (1.2)	1.4	20 (0.8)	1.3	66 (2.8)	4.4	21 (0.8)	1.9
Sarcoma, NOS	10 (0.4)	1.0	7 (0.3)	0.7	40 (1.7)	2.5	17 (0.7)	1.6
Squamous cell papilloma	29 (1.2)	1.7	6 (0.3)	0.7	3 (0.1)	0.5	6 (0.2)	0.7

[a] Includes all tumors occurring with a frequency of 0.5% or greater, as of March 1983.
[b] Number of animals examined histopathologically (or, for certain lesions, the number of animals necropsied).
[c] This combination is included because certain early studies in the data base tended to use these terms interchangeably.

Although this particular example is fairly straightforward, others are less obvious. For example, the following terms for leukemia have been used in NCI/NTP studies: leukemia NOS, mast-cell leukemia, monocytic leukemia, myelomonocytic leukemia, mononuclear cell leukemia, granulocytic leukemia, lymphocytic leukemia, erythrocytic leukemia, and undifferentiated leukemia. To those unfamiliar with tumor pathology, it may not be clear which of these diagnoses represent synonymous terms for the same lesion and which represent histologically distinct leukemias, and therefore require separate analyses. The NTP position on this particular issue is that the most meaningful analysis is for *all* leukemia, rather than for any one particular type.

Another issue is the use of different sets of criteria for diagnosing a lesion. For example, some pathologists diagnose all thyroid C-cell proliferative lesions extending beyond the boundary of one follicle as C-cell carcinoma. Others diagnose all C-cell lesions located within the thyroid lobe as C-cell adenoma, regarding only lesions that extend beyond the thyroid capsule or having distant metastases as carcinomas.

Thus, the nomenclature conventions and diagnostic criteria for each study should be identical to insure unambiguous identification of all relevant tumors in the historical control database. As an initial step toward achieving this objective, the NTP has held workshops on kidney, liver, and pancreas pathology; each of the testing laboratories as well as leading diagnostic pathologists in the particular organ system have participated. During these workshops, examples of specific lesions were illustrated, discussed, and standardized diagnostic criteria formulated. These criteria have been incorporated into NTP's quality assurance and review procedures. Any diagnoses that do not conform to

TABLE II—*Continued*

	MALE RATS		FEMALE RATS		MALE MICE		FEMALE MICE	
	Number of Tumors (%)	SD (%)	Number of Tumors (%)	SD (%)	Number of Tumors (%)	SD (%)	Number of Tumors (%)	SD (%)
Squamous cell carcinoma	20 (0.9)	1.3	15 (0.6)	1.2	4 (0.2)	0.7	6 (0.2)	0.7
Basal cell neoplasms	22 (0.9)	1.6	6 (0.3)	0.7	2 (0.1)	0.4	5 (0.2)	0.8
Keratoacanthoma	20 (0.9)	1.4	6 (0.3)	0.8	0 (0.0)	0.0	0 (0.0)	0.0
Lipoma	12 (0.5)	0.9	1 (<0.1)	0.3	0 (0.0)	0.0	0 (0.0)	0.0
Musculoskeletal System	2320		2370		2343		2486	
Osteosarcoma	12 (0.5)	1.0	7 (0.3)	0.8	3 (0.1)	0.7	14 (0.6)	1.1
Rhabdomyosarcoma	0 (0.0)	0.0	2 (0.1)	0.4	12 (0.5)	1.6	2 (0.1)	0.4
Nervous System								
Brain	2301		2348		2303		2378	
Astrocytoma	9 (0.4)	1.0	12 (0.5)	1.1	0 (0.0)	0.0	0 (0.0)	0.0
Reproductive system								
Mammary gland	2320		2370		2343		2486	
Fibroadenoma	51 (2.2)	2.0	572 (24.1)	10.1	0 (0.0)	0.0	8 (0.3)	1.1
Adenocarcinoma	6 (0.3)	0.7	48 (2.0)	2.4	0 (0.0)	0.0	40 (1.6)	2.3
Preputial gland	2320				2343			
Adenoma	50 (2.2)	3.4			2 (0.1)	0.4		
Carcinoma	63 (2.7)	3.0			0 (0.0)	0.0		
Prostate	2154				2343			
Adenoma	14 (0.6)	2.0			0 (0.0)	0.0		
Testis	2285				2312			
Interstitial cell tumor	2002 (87.6)	8.9			8 (0.3)	0.9		
Clitoral gland			2370				2486	
Adenoma			28 (1.2)	1.8			0 (0.0)	0.0
Carcinoma			46 (1.9)	2.7			0 (0.0)	0.0
Uterus			2318				2360	
Endometrial stromal polyp			424 (18.3)	8.1			22 (0.9)	1.4
Endometrial stromal sarcoma			25 (1.1)	1.7			13 (0.6)	1.2
Ovary			2321				2167	
Granulosa cell neoplasms			13 (0.6)	1.0			2 (0.1)	0.4
Tubular adenoma			0 (0.0)	0.0			19 (0.9)	1.4
Respiratory System								
Lung	2305		2354		2328		2388	
Alveolar/bronchiolar adenoma	35 (1.5)	2.1	18 (0.8)	1.4	282 (12.1)	6.7	131 (5.5)	3.6
Alveolar/bronchiolar carcinoma	20 (0.9)	1.6	9 (0.4)	0.9	119 (5.1)	4.3	47 (2.0)	2.3
Special Sense Organs								
Harderian gland	2320		2370		2343		2486	
Adenoma	1 (<0.1)	0.3	0 (0.0)	0.0	50 (2.1)	2.8	32 (1.3)	1.7
Carcinoma	1 (<0.1)	0.3	0 (0.0)	0.0	2 (0.1)	0.4	1 (<0.1)	0.3
Other Tumors	2320		2370		2343		2486	
Mesothelioma (tunica vaginalis)	30 (1.3)	1.7			0 (0.0)	0.0		
Mesothelioma (other)	23 (1.0)	1.7	1 (<0.1)	0.3	3 (0.1)	0.5	0 (0.0)	0.0

these standards are returned to the testing laboratory pathologist for reconsideration.

Another issue involves combining benign and malignant tumors (e.g., hepatocellular adenoma and carcinoma) for biological and statistical interpretation. For example, in their study of the variability of tumor rates in F344 rats and B6C3F$_1$ mice, Tarone, Chu and Ward [4] combined certain benign and malignant neoplasms, since "these combined types represent the histogenetic development of the tumors, and the groupings should minimize the effect of various pathologists in the program using different terms for the same stage in the development of a given tumor type." Ward [8] presents data illustrating different diagnostic criteria employed by four pathologists in the evaluation of liver lesions. The issue of tumor combinations should be carefully studied in advance, so that the historical control database can summarize the incidences of appropriate tumor combinations.

Defining the Historical Control Database. Criteria should be established that will aid in determining whether or not a particular study should be included in the database. This will assure a homogeneous set of studies upon which to base statistical comparisons. Previous investigators [3, 7] have recognized this need and have emphasized that historical control databases should contain studies that are similar with respect to experimental factors known or suspected to affect the magnitude of tumor rates.

Certainly species, strain, sex, study duration, pathology protocols, nomenclature conventions, quality assurance and review procedures should be the same for each study in a particular historical control database. Ideally, diets, caging regimens, and various environmental parameters should also be comparable. Different types of control groups (e.g., untreated, corn oil gavage) should be dealt with separately. Other potential sources of variability (calendar year, laboratory, pathologist, supplier) should also be investigated, identified and controlled.

In June, 1982, a meeting of NTP pathologists and statisticians was held to establish an "updated" historical control database for tumor incidences. After considering the factors mentioned above, the group decided that this database should consist of all chemicals whose technical report drafts were peer reviewed in 1980 or later. This corresponds to those chemicals whose Technical Reports begin with number 193. Thus, many early NCI studies were excluded from the database. This action was not meant to indicate that these studies were flawed or that the pathology diagnoses were unreliable. These studies were excluded primarily because the pathology protocols, nomenclature conventions, quality assurance and review procedures, and other experimental factors noted above were different in some respects from those currently employed.

A further decision had to be made: when in the overall pathology evaluation process were diagnoses to be regarded as final and the study formally included in the database. It was decided that approval of the laboratory's pathology diagnoses by the NTP Pathology Working Group (PWG) should be the point in time in which a study becomes part of the database (The PWG consists of NTP pathologists and other experts in rodent pathology from academia and industry; their primary function is to review the pathology data and resolve any discrepancies in pathology diagnoses).

Table II summarizes the incidences of the more frequently-occurring tumors in the NTP historical control database; included are tumor incidences from untreated control male and female F344 rats (47 studies) and B6C3F$_1$ mice (51 studies). Most control groups had 50 animals/species/sex and all were from two year carcinogenicity studies. All neoplasms occurring with a frequency of 0.5% or more are listed. The current database contains information beginning with those studies reported in Technical Report 193 through those studies whose pathology diagnoses were finalized in CBDS as of March, 1983.

Comparing these rates with previous tabulations of control tumor incidences for F344 rats and B6C3F$_1$ mice [1, 4, 8–10, 13–17] showed that the incidence of several neoplasms are significantly higher in the current database. For F344 rats, the most notable increases as compared to Goodman et al. [9] are mononuclear cell leukemia (males: 28% vs. 12%; females: 17% vs. 10%), pituitary adenoma (males: 22% vs. 11%; females: 44% vs. 29%) and adrenal pheochromocytoma (males: 18% vs. 9%). Similarly, for B6C3F$_1$ mice benign and malignant liver neoplasms (males: 31% vs. 21%; females: 8% vs. 4%) and pituitary adenoma (males: 0.6% vs. 0.1%; females: 8% vs. 3%) showed an increased incidence in the current data base compared to those reported by Ward et al. [10]. These differences in tumor rates are all significantly ($P < 0.01$) greater than what would be expected by chance alone.

These time-related trends are similar to those found by other investigators. When considering data from the early NCI studies, Ward [8] noted that "there is real evidence that tumor incidence at several sites in 2-year-old F344 rats has increased significantly over the past 8 years. The cause(s) is not known." One possible explanation is that over time more uniform criteria have been established for the diagnosis of these neoplasms. In addition, an in depth three-phase review of the pathology data has been developed and implemented by the NTP [18]. These time-related differences in tumor incidence are probably also affected by increased survival in the more recent studies due to improved animal husbandry, diets and environmental conditions. Moreover, not all studies summarized by Ward et al. [10] were of two year duration. One should not exclude the possibility that the incidence of these neoplasms is increasing due to one or more factors such as genetic drift or the presence of low level carcinogens in the diet (especially nitrosamines), water, bedding, etc.

Identifying Sources of Variability. Study-to-study variability in tumor rates may exceed what would be expected by chance alone. These sources of extra-binomial variability should be identified and controlled before attempting to use the database.

Time (calendar year) appears to be an important source of variability. Certain tumors show increased incidences in recent studies relative to earlier experiments. This variable can be controlled to some extent by limiting the historical control data to the more recent studies, as has been done by NTP. An additional strategy would be to employ a 3–4 year "window" for historical control data, i.e., to include in the database only those studies conducted within 3–4 years of the study being evaluated.

The laboratory is also an important source of variability for certain tumors. When all

TABLE III—Interlaboratory Variability in Control Tumor Incidence: Male F344 Rats[a]

	Laboratory[a]									
	A		B		C		D		E	
Number of Studies	9		5		14		6		7	
Number of Animals Necropsied	439		249		699		340		344	
	Rate	Range	Rate	Range	Rate	Range	Rate	Range	Rate	Range
Overall Survival	68	44–78	62	46–78	62	50–76	67	56–78	65	56–72
Integument: Fibroma/Fibrosarcoma	5	0–10	5	0–12	4	0–12	7	6–10	5	2–12
All sites: Leukemia	27	12–40	28	16–44	24	0–46	31	20–46	32	24–40
Liver: Neoplastic Nodule	2	0–5	2	0–8	3	0–12	5	0–10	6	0–12
Liver: Carcinoma	<1	0–2	<1	0–2	1	0–2	1	0–2	1	0–4
Pituitary: Adenoma	17	5–29	18	6–28	24	7–52	18	8–41	30	19–44
Adrenal: Pheochromocytoma	19	6–43	23	14–31	19	6–38	19	12–35	14	8–23
Thyroid: C-Cell Tumor	11	4–20	9	4–14	8	2–20	7	2–12	10	4–15
Pancreas: Islet Cell Tumor[b]	6	2–10	5	0–14	5	0–11	5	2–8	10	6–15
Mammary Gland: Fibroadenoma	3	0–6	2	0–4	3	0–8	3	0–6	2	0–4
Testis: Interstitial Cell Tumor[b]	88	68–95	85	71–96	86	72–96	96	94–98	91	86–96

[a] Values in the table represent % incidences.
[b] Significant ($P < 0.05$) interlaboratory variability.

TABLE IV—Interlaboratory Variability in Control Tumor Incidence: Female F344 Rats[a]

	Laboratory[a]									
	A		B		C		D		E	
Number of Studies	9		5		15		6		7	
Number of Animals Necropsied	439		249		747		337		350	
	Rate	Range	Rate	Range	Rate	Range	Rate	Range	Rate	Range
Overall Survival	75	66–84	73	68–80	71	50–84	74	66–78	77	62–86
Integument: Fibroma/Fibrosarcoma	2	0–6	<1	0–2	2	0–4	2	0–4	2	0–6
All sites: Leukemia	16	8–28	22	14–38	15	0–24	17	12–20	17	6–32
Liver: Neoplastic Nodule[b]	<1	0–2	4	0–8	3	0–8	3	2–4	5	0–12
Liver: Carcinoma	0	—	1	0–4	<1	0–2	0	—	<1	0–2
Pituitary: Adenoma	37	18–50	45	42–52	49	30–70	45	30–64	42	26–67
Adrenal: Pheochromocytoma	4	0–16	5	2–8	3	2–8	5	0–8	4	2–6
Thyroid: C-Cell Tumor[b]	14	10–18	6	0–10	6	2–12	5	2–11	11	4–16
Pancreas: Islet Cell Tumor	1	0–4	<1	0–2	1	0–7	2	0–4	2	0–6
Mammary Gland: Fibroadenoma[b]	28	18–35	21	16–26	31	20–44	18	10–23	15	2–38
Uterus: Endometrial Stromal Polyp[b]	15	8–22	26	21–31	21	4–35	22	10–37	12	8–16

[a] Values in the table represent % incidences.
[b] Significant ($P < 0.05$) interlaboratory variability.

contract laboratories with five or more studies in the NTP historical control database were considered, the following tumors showed significant ($P < 0.05$) interlaboratory variability (see Tables III–VI): pancreatic islet cell and testis interstitial cell tumors (male rats); liver nodules, thyroid C-cell tumors, mammary gland fibroadenomas, and uterine endometrial stromal polyps (female rats); lymphomas and pituitary tumors (mice); and lung tumors (male mice). No one laboratory appeared to report consistently high (or low) tumor incidences relative to the others, with the possible exception of Laboratory C, which tended to diagnose more tumors for mice than did the other four laboratories (Tables V and VI).

A specific example of inter-laboratory variability is given in Table VII. For male $B6C3F_1$ mice, the incidence of lung alveolar/bronchiolar adenoma or carcinoma is nearly three times as great in Lab C as in Lab D; and there is essentially no overlap of reported tumor rates between these laboratories (Table VII).

While this is admittedly a "worst case" example, differences of this magnitude may be important, and NTP is currently studying this issue in an effort to determine the underlying causes of laboratory-to-laboratory variability in tumor incidences.

A certain amount of interlaboratory variability is attributable to different diagnoses of a given neoplasm at different laboratories. Even though much effort is devoted to uniformity of diagnosis, histopathology is a judgmental science, with subsequent differential interpretation. Differentiations between hyperplasia and adenoma or between adenoma and carcinoma are sometimes not clear, and subjective differences in interpretation of these diagnoses can result in significant interlaboratory variability. Secondly, differences in laboratory geography with concommitant differences in the environment of the test animals may have an effect on the frequency of certain neoplasms. Tarone, Chu and Ward [4] hypothesize that "... unknown factors involving the diet, air, water, or bedding may play a role.... The unknown natural causes of certain tumors may allow slight modifications of ambient factors to greatly alter tumor incidence." Interlaboratory variability in tumor incidences in the NTP historical control database could not be attrib-

TABLE V—Interlaboratory Variability in Control Tumor Incidence: Male B6C3F$_1$ Mice[a]

	Laboratory[a]									
	A		B		C		D		E	
Number of Studies	9		5		15		8		10	
Number of Animals Necropsied	448		248		745		398		280	
	Rate	Range	Rate	Range	Rate	Range	Rate	Range	Rate	Range
Overall Survival	76	64–84	80	74–86	73	58–88	76	64–88	74	62–82
Integument: Fibroma/Fibrosarcoma	5	0–14	1	0–4	2	0–8	4	0–8	6	0–23
Lung: Alveolar/Bronchiolar Tumor[b]	19	8–29	16	8–27	22	12–34	8	2–12	11	2–15
All sites: Lymphoma[b]	9	2–14	8	2–18	16	4–32	12	6–18	8	2–10
All sites: Hemangioma/Hemangiosarcoma	4	0–6	2	0–6	6	0–20	3	0–6	2	0–7
Liver: Adenoma	9	6–14	6	2–10	12	0–22	9	2–14	9	2–17
Liver: Carcinoma	23	12–30	22	10–32	21	10–36	22	8–28	19	13–27
Pituitary: Adenoma[b]	0	—	0	—	2	0–6	0	—	0	—

[a] Values in the table represent % incidences.
[b] Significant ($P < 0.05$) interlaboratory variability.

TABLE VI—Interlaboratory Variability in Control Tumor Incidence: Female B6C3F$_1$ Mice[a]

	Laboratory[a]									
	A		B		C		D		E	
Number of Studies	9		5		15		8		7	
Number of Animals Necropsied	446		247		748		400		371	
	Rate	Range	Rate	Range	Rate	Range	Rate	Range	Rate	Range
Overall Survival	76	64–88	78	74–84	71	48–84	77	68–88	74	62–84
Integument: Fibroma/Fibrosarcoma	<1	0–2	1	0–4	1	0–4	1	0–8	1	0–4
Lung: Alveolar/Bronchiolar Tumor	7	2–9	5	2–11	10	0–16	6	0–12	6	0–12
All sites: Lymphoma[b]	20	10–30	28	18–34	31	8–62	23	18–34	19	10–29
All sites: Hemangioma/Hemangiosarcoma	2	0–8	4	2–6	4	0–8	4	0–8	4	2–10
Liver: Adenoma	3	0–14	4	0–8	6	0–18	2	0–4	6	2–9
Liver: Carcinoma	4	0–6	4	0–10	4	0–8	6	2–15	4	0–9
Pituitary: Adenoma[b]	3	0–10	6	0–10	12	0–30	4	0–12	7	0–19

[a] Values in the table represent % incidences.
[b] Significant ($P < 0.05$) interlaboratory variability.

TABLE VII—Historical Incidence of Lung Tumors (Adenoma or Carcinoma) in Male B6C3F$_1$ Mice at Five NTP Laboratories[a]

LABORATORY				
A	B	C	D	E
4/50 (8)	4/50 (8)	6/50 (12)	1/49 (2)	1/47 (2)
5/50 (10)	5/47 (11)	6/50 (12)	3/50 (6)	3/46 (7)
8/49 (16)	7/48 (15)	6/49 (12)	4/50 (8)	5/46 (11)
9/50 (18)	10/50 (20)	7/48 (15)	4/46 (9)	6/44 (14)
9/50 (18)	13/49 (27)	8/50 (16)	5/49 (10)	7/47 (15)
10/50 (20)		10/50 (20)	5/49 (10)	7/46 (15)
11/50 (22)		10/50 (20)	5/50 (10)	
13/49 (27)		11/50 (22)	6/50 (12)	
14/48 (29)		12/50 (24)		
		12/49 (24)		
		13/49 (27)		
		13/50 (26)		
		14/50 (28)		
		16/50 (32)		
		17/50 (34)		
Total:				
83/446 (19)	39/244 (16)	161/745 (22)	33/393 (8)	29/276 (11)

[a] All NTP laboratories with five or more studies included.

uted to differences in survival, since this variable showed no significant differences among laboratories for any of the four sex-species groups (Tables III–VI).

The finding of significant laboratory-to-laboratory variability is consistent with the results of Tarone, Chu and Ward [4] who carried out a similar investigation with earlier NCI data. They found significant interlaboratory variability for several tumor types in both the F344 rat and B6C3F$_1$ mouse. An obvious solution to the problem of inter-laboratory variability in tumor incidence would be to limit historical control comparisons to the laboratory that carried out the particular study in question. The one possible exception might be rare tumors, which occur so infrequently that laboratory-to-laboratory variability will generally not be a problem.

For certain tumors pathologist-within-laboratories was a significant source of variability. Thus, one could argue that historical control comparisons should be limited to those diagnoses generated by the same pathologist as well as being restricted to the same laboratory at the same time period. However, the differences among pathologists were not as striking or as frequent as the laboratory-to-laboratory variability, due perhaps in part to the quality assurance and the PWG review procedures which minimize this source of variability (as noted earlier, the original pathologist is asked to reconsider any diagnosis that does not conform to the standard diagnostic criteria established by the NTP). Thus, it may be somewhat too restrictive as a general rule to require that both laboratory and pathologist be identical for historical control comparisons. Animal supplier did not seem to be a major source of variability in NTP studies. This may be due to animals from all sources being derived from a single genotype and reared under standardized conditions.

Although further evaluation is in progress, when NTP utilizes historical control data, it generally limits comparisons to relatively recent (e.g., past 3–4 years) studies at the laboratory that conducted the study in question. This eliminates much (but not all) of the extra-binomial variability and is consistent with the recommendations of other investigators who have considered the historical control issue [3, 4].

Developing Appropriate Statistical Methodology. As indicated earlier, one simple strategy for utilizing historical control data is to examine the historical control range and determine whether or not the interval includes the tumor incidence observed in a particular group. Although there are situations in which the range may be helpful, there are problems associated with its use as a formal statistical analysis in the evaluation of tumor incidence data.

The range is sample-size-dependent, and tends to broaden as more studies are completed. If the range is based on only a few studies, then it is frequently narrow and a tumor rate in a test group could easily fall outside the range by chance alone. Conversely, if the historical control range is based on many studies, and hence potentially quite wide, a tumor rate in a test group may well be a chemically related effect even though the incidence is inside the upper bound of the historical control range.

Since the historical control range gets wider and wider as additional data are generated, it becomes progressively *more* difficult to obtain significant treatment-related effects (i.e., a tumor incidence outside the range) as more information is accumulated regarding control tumor rates. Intuitively, the opposite phenomenon seems more logical. Thus, a more appropriate statistical procedure is necessary before historical control data can be used in a formal testing framework.

Recently, three procedures were derived for the utilization of historical control data. The first was proposed by Tarone [7], who assumed a logistic model for dose response and an underlying beta distribution for the probability of tumor in the control popula-

tion. Thus, a beta-binomial model was assumed, with parameters estimated from historical control data. Setting up the likelihood function, an asymptotic (large sample) test based on a modified Cochran-Armitage statistic was obtained for the existence of a dose response. The control tumor rate used in the test procedure was in essence a weighted average of the historical and concurrent control group rates, with the relative weights determined in part by the magnitude of the extra-binomial variability in the historical control data.

A second method used a Bayesian approach [19]. The authors assumed that logits of the historical control rates were normally distributed and integrated out nuisance parameters to obtain a distribution for the slope of the linear effect. The slope was then tested by computing a Bayesian p-value, defined as the posterior probability of a positive or negative slope (whichever is smaller). Dempster et al. [19] stated that their Bayesian Z score principle and the asymptotic chi square sampling theory principle of Tarone yielded equivalent results in large samples.

The third method [5] was an exact conditional test rather than an asymptotic procedure, and like the Tarone procedure, it assumed an underlying beta-binomial model. An exact conditional test was derived by calculating the tail of the beta-binomial distribution, assuming the beta-binomial parameter values were known. This test was derived for pairwise comparisons rather than dose-response trends, but the method can be extended to include this more general case as well.

Hoel and Yanagawa [20] derived a locally most powerful test of trend for binomial response data using a beta prior distribution for the historical control information. This test provided a generalization of both the Tarone and Hoel procedures. The gain in asymptotic efficiency by incorporating historical control information was calculated and small sample methods were given. One major conclusion of their research was that a conditional exact test was preferred over an asymptotic test because of the poor operating characteristics of the asymptotic procedure for tumors having low background rates. A possible area of future research would be the extension of the methods described above to adjust for survival differences (and time-to-death-with-tumor). Considerations should also be given to possible time-related trends.

Finally, if the tumor rates observed in concurrent controls are inconsistent with past historical experience at that laboratory, then utilizing historical control data becomes more difficult. In this situation Cox and McCullagh [21] stated "it is far from clear how the historical controls could be used, or indeed whether they should be used, in formal comparisons."

In summary, when the biological significance of an observed increase in tumor incidence relative to concurrent controls is uncertain, historical control rates can aid in the overall evaluation. Current NTP philosophy is that the most appropriate comparisons are with concurrent controls. Supplemental comparisons with historical control rates may occasionally be made and should generally be limited to data from the same laboratory. For certain uncommon or rare tumors use of Program-wide rates may be appropriate. If, however, historical control data are to be used in a formal testing framework, several issues must be resolved: (1) defining the historical control database; (2) standardizing pathology nomenclature and diagnostic criteria; (3) identifying major sources of variability; and (4) developing and utilizing statistical procedures that adjust for extrabinomial variability and survival differences.

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