Sandra A. Edwards (State Bar No. 154578)
Joshua W. Malone (State Bar No. 301836)
Farella Braun + Martel LLP
235 Montgomery Street, 17th Floor
San Francisco, CA 94104
Telephone: (415) 954-4400; Fax: (415) 954-4480
sedwards@fbm.com
jmalone@fbm.com

Joe G. Hollingsworth (appearance *pro hac vice*)
Martin C. Calhoun (appearance *pro hac vice*)
Kirby T. Griffis (appearance *pro hac vice*)
William J. Cople (appearance *pro hac vice*)
Hollingsworth LLP
1350 I Street, N.W.
Washington, DC 20005
Telephone: (202) 898-5800; Fax: (202) 682-1639
jhollingsworth@hollingsworthllp.com
mcalhoun@hollingsworthllp.com
kgriffis@hollingsworthllp.com
wcople@hollingsworthllp.com

George C. Lombardi (appearance *pro hac vice*)
James M. Hilmert (appearance *pro hac vice*)
Winston & Strawn LLP
35 West Wacker Drive
Chicago, IL 60601
Telephone: (312) 558-5969; Fax: (312) 558-5700
glombard@winston.com
jhilmert@winston.com

Attorneys for Defendant
MONSANTO COMPANY

ELECTRONICALLY
FILED
Superior Court of California,
County of San Francisco
06/12/2018
Clerk of the Court
BY: VANESSA WU
Deputy Clerk

SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

vs.

MONSANTO COMPANY,

Defendant.

Case No. CGC-16-550128

DECLARATION OF SANDRA A. EDWARDS ISO REPLIES ISO MONSANTO'S MOTIONS *IN LIMINE* NOS. 6-30

Trial Date: June 18, 2018
Time: 9:30 p.m.
Department: TBD

I, Sandra A. Edwards, declare as follows:

1. I am an attorney duly admitted to practice before this Court. I am a partner with Farella Braun + Martel LLP, attorneys of record for Monsanto Company ("Monsanto"). I submit this Declaration in support of Monsanto's Replies in support of Motions *In Limine* Nos. 6-30 to exclude certain evidence.

2. Attached hereto as **Exhibit 1** is a true and correct copy of excerpts from the deposition of Charles Benbrook on May 23, 2018 in *Peterson and Hall v. Monsanto Company*, No. 1622-CC01071 (Cir. Ct. Mo.).

3. Attached hereto as **Exhibit 2** is a true and correct copy of excerpts from the deposition of Christopher Portier on Jan. 12, 2018 in *In re: Roundup Prod. Liab. Litig.*, 3:16-md-02741-VC (N.D. Cal.).

4. Attached hereto as **Exhibit 3** is a true and correct copy of an excerpt from the Expert Report of Charles Benbrook.

5. Attached hereto as **Exhibit 4** is a true and correct copy of an excerpt from the deposition of Charles Benbrook on Feb. 8-9, 2018.

6. Attached hereto as **Exhibit 5** is a true and correct copy of TNO, *In vitro percutaneous absorption study with [^{14}C]glyphosate using viable rat skin membranes,* TNO Report (July 9, 2003).

7. Attached hereto as **Exhibit 6** is a true and correct copy of excerpts from the deposition of Kirk Azevedo on June 8, 2016 in *Phyllis Kennedy v. Monsanto Company*, No. 16M-CC00001 (Cir. Ct. Mo.).

8. Attached hereto as **Exhibit 7** is a true and correct copy of excerpts from the deposition of William Sawyer, Ph.D., on Feb. 26-27, 2018.

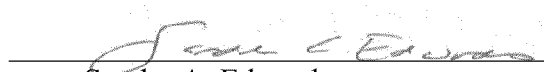
9. Attached hereto as **Exhibit 8** is a true and correct copy of an excerpt from the Expert Report of William Sawyer, M.D.

10. Attached hereto as **Exhibit 9** is a true and correct copy of an excerpt from Durkin, et. al, "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997.

Farella Braun + Martel LLP
235 Montgomery Street, 17th Floor
San Francisco, California 94104
(415) 954-4400

11. Attached hereto as **Exhibit 10** is a true and correct copy of Waldman, et. al, "Monsanto Was Its Own Ghostwriter for Some Safety Reviews," Aug. 9, 2017, https://www.bloomberg.com/news/articles/2017-08-09/monsanto-was-its-own-ghostwriter-for-some-safety-reviews.

I declare under penalty of perjury under the laws of the State of California that the foregoing is true and correct, and that this declaration was executed on June 12, 2018, at San Francisco, California.



Sandra A. Edwards

Farella Braun + Martel LLP
235 Montgomery Street, 17th Floor
San Francisco, California 94104
(415) 954-4400

Exhibit 1

IN THE CIRCUIT COURT OF THE CITY OF ST. LOUIS

STATE OF MISSOURI

RONALD PETERSON and JEFF HALL, Plaintiff(s), vs. MONSANTO COMPANY; OSBORN & BARR COMMUNICATIONS, INC.; OSBORN & BARR HOLDINGS, INC., Defendant(s).	)	1622-CC01071

VIDEOTAPED DEPOSITION UPON ORAL EXAMINATION OF

CHARLES BENBROOK, Ph.D.

CONFIDENTIAL

8:30 A.M.

MAY 23, 2018

QUALITY INN & SUITES CONFERENCE CENTER

700 PORT DRIVE

CLARKSTON, WASHINGTON

REPORTED BY: PATSY D. JACOY, CCR 2348

noncarcinogenic to humans in 2017 that there's been several additional epidemiological studies, correct?

A. Correct.

Q. Do you know how many epidemiology studies have been conducted between 1991 and 2017 on glyphosate and non-Hodgkin's lymphoma?

A. They're -- they're conducted in probably all continents on the planet and -- and several are not published in English language journals so I wouldn't say that I know all of them. I have -- in my expert report I discuss several of the most prominent ones in terms of the attention that both EPA gives to them in -- in their evolving reports and as well as the attention and focus that the IARC working group devoted to them.

Q. Indeed. And let me know if you agree. Nearly the entire if not the entire epidemiology database on glyphosate has occurred between 1991 and 2017 in terms of when the studies were published, correct?

A. Certainly the vast majority of it. I can't think of a single one that came out before '91.

Q. And in terms of epidemiology, epidemiology is the study of the formulated product used in real world dosing situations by farmers and whoever else would apply the formulated product, correct?

A. Correct.

Q. The most recent epidemiology study published on glyphosate, the Agricultural Health Study published in 2018 has found that there's no association between glyphosate and non-Hodgkin's lymphoma or any of its subtypes, correct?

MR. LITZENBURG: Form.

A. Correct.

Q. (BY MR. HOLLINGSWORTH) Dr. Benbrook, I want to go back to what you've reviewed in this case. I recall at the last deposition you said that you had reviewed a few depositions, and I'll let you name them again today, but have you reviewed any additional depositions since that time?

A. No.

Q. And do you recall what depositions you've reviewed?

A. I'm sure it's in my testimony from -- from before. I -- I didn't go back and look at any of that part of the record in preparing for this deposition, so I just would assume that my memory from back -- from three months ago served to answer that question.

Q. You have not reviewed --

A. Yeah.

Q. You have not reviewed Dr. Heydens' deposition;

these individuals had amongst themselves under circumstances where I believe they were being forthright and not -- not trying to shield the truth in any way. The -- the -- the discovery record in terms of these individuals' opinions, actions, knowledge of the science is extremely extensive, tens of thousands of documents. Obviously I only reviewed a small fraction of them, but I -- I became quite confident that the 15 or 20,000 pages of documents that I -- I read and multiple exchanges among these individuals that I had a -- a clear and reasonably accurate understanding of what their -- their feelings were, what their knowledge was, what their interpretation of the different scientific issues were.

So I -- you know, there really -- it wasn't a question of another side of the story. I just simply read what they said amongst themselves. It was -- you know, to me it was quite clear and I tried to include in my expert report a number of direct quotes from, you know, dozens of internal e-mails which I think speak for themselves.

Q. Your opinions on Dr. Heydens, Dr. Farmer, Dr. Saltmiras, Dr. Goldstein are based on company e-mails and documents given to you by the Miller Firm, correct?

A. Yes, correct.

Q. Your opinions on Mr. Rowland are based on company e-mails and documents as well as perhaps some FOIA e-mails given to you by the Miller Firm or otherwise available online, correct?

A. Well, let's be clear here. I mean, I don't -- I've never met Jeff Rowland. I've never talked to him. I don't really have an opinion on him. I do have an opinion about what his role was in the EPA review of glyphosate oncogenicity, and I base that opinion on his own statements to the -- for the most part, either statements by him or statements by Monsanto scientists and representatives about him. So it -- it's less of an opinion and -- and more of just a factual accounting of the exchanges that -- and communications that occurred between them.

Q. You reviewed company documents and e-mails on Drs. Farmer, Heydens, Saltmiras, Goldstein and determined what their feelings were, what their knowledge was and what their interpretations of the scientific issues were, correct?

A. Correct.

Q. And that was based entirely on documents given to you by the Miller Firm, correct?

A. I -- I may have had a few of these e-mails

am well aware that I have not reviewed anywhere near the totality of it, and so I felt it was my obligation to try to, as effectively as I could with the time that I had, track down the documents that seemed most important. So I did some of my own searches and got some of them that way, and in other cases I sent e-mails to -- to Mr. Litzenburg and Mr. Travers, and in -- and generally they were able to find what I asked for. And then they would e-mail it to me and then I would take it from there.

Q. If you wanted documents on a particular issue, you would often send an e-mail to the Miller Firm and ask for more company documents on that subject, they would conduct a search and then return you a search that lined up with the documents you requested. Is that fair?

A. They would -- they would e-mail the documents.

Q. Sure.

A. Yeah, correct.

Q. But is that -- is that fair? Is that how it would go that you would request more company e-mails or documents on a particular issue, you would ask the Miller Firm for more documents on that issue, they would conduct a search and then e-mail those documents to you; is that correct?

A. Certainly not. You know, they're -- Monsanto is sending such data to regulatory authorities around the world. I don't know what the total number is, but it's got to be over 100, and so no, I didn't -- didn't try to track all that. It would have taken a team of 50 people several years to do that. No, I didn't do that. It wasn't feasible. It wasn't needed either because, again, as I said, the internal record is quite clear what -- what Monsanto did and why they did it relative to the testing of formulated product for genotoxicity.

And, you know, what -- what EPA said in a 2017 report, you know, will -- would not affect and has not affected, you know, certainly my opinion because there's -- there isn't -- there is not a section in that report discussing this substantial database of Monsanto-commissioned studies on the genotoxicity of formulated product because they didn't commission the studies.

Q. (BY MR. HOLLINGSWORTH) The internal record that you reviewed on the genotoxicity of formulated products is based on company e-mails either given to you by the Miller Firm or your own search, correct?

MR. LITZENBURG: Object to form.

A. Correct.

of the extent of the raw database of genotox studies on formulated product and that based on the records that I had and that I have requested and that I reviewed and EPA documents, I was quite confident that there were no such studies. So I -- I didn't -- I didn't conduct any further searches or spend any additional time trying to track down studies which I was quite confident didn't exist.

Q. You were quite confident studies didn't exist with respect to Monsanto's formulated product genotoxicity studies based on your review of the company e-mails given to you by the Miller Firm, correct?

A. Correct.

Q. Sir, are you familiar with the EPA-required guideline testing that every pesticide product is required to go through before it's registered?

A. Yes.

Q. Agree that FIFRA places the burden to demonstrate the pesticide is safe on the manufacturers and registrants?

A. Yes.

Q. Sir, you recall reviewing the December 12, 2017 draft human health risk assessment in support of registration review?

(Recess taken.)

VIDEO OPERATOR: We are going back on the record. The time is 2:42.

MR. LITZENBURG: Off the record -- this is Tim Litzenburg, plaintiffs' counsel -- I have just informed counsel that I had a death in the immediate family this week and we will have to suspend this deposition for a 5:00 a.m. flight tomorrow. Counsel have agreed to finish today's portion of the deposition at around 5:00 p.m. and then continue to meet and confer on when we can complete Dr. Benbrook's deposition in the Peterson/Hall matter, and you all may say whatever you like.

MR. HOLLINGSWORTH: Sure. And, you know, we agree to go to 5:00 today and then see where we are at that moment. We may request, and I think you stated earlier, that you could go until as late as 10:00 tonight. We may take you up on that, but we will let you know at 5:00.

MR. LITZENBURG: Okay, that's fair.

Q. (BY MR. HOLLINGSWORTH) Change up a little bit.

A. As long as we can have dinner before 10:00.

Q. Hmm?

A. A dinner break before 10:00 because somebody

A. Correct, in this six-pack set of tests that we talked about and -- and a few others, yeah.

Q. All -- all formulated products must undergo dermal testing, correct?

A. Yes.

Q. EPA does not require chronic animal carcinogenicity testing on the formulated product, correct?

A. That's correct.

Q. EPA does not require chronic animal carcinogenicity testing on Roundup, correct?

A. Correct.

Q. EPA does not require chronic animal carcinogenicity testing on Ranger Pro, correct?

A. Correct.

Q. EPA does not require chronic animal carcinogenic testing on any end use formulated pesticide product, correct?

A. Not -- certainly not as a routine approach, no.

Q. Do you know why EPA doesn't require chronic animal carcinogenicity testing on the formulated product whether it be Roundup, Ranger Pro or some other pesticide?

A. I think there's a --a couple reasons. I think

the workload of dealing with just the two chronic studies on active ingredients is -- places considerable strain on the agency, and if they were to, say, include even one formulated product for each active ingredient, that would double the workload to evaluate those studies. So I think there's workload considerations. And then there's -- there's valid considerations that the registrants, including Monsanto, have argued that there's -- you know, there's 100-plus Roundup labels which probably include a dozen different surfactants and adjuvants in various different proportions, and it would be -- it would be infeasible and inappropriate to require, you know, $4 million worth of chronic testing on every single one of them.

So part of the practical issues was, you know, which formulated products to choose, if EPA were to require such testing, so there -- there are valid regulatory policy and efficiency of decision-making reasons why EPA has not as a matter of course required chronic testing on formulated products.

Q. So there are valid regulatory policy and efficiency decision-making reasons including the workload that's put on EPA for potentially reviewing a long-term cancer study of every formulated product, and then also the expense and workload that would be put on

companies in developing that those data -- those tests and data packages, correct?

A. That is why at this point EPA does not include routinely chronic testing of, say, at least one of the major formulations for all pesticides, that is correct.

Q. Are there any other reasons?

A. Well, I -- I think those are the two major ones.

Q. Do you know of any pesticide company that conducts long-term rodent carcinogenicity studies on its formulated pesticide products?

A. Certainly not as a -- not as a routine practice and certainly not that I'm aware of where they've submitted them to -- to EPA, but I would imagine -- I would imagine that even Monsanto maybe in another country has done some further testing of formulated product, whether it's Q testing or genotox or cancer, but -- but where there would be no -- no knowledge or record of that in the US. It's a big world. There's a lot of different people doing a lot of different testing and, you know, my review of the record really was limited to toxicity testing done by Monsanto to submit to the EPA, and so I -- you know, it's just -- it's hard for me to know what might have been done in China or Japan or Turkey.

in the pure glyphosate.

You know, there's -- there's no question but that the record in this case shows that, you know, by the early 2000s, Monsanto was -- knew that its formulated product was more toxic to mammals than its pure active ingredient, and I think as -- as the use of glyphosate expanded, as the GE crops came on and, you know, became so popular around the world, a responsible company would have in that -- in that instance done a battery of -- of chronic feeding studies on at least one of its major formulated products, and I think had they done that and had the study produced no indications of toxicity beyond what was already aware from the long-term studies on glyphosate alone, then we wouldn't be here today, but I think it -- it -- in this unusual and unique circumstance it was the company's responsibility without being asked by EPA to do such studies. That is my opinion.

Q. Finished?

A. Yeah.

Q. Given there's not a single pesticide company in the US or abroad that has conducted a long-term rodent study on one of its formulated pesticide products, it certainly isn't industry standard for a company to do that, correct?

A. Well, I'll agree with you, it's not a routine industry standard, but I'm not prepared to say that no company has ever done a chronic feeding study on a formulated product. I -- I don't -- I have not done the research to agree or disagree with that statement of yours.

Q. Given you're not aware of a single pesticide company in the US or abroad that has conducted a long-term rodent carcinogenicity study on one of its formulated pesticide products, it certainly isn't industry standard for a company to do that kind of testing, correct?

MR. LITZENBURG: Object to form.

A. Yes, sir, that's exactly what I just said. I agreed with you on that part of your statement.

Q. (BY MR. HOLLINGSWORTH) You testified above -- earlier today that your definition of a reasonable company is based, in part, on following the industry standards, correct?

A. Certainly at a minimum, yes.

Q. So it's certainly not unreasonable that Monsanto has not tested Roundup in a long-term rodent carcinogenicity study, correct?

A. No, no, it is not.

MR. LITZENBURG: Wait a second.

testing of formulations, and I say it does and I just read the passage where --

Q. (BY MR. HOLLINGSWORTH) Sure.

A. -- it's spelled out.

Q. And this paper certainly isn't a formal request to EPA or another worldwide regulator to consider long-term rodent carcinogenicity testing on the formulated product, correct?

A. Correct.

Q. Are you aware of anyone who has formally raised objections to it with EPA or another worldwide regulator?

A. Well, I'm not, but there's no reason why it would be if somebody hadn't. There's regulators all over the world, I mean, all sorts of petitions and requests from concerned citizens and scientific organizations. So, I mean, I -- I'm sure that there have been formal requests to regulators somewhere in the world to call for, you know, more in-depth testing of formulated product. It's a -- it's a common concern.

Q. You're not required [verbatim] of any formal response from EPA or another worldwide regulator with respect to that request, are you?

MR. LITZENBURG: Object to form.

A. Excuse me?

Q. (BY MR. HOLLINGSWORTH) You're not re -- you're not aware of any response from EPA or another worldwide regulator with respect to that request, correct?

A. No, I'm not.

Q. Sir, have you designed a long-term rodent carcinogenicity study on a formulated pesticide before?

A. No.

Q. Has anyone designed a GLP or OECD-approved study on the Roundup formulated product?

A. I'm -- I don't know the answer to that question.

Q. As far as you know, has anyone designed a GLP or OECD-approved study on the Roundup formulated product?

A. Well, I don't know if Seralini's study would qualify under OECD guidelines. It certainly qualified as a chronic feeding study. It was not designed to be a cancer study. So that would probably be the only one that I'm aware of that certainly arguably was designed in accord with OECD chronic feeding requirements, but as I said, not oncogenicity requirements which would have required many more animals per treatment group.

Q. Right. And you're aware that EFSA had a

Q. Right. If you look at Appendix F?

A. F -- F.1.1, page 203.

Q. Correct. These are listing genotoxicity studies on the formulated product -- glyphosate formulated product that are in the possession of EPA, correct?

A. Yeah, looks like that's what it is.

Q. And if you turn to page 206 of 216?

A. Okay.

Q. It notes Perina 1998. Do you see that?

A. Oh, I do, yeah.

Q. And it notes that it was done on MON 77280. Do you see that?

A. Correct, okay.

Q. That's the same study that we just reviewed in the prior exhibit, correct?

A. Seems to be, yeah.

Q. Okay. So this shows that Monsanto has conducted genotoxicity studies on the glyphosate formulated product and that the EPA is in possession and has reviewed those studies, correct?

MR. LITZENBURG: Object to form.

A. Well, at least one.

MR. HOLLINGSWORTH: We'll mark another exhibit here.

reverse mutation test with five histidine deficient mutant tester strains of Salmonella typhimurium. Do you see that?

A. Yep, standard Ames test.

Q. And down at the bottom it says: The results -- the results revealed that the test substance MON 77280 provided no positive mutagenic effect. Do you see that?

A. I do.

Q. So this is another negative mutagenicity or genotoxicity test on the glyphosate formulated product, correct?

A. Right, right, in this Salmonella strain of which there are many, many in the record.

Q. Sure. And if you turn again to EPA 2017 OPP report, and the list of glyphosate formulations that were studied for genotoxic effect.

A. I'm guessing it shows up.

Q. Do you see the Camolesi is one of those studies? It's on the first page, page 203?

A. Yes, I do.

Q. So Monsanto, for purposes of registration in Brazil, conducted genotoxicity tests on the formulated glyphosate product and the EPA is in possession and has reviewed those studies, correct?

A. According to this table, yes.

Q. So you certainly cannot say that Monsanto did not conduct any cancer testing on the glyphosate formulated product, correct?

MR. LITZENBURG: Object to form.

A. Any cancer testing?

Q. (BY MR. HOLLINGSWORTH) Yes. Sir, you testified previously that genotoxicity studying is a form of cancer study, correct?

A. No, I did not testify to that.

Q. What did you mean when you said that?

A. I testified that regulators and scientists consider mechanistic data or genotoxicity studies as an important part of their evaluation of whether a pesticide poses a cancer risk. It -- a genotoxicity study is not the same thing as a cancer study, but it's important evidence that the EPA under its new guidelines takes into account in making a weight of evidence determination, just as IARC took account of the genotoxicity data in its weight of evidence determination that glyphosate and glyphosate-based herbicides are, in their judgment, probable human carcinogens.

So a genotox study is not the same as a cancer study, but it is drawn upon by scientists to gain

insight on the -- the mechanism through which exposure to glyphosate-based herbicides could trigger abnormal cell growth that could progress to a -- a frank tumor.

Q. Right. And EPA was in possession of these Monsanto studies on the glyphosate formulated product that are used by scientists to gain insight on the mechanism through which exposure to glyphosate-based herbicides could trigger abnormal cell growth that leads to a tumor, correct?

MR. LITZENBURG: Object to the form.

A. Yes, correct. I don't know when, but...

MR. LITZENBURG: Dr. Benbrook, would you -- I think Number 15 is the thing we only have one copy of. Can I look at it while you all are looking at other things?

THE WITNESS: Sure. 17, 16, 14, 20, 18, 13.

Q. (BY MR. HOLLINGSWORTH) Are we good to continue?

A. Sorry. There's just a lot of paper here.

MR. LITZENBURG: You're doing better than me.

THE WITNESS: There's 15.

MR. LITZENBURG: Thank you.

A. Okay.

glyphosate-based herbicides at levels below EPA certified limits can cause non-Hodgkin's lymphoma?

A. I -- I have no -- no reason to believe that, and I would -- would find that unlikely, but, you know, it's -- it's possible I suppose.

Q. You don't have the expertise to determine whether impurities found in glyphosate-based herbicides at levels below EPA certified limits can cause NHL, correct?

A. I'm -- I certainly don't have a crystal ball that could make that determination, and I -- I doubt that anybody has -- has done the kind of in-depth work that would be required to definitively judge that, and I know that Monsanto actually did commission a two-year feeding study on NNG in the early days, but it -- the study was terminated because of excessive mortality in one of the treatment groups and it wasn't repeated and -- but, you know, the levels are -- the levels that have been consistently reported were very low and it was a -- it has been the judgment of EPA all along that they didn't -- they didn't feel that the level of risk was high enough to warrant any further assessment.

Q. Right. And you don't hold the opinion that impurities in glyphosate-based herbicides at the level in which they actually exist are causing NHL, correct?

worked for the National Academy of Sciences, the integrity of science and scientific ethics, the quality of scientific communications has been a important and recurrent theme throughout my career and, you know, clearly ghostwriting and inaccurate attribution of published papers is a -- is a matter taken very seriously in the scientific community throughout my career and will continue to be a very important thing. So if that's what you or a reasonable person would regard as the knowledge and experience of an expert in ghostwriting, then yes, I would characterize myself as such an expert.

Q. So you don't want to withdraw your testimony from the last deposition that you're an expert in ghostwriting, you stand by that?

A. I -- I stand by it.

Q. The first subsection, Subsection 6D.1, is about Dr. John Acquavella, correct?

A. Correct.

Q. He's a former Monsanto employee and also worked on the Intertek expert panel publications after his employment with Monsanto, correct?

A. Yes.

Q. And you authored this report starting last October, finished up sometime in December 2017,

correct?

A. Yes.

Q. Okay. And during that time and since that time, you know, roughly six months, you still haven't taken the time to review Dr. Acquavella's deposition and see what he had to say about your claims with respect to him and ghostwriting, correct?

A. I -- as I said, I -- I haven't reviewed Dr. Acquavella's deposition.

Q. Do you wish you had reviewed Dr. Acquavella's deposition to determine whether the claims you made about Dr. Acquavella and ghostwriting were, in fact, true?

MR. LITZENBURG: Object to form.

A. I -- I based my discussion of Acquavella's complaints to his colleagues in Monsanto about inaccurate attribution of the authorship of papers in the volume that he was working on on his own words and the e-mails that he exchanged and, you know, I -- I probably would gain sort of -- you know, further understanding of the context and -- but I -- I -- Acquavella is a pretty straight shooter kind of guy. He sort of calls it like he sees it, and I have no reason to believe that he was lying or misleading his colleagues in all of the e-mails that I saw where he

Q. (BY MR. HOLLINGSWORTH) So you're reading this company e-mail by Dr. Acquavella and interpreting what he means to say with certain text in this company e-mail, correct?

A. Yeah, this and the other e-mails, it's laid out here, you know, I -- I think pretty clearly and, you know, if you want to pull out the original e-mails we can talk some more about it.

Q. But you never reviewed Dr. Acquavella's deposition when you made your claims about him and Monsanto's ghostwriting, correct?

MR. LITZENBURG: Asked and answered as with everything today.

A. Yep, yep, as I -- you know, I have no reason to change my previous answer to that question.

Q. (BY MR. HOLLINGSWORTH) So your opinions on ghostwriting with respect to Dr. Acquavella are based entirely on company e-mails, correct?

A. And reviews of the -- the various drafts and the papers and my reading of the actual final paper and my understanding of where the parts of that paper came from as well as the other chapters. For example, the introductory chapter which Dr. Heydens wrote, drafted the introductory chapter that appeared under the name of other people and not his. So, yes, the -- the

he was on one or maybe two of the other papers.

Q. So your claim that the Acquavella 2016 review article is ghostwritten is based on Dr. Kier's name not being included as an author, correct?

A. Well, first of all, to go back to the -- the reason that I included Acquavella calls Monsanto out for unethical behavior, the -- the focus and the substance of that episode was Heydens telling Acquavella that his name could not appear on this chapter that he had written. And Acquavella said back to Heydens, "Well, I'm not okay with that, my panel is not okay with that because that would be unethical." And presumably because of Acquavella's objection, Acquavella's name now appears on the paper as published.

Q. Dr. Kier is a genotoxicity expert, and you're claiming that he should be an author on the epidemiology expert panel review?

A. I didn't make that claim. I didn't make that statement. I said in the early discussion in e-mail traffic Dr. Heydens asked Dr. Acquavella and Dr. Kier to work on this chapter together. Dr. Kier also drafted -- I think he was the -- probably the principal author of the genotox chapter. I'm simply noting that the written record shows that Dr. Kier was involved at

was --

A. Correct.

MR. LITZENBURG: -- as with every paper, right? Which -- which question are you asking him?

Q. (BY MR. HOLLINGSWORTH) Monsanto's name is all over this declaration of interest and every declaration of interest that you have a problem with, correct?

MR. LITZENBURG: No.

A. The declarations of interest are different somewhat across the papers. The one I was just talking about, it wasn't a Monsanto declaration of interest. It was a statement by the editor of the journal.

Q. (BY MR. HOLLINGSWORTH) I'm talking about the declarations of interest, sir. Monsanto's name is all over these; isn't that true?

A. Correct. Yeah.

Q. Okay.

VIDEO OPERATOR: We're going off the record. The time is 9:27.

(Discussion off the record.)

Q. (BY MR. HOLLINGSWORTH) Dr. Benbrook --

MR. LITZENBURG: Hang on a second. We have previously had a --

VIDEO OPERATOR: We're not on the record yet.

but I'm going to continue.

Q. (BY MR. HOLLINGSWORTH) Dr. Benbrook, you are aware that regulatory agencies, EPA, EFSA, they do not consider review articles of -- of any importance when they have the primary studies to review, correct?

A. I think that's generally a correct statement.

Q. Okay. The regulator is going to take an independent review of those primary studies rather than rely on a review paper, correct?

A. Well, it's funny that you would ask that question because in the case of the BFR review of glyphosate genotoxicity studies done and submitted to the agency or published in the peer-reviewed literature before 2000, the year 2000, it's been shown very clearly that the BFRA review of that body of literature was in effect ghostwritten by Dr. Kier who had written a report for the glyphosate task force reviewing the pre-2000 genotoxicity data, and a word-for-word comparison of the glyphosate task force review of these early genotoxicity studies written by Dr. Kier appears verbatim in the BFRA review of that information.

In addition, it -- it is -- it's been shown that the -- much of the text of Dr. Kier's task force report is essentially verbatim -- repeats essentially verbatim the conclusions in a Williams, et al., 2000

I've put in the expert report.

Q. (BY MR. HOLLINGSWORTH) Go -- go to paragraph 798, sir. That's where you made the claim.

A. 798. Okay. As part of his 2015 performance evaluation Saltmiras summarized his glyphosate-related activities which included ghostwrote cancer chapter -- cancer review paper Greim, et al., 2015. Coordinated care 2015 --

Q. We're talking about Greim, sir.

A. Okay.

Q. You claim that Dr. Saltmiras ghostwrote the Greim publication, correct?

A. That's what he says in -- that's what he says in this e-mail.

Q. But by your definition and the first thing an expert in ghostwriting checks is who is an author on the paper, correct?

A. Correct.

Q. And Dr. Saltmiras is an author on the paper, correct?

A. His name does appear as the paper was published.

Q. So Dr. Saltmiras can't by your own definition have been a ghostwriter on the Greim publication, correct?

A. Because his name was added, but he obviously thought that he did. I don't -- I don't -- I can't explain why he made this claim in his performance evaluation when, in fact, he appears on -- you know, on the list of authors. You know, it's a -- I don't -- I don't know what he was referring to, but by his own words, he said that he ghostwrote the cancer review paper.

Q. Right. You based your opinion as to ghostwriting on company e-mails and company documents?

A. Right.

Q. Rather than looking at the first place you should have looked, which is the authorship --

A. Right.

Q. -- of the paper as published, correct?

A. And --

MR. LITZENBURG: Asked and answered, argumentative.

A. Now that I've thought for a minute about it, what Saltmiras is complaining about is that he wrote the -- the paper, he wrote the whole paper, and he -- he is, I think, saying, "I really deserve the credit for this paper despite the fact that there were three other coauthors." Because he wrote the paper. Now, whether these other coauthors contributed substantially

enough to legitimately be listed as coauthors, I -- I'm not -- not prepared to address at this late hour without going back and looking at what's in the record about who did what, but I'm -- I'm -- I believe that that's the explanation for why Saltmiras reported to his supervisor that he -- he deserves credit for ghostwriting this paper because he wrote it. So instead of it just being David Saltmiras, it's these three other people added. That -- that's the explanation.

Q. (BY MR. HOLLINGSWORTH) You're speculating in that explanation and Dr. Saltmiras is included as an author in this publication and, therefore, could not have ghostwritten it, correct?

A. He --

MR. LITZENBURG: Object, asked and answered.

A. I think the -- what Saltmiras was reporting to his supervisor was that he deserves credit for being the principal author, the major author, perhaps the sole author, I don't really know, of this particular paper, and he himself characterized his role as ghostwriting it and I took him at his word.

Q. (BY MR. HOLLINGSWORTH) Dr. Benbrook, even in the company e-mails and company documents on which you

REPORTER'S CERTIFICATE

I, PATRICIA D. JACOY, the undersigned Certified Court Reporter, pursuant to RCW 5.28.010 authorized to administer oaths and affirmations in and for the State of Washington, do hereby certify that the sworn testimony and/or proceedings, a transcript of which is attached, was given before me at the time and place stated therein; that any and/or all witness(es) were duly sworn to testify to the truth; that the sworn testimony and/or proceedings were by me stenographically recorded and transcribed under my supervision, to the best of my ability; that the foregoing transcript contains a full, true, and accurate record of all the sworn testimony and/or proceedings given and occurring at the time and place stated in the transcript; that a review of which was requested; that I am in no way related to any party to the matter, nor to any counsel, nor do I have any financial interest in the event of the cause.

WITNESS MY HAND AND DIGITAL SIGNATURE this 28th day of May, 2018.

Patricia D Jacoy

PATRICIA D. JACOY
Washington State Certified Court Reporter, #2348

Exhibit 2

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	)	MDL No. 2741
	)	Case No. 16-md-02741-VC

DEPOSITION OF DR. CHRISTOPHER PORTIER

Friday, January 12th 2018

AT: 11.00 am

Taken at:

Hilton London Heathrow Airport
Terminal 4
Hounslow TW6 3AF
United Kingdom

Job ref: 173050

Pages: 1 - 126

Reporter: Claire G. Hill RPR CRC

published case control studies of glyphosate and non-Hodgkin's lymphoma combined, correct?

MS. GREENWALD: Same objection.

A. I don't know what "significantly" means here. We can add the numbers up and I can tell you if it's double or if it's triple or if it's 1.5 times, but I don't know what "significant" means, so I can't.

Q. You would agree that there are more exposed non-Hodgkin's lymphoma cases in the 2018 National Cancer Institute study than in all of the published case control studies combined, correct?

A. That is correct.

Q. The scientists, I guess it's ten scientists from the National Institutes of Health, state in the abstract of the 2018 NCI study, that -- in their conclusion:

"In this large prospective cohort study, no association was apparent between glyphosate and any solid tumours or lymphoid malignancies overall including non-Hodgkin's lymphoma and its subtypes."

Correct?

A. First, let me correct something. This is not an NCI study. Having worked at NIH, I know what this is, this is a study produced by

CERTIFICATE OF COURT REPORTER

I, Claire Gwyneth Hill RPR MBIVR, Accredited Real-time Reporter, of Planet Depos, hereby certify that the foregoing testimony was recorded by me stenographically and thereafter transcribed by me, and that the foregoing transcript is a true and accurate verbatim record of the said testimony.

I further certify that I am not a relative, employee or counsel of any of the parties of the within cause, nor am I an employee or relative of any counsel for the parties, nor am I in any way interested in the outcome of the within cause.

Signed:

Claire Gwyneth Hill

Dated: 1/15/2018

Exhibit 3

SUPERIOR COURT OF THE STATE OF CALIFORNIA
FOR THE COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON, Plaintiff, v. MONSANTO COMPANY, Defendants.	Case No. CGC-16-550128

EXPERT REPORT OF CHARLES BENBROOK

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Notes:

1. Several documents are cited by reference to their MONGLY number; others are referenced as a numbered exhibit. In some cases, a reference lists just the first page of a cited source, while in other cases, all pages in the source, or a selected subset of pages, are listed. In all cases where only the first page of a cited source is listed, I may have relied on content throughout the document in forming my opinions.

2. I had in my files many of the documents that appear in the discovery record of this case. At the suggestion of Counsel in such instances, I identify these documents with their MONGLY or exhibit number.

I. Summary of Opinions

1. I was asked by the Plaintiff's lawyers in this case to review extensive material on Roundup® and to give an opinion as to whether Monsanto® should have warned the public about the risk of non-Hodgkin Lymphoma (NHL) associated with use of and exposure to glyphosate and glyphosate-based formulations.

2. It is my opinion that Monsanto failed to adequately warn about the risk of NHL associated with the use of Roundup® and RangerPro®[1] beginning in, or before 2001 for reasons explained below. I was also asked to opine whether Monsanto fulfilled its duty as a pesticide manufacture with respect to the stewardship of Roundup®. It is my opinion they did not as further detailed and for the reasons below.

3. Prior to being contacted by Plaintiff's lawyers I had been independently researching, for many years, the use, toxicological properties, and regulation of glyphosate in the United States. My research findings have been published in peer-reviewed science journals. And have included the need for reform in the regulation of herbicides in general, and glyphosate in particular.

4. In order to inform these opinions, I carried out independent research using online EPA resources, publicly available literature, and regulatory documents. I also have long professional experience researching glyphosate and Roundup®. Plaintiff's lawyers sent me several volumes of documents containing mostly internal Monsanto communications. I requested follow-up information in several areas, drawing on the discovery record in this case.

[1] In this report Roundup® and RangerPro® are used interchangeably. They are similar products manufactured by Monsanto containing the active ingredient glyphosate and the surfactant POEA. Both products were used by Dewayne Johnson.

5. The opinions in this report are based on my education, experience, review of the documentation, and independent research. These opinions are held to a reasonable degree of certainty.

A. Focus of Case

6. This case is about the way Dewayne Johnson used and applied RangerPro and Roundup ProConcentrate in the course of carrying out job-related, weed management duties for the Benicia Unified School District.

7. Dewayne Johnson applied glyphosate-based herbicides in 2012-2014. In those years, farmers and ranchers applied about 90.3% of the total pounds of glyphosate herbicide used in the U.S., while non-agricultural uses accounted for about 9.7%. (Benbrook C. [2016]. Trends in glyphosate herbicide use in the United States and Globally, *Environmental Sciences Europe* Vol 28:3; DOI 10.1186/s12302-016-0070-0).

8. Of the 9.7% of total glyphosate use that is non-agricultural, I estimate that at least two-thirds of that was applied on golf courses, along roads and rights-of-ways (railroad tracks, power lines), and on industrial facilities. The majority of these non-ag applications were carried out using mid- to large-scale spray equipment with cabs and air filtration systems, or by airplanes or helicopters.

9. Hence, glyphosate applications made using a hand held or backpack sprayer likely accounted for under 3% of the total U.S. use of glyphosate-based herbicides in the 2012-2014 period.

10. Government statistics, and the records in this case, show that over the years, a highly disproportionate share of the glyphosate-related, worker-safety poisoning and illness episodes arise from hand-held, backpack, or other application methods that result in markedly

higher exposures and risks than typical, larger-scale applications of Roundup.

11. By "highly disproportionate," I mean, for example, one-half or more of the reported, glyphosate-based herbicide illness episodes arise from hand held/backpack applications of the herbicide that account for well less than 3% of the total volume of glyphosate applied.

12. The reason is clear. Most glyphosate applied on farms is sprayed using large equipment with enclosed cabs that have air filtration systems, where the operator/driver/pilot is far-removed from the spray, and also protected from exposure by a glass/metal cab and an air filtration system.

13. The sizable differential in routine, expected exposures between ag and many non-ag uses of glyphosate arises because of the proximity of people using a hand held or backpack sprayer to the spray solution, their need to walk within and through an area that was sprayed just minutes before, the absence of a barrier or shield to protect them from spray drift, and the absence of an air filtration system (since a respirator is not required on any Roundup labels).

14. Since the 1980s, Monsanto has known that individuals applying a glyphosate-based herbicide through a hand-held or backpack sprayer face markedly higher exposures and risks, especially on windy days.

15. The company has also known that risks are higher for individuals that apply the herbicide for many days a year and/or many hours during a given day, yet there are no statements on Roundup labels or label provisions that require stricter worker protection measures as a function of how many hours in a work week, or over a year, that a person sprays glyphosate herbicides as part of their job.

16. Accordingly, a key question at the heart of this case is whether Monsanto acted responsibly in the face of information pointing to greatly elevated exposures and risks of cancer,

specifically non-Hodgkin Lymphoma ("NHL") for some individuals like Dewayne Johnson, who applied Roundup herbicides in known, high-exposure scenarios.

B. Monsanto's Responsibilities

17. Monsanto was responsible for four things that are central to this case. First, the company was responsible for assuring that the specific herbicide products sold to the school district for which Mr. Johnson worked were as safe as they could be, given existing knowledge and technology.

18. Second, Monsanto was responsible for the content, scope, and effectiveness of the label directions for use, use restrictions, warnings about high-risk scenarios, and worker-safety requirements on the RangerPro and Roundup ProConcentrate labels.

19. While Monsanto had to comply with several generic, EPA requirements regarding what and how such worker safety information appears on an herbicide label, the company bore the primary responsibility to assure that the label directions on its products, as well as any restrictions, warnings, and precautions, were adequate to avoid any "unreasonable adverse effect on man or the environment."

20. Third, Monsanto bore an obligation to draw upon its extensive field testing and scientific resources to progressively improve the utility and safety of its products in two basic ways: (1) through progressively safer formulations, and (2) through label directions and worker-safety provisions that both adequately warn those handling, mixing, and applying Monsanto-brand herbicides about potential high-exposure scenarios, and require adoption and adherence to worker-safety provisions sufficient to prevent significantly elevated exposure episodes.

21. Fourth, Monsanto was and remains obligated to work cooperatively and openly with the EPA to assure that both the company's internal assessments of risk, including worker

risks, and those done by the EPA, are as accurate as possible. This obligation flows from the company's product stewardship pledges, as well as provisions in federal law.

22. Accuracy in worker risk assessments is an essential foundation upon which the company and EPA can then develop effective, commonsense methods to reduce applicator exposures and risk.

23. The record of this case shows that Monsanto repeatedly failed in carrying out each of these four, essential tasks and responsibilities. Monsanto failed to warn about the risk of NHL, other forms of cancer, or damage to the liver or kidneys, stemming from the use of Ranger Pro and Roundup Pro.

24. Instead, the company overstated the benign nature of its glyphosate-brand herbicides, calling them biodegradable and safe to use, without any qualification. Monsanto also did little to counter the often-heard claim that "Roundup is safe enough to drink."

25. In dozens of instances, the company generated, or came into possession of, scientific information pointing to higher risks than previously recognized. Instead of sharing the information with the EPA, as often required by law, and acting on the new information to update risk assessments and determine whether new, exposure and risk-reduction measures were warranted, Monsanto took active steps to not disclose the information and keep it from becoming public knowledge.

26. In many instances, the company sought ways to undermine the relevance or legitimacy of results in studies that it had commissioned and paid for. Monsanto's determination to change the results of a Bio/dynamics mouse oncogenicity study is a case in point discussed at length in this report.

27. Furthermore, it is important to emphasize that it is Monsanto's responsibility to

take steps to increase margins of safety for users of its products like Dewayne Johnson, through alteration of formulations and addition of new worker-safety language on labels.

28. Such changes should be made whenever the company recognizes an opportunity to make their products safer. Across the pesticide industry, the majority of proactive steps taken to increase margins of safety in the use of specific pesticides are initiated by companies, not the EPA.

29. The number of label amendments proposed by pesticide registrants, and approved generally without change by the EPA, greatly outnumbers label changes required by the EPA.

1. Product Stewardship Standards for Communicating Warnings

30. A company selling a pesticide to the public is responsible for the testing of its product to ensure it can be used safely. It is not the EPA's responsibility to test the product, nor does the agency have the financial resources required to do so.

31. In addition, a company selling a pesticide product to the public bears responsibility for adequately warning users about any potential risks associated with the use of its product. Companies are also obligated to require on product labels practical and effective steps that users must take, or should take to mitigate (reduce) such risks (referred to throughout this report as worker-safety requirements or provisions).

32. While EPA requires and oversees adherence to generic, worker safety labeling requirements, it is crystal clear in the industry that companies bear the primary responsibility to assure that label directions and restrictions are clear, effective, and comprehensive in addressing possible risks from the use of a given product.

33. The purposes for which Dewayne Johnson applied Ranger Pro and other Roundup herbicides, and the methods he used to apply them, were common and routine, as were the

factors giving rise to potentially unsafe exposures from Johnson's lawful applications.

34. This responsibility to warn and mitigate extends to the full range of foreseeable circumstances and situations in which a pesticide can be applied in accord with the directions on its label (e.g., a leaky hose fitting on a backpack sprayer, or an application on a windy day).

35. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), "a manufacturer seeking to register a pesticide must submit a proposed label to EPA as well as certain supporting data." (7 U.S.C. §§ 136a(c)(1)(C), (F))

36. Manufacturers have a duty to update pesticide product labels when new safety information and insights are discovered, for example from tracking documented poisoning episodes. The routine method for them to do so is by requesting EPA to approve a label amendment that builds into a product's existing label, new language imposing additional safety precautions and worker safety provisions.

37. EPA almost always approves such requests for label amendments, and in most cases, quickly.

38. A pesticide product is considered misbranded under FIFRA if:

> "(F) the labeling accompanying it does not contain directions for use which are necessary for effecting the purpose for which the product is intended and if complied with, together with any requirements imposed under section 136a(d) of this title, are adequate to protect health and the environment; [or] (G) the label does not contain a warning or caution statement which may be necessary and if complied with, together with any requirements imposed under section 136a(d) of this title, is adequate to protect health and the environment..." § 136(q)

39. A pesticide product can be misbranded even if the EPA has registered the pesticide and approved its label, because manufacturers bear the responsibility to assure that labels incorporate new and/or adequate safety information and worker safety restrictions to prevent applications leading to excessive exposures and risks.

40. FIFRA explicitly states that "registration does not provide a defense to the violation of the statute." 7 U.S.C. § 136a(f)(2)

41. Additionally, manufacturers are not limited to warning the public through just the text appearing on a product label. Indeed, many product labels are long, complex, and technical documents, which are often not carefully read by users.

42. For this reason, manufacturers also need to utilize other methods to communicate safety information to users. Common methods include advertising, media interviews, websites, blogs, trade and scientific publications, training materials, phone calls, email, information shared by their sales force, and point-of-sale warnings and use directions.

43. Manufacturers can also warn about the risks of pesticides through safety data sheets governed by OSHA. Safety Data Sheets are often provided to employers of chemical applicators, as Dewayne Johnson was by his supervisor working for the Benicia Unified School District.

44. An important provision in OSHA regulations provides that:

> "Chemical manufacturers, importers, distributors, or employers who become newly aware of any significant information regarding the hazards of a chemical shall revise the labels for the chemical within six months of becoming aware of the new information, and shall ensure that labels on containers of hazardous chemicals shipped after that time contain the new information." (29 CFR 910.1200(f)(11))

45. Manufacturers must include information about the carcinogenicity of their product on safety data sheets.

46. They may conduct their own assessment of the oncogenic potential of their products, or rely on testing and cancer risk assessments made by another organization or company. However, an assessment by IARC, if available, must be included on OSHA safety data sheets, because IARC determinations are regarded by governments around the world as

credible, data-driven, and authoritative. (29 C.F.R. § 1910.1200, Appendix A)

2. Failure to Adequately Warn and Prevent Risks is Misbranding

47. Since 1985 when EPA toxicologists concurred that glyphosate was a potential human carcinogen, the labels for Roundup and other glyphosate based formulations have been misbranded because they did not contain adequate instructions to protect the health of people applying the products.

48. Beginning in 1985, Monsanto could and should have added a warning to the labels on glyphosate-based herbicides, and utilized other methods to inform the public that glyphosate had been shown to be oncogenic in animal studies. A reasonable and prudent manufacturer would have accepted the EPA's position that glyphosate was possibly oncogenic, and as a result, included that information on the label, in chemical safety data sheets, and in its marketing material.

49. A reasonable and prudent pesticide manufacturer would have added such a warning to adequately safeguard the health of the people using its products, and coupled the warning statement with the addition of a set of practical worker safety provisions that would markedly reduce potential exposure (e.g., wearing gloves, a requirement ***not*** on the labels of the Monsanto herbicides Johnson applied).

50. Monsanto was well aware that such added worker safety requirements were especially needed in the case of high-exposure application methods and scenarios, like those encountered by Dewayne Johnson in the course of his job.

51. A year later, in 1986, the EPA issued a new Registration Standard document on glyphosate. It set forth just such a set of prudent and practical worker safety requirements designed to markedly reduce the frequency and severity of high-exposure episodes.

52. These new provisions were supposed to be on all labels sanctioning use of glyphosate-based herbicides by June 30, 1988, except for very dilute products marketed to homeowners in ready-to-spray bottles.

53. But Monsanto resisted the new worker safety provisions called for in the 1986 Registration Standard, and the most important of them are ***still are not included on most of Monsanto's glyphosate product labels in the U.S***.

54. Cancer is not the only adverse health effect possibly associated with use of glyphosate herbicides that Monsanto should have warned users about via product label amendments.

55. Beginning in 1999 Monsanto could and should have added a warning to their labels, and otherwise informed the public, that exposure to formulated glyphosate products can cause oxidative stress and lead to genotoxic damage. In lay terms, such a warning might state "exposure to this product can damage cells and trigger disease."

56. The company was aware of new genotoxicity studies reporting such impacts. To determine the proper course of action moving forward, Monsanto commissioned an internationally respected expert, Dr. James Parry, to review recent genotoxicity studies and render his opinion whether the findings reported were credible.

57. Dr. Parry concluded that some were, and recommended Monsanto take a number of steps to better understand the nature, magnitude and likely causes of newly discovered genotoxic risks stemming from, especially, exposure to formulated glyphosate herbicides.

58. After receiving Dr. Parry's expert report, a reasonable and prudent pesticide manufacturer would have added a genotoxicity warning to Roundup labels, and conducted the additional, more sophisticated and sensitive testing that Dr. Parry had recommended to resolve

"outstanding issues."

59. Instead, Monsanto ended its association with Dr. Parry and refused to do the testing he recommended.

60. Beginning around 2002, Monsanto could and should have added a warning to their label, and otherwise informed the public and biomedical community, that exposures to Roundup formulations increase the risk of a specific cancer, NHL, after learning about the results of two epidemiological studies showing a statistically significant increase in the risk of NHL among users of glyphosate-based herbicides. (Hardell and Eriksson (1999). A case-control study of non-Hodgkin lymphoma and exposure to pesticides, *Cancer* 85: 1353-1360; McDuffie et al. (2001) Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health, *Cancer Epidemiology, Biomarkers & Prevention* Vol 10: 1155-1163)

61. Had Monsanto amended the label to include a risk of NHL in 2002, the EPA would have approved that amendment.

62. These initial NHL results were reinforced in 2003 and 2008 in studies by DeRoos et al. and Eriksson et al.

63. These human epidemiological findings in peer-reviewed science journals take on added importance in light of the confidential, Monsanto commissioned report by Dr. Parry.

64. A reasonable and prudent pesticide manufacturer, aware of recently published evidence of genotoxicity, Dr. Parry's evaluation of these studies, and now a series of positive epidemiological studies, would have added a NHL warning to its glyphosate-based herbicide labels, and added long-overdue worker safety requirements, in order to more adequately safeguard the health of applicators and others exposed to elevated levels of glyphosate herbicide.

65. Beginning in at least by June 30, 1988 in response to the 1986 glyphosate Registration Standard, Monsanto could and should have added the EPA-required worker safety provisions to all their glyphosate labels. These would have included instructions to applicators regarding the additional steps needed to reduce their exposure to Roundup formulations, particularly in the case of high exposure-risk scenarios (e.g., when an applicator is using a backpack or hand held sprayer).

66. Such steps for backpack or hand-held application methods would include wearing a face shield or googles to avoid exposure to drift; wearing chemical-resistant gloves and shoes or boots; walking perpendicular to the direction of the wind; and, more cautious handling of clothing and other gear used during spraying operations, including disposal of heavily contaminated clothing and equipment.

67. A reasonable and prudent pesticide manufacturer would have added the EPA-required provisions in 1987-1988, at a minimum, as well as new warning language to more assuredly safeguard the health of applicators on, for example, windy days.

68. In addition to new label language, beginning on the above referenced dates, Monsanto should have conveyed the above warnings and instructions through media outreach, applicator training sessions, scientific publications, its website, third-party bloggers it influences, training materials, advertisements, OSHA safety data sheets, and direct communications by sales and technical support staff.

69. Without doubt, Monsanto should have conducted long-term carcinogenicity tests of at least its top two or three Roundup formulations in the 1990s (ranked by sales), in the wake of the near-decade long fight with EPA over the 1983 Bio/dynamics mouse oncogenicity study.

70. Having learned from multiple, credible published studies, its hired scientific

advisers, and its own internal research that formulated glyphosate-based products are far more toxic than 100% pure glyphosate, a reasonable and prudent pesticide manufacturer would have tested at least the most widely sold, formulated Roundup products to determine if they were genotoxic and/or carcinogenic.

71. A reasonable and prudent manufacturer that repeatedly pledges allegiance to sound science would not engage in a campaign to "orchestrate outcry," "invalidate the relevance," and cut the funding of IARC, one of the most respected and authoritative scientific bodies in the world charged with a serious, difficult task -- determining the causes of cancer in the hope of reducing the burden of disease worldwide.

72. Monsanto's failure on the label of Ranger Pro herbicide to adequately warn users about the risk of NHL, and reduce exposures in high-risk application scenarios via prudent worker safety requirements, increased Mr. Johnson's exposure to glyphosate and therefore increased his risk of NHL.

73. Instead of warning the public about the risk of NHL, Monsanto has devoted enormous resources to try to sow doubt and discredit scientifically valid claims that Roundup and RangerPro formulations increase the risk of NHL, as extensively detailed in this report.

3. Responses to Mr. Johnson's Inquiry

74. Importantly, Dewayne Johnson reports that he called a number listed on the RangerPro packaging and was connected to the Missouri Poison Control Center on March 27th 2015. Mr. Johnson asked whether RangerPro was a cause of his NHL, and whether it was safe for him to keep using RangerPro. The operator at the poison control center stated that his symptoms were not consistent with the symptoms following glyphosate exposure, and as a result Mr. Johnson continued to spray RangerPro. (MONGLY00500667). Mr. Johnson reports that the

operator further advised that an employee from Monsanto would contact him with additional information.

75. A report of Mr. Johnson's call to the Missouri Poison Control Center was sent to Monsanto in April of 2015. Monsanto did not follow-up to inform Mr. Johnson that IARC had, just a week before, determined that glyphosate was a probable human carcinogen associated with NHL. Mr. Johnson was unaware of the IARC classification at the time he called.

76. A Monsanto employee utilized email to contact California School District employees to deny that Roundup was associated with NHL. For example, in a 2010 email responding to a grounds supervisor relaying a parent's concern about RoundupPro and NHL, an employee stated. "I want to assure you that Roundup Is almost non-toxic to all species except plants. It has a caution label and has been shown not to cause cancer. The first place to go to look for information about Roundup is our website www.monsanto.com/ito."

77. Horizon, the distributor that sold Monsanto herbicides to Mr. Johnson's school district, utilized a Powerpoint created by Monsanto for training people such as Mr. Johnson. This Powerpoint states that "Based on laboratory studies conducted with animals, Roundup® Brand IT&O Herbicides: Do not cause cancer." However, Monsanto has never conducted a carcinogenicity study of Roundup on animals.

78. This unequivocal and reassuring statement also contradicts Donna Farmer's warning to Monsanto scientific and outreach personnel to ***not*** say that "Roundup does not cause cancer," because the company has never tested formulated Roundup for carcinogenicity.

C. Monsanto's Ethics and Behavior

79. Monsanto's stated, primary goals driving its herbicide business is opening up new markets for Monsanto products (i.e., gaining new registrations), and minimizing any possible

adverse impacts on the sale of Monsanto products already on the market.

80. The later sort of impact – protecting the company's existing pesticide products and sales -- is often referred to inside Monsanto as preserving glyphosate's "Freedom to Operate" (FTO).

81. Monsanto's rejection of new and better science as a way to reduce pesticide risks is evident in essentially all of the key actions and initiatives taken by the company over the last 40 years to first expand the uses of glyphosate, and in later years, protect the glyphosate FTO.

1. Failure to Repeat Key 1983 Mouse Oncogenicity Study

82. A contract laboratory called Bio/dynamics conducted a Monsanto-commissioned mouse oncogenicity study in the early 1980s. The study results were submitted to EPA in 1983. The agency's preliminary review of the study concluded that glyphosate had caused a dose-related increase in renal tubule adenomas, a rare tumor, and as a result was a possible human carcinogen.

83. This EPA determination contradicted the Bio/dynamics interpretation of the results, as well as Monsanto's. The conflicting conclusions based on the results of this pivotal study set the stage for an intense, high-stakes conflict between Monsanto and the EPA.

84. To gain approval of new tolerances covering glyphosate residues in food, and new agricultural registrations for Roundup, Monsanto simply ***had to reverse*** the EPA Office of Pesticide Programs (OPP) cancer classification of glyphosate.

85. When such disagreements arise over the interpretation of a specific study, the routine response by OPP/EPA is to require the company to conduct a new, and hopefully more carefully designed study. And so, OPP required Monsanto to conduct a new, much more powerful (statistically) mouse oncogenicity study.

86. Monsanto responded to EPA's request by arguing no such study was needed. OPP/EPA responded by stating why it felt such a study was indeed essential.

87. After eight years of back and forth covered in detail in this report, Monsanto had displayed to the OPP that it would always be willing and able to take whatever next step was necessary to raise new scientific issues in need of exploration, prior to a final OPP decision on whether the 1983 Bio/dynamics study was positive or negative for cancer, or needed to be repeated.

88. Monsanto also had demonstrated multiple times both its ability and willingness to direct political pressure on the agency. The company's clout in Congress, and at senior levels in Executive Branch agencies, made it possible for Monsanto to continuously raise the stakes facing OPP/EPA, until OPP brought its evaluation of the Bio/dynamics study into alignment with Monsanto's, and as a result, changed the cancer classification of glyphosate in a way acceptable to the company.

89. In short, Monsanto convinced the OPP that it was not an effective use of the agency's limited resources to continue the fight.

90. In 1991, EPA changed its interpretation of the 1983 mouse oncogenicity study, on account of one seemingly "magic" tumor found by a Monsanto-commissioned pathologist, who had been asked to reread the kidney slides in the study. This one magic tumor in the male mouse control group turned the seemingly positive Bio/dynamics mouse study into a negative one.

91. All of the pathologists that worked for the EPA and viewed the mouse kidney slides from the Bio/dynamics study could not see, and did not agree that the magic tumor existed in the kidney of one male, control mouse.

92. All of the pathologists paid by Monsanto to assess the kidney slides for the male

mouse control group agreed that there was one tumor in the control mouse #1028, ***except*** for the pathologist working for Bio/dynamics who did the initial assessment of the tumors in all animals.

93. This pathologist reported at that time no renal tubule adenomas in control male mouse #1028, nor any other control male mouse. Years later, after re-reading the kidney slides, this pathologist agreed with the other pathologists hired by Monsanto to evaluate the presence of renal tubule adenomas in the control group of male mice.

94. Monsanto still has not repeated the mouse oncogenicity study.

95. The primary reason is clear – legitimate concern in the company that the results of such a study would affirm the key finding in the original Bio/dynamics mouse oncogenicity study, and result in EPA classifying glyphosate as at least a "possible human carcinogen."

2. Monsanto's Third Party Network of Experts

96. Monsanto made heavy use of supposedly independent scientists in carrying out its "Scientific Outreach" (SO) and PR campaigns in support of the safety of glyphosate and Roundup-brand herbicides. Such individuals were appointed to an ad hoc, or standing advisory committee or panel. In other cases, they simply worked on a fee-for-service basis on a defined task.

97. Many of these glyphosate-friendly, consulting experts had once worked for Monsanto. Many have authored or co-authored one to multiple papers commissioned and paid for by the company. In addition, most of these papers contained passages ghost-written by Monsanto scientists, and some were largely ghost-written by Monsanto.

98. "Ghost-writing" refers to contributions to a written document by a person not listed as the author, or among the co-authors of a document. (See VI, C.2 for details).

99. In addition, Monsanto frequently asked and/or sponsored glyphosate-friendly

experts to present oral and/or written comments to regulatory agencies or their advisory groups, make presentations to allied groups, and assist in gaining positive media coverage of glyphosate health issues.

100. While the roles and contributions of dozens of glyphosate-friendly scientists are described in the body of my report, there are far too many instances, and individuals, to provide a comprehensive accounting of this tactic. A list of some members in Monsanto's glyphosate safety third party network appears in IV, section C.

101. After my review of records in this case, I am shocked by the scope, systematic focus, and brazenness of Monsanto's efforts to utilize supposedly independent scientists to: (1) restate and amplify company positions and scientific conclusions, (2) influence and contribute to the literature in peer-reviewed, science journals on glyphosate safety issues, (3) shape and control the information accessible to regulators, and (4) reinforce via repetition key Scientific Outreach and PR messages reaching the farm community, allied organizations, the general public, and political leaders regarding the safety of glyphosate-based herbicides.

102. These actions are inconsistent with applicable industry standards and do not comport with how a reasonable company would act with respect to tapping outside scientific expertise in the hope of elucidating and preventing human health risks.

D. Critical Science Judgements Impacting the Use of Glyphosate

1. Why Glyphosate's Cancer Classification was So Important

103. Various terms are used to refer to the potential of a chemical to cause cancer. The term "carcinogenic risk" used in the Monograph series issued by the International Agency for Research on Cancer (IARC) means that "an agent is capable of causing cancer."

104. In this report, I follow standard practice in EPA and the toxicology community.

The word "oncogen" refers to a chemical thought to cause benign or malignant tumorous growths in animals or humans; the term "carcinogen" refers to a chemical thought to cause malignant tumors in animals or humans.

105. The Toxicology Branch within the EPA's Office of Pesticide Programs (OPP) decided that glyphosate should be classified as a possible human oncogen in 1984. This decision posed a significant economic threat to Monsanto, as stated by Frank Serdy, Monsanto's Manager of Federal and State Regulatory Affairs in his March 13, 1985 letter to the OPP Registration Division Director, Doug Campt.

106. In the 1980s, once glyphosate was classified as a potential oncogen, any significant, future expansion in agricultural use of Roundup herbicides would require the establishment of dozens of Section 409 food-additive tolerances to cover the residues that would be present in certain fractions of grains and oilseed crops.

107. But glyphosate-related Section 409 petitions in the EPA pipeline, and any future Section 409 tolerance petitions, would be blocked by the anti-cancer Delaney Clause under then-current law and policy.

108. The Delaney Clause is a provision in Section 409 of the Food, Drug, and Cosmetic Act that prohibits the use of cancer-causing food additives; when pesticide residues concentrate in certain foods or food ingredients (like wheat bran), they are considered a food additive to which the Delaney Clause applied.

2. Negative Genotoxicity Studies Give Rise to a False Sense of Safety

109. The first round of mutagenicity and genotoxicity studies on glyphosate were commissioned by Monsanto in the 1970s, conducted by IBT, and were found to be invalid and/or fraudulent. The second round was done in the early 1980s, and fulfilled the then-existing OPP

mutagenicity and genotoxicity data requirements.

110. The laboratories conducting these cell-assay studies on nearly 100% pure glyphosate for Monsanto reported no evidence of mutagenic or genotoxic effects, and EPA scientists accepted this determination. So, throughout the 1970s and for the next ~40 years, all EPA documents report that glyphosate, and glyphosate-based herbicides, are not genotoxic.

111. EPA's genotoxicity determination played a central role in the successful effort by Monsanto to change OPP's mind on the results of the highly-disputed, 1983 Bio/dynamics mouse oncogenicity study.

112. Despite what EPA regarded as clear evidence of a dose-response increase in renal tubule adenomas in male mice in that mouse study, Monsanto argued, and EPA eventually accepted, that the absence of any evidence of genotoxicity provided strong support for the conclusion that the increase in renal tubule adenomas in male mice was not treatment related.

113. Over and over for decades, the absence of evidence of genotoxicity is cited by Monsanto and the EPA as a reason, if not the major reason, to ignore other evidence of mammalian toxicity following exposure to glyphosate-based herbicides.

114. Unfortunately, glyphosate-based herbicides had always been genotoxic to multiple organisms, and via several mechanisms, but the testing methods available in the 1970s and 1980s had not yet detected such effects.

115. Critically, essentially all of the genotoxicity testing required by the EPA and commissioned by Monsanto was carried out on nearly pure glyphosate, rather than on the formulated glyphosate herbicides people use and are exposed to.

116. The first evidence of genotoxicity of glyphosate-based herbicides appeared in the open, scientific literature in the 1990s (see the genotoxicity study subsection in VI., C.1).

117. By 2003, there was considerable evidence in peer-reviewed scientific journals suggesting that at least certain glyphosate-based herbicides were genotoxic.

118. When the International Agency for Research on Cancer (IARC) reviewed glyphosate in 2015, it found "***strong evidence***" of both genotoxicity and the capacity to induce oxidative stress in cells, two mechanisms that can lead to cancer.

119. In the 1980s, Monsanto was aware of the potential, if not probable genotoxicity of formulated, glyphosate-based herbicides, as opposed to pure glyphosate active ingredient.

120. In response and to this day, the company has worked diligently, and with great success, to avoid having to conduct any further, or more sensitive internal or external genotoxicity studies on formulated Roundup and/or other glyphosate-based herbicides.

121. In my opinion, Monsanto did not want to test their formulated glyphosate-based herbicides because they expected such studies to produce positive evidence of genotoxicity.

122. Any positive genotoxicity assay results would have to be, by law, provided to the EPA. Such data would, in turn, almost certainly lead to new, EPA-mandated restrictions on where and how Roundup herbicides could be used, especially on Roundup labels sanctioning non-agricultural applications with backpack or hand-held sprayers, such as those used by the plaintiff in this case, Dewayne Johnson.

123. Almost inevitably, such new studies would curtail glyphosate FTO, at least to some degree.

124. In 1997 Monsanto reached out to Dr. James Parry, a prestigious, independent academic genotoxicity expert that Monsanto was cultivating as a possible "glyphosate-friendly" spokesperson. To test Parry's scientific beliefs and judgements on glyphosate genotoxicity, Monsanto asked Parry to conduct a preliminary assessment of what he learned from a review of

several published genotoxicity studies on glyphosate and/or glyphosate-based herbicides.

125. Following his review, Parry prepared and submitted a detailed report to Monsanto acknowledging some evidence of genotoxicity. Dr. Parry also recommended that Monsanto undertake a set of more sensitive genotoxicity studies on glyphosate ***and*** formulated Roundup herbicides, to determine if the findings reported in earlier studies were replicable, and hence real.

126. Parry and some Monsanto scientists were in agreement that improved, new and more sophisticated genotoxicity studies should be carried out to resolve lingering questions.

127. In response, Monsanto planned to first do similar tests in-house, in order to know what to expect if Dr. Parry, or another scientist, was funded to do the studies.

128. The implication is clear – the results of their internal studies would dictate how, and whether they proceeded to commission the new studies, rather than the recognized need for better studies and more reliable genotoxicity data.

129. Over many years and consistently, Monsanto has provided funding to friendly scientists that invariably challenge and criticize the design, implementation, and/or findings of studies producing results not aligned with Monsanto's internal studies on the genotoxicity of glyphosate and/or Roundup, most of which are negative.

130. Monsanto has commissioned, and ghostwritten portions of at least four purportedly "independent" scientific reviews on the genotoxicity of glyphosate and/or glyphosate-based herbicides. Each one concludes there is no credible evidence to suggest glyphosate or Roundup herbicide poses a genotoxic risk.

131. This fundamental scientific mistake was perpetuated by the reticence of Monsanto to test the genotoxicity of Roundup herbicides formulated with POEA surfactants, and Monsanto's dogged determination to dissuade independent scientists and regulators from

conducting such tests.

132. The failure by Monsanto to properly test for genotoxicity is, in my opinion, one of the primary reasons that the EPA, and other regulatory authorities, have failed for nearly a half-century to recognize the potential for glyphosate-based herbicides to increase the risk of NHL and other cancers in humans.

3. Failure to Test Formulated Glyphosate-Based Herbicides

133. Over the entire history of glyphosate use and regulation, Monsanto has worked diligently, and with considerable success, to ***not*** test its formulated Roundup herbicides.

134. When independent scientists have conducted and published studies on formulated, glyphosate-based herbicides, Monsanto always aggressively challenged the studies, but only if they produced positive results.

135. This pattern of behavior no doubt has discouraged scientists from conducting experiments using formulated glyphosate herbicides.

136. The 40+ year absence of well-designed and carefully conducted short-term genotoxicity and long-term chronic feeding studies using formulated glyphosate-based herbicides is the most significant source of uncertainty in the current appraisal of the link between use of, and exposure to glyphosate-based herbicides and human health risks.

137. Monsanto perpetuated this uncertainty through its systematic actions, and inadvertently set the stage for the explosive impact of the review of the carcinogenicity of glyphosate and Roundup herbicides issued by the IARC in March 2015.

138. The record shows clearly that Monsanto knew that the risks posed by formulated Roundup herbicides were considerably greater than the risks posed by pure glyphosate, because some of the inert ingredients in Roundup are more toxic than glyphosate itself, and the inert

ingredients in Roundup increase the amount of glyphosate reaching and penetrating cell walls, hence increasing the risk of adverse impacts in exposed humans.

139. Instead of using sound science to better understand, and then reduce, the heightened risks stemming from use of the formulated herbicides applied by Dewayne Johnson, Monsanto used its resources and considerable influence to perpetuate the focus of glyphosate testing on an herbicide no one ever used, nor was ever exposed to -- 100% pure glyphosate.

E. Influencing Regulators and the Scientific Community

140. The goal of Monsanto's engagement with independent scientists was succinctly stated in an internal, May 26, 1999 email. The goal is to encourage "… people to get up and shout Glyphosate is Non-toxic." (MONGLY00904009)

141. "Non-toxic" is not an accurate description of glyphosate or Roundup herbicides. Yet through advertising and promotional material, and the messaging advanced by sales staff, Monsanto systematically worked to convince the general public that Roundup is, in fact, safe because it is "non-toxic."

142. Dewayne Johnson was told by his supervisors that Roundup was safe enough to drink, a dangerous and disingenuous claim that is frequently voiced but has rarely been challenged by Monsanto. After his diagnosis, Johnson contacted the Missouri Poison Control Center and asked if it was safe for him to continue applying Ranger Pro herbicides, and was told his symptoms were not an expected response from exposure to the product.

143. The more formal statement of the "Overall purpose" of Monsanto's "Glyphosate Scientific Outreach Plan," or SO Plan, appears at the beginning of a June 1999 document describing the SO plan:

> "Ensure that Monsanto's glyphosate-containing herbicides are widely viewed throughout the scientific community as posing no threat to human health or the environment. This

support will be used to favorably influence current and future possible challenges in the regulatory and public arena." (GLYMON00904774)

1. Cherry Picking Science

144. The record in this case shows that Monsanto does not, in general, use science in the organized pursuit of knowledge and deeper understanding of the potential human and environmental risks associated with use Roundup herbicides, but rather to gain new product registrations, and defend the company's Freedom to Operate, especially when placed in jeopardy by new information regarding potential risks.

145. Monsanto has conducted internal testing to determine what a similar, new study done by another scientist or laboratory is likely to show, prior to committing to pay for the new study by an independent laboratory, the results of which might have to be submitted to the EPA.

146. The reason is clear – Monsanto's priority is to invest testing dollars in gaining new registrations and preserving glyphosate FTO, not to contribute to the science-base needed for refined, more accurate risk assessments and more effective worker-safety label precautions and requirements.

147. Again, in many instances discussed in this report, Monsanto has selectively drawn upon the results of studies, in effect cherry-picking the findings most favorable to its position and desired outcome, while ignoring, or criticizing findings that caste a less favorable light on the safety of glyphosate and Roundup herbicides.

148. In the case of some studies, remarkably, Monsanto does both, highlighting a finding that is aligned with its position, and in general endorsing the quality of the study, only to then elsewhere criticize the study and some negative finding it reports.

149. Monsanto's abuse of science is so systematic and consistent that it seems to track some, perhaps unstated, internal company policy.

150. In every aspect of its "Scientific Outreach" program, in communications with regulators, in public presentations and commentary, and in the ghost-written materials the company or its contractors generate and insert in peer-reviewed papers authored by purportedly independent scientists, Monsanto spins science to support its FTO and attain the company's regulatory objectives.

151. The company almost never uses science as a structured path to deeper insights on the properties and toxicity of its products, so that better ways can be identified to use them safely.

2. Failure to Impose Needed, Commonsense Worker-Safety Provisions

152. Monsanto repeated failures to assist regulators in developing more accurate assessments of worker-safety risks is a clear and consequential breach of the company's pledge to adhere to the best science available, and serve as a responsible steward of Roundup herbicide products.

153. Grave consequences have occurred for some applicators of Monsanto herbicides like Dewayne Johnson, as a result of Monsanto's failure to propose and/or agree to more restrictive worker-safety provisions, especially in known, high-exposure application scenarios.

154. Monsanto's egregious lack of concern for product stewardship, and the safety of applicators spraying the company's herbicides, substantially increased Mr. Johnson's exposures, and hence his risk of NHL.

II. Expert Background and Qualifications

155. I received a B.A. in Economics from Harvard University in 1971, and a Ph.D. in Agricultural Economics from the University of Wisconsin in 1980. I have worked on the impact of agricultural technology on pesticide use, efficacy, and risks, as well as on public health and farmer costs for nearly 40 years.

156. My work has also encompassed the impacts of regulatory policies, requirements, actions, and laws on pesticide use, dietary exposure, worker risks, pest management systems, and food quality and safety.

157. I was the Staff Director of the Subcommittee on Department Operations, Research, and Foreign Agriculture (DORFA) of the House Committee on Agriculture for three years (1981 to 1983). This Subcommittee had jurisdiction over the Federal Insecticide, Fungicide, and Rodenticide Act ("FIFRA"), the primary federal statute governing pesticide regulation.

158. During this period, I organized several DORFA hearings on pesticide issues, and worked with Members of Congress in drafting potential changes in federal laws impacting the Environmental Protection Agency's (EPA) Office of Pesticide Programs (OPP). During my tenure as the DORFA Staff Director, around one-half of the time and focus of the Subcommittee was devoted to pesticide regulatory issues.

159. I made dozens of visits to OPP headquarters during this time-period, collecting information and speaking with OPP management, staff, and scientists on issues that had been brought to the attention of the Subcommittee, as well as issues of concern to OPP. These visits resulted in the flow of substantial information from OPP to the Subcommittee. Information provided by OPP/EPA helped the Subcommittee prioritize the issues addressed in forthcoming

Subcommittee hearings, and/or in need of legislative intervention.

160. On behalf of the Subcommittee, I organized several hearings on pesticide regulatory activities, issues, and controversies. This entailed drafting a hearing charter (purpose, focus, goals), identifying and securing the participation of witnesses, managing the flow of information submitted as part of delivered testimony and follow-up question from Subcommittee members, and preparing the hearing report issued by the House Committee on Agriculture, on behalf of the Subcommittee.

161. The Subcommittee carried out a two-year investigation of pesticide regulatory policy and issues, with a principle focus on OPP/EPA activities. Several controversial areas of EPA action, or inaction, arose during the investigation. These included the OPP/EPA and industry response to the IBT scandal, the role of state versus federal government agencies in pesticide regulation, the way known or possible carcinogenic pesticides were regulated, the timeliness of OPP decision-making, the burden of proof governing OPP/EPA suspension and cancellation actions, the cost of program activities and possible need for user fees, among other issues.

162. During the DORFA investigation of OPP/EPA activities, I visited OPP in Crystal City multiple times. I met many times with managers in the various divisions of OPP, as well as with many staff scientists in the residue chemistry, toxicology, and registration divisions. I interacted with several of the OPP administrators and staff who were responsible at the time, and in subsequent years, for various aspects of OPP's assessment and regulation of glyphosate herbicides.

163. The DORFA Subcommittee investigation culminated in the publication of a Subcommittee report (Volume I), and three supporting volumes of information (Volumes II-IV).

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164. The IBT toxicological data scandal was among the issues explored in the Subcommittee's investigative report and supporting volumes. At the request of the Subcommittee, OPP provided a detailed accounting of the pesticide-company studies submitted to OPP from IBT. The list included several studies commissioned by Monsanto on glyphosate. In fact, most of the initial data supporting the first regulatory decisions on glyphosate in the 1973-1980 period was from IBT, and was subsequently deemed invalid and/or fraudulent. All such studies had to be replicated, and were replicated during the 1980s and 1990s.

165. While serving as the DORFA Subcommittee Staff Director, I met multiple times with Mr. Chester Dickerson. Mr. Dickerson worked for Monsanto and was based in the corporation's Washington, D.C. office. Mr. Dickerson attended virtually every pesticide-related hearing conducted by the Subcommittee in the time period I worked as Staff Director. I had lunch dozens of times with Mr. Dickerson, who was generous with his time and shared his extensive knowledge of the pesticide regulatory process and pesticide issues in general.

166. Mr. Dickerson advanced his, and Monsanto's views regarding the way the OPP was implementing federal law, the OPP response to the IBT scandal, and the subsequent steps Monsanto took to replace fraudulent data. Other common topics of discussion included the need for legislative reforms, a variety of pesticide risk assessment issues, including how known or possible carcinogenic pesticides are regulated.

167. From 1984-1990 I served as the Executive Director of the Board on Agriculture, a major unit of the National Academy of Sciences/National Research Council (NAS/NRC).

168. In February 1985, the EPA "asked the Board on Agriculture (BA) of the National Research Council to study the EPA's methods for setting tolerances for pesticide residues in

food. Specifically, the EPA asked the board to examine the current and likely future impacts of the Delaney Clause on the tolerance-setting process" (quote from preface, *Regulating Pesticides in Food: The Delaney Paradox*, NAS, 1987).

169. My job was to support the BA's work in recruiting the study committee, collecting necessary information and records from the OPP/EPA, commissioning and overseeing analytical work in support of the Committee's deliberations, and drafting the Committee's report, which was entitled *Regulating Pesticides in Food: The Delaney Paradox.*

170. The report was released in 1987, and estimated the level and distribution of potential cancer risk across foods in the diet, stemming from the about 2,500 tolerances covering the residues in food of 53 oncogenic pesticides. It also called for the reform of the Delaney Clause's paradoxical impact on pesticide tolerance setting, and the EPA's and industry's efforts to reduce pesticide-related cancer risk in food.

171. In 1988, the Congress directed the EPA to request the Board on Agriculture of the NAS/NRC to conduct a study on the unique vulnerability of pregnant women, infants, and children following pesticide exposures. This new study was commissioned as a follow-up to the *Delaney Paradox* report.

172. As ED of the Board on Agriculture, I developed the scope of work, helped the Board identify and recruit the study committee, and supported the initial 2.5 years of the Committee's work. I left my position as the ED of the Board on Agriculture in late 1990.

173. The report written by the new NAS/NRC Committee was entitled *Pesticides in the Diets of Infants and Children*. It was released in June, 1993. Hearings on the report were held in both the House and Senate on the day of release. The recommendations were widely embraced both by the pesticide industry and environmental/consumer advocates, and provided the basic

framework for an historic piece of legislation that was passed and signed into law in the summer of 1996, the "Food Quality Protection Act" (FQPA).

174. I started Benbrook Consulting Services (BCS) in late 1990. Since that time BCS has carried out several dozen projects involving pesticide use, risks, and regulation for federal and State government agencies, companies, private institutions, and non-governmental organizations.

175. In the 1990s, several BCS projects involved analytical work on risks stemming from residues of cancer-causing pesticides in food. The impact of the Delaney Clause was a focus of all such projects, as was the long-standing effort by the Congress to pass legislation implementing the recommendations in the 1987 and 1993 NAS/NRC reports.

176. BCS's major client in the 1993-2002 period was Consumers Union (CU), publisher of *Consumer Reports*. I was hired initially to work with senior CU staff in writing a book on pest management and pesticide use/regulatory issues in the U.S. *Pest Management at the Crossroads* (*PMAC*) came out in October 1996 and was widely disseminated and often-discussed in pesticide policy circles.

177. Chapter 3 in *PMAC* addressed human-health risks stemming from pesticide use and exposure, and notes that "More than 70 active ingredients cause cancer in animal tests, and cancer has been the most common reason cited by the EPA in pesticide cancellation and suspension actions."

178. Chapter 4 in *PMAC* focuses on pesticide regulation and includes a detailed explanation of the purpose, provisions, and impact of the recently-passed Food Quality Protection Act, with multiple references to both the 1987 and 1993 NAS/NRC reports.

179. The FQPA changed the basic standard and risk-assessment process governing the

setting of tolerances in the case of possibly cancer-causing pesticides that concentrate in processed foods.

180. The FQPA's core provisions were effective upon enactment, but required the EPA to revisit the 8,066 tolerances covering residues of pesticides then on the market. These included 130 tolerances covering all forms of glyphosate and its metabolites, as well as 14 additional tolerances covering residues of the isopropylamine salt form of glyphosate (the primary form of glyphosate sold by Monsanto).

181. From late-1996 through about 2002 I continued work with Consumers Union on the implementation of the FQPA. I carried out multiple analytical projects for CU, the results of which were typically included in rule-making comments to the EPA on various aspects of FQPA implementation. BCS also worked on FQPA implementation issues for other clients.

182. In 1996, the first genetically-engineered (GE), herbicide-resistant (HR) soybean and cotton seeds were commercially sold. These crops had been engineered to tolerate post-emergent applications of glyphosate (i.e., an application over-the-top of a growing crop), and were labeled "Roundup Ready" crops. Applied in this way, at this stage of crop growth, glyphosate killed actively growing weeds in farm fields, but left the crop unharmed.

183. The commercialization of GE-HR crops triggered rapid growth in the overall sales and pounds applied of glyphosate in the U.S., and globally.

184. I began Ag Biotech InfoNet in 1998, a website covering the use, risks, and regulation of genetically engineered crops. The website grew incrementally through the early 2000s, but was taken off the Internet around 2005. Herbicide-resistant crops, and especially Roundup Ready crops, were a major focus of the website, as was the use and regulation of glyphosate-based herbicides.

185. Beginning in 1996, Monsanto and pesticide and biotechnology industry trade associations and spokespeople claimed repeatedly that GE crops were reducing overall pesticide use.

186. As part of my ongoing analytical work since the early 1990s, I download the pesticide use data collected and released annually by the U.S. Department of Agriculture (USDA). Each year I track changes in herbicide use, as well as overall pesticide use in the three major GE crops – soybeans, corn, and cotton.

187. It was clear to me by the early 2000s that both herbicide and overall pesticide use was rising on acres planted to GE-HR soybeans, corn, and cotton, and that Monsanto claims that its new, GE crops were reducing pesticide use were not supported by official USDA pesticide use data.

188. In 2003 I released the first of several reports on the impacts of GE crops on pesticide use. Ag BioTech InfoNet Technical Paper #6 was issued in 2003, and documented the increase in overall pesticide use on GE soybeans, corn, and cotton from 1996 through 2002. In 2004, Ag BioTech InfoNet released Technical Paper # 7, quantifying the impact of GE crops on pesticide use over the first nine years of use.

189. During my tenure as Chief Scientist of The Organic Center (TOC), I wrote and issued a November 2009 "Critical Issue Report" covering the impact of GE crops on pesticide use over the first 13 years of use. And in October 2012, I published a paper entitled "Impacts of genetically engineered crops on pesticide use in the U.S. – the first 16 years" in the peer-reviewed journal *Environmental Sciences Europe*.

190. Each of the reports I wrote on the impact of GE crops on overall pesticide use highlighted the role of rapidly rising use of glyphosate-based herbicides in pushing upward the

overall pounds of pesticides applied by U.S. soybean, corn, and cotton farmers.

191. The reason why was obvious and not in dispute – farmers who planted Roundup Ready crops switched from herbicides applied at a rate ranging from 0.01 pound per acre to over 1.0 pounds, and averaging about 0.3 pounds per acre, by glyphosate-based herbicides applied at an average rate per crop year of between 1.2 and 2.5 pounds of glyphosate per acre.

192. In 2016, I published the first complete accounting of the use of glyphosate-based herbicides in the U.S. and globally, based on publically available pesticide use data. The paper was entitled "Trends in glyphosate herbicide use in the United States and Globally" and was published in *Environmental Sciences Europe* (Vol 28:3; DOI 10.1186/s12302-016-0070-0).

193. Also in 2016, I was the principle and senior author of a paper entitled "Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement" that was published in the peer-reviewed journal *Environmental Health* (Volume 15:19; DOI 10.1186/s12940-016-0117-0).

194. From late 1990 through 2006, I ran BCS and all my work was via contracts with BCS.

195. From 2006 through mid-2012, I worked as the Chief Scientist of The Organic Center, a small non-profit responsible for tracking new science on the environmental and consumer health impacts of organic food and farming. The impact of organic farming on pesticide use and risks was an ongoing focus during my tenure as TOC Chief Scientist.

196. I took a non-tenure track Research Professor appointment at Washington State University in June 2012, a position I held for three years. During this time, I ran the "Measure to Manage" program. Our focus was development and application of analytical tools useful in quantifying the impact of agricultural technology and farm production systems on agriculture's

environmental footprint and public health outcomes.

197. As a result of multiple research collaborations with Newcastle University scientists, I was appointed as a Visiting Professor in the School of Agriculture, Food and Rural Development, Newcastle University in the United Kingdom.

198. In March 2017, I became a Visiting Scholar in the Department of Environmental Health and Engineering in the Bloomberg School of Public Health, Johns Hopkins University.

199. Both of these academic appointments are ongoing.

200. My resume appears in Appendix A.

III. The EPA Pesticide Regulatory Decision Process

201. The data requirements, risk assessment protocols, and decision criteria supporting pesticide regulatory decisions made by the OPP/EPA change incrementally over time. The changes have, to varying degrees, tracked scientific advances in the underlying residue chemistry, toxicology, and environmental sciences.

202. Sorting out the impact of changes over time in data requirements, study protocols, risk assessment methods, decision criteria governing OPP/EPA regulatory actions, and politics is a complex endeavor, especially in the case of a pesticide like glyphosate that has been registered by EPA since the mid-1970s and gone through so many profound changes in use patterns, test results, and risk assessments.

203. Changes in when, where, how, and how widely a pesticide is used often occur over time, and such changes typically alter exposure and risk levels in ways that are hard to predict, or even detect. This is surely the case with glyphosate, an herbicide that has come to be used in several major ways beyond those covered by the original Roundup labels granted by EPA in the late 1970s.

A. Three Major OPP/EPA Actions and Decisions

204. There are three major types of pesticide regulatory actions and/or decisions made by the OPP/EPA: (1) a "yes"/"no" response, or a conditional or amended "yes," to a petition from a pesticide manufacturer asking the EPA to establish new tolerance(s) covering residues of a pesticide in food(s) derived from a crop or crops for which the pesticide will be labeled for use; (2) a "yes"/"no" response, or an amended or conditional "yes," to an application from a pesticide manufacturer for a registration (i.e. label) authorizing a new pesticide product for use on specified crops under defined conditions; and (3) a cancellation, suspension, or refusal to re-

register an existing registration for a pesticide already on the market; or, re-registration of an existing product under different, and usually restricted terms and conditions.

205. Each of these three major types of decisions/actions arises from well-defined OPP/EPA application, review, risk assessment, and approval/denial processes. These processes typically require companies to conduct new studies and submit new data to the agency.

206. Once all, or most of the requested and/or required information is submitted to OPP, a scientific review is undertaken of submitted studies in the residue chemistry, toxicology, or environmental effects branches.

207. OPP staff determine whether: (1) all required studies have been undertaken and submitted, (2) the studies were conducted in accord with Good Laboratory Practices (GLP) and other requirements set forth in EPA guidance and policy documents, and (3) study results support the "gateway" OPP action(s) or decision(s) requested by the applicant/registrant.

208. By "gateway actions," I mean actions or decisions that OPP/EPA must make prior to approving a new registration application. The three most important are:

(1) The setting of a tolerance level at "x" parts per million in food "y." Tolerances are set at a level to cover residues of the pesticide likely to be in crop "y" at harvest after an application made in accord with all label directions, or in foods made from crop "y".
(2) Establishing a mammalian (i.e. human) chronic Reference Dose at "z" milligrams of pesticide per kilogram of bodyweight. A cRfD is the key human-exposure benchmark that approved registrations of a pesticide cannot exceed.
(3) Whether the pesticide has potential to cause cancer. Pesticides are classified by OPP/EPA as a possible, probable, or proven oncogene, or not carcinogenic, or unknown.

1. Applications to Register a New Pesticide

209. In the case of an application for a food crop use, or uses, of a new pesticide active ingredient, the OPP must decide which data requirements must be satisfied prior to making a final "yes"/"no" decision. Required and submitted studies must be evaluated by OPP for adherence to study protocols and GLPs set forth in OPP's detailed data requirements spelled out

Section 408 of the Code of Federal Regulations.

210. Any required tolerances covering residues of the pesticide in foods derived from treated crops must be approved and in place prior to OPP action in response to a registration application.

211. Companies generate studies and collect other data to submit to the OPP in support of requested actions. Registrant-generated materials submitted to OPP include: (1) suggestions and/or requests to establish tolerances in specific foods at a defined level expressed in parts per million of the pesticide (measured by weight of the pesticide and food); and (2) a suggestion to establish the pesticide's chronic Reference Dose at a given level, expressed as milligrams of pesticide per kilogram of bodyweight per day. (A pesticide's chronic Reference Dose (cRfD) establishes the maximum amount of the pesticide that a person of known weight can be exposed to in a day, without exceeding the EPA's "level of concern").

212. In the event estimated exposures exceed the EPA's "level of concern," the agency will either request additional data to refine its estimates of exposure and risk, or impose restrictions on labeled uses that bring expected exposures below the agency's "level of concern".

213. Once all requested data is submitted and deemed acceptable (i.e., it satisfies OPP-imposed data requirements), OPP science-branch managers must then determine whether submitted studies support the actions requested by applicants (set a tolerance, register a new use of a pesticide). The key decision criterion is whether the exposure levels likely to occur following use of a pesticide in accord with its label directions might exceed EPA's "level of concern."

214. Such "levels of concern" vary depending on: (1) the exposed organism; (2) the age and vulnerability of population groups; (3) the type of risk under review (e.g., acute, chronic,

reproductive); and (4) the magnitude, persistence, and reversibility of any possible adverse effects.

215. The level of certainty/uncertainty in OPP/EPA exposure or risk assessments also plays a role in determining whether the agency's "level of concern" has been exceeded.

216. The EPA will approve the registration of a new pesticide if all applicable data requirements are satisfied, and no estimated exposure levels for non-target organisms (e.g., people, birds, bees, fish), exceed EPA's "level of concern."

217. In some cases, the OPP/EPA will grant a "conditional registration" for a new pesticide, or a new use of a previously registered pesticide. Such registrations are accompanied by a requirement that the registrant must conduct and submit additional studies or data to OPP by a given date.

2. Actions Impacting the Future Use of an Already-Registered Pesticide

218. In the case of re-registration, cancellation, and suspension actions impacting already-registered pesticide uses, the EPA is bound by the FIFRA statute to balance the risks and benefits associated with ongoing, or altered use of the already-registered pesticide.

219. As stated in the 1996 Consumers Union book *Pest Management at the Crossroads*, "New pesticides are guilty until proven innocent, with applicants bearing the burden of proof. Old pesticides are innocent until proven guilty, with EPA bearing the burden of proof" (page 93).

220. Before restricting the use of a previously registered pesticide, OPP must first show that: (1) exposure levels to one or more non-target organisms (and especially people), exceed the EPA's level of concern, and (2) the risks stemming from the ongoing use of the pesticide exceed the benefits flowing from such uses.

221. To make judgements regarding risks versus benefits, the OPP must carry out detailed assessments of how a given pesticide is used on a given crop, pesticide efficacy (number and severity of pests controlled, how well are they controlled, and for how long), how use varies across the country, the cost of the pesticide plus its application, and what combination of factors can lead to exposures above EPA's level of concern.

222. This use-specific information is essential for EPA to identify relatively high-risk uses, as well as options to reduce exposure levels. At the end of its assessment of pesticide uses, benefits, and risks, the OPP must decide whether restricting or cancelling the use of a pesticide will cause unacceptable crop losses or damage, and/or force farmers to increase reliance on another pesticide that might pose even more serious risks.

B. Impacts of OPP Cancer Determinations in Tolerance Setting

223. The terminology used in describing the potential of pesticides to cause or increase the risk of cancer is important, and can be confusing. This report adheres to the common definitions of terms in the OPP/EPA, as well as in the scientific community.

224. An *oncogen* is a chemical thought to possibly increase the risk of triggering growth of benign and/or malignant tumors. A *carcinogen* is a substance thought to trigger the growth of malignant tumors. *Oncogenicity* is the capacity to cause or amplify growth of benign or malignant tumors, while *carcinogenicity* is the capacity to trigger or amplify growth of cancerous, malignant tumors.

225. The EPA was formed in 1972. According to a 1994 EPA document, cancer risk had been, at that point in the agency's history, the most commonly cited reason for OPP pesticide cancellation and suspension actions (*Status of Pesticides in Reregistration and Special Review*, 738-R-94-008).

226. As of the mid-1980s, the NAS/NRC report *Regulating Pesticides in Food – The Delaney Paradox* identified about 2,500 tolerances covering residues of 53 food-use pesticides thought by EPA to pose some level of cancer risk (NAS/NRC, 1987).

227. As of June 1986, there were 8,477 food tolerances in the Code of Federal regulations, so about 30% of all tolerances covered uses of possibly oncogenic pesticides (data on number of tolerances from Table 2-1, p. 35, NAS/NRC, 1987)

228. Congressional hearings conducted by the DORFA Subcommittee in 1981-1983 included extensive testimony from OPP officials, the pesticide industry, and consumer health advocates on OPP/EPA methods and policies governing the regulation of possibly cancer-causing pesticides.

229. Special focus was directed to the conundrum faced by OPP/EPA in working through sometimes conflicting statutory standards applicable to the tolerance setting process in the case of certain possibly oncogenic pesticides. The "Delaney Paradox" arises from the conflicting mandates in the two statutes governing the tolerance setting process.

230. The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) is the dominant statute governing pesticide regulation. It directs the OPP/EPA to apply a risk/benefit balancing standard in deciding whether to approve a pesticide registration, reregister an already-approved pesticide use, or cancel or suspend an existing registration.

231. According to the OPP –

> "Before EPA may register a pesticide under FIFRA, the applicant must show, among other things, that using the pesticide according to specifications 'will not generally cause unreasonable adverse effects on the environment.' FIFRA defines the term 'unreasonable adverse effects on the environment' to mean: '(1) any unreasonable risk to man or the environment, taking into account the economic, social, and environmental costs and benefits of the use of any pesticide, or (2) a human dietary risk from residues that result from a use of a pesticide in or on any food inconsistent with the standard under section 408 of the Federal Food, Drug, and Cosmetic Act.'" (quote from *Summary of the Federal*

Insecticide, Fungicide, and Rodenticide Act, https://www.epa.gov/laws-regulations/summary-federal-insecticide-fungicide-and-rodenticide-act)

1. Setting Tolerances under Sections 408 and 409 of the FDCA

232. A second federal statute establishes the authority for OPP/EPA to set tolerances -- the Food, Drug, and Cosmetic Act (FDCA). Section 408 was added to the FDCA in 1954 in order to provide a mechanism for the Food and Drug Administration (FDA) to control pesticide residue levels in food.

233. Section 408 authorizes the establishment of tolerances in raw agricultural products at the point such products would typically leave the farm gate. Section 408 requires that such tolerances be set at levels deemed necessary to protect public health. Residues in excess of the applicable tolerance render food adulterated, and hence unlawful for sale.

234. Responsibility for establishing tolerances under Section 408 was granted to the EPA upon formation of the agency in 1972.

235. Section 409 of the FDCA provides the FDA general authority to regulate food additives – "any substance the intended use of which results or may reasonably be expected to result…in its becoming a component of the food." (21 USC § 321(s) [1984]).

236. Section 409 goes on to exempt pesticide residues in food up to the level authorized by a Section 408 tolerance applicable to the given food, in recognition of the fact that such levels are subject to control via the tolerance setting process.

237. However, in some cases, pesticide residues in raw agricultural commodities concentrate in processed agricultural products, or food ingredients derived from the raw agricultural commodities. Common examples include residues in raisins, in contrast to the grapes the raisins come from (and indeed any dried food); milling wheat to produce wheat germ and flour; making tomato paste or ketchup from raw tomatoes; or, extracting oils from crops like

canola, soybeans, or olives.

238. As in the case with Section 408, EPA has been granted the responsibility of setting tolerances under the authority granted in Section 409 of the FDCA.

239. In the 1958, Congress amended Section 409 of the FDCA to include the so-called Delaney Clause (named after its author, New York Congressman James Delaney). The clause states that "the Secretary of the Food and Drug Administration shall not approve for use in food any chemical additive found to induce cancer in man, or, after tests, found to induce cancer in animals."

240. The Delaney Clause applies to all food additives regulated under Section 409 of the FDCA, including pesticide residues in processed foods that concentrate above the level in the corresponding raw agricultural commodity.

241. Based on the EPA's interpretation of the requirements in Section 409, the key factor in determining whether a Section 409 tolerance must be granted is whether a pesticide residue concentrates in a processed food above the level typically found in the raw agricultural commodity, ***not*** whether the level in the processed food is expected to exceed the Section 408 tolerance level.

242. In the 1980s and 1990s, EPA denied the registration of several new pesticides and/or new uses of an already-registered pesticide that OPP had classified as a possible oncogen, because a Section 409 food-additive tolerance was required.

243. Glyphosate was among the pesticide active ingredients that was directly impacted by the Delaney Clause from 1983 into the 1990s, by virtue of OPP's classification of glyphosate as a possible human carcinogen in 1983.

IV. Early EPA Actions on Glyphosate Herbicide and Monsanto Efforts to Influence the OPP's Evaluation of Glyphosate Toxicity

244. The Office of Pesticide Programs in EPA processed the initial tolerance petitions and registration applications for Monsanto's new herbicide, glyphosate, in the 1974-1977 period, just after the formation of the EPA in 1972.

245. Glyphosate is a broad-spectrum herbicide that kills any growing plant, whether regarded as a weed or a crop. It also kills most vines, shrubs, and trees. The herbicide is most effective when sprayed on young and immature plants; higher doses are required to kill well established, mature plants, vines, and trees.

246. By virtue of the indiscriminate nature of glyphosate, the herbicide cannot be sprayed on any crops, trees, vines, or other desirable vegetation after the plants had germinated and were growing above the ground. Glyphosate could be sprayed after crop harvest to kill any surviving weeds and plants.

247. At the time Monsanto requested the first registrations for its Roundup herbicide containing the active ingredient glyphosate, the company envisioned that glyphosate would be used for general weed control: (1) in industrial settings like lumber yards, electrical transmission facilities, along roads and railroad tracks, and within a variety of other rights of way, (2) to kill early-germinating weeds prior to the planting of a crop, or the crop's emergence, (3) on fields that farmers want to remain fallow, but largely weed free, and (4) after a crop is harvested.

A. Initial Approved Uses and Tolerance Actions

248. The first EPA actions on glyphosate occurred in 1974, and approved of temporary tolerances for the combined residues of glyphosate and its metabolite aminomethylphosphonic acid (AMPA) in the crops harvested from 9,715 acres of experimental uses of glyphosate. The

temporary tolerances requested were: corn fodder and foliage at 0.5 ppm; cottonseed and cotton forage and hay at 0.5 ppm; and corn, soybean, and wheat grain at 0.1 ppm.

249. The above temporary tolerances, along with similar tolerances on several other crops, were approved and eventually became permanent tolerances, in response to tolerance petitions 4G1444, 5G1523, 5G1561, and 5F1560.

250. The first agronomic crops on which glyphosate herbicides were registered for use were cotton and soybeans. On March 5, 1976 Monsanto requested EPA to establish temporary tolerances on cottonseed and cotton forage, and soybean grain, hay, and forage, in order to allow harvest and use of crops grown under an Experimental Use Permit. (MONGLY03579293)

251. EPA approved Monsanto's request for temporary cotton and soybean tolerances in a letter dated September 7, 1976. The tolerances would be in effect for one year.

252. The letter goes on to alert Monsanto that: "A food additive tolerance is being established for residues of glyphosate and its metabolite in soybean hulls at 20 ppm." So, from September 1976, Monsanto was aware that it would have to request, and EPA approve, food additive tolerances for at least some, and indeed likely most, proposed glyphosate food crop uses.

253. Such tolerances were then subject to the Delaney Clause and would not be approved by EPA in the event glyphosate was determined to be a possible animal or human oncogen.

254. Over the next 10+ years, several other applications for Experimental Use Permits were submitted and most were granted by EPA, sometimes in a modified form. In addition, most of the requests for the temporary tolerances required to allow crop harvest and use were approved. Several approval letters from EPA to Monsanto contained a similar paragraph

explaining that the agency had also established Section 409 food additive tolerances, on a temporary basis.

255. Both the number and scope of pending temporary and permanent tolerance petitions expanded steadily during the late 1970s, as did the number of tolerances that were granted.

256. The status of OPP actions on 21 pending glyphosate tolerance petitions is discussed in a March 15, 1977 Toxicology Branch memo by Raymond Landolt. It identifies the data supporting existing tolerances, the need for some additional studies, and corrects an error in an earlier memo regarding the no effect level in a three-generation rat reproduction study.

257. It also includes the following passage: "TB [Toxicology Branch] memo of June 4, 1974 concluded that 'the residue on human food crop are negligible and the fraction that is non-extractable would be sufficiently low to be toxicologically insignificant.'"

258. In 1975, permanent tolerances covering the combined residues of glyphosate and AMPA were established at 0.1 ppm for corn and soybean forages and grain, as well as for wheat, sorghum, oats, and barley grain and forages. With the exception of soybeans and the wheat straw tolerances, the above tolerances remained in place at the 0.1 ppm until 1996.

259. The tolerances were increased 10- to 40-fold in 1996, to cover the much higher residues stemming from new and emerging uses of Roundup herbicide.

260. On February 21, 1986, Monsanto submitted an application to OPP/EPA seeking registration of preharvest use of glyphosate on soybeans. Such uses were intended to kill the growing plants to accelerate harvest and/or prepare the fields for the planting of another crop. (MONGLY03692349) The application included a list of proposed changes in soybean tolerances required to cover residues in soybean grain (up to 20 ppm, from 6 ppm), and soybean hay (up to

200 ppm, from 15 ppm). In addition, Monsanto acknowledged that a Section 409 food additive tolerance in soybean hulls would be required, and proposed that it be set at 100 ppm.

261. As long as EPA considered glyphosate a possible oncogene, approval of the Section 409 tolerance would likely not occur. For example, in an April 18, 1985 memo to the Registration Division and Toxicology Branch from the Residue Chemistry Branch, R.W. Cook reviews a pending tolerance petition that requests increases in glyphosate plus AMPA tolerances in wheat grain and wheat straw. The memo states: "4b. TOX has concluded (W. Dykstra, 3/19/85) that food additive tolerances for glyphosate are not appropriate due to the Delaney rule." (page 4)

262. The soybean grain tolerance was increased from 0.1 ppm to 6.0 ppm in 1985, and to 15.0 ppm in 1990, to cover residues in soybeans harvested from fields sprayed with preharvest glyphosate as a desiccant (i.e., to kill the mother plants). The soybean hay tolerance was raised to 200 ppm, and the soybean straw tolerance was set at 100ppm. The wheat straw tolerance was raised to 40 ppm.

B. Studies on Glyphosate Conducted by IBT Create Massive Hole in Toxicology Dataset

263. Early interactions between OPP and Monsanto were complicated by the IBT pesticide data scandal.

264. IBT was a major contract laboratory doing toxicological studies destined for submission to OPP/EPA for many pesticide manufacturers in the 1970s and 1980s.

265. In 1976, a routine FDA audit of an IBT test facility uncovered problems with the conduct of some studies and lead to a thorough EPA assessment of all studies done by IBT that supported regulatory actions by OPP.

266. Most of the initial toxicological database supporting the early tolerance petitions

and registrations of glyphosate were done by IBT. The "IBT Tracking System Report" released in 1983 notes 30 studies done by IBT on glyphosate, of which 17 were invalid and 2 were pending final judgements (Exhibit B, "Summary of the IBT Review Program," OPP, July 1983).

267. On July 1, 1977, OPP generated a one-page summary of the eight toxicology studies used to support establishment of all existing glyphosate tolerances. All eight studies were submitted between 1972 and 1974, and all eight were done by IBT.

268. An August 21, 1978 memo from William Dykstra of the Toxicology Branch to Robert Taylor in the Registration Branch discusses the EPA's assessment of the validity of a key, 2-year chronic oral toxicity study done in Albino rats by IBT. For a variety of reasons, the EPA judged the study to be invalid, yet it served as the basis of the then-current chronic Reference Dose of 0.1 mg/kg/day (called an ADI, or Acceptable Daily Intake in 1978).

269. A July 27, 1982 memo from the Toxicology Division to the Registration Division reported EPA's judgement that the 2-year dog study (No. 651-00565) done by IBT for Monsanto and completed in 1973 was invalid because of missing data, failure to record diet preparation records, and other deficiencies.

270. Accordingly, it took about a decade for EPA to determine that most of the toxicological database submitted to the agency by Monsanto in the mid-1970s, and used by EPA to support all early EUP, tolerance, and registration actions, was invalid.

271. Problems also arose with some of the replacement studies that Monsanto commissioned to replace invalid IBT studies. In July 1979, Monsanto decided to terminate a 2-year mouse study on NNG because of excessive mortality in treated groups of animals (MONGLY04272266).

272. Via an agreement with OPP, Monsanto repeated all of the invalid IBT studies at

different laboratories. In the interim, EPA allowed existing registrations and tolerances to remain in place.

273. The first of the replacement studies were submitted to OPP beginning in the early 1980s. For about a decade, the early registrations and tolerances covering all uses of glyphosate were not supported by a complete set of valid toxicology studies.

C. Contaminants, Adjuvants, and Surfactants

274. The EPA grants two basic types of registrations and labels for pesticides: technical use registrations and labels, and formulated, "end use" product registrations and labels.

275. A first step in the regulatory process typically entails a chemical company applying for and gaining a technical use product label covering a product composed of 100%, or nearly 100% pure active ingredient. Such registrations are granted to basic manufacturers that are involved in pesticide discovery research and development, and own and/or operate chemical plants synthesizing pure, 100% pesticide active ingredients.

276. The EPA labels issued for technical use products generally do not include detailed lists of approved crop or industrial uses, rates of application, or other specific use instructions. They do address proper handling, storage, and transport methods and precautions.

277. Technical use pesticides may be used internally by the basic manufacturer to make its own brand-name formulated product, like Roundup herbicide containing glyphosate as the active ingredient and various adjuvants and surfactants.

278. Technical use products are also sometimes sold to pesticide companies that formulate "end use" products labeled for specific uses. Such "end use" products are ready to be used and applied by farmers, applicators, home owners, land managers, or other people involved in pest management.

279. The distinctions between technical use and end-use products are important for many reasons. Different data requirements apply. End use products often have a substantially different set of environmental fate properties, compared to the pure active ingredient(s) in them. These differences can dramatically alter the nature and outcome of both environmental and human-health risk assessments and outcomes.

280. End-use products are often more toxic than pure active ingredients. Companies seeking and obtaining end-use product labels are responsible for a much more extensive set of decisions regarding uses, rates, and methods of application, than companies just seeking and gaining technical use registrations.

281. In addition, end-use pesticide products contain much more complete label directions and safety precautions that collectively will, hopefully, assure that the pesticides do not cause any "unreasonable adverse effect on man or the environment."

282. The "label is the law" is the basic statutory provision in federal law that applies to all pesticide labels. The presumption, and hope, is that when a pesticide is applied in accord with all label directions, there will be no "unreasonable" adverse impacts on people or the environment.

1. Sources of Pesticide Product Risk

283. Human health and environmental risks from pesticide use can arise from three general categories of ingredients, or components, in a commercial pesticide product: (1) the active ingredient itself, (2) any impurities in the active ingredient that are formed during the manufacturing process, or as a result of a chemical reaction that occurs between the time the pesticide is made and/or mixed at a plant and applied by a user, and (3) the so-called "inert ingredients" added to essentially all end-use pesticide products (e.g., surfactants and adjuvants).

284. "Inert ingredients" are added to liquid, end-use pesticide products like Roundup herbicide to assure that the active ingredient (glyphosate) remains thoroughly mixed and stable, is compatible with other pesticides or liquid fertilizers that might be combined in a tank-mix and applied via a single pass through a field, and sticks or adheres to whatever weeds or unwanted vegetation the herbicide is sprayed on.

285. Herbicide adjuvants and surfactants are labeled "inert ingredients" because they do not contribute directly to the capacity of the herbicide to kill or control weeds. But several inert ingredients, by themselves, pose toxicological and/or environmental risks, and hence are not "inert" in the sense of contributing to the risk profile of an end-use herbicide product.

286. Some of the most important, unresolved scientific and regulatory issues and uncertainties arise because of impurities in glyphosate-based herbicides and the inert ingredients incorporated in formulated, end-use glyphosate-based herbicides.

287. Indeed, in my opinion, the near-complete, 40+ year absence of well-designed and rigorously conducted long-term chronic feeding studies on formulated glyphosate-based herbicides is the largest single source of uncertainty in the existing appraisal of the link between use of and exposure to glyphosate-based herbicides, and human health risks.

2. Impurities in Glyphosate Active Ingredient

288. Since the 1970s, Monsanto scientists were aware of two impurities associated with Roundup herbicides: NNG and formaldehyde. NNG is formed when glyphosate interacts chemically with nitrosating agents, to form the oncogenic nitrosamine contaminant NNG. The later contaminant is an unavoidable, low-level contaminant in glyphosate that occurs as a result of the manufacturing process used by Monsanto.

289. In addition, Monsanto was aware that the "glycine process" for manufacturing

glyphosate (used by Syngenta) "may rightly avoid formaldehyde." (Wratten email of April 19, 2008 in MONGLY02530945; more detailed discussions of both NNG and formaldehyde in glyphosate appear in MONGLY03909609)

3. Adjuvants and Surfactants in Roundup End Use Products

290. There are substantial differences between pure, 100% glyphosate and the formulated, glyphosate-based herbicides that people purchase and apply. The differences arise from the so-called "inert ingredients" added to the active ingredient, i.e. glyphosate in the case of formulated Roundup herbicides.

291. The two major categories of inert ingredients are surfactants and adjuvants. Surfactants are added to formulated herbicides to "interfere with proper membrane function" (MONGLY01700591), such as keeping foreign chemicals, viruses, and bacteria out of cells.

292. Such differences can be important to regulators, applicators, and public health outcomes in cases where the inert ingredients in a pesticide alter the toxicity profile of the formulated pesticide product, in contrast to the pure active ingredient. This can happen in several different ways.

293. For example, the primary surfactant used for years Roundup formulations is polyoxyethkene alkylamine (POEA). According to Monsanto, it was generally present at in a 3:1 ratio of glyphosate to POEA in the early years of commercial use, with the concentration of POEA falling to ratios around 7:1 in Roundup brands since ~2000. (MONGLY01700591)

294. Some inert ingredients change the properties of formulated pesticides, for example by increasing the persistence of a pesticide or its ability to penetrate cell walls, or both.

295. This distinction between the risks associated with 100% pure active ingredients (i.e. glyphosate), in contrast to formulated products containing inert and active ingredients (i.e.,

Roundup), is a central issue in this case, because almost all the testing and government risk assessments – and claims of safety for Roundup – are based on tests conducted using pure glyphosate, rather than tests using Roundup.

296. But people applying Roundup are never exposed just to glyphosate, they are always exposed to glyphosate and a mix of inert ingredients.

297. In the case of pure glyphosate versus formulated Roundup, the risks posed by the latter are considerably greater than the former, both because the inert ingredients in Roundup are more toxic in some ways than glyphosate itself, and the inert ingredients increase the amount of glyphosate reaching and penetrating cell walls, and hence posing risks of adverse impacts in exposed humans.

298. A short paper in the prestigious medical journal *The Lancet* appeared in 1988 (Sawada et al., Probable toxicity of surface-active agent in commercial herbicide containing glyphosate, *The Lancet*, 1(8580): 299). It attributed acute, glyphosate-herbicide poisoning symptoms among several Japanese patients to the "inert ingredient" surfactant POEA in formulated Roundup, and not the active ingredient (glyphosate).

299. The Japanese team reported that the acute lethal dose (i.e., LD-50) of POEA is one-third that of glyphosate, which explains why the LD-50 of glyphosate active ingredient is much higher than the LD-50 of Roundup herbicides formulated with the surfactant POEA.

300. While both Monsanto and EPA were aware of the differential toxicity of glyphosate and POEA when the first glyphosate tolerances and registrations were moving through the agency in the late 1970s, this article in *The Lancet* triggered, to my knowledge, the first attention by independent scientists on the possible human health impacts of the inert ingredients in Roundup herbicides.

301. Among the adverse mammalian impacts of POEA noted by the Japanese scientists was damage to red blood cells.

302. Inert ingredients in formulated pesticide products can also, themselves, contain toxic impurities and contaminants. While pure glyphosate contains the nitrosamine-impurity NNG, the POEA surfactant in formulated Roundup products contains 1,4-dioxane.

303. A U.S. National Cancer Institute bioassay of 1,4-dioxane found that the chemical causes hepatocellular adenomas and carcinomas in the kidneys of rats. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr080.pdf In 1982, the International Agency for Research on Cancer classified 1,4-dioxane as a possible human carcinogen (IARC, *IARC monographs on the evaluation of the carcinogenic risk of chemicals in humans. Supplement 4*, WHO, 1982). An EPA report from 1986 listed 1,4-dioxane as a probable human carcinogen.

304. In July, 1999 the Italian Pesticide Committee, a European regulatory body, held a meeting on the regulation of Roundup herbicide. It decided that new genotoxicity studies on both glyphosate and formulated Roundup would be required to assess DNA reparation, following OECD Guideline 486 (1998). Such studies were needed to address lingering and complex risk issues arising from impurities in both pure glyphosate, and the inert ingredients used to make formulated glyphosate-based herbicides, including Roundup.

305. Monsanto employee [redacted] forwarded the news regarding this new genotoxicity study requirement to senior Monsanto officials including [redacted], William Heydens, Donna Farmer, Larry Kier, and [redacted] in a July 29, 1999 email. (MONGLY00877684)

306. In response, [redacted] said that the OECD 486 test "is not an unreasonable request but suggest some liver toxicity along with it to explain bumpy responses at the high dose. This

test has also been requested by the French for MON 4660 and there the risk is greater because of extreme liver toxicity." (MONGKY0877684)

307. A few hours later, William Heydens adds to the email chain this comment: "I don't think an in vivo UDS [the OECD 486 test] is reasonable for glyphosate…Now, formulations are obviously another issue…liver toxicity with formulations could be a confounding factor, and we would have to design and conduct the study very carefully (using our alachlor & acetochlor experience) if we are ultimately forced to do it."

308. This is one of dozens of examples in the record where the response of Monsanto to a new issue or concern, or a request from a regulatory for a new study, amounts to "how can avoid doing any new, possibly damaging lab studies," rather than how can Monsanto conduct, or commission the best possible science to deepen understanding of the impacts of exposure to glyphosate-based herbicides, in order to more assuredly recognize and reduce human health risks.

309. Two days later, Donna Farmer adds to this email chain, and writes: "Sorry I am weighing in on this late…It is too premature to discuss conducting any studies. I will not support any studies on glyphosate formulations or other surfactants at this time…". (MONGLY00877684)

310. Despite a steady stream of new studies over three decades pointing to the heightened toxicity of Roundup formulations including POEA surfactants, Monsanto continued to defend their safety and use worldwide.

311. In January 30, 2010 email, William Heydens shared two reasons to continue defending POEA tallowamine surfactants: first the prospect of a "'domino effect' on etheramines; defend other world areas to the best of our ability." The second reason for concern

was that "they [Brazilian Monsanto employees] are worried about this coming across the Atlantic to their part of the American hemisphere." (MONGLY02062439)

312. Heydens was responding to a January 25, 2010 email from his colleague [redacted] on the question of whether to phase out POEA surfactants. After discussing some new studies underway on an alternative surfactant, [redacted] wrote: "Anyway, there are non-hazardous formulations so why sell a hazardous one?" (MONGLY02062440)

313. In a June 8, 2010 email on the vulnerability of Roundup formulations containing POEA surfactants in Argentina, William Heydens wrote to colleagues in Argentina and at Monsanto headquarters in St. Louis:

> "So I would think that a backup plan of reducing POEA content is not sufficient, but rather a POEA-free formulation (or formulations) would be necessary to totally protect your business in Argentina." (MONGLY02013061)

314. In the slide deck prepared for "Regulatory Leadership Meetings" in November 2010, a slide addresses the business impact of the loss of POEA surfactants. "Germany is major concern" noting that "restrictions on POEA uses pre-harvest had significant negative impact on sales in 2010." (MONGLY02721133)

315. The "Strategy in Germany" included three core elements: (1) defend POEAs; (2) register non-POEA formulations; and (3) "Managed exit from POEA" to "Avoid a ban"; "Focus: voluntary non-renewal of registrations (e.g. MON 14420 end 2012)"; and, (3) "No sales of any POEA products after 2012." (MONGLY02721133)

316. Over the last decade or so, European regulators forced Monsanto to phase out POEA surfactants in all glyphosate-based herbicides, including Roundup, but POEA surfactants are still present in several Roundup products in the U.S.

4. Assessing Glyphosate's Capacity to Disrupt the Endocrine System

317. The European Commission had put in place a new set of testing guidelines to assess the degree to which pesticides have the potential to disrupt the functioning of the endocrine system. Such chemicals are generally referred to as "endocrine disruptors."

318. In April 2002 Monsanto employees in Europe report to headquarters that European regulators are working on development of a list of possible endocrine disrupting pesticides, and that some new assays might be required on glyphosate and/or formulated Roundup herbicides.

319. In response to this news, William Heydens sends an email at 7:20 a.m. on April 25th to Donna Farmer. In it, he suggests a call to "…to see if there is anything more we should be doing besides the usual 'pay no attention to the man behind the curtain'." He ends this email by saying "…this damn endocrine crap just doesn't go away, does it."

320. Farmer replies to Heydens at 8:19 a.m. (just under an hour later), and writes that the "interest[ing] point" is that published tests of possible glyphosate-endocrine disruption show that pure glyphosate has no effect, but formulated product (i.e. Roundup) does. (MONGLY00885551).

321. In response to Farmer, Heydens responds at 10:47 a.m. the same day, and reports that after discussions with other Monsanto experts, they: "…concluded, not surprisingly, that we are in pretty good shape with glyphosate but vulnerable with surfactants."

D. Patterns Emerge in OPP-Monsanto Interactions over Glyphosate's Toxicology Database

322. Applicants seeking registration of pesticide products and/or petitioning for the establishment of tolerances routinely submit studies that satisfy OPP/EPA data requirements. Submissions of such studies typically include the applicant's interpretation of the study results,

as well as the regulatory actions or decisions that the applicants believe the study results support. This is a standard feature of pesticide manufacturer-OPP interactions.

323. When OPP science branch reviews find studies to be acceptable (i.e., conducted in accord with Good Laboratory Practices, proper reporting of results, acceptable statistical analyses), agency scientists then determine whether they agree with the applicant's interpretation of the study results. When there is at least general agreement, scientific reviews usually include a finding that the request to establish a tolerance or grant a new registration is "supported" in terms of the purview of the relevant science branch.

324. In many cases, a recommendation is made to ask the applicant to satisfy some minor deficit in the supporting data, or information about how a given study was conducted. In other cases, an issue possibly impacting the interpretation of a study, or altering estimates of exposure or environmental risks, might be flagged as a way to trigger an assessment by another part of OPP.

325. General patterns emerge from a review of Monsanto-OPP interactions from 1974 to the present relative to glyphosate's toxicological data base, OPP reviews of submitted studies, and OPP risk estimates and regulatory actions.

326. Monsanto agrees and supports OPP/EPA assessments when they generally are consistent with the assessments advanced by Monsanto and support requested or proposed agency actions.

327. When OPP's assessment of a study deviates from Monsanto's and results in, or points toward a decision or action by OPP/EPA that Monsanto regards as unfavorable, the company typically first presents arguments bolstering its initial interpretation of study results, and the EPA actions supported by the study.

328. In cases where OPP and Monsanto continue to disagree about a given study, Monsanto will sometimes come around to agreeing with OPP that certain study deficiencies should be corrected, or that a study protocol could somehow be improved.

329. On this basis, Monsanto would often then offer to generate a replacement study on the understanding that the status quo, or some acceptable, interim change in a pesticide product's label provisions, will suffice until the replacement study is completed, submitted to OPP, and reviewed.

330. In other cases, OPP has requested a replacement study on some aspect of glyphosate toxicity and Monsanto has resisted, arguing that the existing study is valid and should satisfy agency data requirement.

V. Bio/dynamics Mouse Oncogenicity Study Triggers a Change in Glyphosate's Cancer Classification

331. Based on the flawed, long-term glyphosate cancer study in rats conducted by IBT in the 1970s, OPP classified glyphosate as "not oncogenic in the rat" in or around 1977, and hence not likely to pose human oncogenic risk. This classification remained in place until EPA's March 4, 1985 "Consensus Review of Glyphosate" classified glyphosate as a category C, possible oncogene.

332. Throughout the 1977-1983 period, there was rapid growth in the number of approved tolerances and registered agricultural uses of Monsanto's glyphosate-based herbicides, despite the lack of a valid set of long-term feeding studies in mice and rats.

333. A new mouse oncogenicity study on glyphosate was among the IBT replacement studies submitted by Monsanto to OPP (EPA Accession #: 251007-014; Bio/dynamics Project No. 77-2061). It was conducted by the contract laboratory Bio/dynamics to fill a pending data gap, and was submitted to EPA on July 29, 1983.

A. Results of Bio/dynamics' Mouse Oncogenicity Study

334. The study followed routine design protocols for a chronic feeding study. There were four groups of Charles River CD-1 mice: control, 1,000 ppm glyphosate technical in the animals' diet, 5,000 ppm, and 30,000 ppm. There were 50 male mice and 50 female mice in each group. Animals were observed twice daily, and mortality during the study was reported as "normal for this age and strain of mice." (MONGLY04275682)

335. In the section "Results" in its summary report to Monsanto, Bio/dynamics states: "No treatment-related effects were demonstrated." In other words, the study was "negative" for oncogenicity.

336. But the Bio/dynamics summary report does address a number of statistically

significant increases in tumors observed in the study. Table 1 in the report lists four "microscopic changes" that were elevated in the treatment groups in a statistically significant way: central lobular hepatocyte hypertrophy (elevated in male mice), central lobular hepatocyte necrosis (elevated in males), chronic interstitial nephritis (elevated in males), and proximal tubule epithelial basophilia and hypertrophy (elevated in females).

337. Bio/dynamics dismisses all four types of lesions noted in their Table 1 by saying "All these findings, however, were of the type and severity common to long-term mouse studies."

338. The central issue of debate over the results of the Bio/dynamics mouse study -- the incidence of renal tubule adenomas -- was addressed in the summary:

> "The incidence of renal tubule adenomas was 0/49, 0/49, 1/50, and 3/50, in control through high-dose males, respectively. This lesion, however, was not observed in any of the female treatment groups, and, as mentioned previously, this data was not statistically different from control. While not observed in control animals in this study, renal tubule adenomas have previously been observed in control male CD-1 mice of comparable age. ***The slightly increased incidence of adenomas in the high-dose males was considered spurious and unrelated to glyphosate administration***." (Emphasis added; MONGLY04275683)

339. The debate over these renal tumors in the Bio/dynamics mouse study continues to this day. In March 2015, it arose anew in the development and wake of the classification of glyphosate, and glyphosate-based herbicides as "probably carcinogenic to humans" by the International Agency for Research on Cancer (IARC) (see section VI., D. The IARC Bombshell).

340. In the male mice, the incidence of renal tubule adenomas reported by Bio/dynamics was 0/49 male mice in the control group, and 0/49, 1/50, 3/50 in the three treatment groups (1,000 ppm, 5,000 ppm, 30,000 ppm).

341. Three aspects of this Bio/dynamics summary statement no doubt attracted the

attention of OPP scientists when they evaluated this study: (1) the rarity and seriousness of renal tubule adenomas, (2) the hail-Mary like statement that renal tubule adenomas had been observed in control, male CD-1 mice in other studies (and so the absence of tumors in the control male mice in this study means that this study's control group data should be discounted), and (3) the Bio/dynamics assertion that the increase in renal tubule adenomas in the treated, male mice is spurious and not statistically significant, when there is a clear, treatment-related, dose-response trend in the occurrence of renal tubule adenomas in the male mice (i.e., 0, 0, 1, 3).

1. The High Stakes Review of the Bio/dynamics Mouse Oncogenicity Study

342. The importance of OPP's evaluation of the Bio/dynamics mouse oncogenicity study on glyphosate was widely recognized inside EPA and Monsanto, and among many others following pesticide regulatory decisions.

343. Interested parties included members of Congress and their staffs (then including C. Benbrook), senior Administration political appointees, pesticide trade associations, farm groups, environmental and consumer advocates, the media, and other state and federal government agencies.

344. The importance of OPP's assessment of the study would be markedly heightened if the agency determined that the study was "positive." Such a judgement would reverse the status quo classification of glyphosate as "not oncogenic," and dramatically alter the outcome of a number of pending and forthcoming tolerance petitions and registration applications, both in the U.S. and globally.

345. Two memos dated January 31, 1984 were sent from Monsanto toxicologist Lyle Gingerich to four colleagues (MONGLY04269118; MONGLY04269119-20). The first memo reports on a recent conservation Dr. Gingerich had with Robert Taylor.

346. Taylor was the senior official in OPP's Registration Division responsible for managing the flow through OPP/EPA of glyphosate-Roundup herbicide tolerance petitions and registration applications, as well as managing interactions between Monsanto and OPP on the fulfillment of data requirements, label changes, data compensation, and other issues that arise regarding the regulatory status of Monsanto's glyphosate-based herbicides.

347. In the first 1/31/1984 memo, Dr. Gingerich reports on presumably separate, face-to-face meetings on January 31, 1984 at OPP with Robert Taylor of the Registration Division and W.L. Burnam, Deputy Director of the Hazard Evaluation Division.

348. The Gingerich memo reports that Mr. Taylor told him that W.G. Dykstra of the OPP toxicology division had reviewed the new mouse oncogenicity study done by Bio/dynamics. The memo states: "R.J. Taylor said that he saw something in writing to indicate that when the review is sent to him it will state that Roundup is an oncogen."

349. The memo goes on to report that according to OPP's Mr. Taylor, various pending tolerance petitions will be denied, presumably as a result of this important change in OPP's characterization of glyphosate's chronic toxicity.

350. Dr. Gingerich reports in this first of two January 31, 1984 memos that he intends to speak later the same day, again, with R.J. Taylor and W.L. Burnam of the toxicology branch, in order to request "W.G. Dykstra's review and [discuss] what would be an appropriate forum for Monsanto inputs."

351. The first of two 1/31/1984 Gingerich memos to colleagues closes with an unusual question: "Do you think it would be appropriate for our legal department to caution EPA on possible premature leaks of this review's conclusions prior to Dr. Kasza's [senior OPP pathologist] re-review and final disposition of the matter?"

352. If such a caution had been communicated, through any channel, it would have constituted an unambiguous "shot across the bow" from Monsanto to OPP. The fact that Monsanto officials even considered expressing such "caution" to OPP's legal department reflects how serious this turn of events was in terms of OPP actions on pending and future glyphosate tolerance petitions and registration applications.

353. This Monsanto position regarding OPP communication of preliminary OPP science determinations relative to glyphosate oncogenicity stands in sharp contrast to Monsanto efforts three decades later to encourage a premature EPA release of the Cancer Assessment Review Committee's (CARC) re-assessment of glyphosate's carcinogenicity.

2. Second 1/31/1984 Gingerich Memo to Monsanto Colleagues

354. Later during January 31, 1984, Dr. Gingerich either met with, or spoke on the phone again with W.L. Burnam of the OPP toxicology branch, according to the second of two memos to Monsanto colleagues sent by Dr. Gingerich on January 31, 1984.

355. In this second memo, Gingerich reports to his colleagues that Burnam told him that:

> "A 'complete' review of the glyphosate mouse study has not been done. There has been no section or branch sign-off of W.G. Dykstra's review. The question of kidney tumors was pointed out by W.G. Dykstra and is being evaluated by either C. Chaisson or Dr. L. Kasza. W.L. Burnam asked that we send in historical control data to document the claims made in our summary. He cautioned that these be from the same laboratory and time period. He said to be sure to report the numbers study by study, rather than as an overall average."

356. This second 1/31/1984 memo goes on to say that "R.J. Taylor continues to be concerned that Roundup actions will be held up for a few months until this is resolved." By "this," Dr. Gingerich is referring to the classification of glyphosate as a possible oncogen, an OPP action that would have major implications for several pending OPP decisions and

regulatory actions.

357. It is remarkable and worth noting that on the same day that Monsanto learned that the then-incomplete OPP evaluation of the new Bio/dynamics mouse oncogenicity study was likely to lead to OPP classifying glyphosate as a possible oncogen, a representative of Monsanto stationed in the company's Washington D.C. office (Dr. Gingerich) had at least two face-to face meetings with senior representatives of the OPP Registration and Toxicology Divisions, at least two follow-up calls or meetings with these same individuals, and furthermore, had received a clear, substantive request from Dr. Burnam for more data relevant to the primary issue explaining why Monsanto and OPP reached different conclusions regarding the results of the Bio/dynamics mouse oncogenicity study (the number of kidney tumors in the control group of male mice).

358. On February 10, 1984, Hoyt Jamerson of the OPP Registration Division received a memo from William Dykstra of the Toxicology Branch addressing the results of the newly submitted Bio/dynamics mouse study. Under "Recommendations," it states: "Review of the mouse oncogenicity study indicates that glyphosate is oncogenic, producing renal tubule adenomas, a rare tumor, in a dose-related manor. Therefore, Toxicology Branch considers that the PP#3E2845 [pending tolerance petition] is not toxicologically supported."

359. This memo confirms that only 10 days transpired between the OPP-Monsanto discussions on January 31, 1984 regarding the then-incomplete Dykstra review of the new mouse study, and presumably both section and Toxicology Branch sign-off on Dykstra's conclusion that glyphosate caused an increase in a rare kidney tumor in male mice in a dose-related manner.

360. The conclusion set forth in the February 10, 1984 memo is the first known written confirmation that OPP now regarded glyphosate as a possible oncogen. This conclusion had

significant implications known to both OPP and Monsanto.

361. As noted earlier, once glyphosate was classified as a possible oncogen, the OPP would no longer be able to approve any required, Section 409 food additive tolerances. Moreover, final action on any pending tolerance petitions or major, new food use registrations would likely also be delayed or denied.

362. On March 20, 1984, Monsanto submitted to OPP historical control data on the incidence of renal tubule adenomas in the control groups of CD-1 mice in past studies, as requested by Toxicology Branch Deputy Chief Bill Burman in his second conversation on January 31, 1984 with Monsanto's Lyle Gingerich.

363. Burman had suggested Monsanto submit historical control data from the same laboratory, and roughly from the same time period (i.e. within 3-4 years of the time the glyphosate mouse study was conducted). Monsanto submitted such historical control data from Bio/dynamics, as well as from two other "major" contract laboratories. (MONGLY04276057)

364. The final memo codifying Dykstra's review of the mouse oncogenicity study was sent to Taylor in the Registration Division on September 4, 1984. In its "Recommendations" section, the Toxicology Division states that "1. Glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner. The study is acceptable as core-minimum data. 2. A [cancer] risk assessment by Toxicology Branch is required."

365. On February 5, 1985 Monsanto sent the Director of the OPP Registration Division another letter advancing similar arguments in support of the company's conclusion that the renal tubule adenomas in the male mice were not treatment related nor statistically significant.

366. The 2/5/85 Monsanto letter sets forth six arguments in support of the company's assertion that the observed renal tubule adenomas were not treatment related: (1) tumors were

only observed in male mice, (2) renal tubule adenomas were only present at the end of the study, suggesting they were caused by the age of the male mice, rather than exposure to glyphosate in the animal's feed, (3) Only benign tumors were observed, (4) another Bio/dynamics, 2-year chronic feeding study in the same strain of mice with N-nitrosoglyphosate (NNG) produced no renal tubule adenomas in any control or treatment group, (5) glyphosate was not mutagenic in a number of assays, and (6) a complex statistical argument suggesting that the dose-related increase in renal tubule adenomas in the male mice was not statistical significant.

367. Toxicology Branch scientists assessed the data and arguments in this Monsanto letter prior to deciding whether to re-open their consideration of the renal tubule adenoma data. The review was conducted by Herbert Lacayo, and after a complex statistical analysis, he concluded that "a prudent person would reject the Monsanto assumption that Glyphosate dosing has no effect on kidney tumor production" (2/26/1985 memo, Lacayo to Reto Engler; Benbrook files).

368. It is worth noting that the 2/5/85 Monsanto letter contains two pieces of information that actually undercut two of the points raised in it.

369. First, regarding the differential rates of renal tubule adenomas in male and female mice in the glyphosate mouse study, Monsanto reports that "Historically, this lesion is observed only in male mice [four references are cited]. Control animal data from several laboratories indicate an historical control incidence in females of zero." Accordingly, the difference in incidence in this tumor, in this strain of mice, should not have been surprising, nor a reason to call into question the study's outcome.

370. Second, in the letter's point number 4, Monsanto reports zero incidence of renal tubule adenomas in the male and female control group of Charles River CD-1 mice in a similar, Monsanto-commissioned Bio/dynamics mouse study on NNG, undercutting their effort to convince OPP that the absence of renal tubule adenomas in the male mice control group was not supported by similar control-group data from other studies.

371. This and earlier letters, and multiple contacts with Monsanto officials, had made

OPP well aware that the company was determined to reverse the OPP determination that the mouse oncogenicity study was positive. So, to determine whether there was consensus among senior EPA toxicologists and cancer experts, the OPP held a meeting on February 11, 1985 attended by eight senior scientists in the Toxicology Branch.

372. The 2/11/85 meeting's stated purpose was to "evaluate and discuss the data base on Glyphosate, and in particular the potential oncogenic response of Glyphosate." The attendees reviewed the OPP assessment of the new mouse study, as well as the arguments and data submitted by Monsanto in its February 5, 1985 letter.

373. The attendees concurred unanimously that: "In accord with EPA proposed guidelines (FR of Nov. 23, 1984) the panel has classified Glyphosate as a Category C oncogen."

374. On February 21, 1985, another, Monsanto-requested meeting was held with the OPP Toxicology Branch (TB), attended by the TB Chief Ted Farber and then-Assistant Chief Bill Burnam. Dr. Gingerich, Frank Serdy, and Fred Johannsen represented of Monsanto.

375. A February 22, 1985 memo from Dr. Gingerich to Monsanto colleagues characterized the meeting mood as "relaxed, informal, and open." The memo states that Dr. Farber called the February 11, 1985 decision by OPP to classify glyphosate as a possible oncogen "an extremely close call and that EPA remains open to any new information that would make their decision easier." (MONGLY04269072)

376. The memo sets forth Monsanto's goals for the meeting, which including: "(1) see if we could respond to their concerns [the renal tubule adenomas] before any unnecessary comments became a part of the Roundup permanent file. (2) determine exactly what their concerns are. (3) gauge the level of their concern."

377. Under the heading "Concerns of Toxicology Branch" in the February 22nd memo

by Gingerich, he reports that Dr. Farber opened the meeting by describing the conclusions of the OPP toxicology branch review of the mouse oncogenicity study. Specific points noted were: "Oncogenic in mouse, IARC ranking 'c' [possible human carcinogen]; Company's letter [Monsanto's February 5th letter] was too weak to be convincing; Biologically significant rare tumors; Historical controls [data] not helpful; Will ask to re-section tissues, consider crystal formation, etc."

378. The meeting memo then states that "Dr. Farber indicated that a substantial re-look at tissues may cause the EPA pathologist [Dr. Kasza] to change his position. If no carcinomas are found the second time, our arguments about 'only benign' tumors would be stronger. I [Gingerich] read this to mean that the EPA pathologist (Kasza) is open to persuasion."

379. Next, the memo reports on several questions raised during the meeting, and their answers. Monsanto representative FJ (Frank Johannsen) then asked OPP's Dr. Farber "…what the EPA would be likely to do if we [Monsanto] re-sectioned the slides and found no carcinomas. Dr. Farber said that it would force them to get the internal peer review group together again."

380. This and other questions raised during the February 21, 1985 meeting demonstrated that Monsanto acted to find some basis, any basis, to change OPP's conclusion on the mouse oncogenicity study, and the classification of glyphosate as a possible oncogen.

3. OPP Dismisses Monsanto's Historical Control Data Argument

381. On February 5, 1985, Monsanto sent to the Director of the OPP Registration Division a four-page letter transmitting additional information related to the Bio/dynamics chronic mouse study.

382. Four days later, on February 26, 1985, a memorandum was sent to OPP

statistician Reto Engler, an individual involved in the Toxicology Branch science review of glyphosate's oncogenicity and responsible for carrying out the recommended quantitative risk assessment of glyphosate's oncogenicity. The memo was written by an OPP statistician Herbert Lacayo, and sent through and signed off by Bertram Litt, OPP's Statistics Team Leader.

383. The memo focused on whether the additional, mouse historical control data for kidney tumors submitted by Monsanto alters the OPP assessment of the significance of the reported tumors in the Bio/dynamics study. It begins by noting that Monsanto submitted "historical control data from Bio/dynamics and two other laboratories," despite Dr. Burnam's unambiguous request during the February 22nd meeting that Monsanto only consider, and submit historical control data from the same laboratory where the Bio/dynamics study was conducted, and within an appropriate window of time (3-4 years).

384. The summary of the Lacayo statistical review of the historical control data states that "…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" (i.e., highly statistically significant, since the usual cut-off for significance is the p = 0.05 level).

385. A March 4, 1985 memo on the subject "Consensus Review of Glyphosate" codified the conclusion reached by the eight Toxicology Branch scientists, each of whom signed the consensus review document (MONGLY04269067). The signatories included the Chief of the Toxicology Branch Theodore Farber, OPP's senior pathologist who read the Bio/dynamics mouse study histopathology slides, Bertram Litt, OPP's senior statistician, and William Dykstra, author of the original OPP review of the mouse study.

386. This is an unusual memo, and clearly was written to codify in the glyphosate registration file, and communicate to Monsanto, that senior scientists in the Toxicology Branch

were united in their classification of glyphosate as a possible oncogen, despite all the back and forth with Monsanto, and the review and assessment of historical control data.

387. The memo was sent to Robert Taylor in the Registration Division, and marked the end of the beginning of a protracted debate between OPP and Monsanto over the results of the Bio/dynamics mouse study.

388. The managers and scientists in OPP's Toxicology Branch were aware of the significance of this change in glyphosate's cancer classification. The memo was prepared in anticipation of a vigorous response from Monsanto to senior officials in OPP and at political levels within EPA, and possibly as well in the White House and Congress on OPP.

4. Monsanto Takes Its Case to the Director of the OPP Registration Division

389. Only two days passed before Monsanto again wrote to OPP, this time to Douglas Campt, then Director of the OPP Registration Division. The five page, March 13, 1985 letter was sent by Frank Serdy, the Monsanto Manager, Federal and State Registration Affairs.

390. The letter recounts the recent history of OPP's evaluation of the Bio/dynamics mouse oncogenicity study, the numerous meetings and back-and-forth involving OPP and Monsanto scientists, and asserts that the renal tubule adenomas observed in the male mice in the study are not treatment related, nor statistically significant. It also restates the many Monsanto arguments advanced over the past six weeks.

391. In closing his letter to Mr. Campt, Mr. Serdy states that:

> "As you know, glyphosate is an extremely important herbicide to agriculture in the U.S. and around the world. Monsanto is concerned that even the initiation of formal regulatory action would have serious negative economic repercussions which we believe are not justified by the scientific evidence."

392. In 1984, an estimated 8.9 million pounds of glyphosate active ingredient were applied nationwide by U.S. farmers and ranchers (Benbrook, C [2016]. Trends in glyphosate use

in the United States and Globally, *Environmental Sciences Europe*, Vol. 28:3; data on use in the U.S. is from Supplemental Table S18, data on global use is from S24). In 2014, agricultural use in the U.S. had risen to 249.9 million pounds, 28-times higher than the level of use in 1984.

393. Globally in 1994 (first year a global estimate is possible), an estimated 124 million pounds of glyphosate active ingredient were applied. In 2014, 1.65 billion pounds of glyphosate were applied, 13-times more than in 1994, and likely well over 25-times more than global use in 1984.

394. The "negative economic repercussions" referenced in Serdy's letter would have included curtailment of much of the dramatic rise in glyphosate use that began in 1996 with the commercial launch of genetically engineered crops able to withstand post-emergence applications of Roundup.

395. In an April 3, 1985 memo from William Dykstra to the Registration Division's Robert Taylor, the official Toxicology Branch judgement regarding glyphosate's oncogenicity was stated as it had been previously: "Glyphosate was oncogenic in male mice causing renal tubule adenomas, a rare tumor, in a dose-related manner."

5. Monsanto's Next Move – Hire Another Pathologist to Re-read the Kidney Slides

396. Also on April 3, 1985, Dr. George Levinskas, a scientist in the Monsanto Department of Medicine and Environmental Health, circulated a brief update inside the company stating that "Senior management at EPA is reviewing a proposal to classify glyphosate as a class 'C' possible human carcinogen' because of kidney adenomas in male mice. [Private, consulting pathologist] Dr. Marvin Kuschner will review kidney sections and present his evaluation of them to EPA in an effort to persuade the agency that the observed tumors are not related to glyphosate." (MONGLY04277789)

397. Dr. Kuschner had not been involved with the design, conduct, or evaluation of the Bio/dynamics mouse oncogenicity study, and had not previously reviewed the study's histopathology slides.

398. When Dr. Levinskas wrote that Dr. Kuschner will review the slides "in an effort to persuade the agency that the tumors are not related to glyphosate," the implication is clear. Dr. Kuschner was chosen for a specific assignment – turning the EPA review of the Bio/dynamics mouse study from "positive" to "negative" for oncogenicity. Moreover, based on previous discussions with OPP toxicology branch managers, Monsanto officials recognized that the identification of even one tumor in the group of male control mice was one way to do so.

399. Also on April 3, 1985, a letter is sent by Dr. Aleksanday Knezevich, Senior V-P, Pathology at Bio/dynamics to Dr. Marvin Kushner, a private consulting pathologist living in New York. (MONGLY04269049) The letter informs Dr. Kushner: "The enclosed shipment is being sent to you at the request of Dr. Tim Long of Monsanto. It contains slides of kidney sections from all animals on the references study [mouse oncogenicity study]."

400. On April 14, 1985, Dr. Kushner signed for the receipt of a box from Federal Express containing 422 slides of kidney sections representing 399 animals in the Bio/dynamics mouse oncogenicity study.

B. Pending Actions Heighten Monsanto's Concern Over Public Release of Glyphosate's Cancer Classification

401. Clearly, Monsanto was working hard to turn around OPP's judgement on the Bio/dynamics mouse oncogenicity study before there was any public acknowledgement of the EPA's change in the cancer classification of glyphosate. Monsanto had responded, or began to fashion its strategy, at each step in the EPA process on the same day, or within days of learning new information about the OPP review of the study.

402. The company realized it would need time to generate new data sufficiently persuasive to change what was now stated as a firm, consensus OPP judgement. In the interim, it Monsanto attempted to prevent the new cancer classification from being acknowledged in the normal course of OPP public statements and federal register notices, and especially notices pertaining to the many glyphosate tolerance petitions at various stages of OPP review.

403. Two such circumstances that might have led to OPP stating its new position on glyphosate oncogenicity are addressed in an April 10, 1985 update memo to company colleagues by T.F. Armstrong, a Monsanto scientist working with the EPA. In the memo, he reports on an April 9, 1985 phone call with Jim Ackerman of OPP, involving Frank Serdy, Lyle Gingerich, and himself.

404. OPP's Ackerman reportedly told Armstrong that the glyphosate mouse oncogenicity peer review would be completed in a few weeks, and that the Assistant Administrator for Pesticides and Toxic Substances, Dr. Jack Moore (a Presidential appointee and individual responsible for actions by OPP), had assigned a Dr. Barnes in his office to assess the outstanding issues in the evaluation of the mouse study.

405. Dr. Moore's office had been drawn into assessment of the status of the glyphosate oncogenicity study because of the need for a timely EPA response to a pending Section 18 emergency exemption label request on behalf of the National Wheat Growers for use of glyphosate "through selective equipment on wheat." (MONGLY04269047). In this context, "selective equipment" is referring to a rope-wick applicator, and a pending 1983 application for a Section 18 emergency exemption from the State of Oklahoma.

406. This Section 18 request from Oklahoma is historically important, because it marks the first, known instance in which OPP indicated that it would deny a necessary Section 409

food-additive tolerance because of the Delaney Clause in the Food Drug, and Cosmetic Act (FDCA).

407. There was a second public event in which Monsanto worried that EPA would be forced to respond, on the record, to a direct question about the status of OPP's assessment of the glyphosate mouse oncogenicity study.

408. On April 17, 1985, a public hearing was scheduled on the use of glyphosate in the aerial herbicide-spray program targeting marijuana cultivation in South America. The meeting was organized by the Drug Enforcement Agency and a representative of the OPP would be in attendance.

409. Monsanto expected that "at this public hearing, we suspect the Drug Enforcement people will ask the EPA if glyphosate is safe to use, and if the EPA answers anything but Yes, the mouse study situation could be released to the public at this hearing." (MONGLY04269047)

410. The DEA's concern over glyphosate human health effects included acute effects on people living in and around treated areas, as well as acute and chronic effects among U.S. citizens smoking marijuana contaminated with residues of glyphosate and AMPA, glyphosate's major metabolite.

411. Armstrong's April 10th memo to his Monsanto colleagues ends with this statement: "Based on the foregoing points, a possible Monsanto action on the glyphosate mouse study would be to submit a letter to the EPA to prevent an inappropriate release of the 'tentative' mouse study conclusions. This letter needs to be received by the EPA prior to next week's Marijuana Public Hearing, and preferably it should be written by a toxicologist that is highly respected by Dr. Barnes and/or Dr. Moore."

412. The above "should we warn OPP" instance is one of several since the January 31,

1984 Gingerich memo in which Monsanto officials considered having its legal department "caution" EPA over pre-mature public discussion of information on OPP's evaluation of the mouse oncogenicity study.

413. This extraordinary series of events drives home the magnitude of the negative repercussions that Monsanto expected, if the OPP officially and publicly announced its conclusion that glyphosate possibly causes cancer.

414. Sometime in or around mid-May 1985, Kushner submitted his report to Bio/dynamics and Monsanto. The company reviewed the report, and submitted it to OPP.

415. In a June 14, 1985 memo from OPP's senior statistician Reto Engler to Robert Taylor of the Registration Division, Dr. Engler reports that after a TB peer-review process:

> "We have determined that the incidence of renal adenomas in male mice (a rare tumor) is inconsistent with the historical control incidence of this tumor. The registrant, in several letters, has refuted our statistical analysis of the data. Basically the registrant contends that the highest incidence ever observed in historical controls should be used to judge the incidence in the Glyphosate study. The use of any historical control data in this manner is biologically as well as statistically inappropriate and misleading." (Underlining in original).

416. Then, Dr. Engler goes on to report that the registrant has now submitted a report (presumably from Dr. Kushner) "which shows that a re-reading of the kidney slides has revealed one (1) kidney tumor in the control group but no additional tumors in the treatment groups." In light of this new information, Engler writes that:

> "Given the overall uncertainty concerning the significance of the observed tumor incidence we believe a systematic reevaluation of this kidney lesion has become necessary in order to fully evaluate Glyphosate."

417. This memo marks at least a temporary victory for Monsanto, since their efforts ro commission, and their submission of the Kushner report delayed OPP's final determination as to glyphosate oncogenicity in the Bio/dynamics study.

418. OPP's decision to re-section the slides also created the possibility that new information would emerge supporting Dr. Kushner's assessment of the slides, and/or changing the number of tumors in the male mice control and three treatment groups in a way that eliminates the dose-related response in the frequency of renal tubule adenomas. (MONGLY00235097 at 5412)

C. Re-sectioning of the Mouse Kidney Slides – Monsanto's Next Effort to Change OPP's Mind

419. "If the results of the kidney re-sectioning do not resolve the glyphosate issue within OPP, we will be faced with an adverse OPP decision," wrote Lyle Gingerich to Monsanto colleagues in an August 20, 1985 memo. (MONGLY04268982)

420. Gingerich also discusses the prospect that OPP might decide to place unresolved science issues before the agency's Scientific Advisory Panel (SAP), especially if a deadlock emerges between the conclusions of Monsanto's and OPP's pathologists.

421. Gingerich goes on to ask "Can we change the focus of the question to the S.A.P. to: 'Is 30,000 ppm too high [a dose] to be used in a meaningful risk assessment?'…If we assembled 10 respected toxicologists, would all ten agree that the feeding level is too high to be meaningful?" He then suggests that the 10 toxicologists agreeing with Monsanto's position should be brought to the SAP meeting and asked to speak in support of the company's assessment of the mouse study, given "…the importance of this issue to Monsanto."

422. Gingerich then explains why he has suggested that all 10 toxicologists should be brought to the SAP meeting: "There is a tendency to 'count the votes' at S.A.P. meetings. We can make a difference by lining up a large number of experts on our side."

423. Eight days later, on August 28th, Frank Serdy, the Director of Federal and State Regulatory Affairs for Monsanto, wrote a memo to his colleague Tim Long, another official

working on the effort to change EPA's mind on the mouse oncogenicity study. Serdy wrote on the topic of "Additional Steps" in the effort to change EPA's mind on the Bio/dynamics mouse study, and the renal tubule adenomas in particular (MONGLY04268980).

424. He voices confidence that glyphosate will ultimately be shown to be not oncogenic, but lays out some "additional steps" if the results of the re-sectioning of the kidneys does not change EPA's mind.

425. First, Serdy writes: "We continue to feel it is important to identify and contact those outside 'experts' who we feel would testify on our behalf both to EPA and SAP that, based on the results, glyphosate is not oncogenic."

426. Serdy's second "additional step" is prefaced by acknowledging that "We do not have a lot of faith, presented with the same evidence, Ted Farber [senior OPP scientist in the Toxicology Branch] will want to back off and change his mind." Serdy then writes: "Hence we feel that it is equally as important to identify and contact 'experts' in the area of statistics who would be willing to testify both to the EPA and SAP that 1-0-1-3 cannot be considered statistically significant."

427. Note that in Serdy's second point he is assuming that EPA has, or will accept Dr. Kushner's conclusion that one mouse in the male control group had a renal tubule adenoma that was not detected, or reported in the original Bio/dynamics report on the results of the study. In the absence of that one, additional adenoma in the male mice control group, the tumor incidence would have remained as originally reported, 0-0-1-3, and reflect a trend which is unambiguously dose-related and highly statistically significant, as Lacayo's 2/26/85 memo had concluded.

428. Driving home the importance of these "additional steps," Serdy writes that:

> "It seems imperative that we continue to do all that is possible in order to have the Agency reverse its decision. Hopefully, the testimony of several respected 'experts' will

be enough to cause EPA to change their minds."

429. The re-sectioning of the male mice kidneys, and the re-evaluation of the slides, was done by Bio/dynamics, at the request of Monsanto. The OPP pathologist Dr. Kasza had been consulted in the process of developing the procedures. R.F. McConnell, a pathologist consulting with Bio/dynamics, read both the original slides, and the slides from the re-sectioned kidneys.

430. The Bio/dynamics report covering the re-sectioned kidney tumors was dated September 26, 1985, and presumably was submitted to the EPA a few days later.

431. The significant result in the Kushner-Bio/dynamics report is finding one renal tubule adenoma in the control group of male mice (mouse # 1028). The report states: "Confirmation of the diagnosis of the original renal tubular adenomas was made, including concurrence with Dr. Marvin Kushner on the presence of a lesion in the control group which represented a developing tumor. No new tumors were found in any of the [other] control or treated groups."

432. The reported conclusion was precisely what Monsanto had hoped for: "The renal tumors observed were considered to be incidental and not toxicologically significant."

433. The technical response from the Toxicology Branch to the September 26, 1985 Bio/dynamics report was done by Dr. Kasza, OPP's senior pathologist, and the scientist who had been consulted by Bio/dynamics on the procedures to be followed in the re-sectioning of the kidneys. The December 4, 1985 memo was sent to William Dykstra, the lead reviewer of the mouse study in OPP's Toxicology Branch.

434. The single, critical question was whether Dr. Kasza agreed with Dr. Kushner and the Bio/dynamics pathologist Dr. McConnell that male mouse #1028 in the control group had a renal tubule adenoma. Kasza requested and carefully re-read the original slides for male mice in

the study with reported kidney tumors, and studied the newly re-sectioned kidney slides. He found no differences in the number of renal tubule adenomas in the treatment groups.

435. In reference to the one, additional control group tumor in mouse # 1028 reported by Kushner-McConnell, Dr. Kasza wrote:

> "It is my opinion that the presence of a tumor cannot be 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."

436. Based on Dr. Kasza's reading of the newly sectioned kidney of animal #1028, there was a group of cells that looked different and that might become a lesion of some sort, but the cell mass had not reached the stage justifying identification as a renal tubule adenoma.

D. The 1986 SAP Review of the Mouse Oncogenicity Study

437. Kasza's interpretation was accepted within EPA. As a result, the EPA and Monsanto were dead-locked, and the stage was set for asking the SAP to help the agency work through the unresolved issues.

438. A January 17, 1986 Federal Register notice announced the two-day SAP meeting on February 11-12, 1986 during which the Bio/dynamics mouse study would be evaluated. Agenda item 1 read: "Review of a set of scientific issues related to apparent oncogenicity being considered by the Agency in connection with the preparation of a Registration Standard for glyphosate."

439. The phrase "apparent oncogenicity" shows that EPA viewed the renal tubule adenomas in the male mice a treatment related, and triggered a swift, firm response from Monsanto.

440. Monsanto's January 23, 1986 letter came a week after the Federal Register notice was published. It was sent to Steven Johnson, a senior EPA official, and signed by Thomas Armstrong, Monsanto's Registration Manager.

441. After noting that EPA said the SAP would assess glyphosate's "apparent oncogenicity," Armstrong wrote: "Monsanto firmly believes that glyphosate is not an oncogen, and we therefore do not agree with this position taken by the Agency. The Agency is in error in reaching this conclusion…"

442. The letter argues that the OPP determination does not follow EPA's Proposed Guidelines for Carcinogen Risk Assessment. Armstrong then writes:

> "In addition to Monsanto's own evaluation, this matter has been reviewed by five independent experts. The unanimous conclusion reached by these scientists is that there is no treatment-related oncogenic effect of glyphosate in the chronic mouse study…"

443. Recall the August 20, 1985 Gingerich memo discussed above. It suggested that Monsanto recruit 10 experts to testify before the SAP, and that "There is a tendency to 'count the votes' at S.A.P. meetings." (MONGLY04268982)

1. SAP Meeting Discussion and Outcome

444. The focus of the glyphosate oncogenicity discussion during the February 11, 1986 SAP meeting was on the histopathology of the kidney slides, and in particular:

- The number of tumors in the male mouse control group;
- The appropriate statistical analysis to use, and whether the renal tubule adenoma incidence reached statistical significance; and
- The proper use of historical control data.

445. The primary presentation by EPA was done by Dr. Farber, and Monsanto's presentation was made largely by Robert Harness, Director of Environmental and Government Affairs, Dr. Timothy Long, in the company's Medical Department, and Mr. Wayne Withers.

446. In addition, Monsanto brought to the SAP meeting, three experts who had been

involved with the study and/or the reading of the controversial kidney slides: Dr. Marvin Kushner, the pathologist who re-read the original mouse study kidney slides; Dr. R.F. McConnell, the consultant to Bio/dynamics that read the original slides, as well as the re-sectioned slides; and Dr. Ira Daly, the Bio/dynamics laboratory director.

447. Each of these individuals brought by Monsanto were given opportunities to make short presentations and participate in the Q & A with SAP members.

448. In addition, Monsanto announced to the SAP that they had submitted the data in question to a panel of four consulting experts (Squires, Olsen, Stemmer, Goodman), all of whom agreed with Monsanto's interpretation of the mouse oncogenicity study results. These experts also participated in the Q&A.

449. One of the invited experts – Dr. Don Goodman – was asked by Monsanto to attend and represent the conclusions of a second review panel convened at the request of Monsanto by Pathco Inc, a pathology consulting group. The Pathco panel reviewing the same mouse oncogenicity data included five scientists (Sourer, Anver, Stranberg, Ward, Goodman).

450. Accordingly, the Monsanto team offering conclusions and presenting data before the SAP included 14 people: three from Monsanto, three individuals involved with the study, four consulting experts, and four additional experts who joined Dr. Goodman (in attendance) on the Pathco Inc panel.

451. The report providing the SAP panel's answers to the two questions EPA asked the panel to address on February 11, 1986 was transmitted to the Director of OPP on February 24, 1986, and was released publicly soon thereafter. The section "Panel response" begins by saying: "In the instance of Glyphosate, the Panel concurs that the data on renal tumors in male mice are equivocal."

452. The SAP report goes on to state: "The vast majority of the pathologists, who examined the proliferative lesion in the male control animal, agreed that the lesion represented a renal adenoma. Therefore, statistical analysis of the data should utilize this datum."

453. This conclusion that the "vast majority" of pathologists agreed with the Monsanto interpretation contradicts a statement made by the EPA in its assessment of the differing views on whether control animal #1028 had a renal tubule adenoma.

454. In Dr. Faber's presentation to the SAP, he states: "we [EPA] do see an increased incidence statistically…" On the critical issue of whether there was a renal tubule adenoma in one male mouse in the control group, Dr. Farber's offered his accounting of the differing views: "…perhaps three pathologists saying no [tumor], perhaps four or more pathologists saying yes."

455. However, given the number of additional experts brought to the meeting by Monsanto, "counting the votes" expressed just during the meeting produced a very different outcome -- 14 to 3 "vote" in favor of Monsanto's position.

456. The three individuals at the SAP meeting supporting the conclusion that there was "no tumor" in control animal #1028 were EPA scientists (Faber, Kasza, Lacayo), while all 14 "yes" votes were expressed by individuals working for, or hired by Monsanto.

457. Taking into account the uncertainty over the number of renal tubule adenomas, the use of historical controls, and the statistical methods used to judge whether the observed tumors were treatment related, the SAP's final judgement was equivocal:

> "…the Panel does not believe that it is possible to categorize Glyphosate clearly into Group C (possible human carcinogen) or Group E (no evidence of carcinogenicity in humans). The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions."

458. Despite requests from OPP to redo the mouse study, Monsanto has refused to do

so, arguing that its interpretation of the Bio/dynamics study has been widely embraced and there is no need to conduct any more long-term, mouse oncogenicity studies on glyphosate.

459. In short, Monsanto considered then, and still does believe and assert publicly that the science issues addressed by the SAP in its 1986 report are "settled."

460. Developments over the last three decades prove this is clearly not the case (see VI., section A.1).

VI. Monsanto Efforts to Influence Scientific Community and Regulatory Assessments of Glyphosate Risks

461. It is entirely appropriate and expected that Monsanto would devote time and resources to the task of persuading regulatory agencies, the scientific community, political leaders, farmers and farm organizations, competitors, the media, and the general public that the health and safety data developed by the company is valid and supports the conclusion that all Monsanto products are "safe." When pushed, the company falls back to statements like "…Roundup herbicides pose 'acceptable risks' when applied in accord with label directions."

462. To one degree or another, and in a wide diversity of ways, all pesticide registrants invest resources in defending the safety of their pesticide products.

463. The tactics, strategies, and messages deployed by Monsanto over the last 40+ years in defense of Monsanto-brand Roundup herbicides is a central issue in this case. A core question is – Did Monsanto grow sales by overstating the safety of Roundup, and by under-protecting people who bought and applied the company's products in a lawful manner in accord with label directions?

A. Ignore, Delay, or Refuse to Fulfill EPA Requests for Information, New Studies, or Label Precautions

464. On August 11, 1986, OPP issued the glyphosate Registration Standard (RS) document setting forth guidance to companies seeking to register new or retain existing pesticide product labels for herbicides containing glyphosate (the date on the RS document is June 1986; the 8/11/86 date of the RS release is from multiple sources, e.g. 10/27/88 letter from Tinsworth to Long in MONGLY00223577).

465. In 1986, Monsanto was the sole manufacturer of glyphosate-based herbicides, so guidance in the 1986 RS document regarding steps that manufacturers of glyphosate herbicides

must take was clearly guidance to Monsanto, and all responses to the RS by industry, and actions taken and not taken, were Monsanto actions/inactions.

466. The RS document is a key historical milestone in the EPA's assessment of glyphosate uses, risks, and benefits, as well as actions that the EPA regards as essential to assure that, on an ongoing basis, benefits stemming from glyphosate uses will routinely exceed any risks.

467. Key functions of the 1986 RS document were to specify required labelling statements and precautions that must appear on product labels, identify data gaps that must be filled, and alert companies to the studies that they must agree to commission and submit to the agency in a timely way, in order to retain existing registrations/product labels, or win approval of new uses/labels in the future.

468. The 1986 glyphosate RS document states on page 2: "Failure to comply with these requirements [e.g. filling data gaps, adding new worker safety rules] may result in the issuance of a Notice of Intent to Cancel or a Notice of Intent to Suspend (in the case of failure to submit data)."

1. OPP Requirement for Repeat Mouse and Rat Oncogenicity Studies

469. Under the heading "Chronic Feeding/Oncogenicity Data," the glyphosate Registration Standard notes that available studies included 2-year mouse and rat chronic feeding studies and a 1-year dog study. But because of limitations in study design and/or questions over the interpretation of equivocal results, none of these studies satisfied core, OPP chronic feeding study data requirements.

470. Hence, the "Summary Science Statement" in the Registration Standard states that "Repeat oncogenic studies are required in mice and rats." (Page 5).

471. EPA required the company to repeat the invalid IBT rat oncogenicity study that, among other things, failed to reach the Maximum Tolerated Dose (MTD) in the high-dose treatment group (maximum doses in long-term feeding studies are supposed to come close to the MTD).

472. About three weeks after the public release of the glyphosate RS, Frank Serdy, the head of product registrations at Monsanto sent an internal memo to Monsanto colleagues involved in the ongoing debate over glyphosate oncogenicity. In this August 28, 1986 memo, Serdy outlines "suggestions" for Monsanto's response to the Registration Standard's data call-in for repeat mouse and rat oncogenicity studies. (MONGLY04278162)

473. After describing possible Monsanto arguments to EPA challenging the need for repeat studies, Serdy writes:

> "If successful [EPA drops the requirement], this approach has the following downside: EPA's response may be: 'Fine, don't repeat either study. We will just put you into class C [a possible oncogene under EPA's classification system]'".

474. The "downside" described by Serdy had, in fact, been the status quo position of the OPP Toxicology Branch since the February 11, 1985 consensus meeting of eight senior scientists in the Toxicology Branch.

2. Monsanto Refuses to Conduct a New Mouse Oncogenicity Study

475. Monsanto's pushback on OPP's determination that the Bio/dynamics mouse oncogenicity study was positive for renal tubule adenomas had been immediate, intense, and non-stop from the day (1/31/84) Monsanto learned that Dykstra's (the Tox Branch reviewer) initial judgement was that the mouse study was positive for a "rare" tumor in mice, renal tubule adenomas.

476. Monsanto's aggressive campaign to change the Toxicology Branch's

determination eventually led to OPP's decision to seek the opinion of the Scientific Advisory Panel (SAP) on two glyphosate-oncogenicity questions during the panel's February, 1986 meeting. Monsanto had, in fact, foreseen such an outcome.

477. The SAP's conclusion was that the results of the mouse study were equivocal, and its core recommendation to EPA was that the agency should require Monsanto to repeat the mouse oncogenicity study.

478. In the 1986 glyphosate Registration Standard, this is precisely what OPP did. In doing so, EPA set the stage for the next, years-long round of arguments and interventions from Monsanto, and supporting political moves, intended to avoid repeating the mouse chronic feeding study.

479. Soon after the release of the glyphosate RS document in August 1986, Monsanto communicated via several channels its vehement disagreement with several aspects of the actions required by EPA in the document.

480. Monsanto's written response to EPA challenging the requirement that the company repeat the mouse oncogenicity study flows directly from the strategic options Serdy presented to his colleagues in the August 28, 1986 memo.

481. Serdy asserts in his RS-response letter to OPP that:

> "The results of the mouse bioassay do not provide positive, or even suggestive, evidence of carcinogenicity. The most that can be said is that the results were equivocal as, in fact, the Scientific Advisory Panel stated."

482. Serdy does not explain the distinction between "suggestive" evidence and "equivocal" evidence, but acknowledges there is some of the later, but not the former.

483. The RS-response letter to EPA from Monsanto/Serdy adds some new and echoes some old arguments: (1) the majority of experts testifying at the SAP meeting concluded the

study was equivocal and did not support a treatment-related effect (reminiscent of the "count the votes" strategy suggested by Gingerich in his August 20, 1985 memo to colleagues (MONGLY04268982); (2) Monsanto had already agreed to redo the rat oncogenicity study, so OPP would have a new, purportedly higher-quality study to use in revisiting its judgement regarding glyphosate oncogenicity; and (3) the mouse study should not be repeated as designed because it is "clear" that the maximum does tested in the study (30,000 ppm), was over the MTD.

484. In the RS-response letter to OPP, Monsanto notes that the company had asked several consulting experts to testify at the SAP meeting, with their time and expenses paid for by Monsanto. The Serdy letter states that the experts "were asked to evaluate the need for a repeat study. All experts agreed that additional testing is not justified…" (page 2).

485. This recounting of the role of the seven consulting experts brought to the SAP meeting by Monsanto, and their testimony at the meeting, is not accurate.

486. The lead person representing Monsanto at the SAP meeting was Robert Harness, Director of Environmental and Government Affairs. In his opening comments to the SAP, Harness said: "Because glyphosate is the largest selling herbicide in the world, with many registered uses, we consulted a group of scientists to advise us ***on the questions raised by the EPA and presented to you by Dr. Farber*** [lead OPP/EPA presenter at the SAP meeting]." (Emphasis added)

487. The two questions presented to the SAP by the EPA were:

> "(1) Based on the Agency's weight of the evidence assessment with emphasis on the mouse kidney tumors, the Agency has classified Glyphosate as a class C (possible human) carcinogen. The Agency specifically requests any comment the Panel may wish to present with regard to its assessment of the weight of the evidence and subsequent determination of carcinogenicity according to the Agency's Cancer Guidelines."

"(2) The Agency requests also that the Panel consider what weight should be given to this marginal increase in kidney tumors, the importance of this type of tumor in the assessment of the carcinogenicity of Glyphosate, and the weight placed on historical and concurrent controls for this type of evaluation."

488. Accordingly, based on Monsanto's own direct statement to the SAP, the consulting experts were not asked to offer an opinion on whether the mouse study should be repeated, as Monsanto claimed in its November 7, 1986 response to the RS document.

489. The transcript of the February 11, 1986 SAP meeting provides further, clear evidence that supports this conclusion.

490. In his opening statement to the SAP, Harness summarizes the key conclusions reached by each of the Monsanto-invited experts, as well as the expert panel convened at Monsanto's request by Pathco Inc.

1. Dr. Marvin Kushner, found an additional tumor in the male mouse control group, no additional tumors in the treatment group, switching the study from purportedly positive to negative for renal tubule adenomas. His concluding statement, quoted by Harness, is that "I see no reason to assign carcinogenic potential to glyphosate."

2. Robert Squires, "In summary, I feel the weight of the evidence strongly suggests the renal adenomas in male mice were naturally occurring and not treatment related."

3. Robert Olsen, "In summary, it is my view that these findings do not support the view that [text cut off]."

4. Dr. Robert McConnell, "It is and has been the opinion of this pathologist that the tumors were incidental and were not toxicologically significant."

5. Dr. Klaus Stemmer, "The incidence of renal tubule adenomas is in all probability biologically by chance."

6. Pathco Inc panel (Drs. Sourer, Anver, Stranberg, Ward, and Goodman, who represented the panel at the SAP meeting), "The incidence of renal tubule cell neoplasms in this study are not compound related."

6. Monsanto's Dr. Timothy Long provided an overview of the back and forth over the mouse study pathology results, and then summarized Monsanto's position by stating, "The overall incidence [of renal tubular adenomas], therefore, remained at 1-0-1-3 [one tumor in controls and mid-range treatment group, 3 in the high-dose treatment group].

> These [kidney section] slides and/or supporting data have now been reviewed by a total of 10 pathologists and toxicologists and the unanimous conclusion of all the experts is that there is no evidence of any treatment related oncogenicity."

491. Two things are clear from the above-cited summary statements presented or quoted by Monsanto representatives at the SAP meeting. First, the consulting experts did, in fact, adhere to their assignment from Monsanto by predominantly addressing the two questions advanced by OPP to the SAP prior to the meeting.

492. Second, the opening remarks provided during the meeting by the Monsanto consulting experts were laser-focused on the incidence of renal tubule adenomas in male mice in the Bio/dynamics mouse study. None of them spoke to the issue of whether the mouse study should be repeated.

493. After Monsanto's prepared presentation, the ensuing dialogue between members of the SAP, EPA scientists, and Monsanto's representatives and invited experts is captured in full in the last, approximate 20 pages of the SAP meeting transcript.

494. In these 20-pages of SAP transcript, there is not a single statement by any of the Monsanto-invited experts addressing whether the mouse study should be replicated.

3. OPP Review of Arguments on the Need to Repeat the Mouse Study

495. Per routine OPP procedures, Monsanto's observations, scientific arguments, and requests for waivers of RS data requirements, including a repeat mouse study, were reviewed by the relevant branches of OPP.

496. Monsanto had formally requested waivers for two RS-document study requirements: (1) an LC-50 inhalation study, and (2) a repeat mouse chronic feeding/oncogenicity study. William Dykstra in the Toxicology Branch reviewed the request, and the supporting data and arguments submitted by Monsanto. He prepared the Tox Branch

memo regarding "Glyphosate – Monsanto Comments to Glyphosate Guidance Document." (MONGLY00223052)

497. Dykstra concurred/approved waiver request (1). On request (2), he wrote: "TB [Toxicology Branch] does not concur with Monsanto regarding the waiver of the repeat mouse oncogenicity study (see discussion in review section [pages 3-6 of the memo])."

498. In his review of Monsanto's arguments in support of a waiver for the mouse study, Dykstra wrote: "Regarding the need to repeat the mouse oncogenicity study with glyphosate, TB fully concurs with the conclusion and recommendation of the Scientific Advisory Panel (SAP)." The SAP had concluded that glyphosate be classified as Group D (not classifiable as to oncogenicity) and recommended that replacement studies in mice and/or rats be carried out.

499. He then writes: "TB believes the oncogenic potential of glyphosate in mice still remains unresolved and that a repeat mouse study is necessary to fully and adequately assess this potential." (MONGLY00223052)

500. Dykstra's memo goes on to say that the new mouse oncogenicity study should be "specially designed" (emphasis in original) to clarify "certain unresolved questions relating to the potential oncogenicity of glyphosate."

501. Dykstra's specific requirements for the new study were unusual, and clearly had to be unwelcomed by Monsanto.

502. First, he recommended retaining the 30,000 ppm high-dose treatment rate, since survival in that group of male mice exceeded survival in the control group (and hence, according to EPA, had not exceeded the MTD). Second, two additional treatment groups should be added to more definitely delineate whether there is a dose-response – 7,500 ppm, and 15,000 ppm. Third, there should be 200 male mice per group, to enhance statistical power.

503. Dykstra also stated that the study should focus just on unresolved questions from the first study. This concession to Monsanto was presumably predicated on the fact that some of his recommendations would have markedly increased the cost of the study (200 male mice in each group, instead of 50; adding two additional treatment groups).

504. First, the study can include only male mice (cutting the size of the study in half). Second, a "tier approach" was acceptable in the pathology examination phase of the study, focusing first on kidney and liver sections in all groups of male mice. If the "first tier" examination produces no evidence of an oncogenic response, "then additional histopathological examination will not be necessary."

505. Last, the memo states: "The registrant should be requested to submit a proposed protocol for the repeat mouse study to the Agency for comment before the experimental work is initiated."

506. Monsanto continued to resist EPA's call for a new mouse oncogenicity study, and indeed has still not redone the study as requested by EPA.

507. The primary reason is clear – legitimate concern in the company that the results of such a study would affirm the key finding in the original Bio/dynamics study mouse oncogenicity study, and result in EPA classifying glyphosate as a "possible human carcinogen."

B. Monsanto Efforts to Delay and/or Defuse Worker Safety Language on Roundup Labels

508. The 1986 glyphosate Registration Standard (RS) specified new worker safety language that must appear on Roundup product labels in channels of commerce as of June 30, 1988.

509. In a February 9, 1987 letter to the Director of the OPP Registration Division, Monsanto argues that the worker-protection language in the 1986 RS is unjustified, for reasons

first set forth in Monsanto's November 7, 1986 letter/response to the RS.

510. The 2/9/87 letter restated and expanded upon the arguments set forth in the 11/7/86 letter. The February 1987 letter also transmitted to OPP a new contact-dermatitis study done by a University of California scientist.

511. OPP's review of the February 1987 letter, the actions it requested, and the newly-submitted dermatitis study was done by Curt Kunchick, a scientist in OPP's Exposure Assessment Branch. His June 18, 1987 review notes that the focus of Monsanto's arguments is contact dermatitis and the newly submitted dermatitis study, while OPP/EPA's principal concerns were eye and skin irritation. (MONGLY00241308)

512. There are three important attachments included with Kunchick's 6/18/87 review: (1) a report on glyphosate poisoning episodes in California, (2) "Worker Safety Rules for Glyphosate Products Containing the Signal Word 'Warning' for Skin or Eye Irritation"; and, (3) "Worker Safety Rules for All Glyphosate Products Intended for Agricultural Uses and Containing the Signal Word 'Caution'".

1. Registration Standard Worker Safety Provisions

513. The required worker-safety protection statements in Attachment 2 were taken essentially verbatim from the 1986 Registration Standard section setting forth "Required Labelling" (page 28-29).

514. Attachment 1 was the primary basis for OPP concern over eye and skin irritation. It included data submitted to EPA by the California Department of Food and Agriculture in a June 6, 1988 report entitled "Glyphosate Poisoning Statistics Summary." The author was Jerome Blondell.

515. Data were recorded and reported by Blondell for three categories of applicators:

ground application using a tractor or spray rig (42 out of 143 total cases); hand application with a backpack sprayer or hand-pump device (100 out of 142 cases); and, other types of application (1 of 142 cases).

516. Blondell's data covered 64 applicator and 24 mixer/loader cases of eye irritation between 1981 and 1985, and 52 applicator and 7 mixer/loader skin injury cases. In addition, there were a total of 24 "Systemic" illnesses reported, 6 cases among spray rig applicators and 18 among hand applicators. Hand applicators like Dewayne Johnson had suffered the majority of total-applicator injury cases: for the eye, 44 out of 64, and for skin, 35 of 52 irritation cases.

517. A section of Blondell's report addresses the relationship between the number of physician-treated occupational illnesses in California and the total pounds of glyphosate applied. The Blondell report contains the following, surprising finding that almost certainly caught EPA's attention:

> "The number of California physician-treated occupational illnesses (average per year, 1981-1985) per million pounds of glyphosate reported sold in California in 1984 was 17.0. On average, for all pesticides, we find 1.3 poisonings per million pounds sold, per year in California."

518. The scope and specificity of the worker-safety provisions required in the 1986 glyphosate Registration Standard (RS), and referenced in Attachments 2 and 3 of the 6/18/87 Exposure Assessment Branch memo are central to this case.

519. Section D, Part 4 of the glyphosate RS states that "Worker Safety Rules must appear on end-use products containing glyphosate except for those labeled for homeowner use only." (page 28). (Products marketed to homeowners contain 2% or less glyphosate; such dilute products require less stringent safety precautions for those applying the products).

520. EPA required worker-safety provisions on glyphosate products like those applied at work by Dewayne Johnson include:

"HANDLE THE CONCENTRATE ONLY WHEN WEARING THE FOLLOWING PROTECTIVE CLOTHING AND EQUIPMENT."

"Wear goggles or a face shield, chemical resistant gloves, chemical resistant apron, chemical resistant shoes, shoe coverings, or boots."

"WEAR THE FOLLOWING PROTECTIVE CLOTHING DURING APPLICATION EQUIPMENT REPAIR, CLEANING, DISPOSAL OF THE SPRAY SOLUTION, AND DURING REENTRY TO TREATED AREAS BEFORE THE SPRAY HAS DRIED."

"Wear goggles or a face shield, chemical-resistant gloves and chemical-resistant shoes, or boots. A helmet with visor may be worn during open cockpit aerial application."

"IMPORTANT! Before removing gloves, wash them with soap and water. Always wash hands, face and arms with soap and water before smoking, eating, drinking, or toileting."

"AFTER WORK, wash protective clothing and equipment with soap and water after each use. Personal clothing worn during use should be laundered separately from household articles. Clothing or protective equipment heavily contaminated or drenched with glyphosate must be disposed of in accordance with State and local regulations."

"HEAVILY CONTAMINATED OR DRENCHED CLOTHING CANNOT BE ADEQUATELY DECONTAMINATED." (Page 29, glyphosate RS)

521. In late 1986 and 1987, OPP was working on a generic policy document setting forth new worker-safety requirements for product labeling that would apply to all registered pesticides. OPP planned on issuing the new worker-safety labeling requirements via what is called a PR Notice (Pesticide Regulatory).

522. In a 11/2/87 letter to Robert Taylor, OPP's registration manager for glyphosate, Monsanto requested a postponement of certain additional protective clothing requirements on Roundup labels. Such added, worker-safety protections for applicators were called for in the 1986 RS, and were supposed to appear on all Roundup-product labels in commerce as of June 30, 1988.

523. EPA assigned the task of reviewing and responding to this Monsanto request for deferral to Alan Nielsen in OPP's Exposure Assessment Branch. He received the assignment on

11/18/87 and a memo setting forth his recommended action is dated 1/28/88.

524. Nielsen agreed to Monsanto's request to postpone additional requirements for personal protective equipment (PPE) on Roundup labels subject to two conditions. The first was that the new worker-protection PR notice would be issued "…in a reasonable time frame…", and hence lead to changes in Roundup worker safety language

525. His second condition for approval of Monsanto's deferral request stands as one of the first clear statements of OPP/EPA concern over adverse health effects suffered by some Roundup herbicide applicators. Nielsen's second condition was that: "…the submitter [Monsanto] begin investigating the high number of eye and/or skin injuries associated with glyphosate use in California."

526. Reinforcing his concern, Nielsen added in his memo to the Registration Division that: "Myself and other members of the Exposure Assessment Branch would like to meet with appropriate representatives of the Monsanto Company to discuss their response to this concern [the adverse impacts data from California] within six months. Please arrange with the submitter."

2. Impact of Monsanto's Refusal to Accept EPA-Required Worker Safety Rules

527. The August 11, 1986 glyphosate RS set forth the detailed worker-safety label language quoted above. This language had to be included on Roundup product labels in commercial channels of trade as of June 20, 1988.

528. Monsanto repeatedly challenged EPA's requirements for stricter worker-safety provisions through multiple communications over several years. Some arguments were procedural (e.g., defer changes in labeling until the new, generic worker-safety labeling PR notice was issued), while others were based on Monsanto-commissioned exposure studies and risk calculations.

529. The impact of Monsanto efforts to delay or defuse the addition of new worker-safety requirements on Roundup labels can be determined by comparing worker-safety language on Monsanto's glyphosate-based herbicides in 1986, the year the RS was issued, to the worker-safety requirements that appear on labels in subsequent years.

530. The plaintiff in this case, Dewayne Johnson, applied two glyphosate-based herbicides from June 2012 through September 2015: RangerPro and Roundup ProConcentrate. He worked as an integrated pest management specialist for a school district, and applied these glyphosate products 20-40 times per year.

531. The RangerPro label in 2012-2014 carried the signal word "Caution" in the section "3.1 Hazards to Humans and Domestic Animals." This concentrated, formulated herbicide was marketed to professional weed managers for "industrial, turf and ornamental weed control." It contained 41% glyphosate and 59% "OTHER INGREDIENTS (including surfactants)."

532. The Roundup ProConcentrate label and the RangerPro labels are nearly identical. There is a modest difference in the concentration of active ingredient and surfactant. Roundup ProConcentrate contains 50.2% glyphosate and 49.8% "OTHER INGREDIENTS (including 13% surfactant)," while RangerPro contains 41% and 59% glyphosate and "OTHER INGREDIENTS."

533. Both herbicides are applied at essentially the same rate of glyphosate and surfactant per area of land, and would pose comparable risks during the mixing and loading process and application.

534. The RangerPro and Roundup ProConcentrate labels include an identical section on human hazards that sets forth mandatory "Personal Protective Equipment (PPE)" and

recommended safety precautions.

535. Both labels include this language:

> **"Personal Protective Equipment (PPE)**
> **Applicators and other handlers must wear:** long-sleeved shirt and long pants, shoes plus socks…[no other PPE is required]"

536. The phrase "other handlers" encompasses those mixing and loading, shipping, storing, or handling these herbicides.

537. Both labels require that PPE be kept and washed separately from other laundry, and then provide this instruction to applicators and other handlers:

> "Discard clothing and other absorbent materials that have been drenched or heavily contaminated with ***this product's concentrate***. Do not reuse them." (Emphasis added).

538. Under the heading "User Safety Recommendations," both labels state that "Users should:

> "Wash hands before eating, drinking, chewing gum, using tobacco or using the toilet. Remove clothing immediately if pesticide gets inside. Then wash thoroughly and put on clean clothing."

539. There is also a "Non-Agricultural Use Requirement" on each label: "Keep people and pets off treated areas until spray solution has dried."

540. During his many applications of RangerPro and Roundup ProConcentrate between 2012 and 2014, Mr. Johnson went well beyond the PPE required on the product labels. He wore a Tyvek suit, googles, and a face mask, none of which were required on either label.

541. He reported that the Tyvek suit only went up to his throat, leaving most of his neck, and the back of his head exposed.

542. Mr. Johnson also reported that when he was applying Ranger or Roundup herbicide with a backpack sprayer, he was often exposed around the neck and on his head from spray drift, especially when the wind was blowing. In his deposition in a worker's compensation

action against the school district he worked for, Johnson stated" "And the mist [spray drift], you know, it happened a lot, where you just – you can't control it. One minute you're spraying and you get a drift of wind and it's on you, you know." (Dewayne Johnson deposition, Dewayne Johnson vs. Benicia Unified School District, 10/28/2015, page 131).

543. He also experienced two significant exposure events to the mixed glyphosate herbicide-water solution. In one, there was a leak in the hose of his backpack sprayer, resulting in the flow of some of the spray solution down his back; the second occurred when a hose on a sprayer in the back of his truck broke and he had to fix it. As a result of the second episode, he reported being drenched with the spray mixture in the tank, and had glyphosate and surfactant on his body for hours.

544. Because of Monsanto's refusal to add to Roundup product labels the new, worker-safety language set forth in the 1986 RS, substantial differences persisted in the worker-safety provisions on the RangerPro and Roundup ProConcentrate labels in 2012-2014, compared to the PPE and other exposure-reduction provisions called for in the RS.

545. For those mixing and loading either herbicide applied by Johnson, the provisions in the RS would have stated, as quoted above:

> "HANDLE THE CONCENTRATE ONLY WHEN WEARING THE FOLLOWING PROTECTIVE CLOTHING AND EQUIPMENT."
> "Wear goggles or a face shield, chemical resistant gloves, chemical resistant apron, chemical resistant shoes, shoe coverings, or boots."

546. The mixer/loader and applicator worker-safety requirements on both the RangerPro and Roundup ProConcentrate products that Dewayne Johnson applied: (1) did not require any gloves, let alone chemical resistant gloves; (2) did not require a chemical resistant apron; and, (3) did not require chemical resistant shoes.

547. The worker-safety language requirements for glyphosate herbicides set forth in

the 1986 RS include:

> "IMPORTANT! Before removing gloves, wash them with soap and water. Always wash hands, face and arms with soap and water before smoking, eating, drinking, or toileting."

548. In addition to not requiring any gloves, the labels on both of the products that Mr. Johnson applied lacked the above "IMPORTANT" instructions regarding washing hands, face, and arms with soap and water. Instead, the RangerPro and Roundup ProConcentrate labels only offer a recommendation that users should "wash hands before eating, drinking, chewing gum, using tobacco or using the toilet."

549. There is another important difference between the worker-safety language required by the 1986 glyphosate RS and the language on the labels of the glyphosate products Mr. Johnson applied. The RS language states:

> "HEAVILY CONTAMINATED OR DRENCHED CLOTHING CANNOT BE ADEQUATELY DECONTAMINATED" and hence should be discarded.

550. Both RangerPro and Roundup ProConcentrate labels require that the herbicide be mixed with water prior to application. The labels provide detailed instructions regarding how much water an applicator should mix with a given volume of the formulated herbicide.

551. Both labels call for discarding clothing or other absorbent materials that "have been drenched or heavily contaminated with ***this product's concentrate***" (emphasis added).

552. Clothing, or other absorbent material, could become drenched with RangerPro or Roundup ProConcentrate ***only*** during the mixing/loading process, or in the event a container of the concentrate herbicide was ruptured during transport or in storage.

553. Neither label requires discarding of clothing drenched during the ***application*** of the products, after the herbicide is mixed with water and poured into a backpack sprayer or spray tank.

3. Monsanto Recognized that the Drift of Roundup Herbicides onto Applicators Using Backpack Sprayers Could Pose Excessive Risk

554. Throughout the 1990s and 2000s, Monsanto aggressively resisted efforts by U.S. and European regulators to place more restrictive worker-safety requirements on Roundup products labeled for use in non-agricultural settings.

555. Regulators in the EU and U.S. were concerned about growing evidence of worker poisoning episodes, as well as the impact of POEA surfactants on the worker risks posed by formulated Roundup herbicides.

556. Monsanto was well aware of the concerns, because there had been a steady flow of new information from their ongoing research and testing around the world that pointed to the need to address high-exposure scenarios and eliminate high-risk surfactants, at a minimum.

557. Regulators in the UK required Monsanto to add a requirement for respiratory protection on certain Roundup labels, as a result of high-exposures around the face when Roundup is applied to trees via a backpack sprayer. (MONGLY06454420)

558. EU forced Monsanto to phase out POEA surfactants in a wide range of Roundup products, a task completed by or around 2010.

559. But in the U.S., Monsanto blocked or curtailed more restrictive worker-safety language on most formulated product labels in the U.S., and retained POEA surfactants in products from which they had been removed in the E.U.

560. In many internal emails and technical presentations (e.g., Powerpoints for scientific staff), Monsanto acknowledges that:

- POEA surfactants increase the risk of worker-safety problems;
- Safer and equally effective alternative surfactants exist, albeit sometimes at higher cost; and
- Regulators will eventually force elimination of POEA surfactants and the addition of new worker-safety requirements.

561. In several instances during which Monsanto employees debated when and whether to make changes in Roundup product formulations and/or add new requirements to reduce worker risks, one or a group of employees voiced the opinion (paraphrasing) "why not just make the changes now?"

4. Monsanto Efforts to Address Concerns over Worker-Risk Assessments

562. [redacted], a European-based Monsanto scientist, sent a November 10, 2008 email to his Monsanto colleagues Saltmiras, [redacted], Farmer, and Kronenberg. In it, [redacted] shares his strongly held view that Monsanto needed to conduct additional studies to obtain better data to address lingering worker-exposure concerns across Europe.

563. The new data and analyses that [redacted] was advocating would be included in an Annex to the dossier Monsanto was developing for submission to the German regulatory authority, as part of the re-registration of glyphosate in the EU.

564. In his email, [redacted] writes: "Dermal exposure is the greatest risk of exposure to operators. Therefor we need to be secure on the ADME of such exposure." ADME stands for **A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion. (MONGLY02155827)

565. A few days earlier (November 7, 2008), [redacted] had sent an email to Monsanto colleagues, including [redacted], a Monsanto employee based in Germany who was interacting with BfR on glyphosate re-registration issues.

566. [redacted] s 11/7/2008 email outlines the topics of discussion on a call addressing adverse worker-exposure episodes the BfR was aware of. Four areas of "preparation" for future interactions with BfR were outlined, including: "3. Toxicology: counter the allegation on synergistic effects of tallow amine [POEA surfactants] with glyphosate." (MONGLY010122033)

567. Achieving this goal would require a successful effort by Monsanto to downplay

the relevance, or reliability of the many published studies showing that formulated Roundup products containing POEA surfactants were more toxic than 100% pure glyphosate alone.

568. In several instances, new data called for by a specific regulatory agency in Europe, South America, or some other foreign country, led Monsanto to conduct new studies that were submitted to the specific regulator that had asked for new or better data.

569. In many cases, such new studies called into question the accuracy of critical parameters and assumptions embedded not just in Monsanto's worker-safety risk assessments, but also the risk assessments carried out by most regulators worldwide.

570. Regulators in Italy and Germany were, in particular, concerned over data published in several peer-reviewed journals showing that Roundup products formulated with POEA surfactants pose greater risks than glyphosate alone, because POEA is more toxic than glyphosate, and the POEA in Roundup products increases the portion of glyphosate that penetrates the skin and cell walls.

571. Regulators base their glyphosate worker-risk assessments on data provided predominantly by Monsanto. If the data from Monsanto is not current or is inaccurate, regulatory risk assessments will also be inaccurate, and hence may poorly reflect actual risks in the field.

572. The failure of Monsanto to submit to the EPA and other regulators updated, more accurate data, as it becomes available to the company, delays the actions that the EPA and other regulators would need to take to produce more accurate, realistic worker-risk assessments.

573. Keeping regulators in the dark, by failing to share new information it gained from its internal research, was a common tactic Monsanto relied on to delay or block stricter worker-safety label requirements. In the U.S., some such failures likely violate the so-called "adverse effects reporting requirement" set forth in Section 6(a)(2) of FIFRA.

574. In the record of this case, there are many instances where Monsanto became aware from its internal research, or studies required by a given country, that some component or parameter in its worker-risk calculations probably, or surely understated actual worker risks.

575. Consistently in such cases, Monsanto's responded in two ways. First, the company would assess whether there was a way to generate new data that contradicts, obscures, or renders irrelevant the new information that suggested current worker risks were understated.

576. Second, and typically on a parallel track, Monsanto would deploy a variety of strategies to avoid having to share such new information with regulators, even when they were seemingly obligated to do so under law.

577. In the interim, Monsanto would often change formulations, or voluntarily alter label provisions in a way that preempted the need to update risk assessments or label requirements. This tactic has often been successfully deployed by Monsanto to hide past sins of omission (i.e., not informing regulators that the risks associated with a given use of Roundup are likely higher than currently estimated).

5. BiF Pushes Monsanto on Worker Risks

578. There is a particularly germane example of these Monsanto behaviors in the company's internal deliberations on how to deal with growing concerns in Europe over worker-exposures and risk.

579. The German regulatory authority, the BfR, was the rapporteur for the EU re-registration review of glyphosate. They had raised with Monsanto concerns over the heightened risk of formulated Roundup herbicides containing POEA surfactants, compared to risks based on data derived from studies focused on 100% pure glyphosate.

580. A published, peer-reviewed genotoxicity paper came out in 2007 that no doubt

was among the papers triggering new concerns in Europe over formulated Roundup products. It was entitled "Cytotoxicty of the herbicide glyphosate in human peripheral blood mononuclear cells (Martinez A, Reyes I, Reyes N, *Biomedica* 27(4):594-604). The results and conclusions sections from the abstract of the paper follow:

> *RESULTS:*
> Both technical grade glyphosate and Roundup formulation were toxic to human peripheral blood mononuclear cells. Cytotoxicity of Roundup was higher than cytotoxicity of glyphosate, since the LC50 (50% lethal concentration) determined by the trypan blue exclusion method at 24 h was the equivalent of 56.4 microg/ml of glyphosate in the form of Roundup and 1,640 microg/ml (1.64 mg/ml) for technical grade glyphosate.
>
> *CONCLUSIONS:*
> This in vitro study confirmed the toxic effects on human cells by glyphosate and its commercial preparations. Commercial formulations were more cytotoxic than the active component alone, supporting the concept that additives in commercial formulations play a role in the toxicity attributed to glyphosate-based herbicides.

581. It is worth highlighting that under the conditions of the 2007 Reyes et al study, the glyphosate-plus-surfactants in formulated Roundup products were 29-times more cytotoxic than pure glyphosate. A 29-fold increase in any pesticide-related risk is substantial and would typically trigger a re-assessment of current risk estimates, and often as a result, changes in relevant label provisions require by the EPA and other regulatory authorities.

582. Plans and initiatives to deal with such concerns were a primary focus of a "Glyphosate Toxicology Peer Review" meeting held in London on June 22, 2007. Three senior, corporate Monsanto scientists were present (Donna Farmer, [redacted], [redacted]), and a fourth participated via the phone ([redacted]). The experts in attendance were Professor [redacted], Dr. [redacted], and Dr. [redacted]. [redacted] is listed as "Consultant." (MONGLY0118777)

583. One section of the meeting overview document is entitled "NOTES TAKEN

DURING THE PRESENTATIONS." It includes sections addressing the most controversial and consequential issues facing Monsanto in preserving its glyphosate-related FTO (Freedom to Operate) in Europe: carcinogenicity, endocrine disruption, co-formulants, and operator exposure.

584. Under "**4. Operator exposure**," there is a section setting forth "**Proposals for Action**." The first bulleted item reads: "Label recommendations for hand held spraying should include recommendation for using shields and not walking through the spray or sprayed area. **ACTION:** [redacted]" (MONGLY0118777)

585. Recall that the EPA-required worker-safety rules in the 1986 glyphosate Registration Standard document included a requirement for googles or a face shield. This requirement is still not on the RangerPro label in the U.S., the herbicide that accounted for most of the glyphosate-based herbicide that Dewayne Johnson applied.

586. In the phrase "**ACTION:** [redacted]," [redacted] stands for [redacted], who was head of Regulatory Affairs for Monsanto in Europe and would be responsible for submitting new or revised glyphosate-based herbicide label directions, including worker-safety requirements, to regulatory authorities.

587. A few years earlier, Monsanto commissioned new studies on the rate of dermal penetration of Roundup herbicides, in response to questions from EU regulators. Studies responsive to this request were needed to sharpen estimates of worker-exposure risk, especially in the case of formulated Roundup products containing POEA.

588. To address evolving worker-risk concerns among European regulators, Monsanto commissioned a dermal penetration study in rats. It was conducted by a Denmark contract laboratory, TNO. The results of the rat skin penetration study using a Roundup formulation suggested that 5% to 10% of the glyphosate in this Roundup formulation was dermally absorbed,

in contrast to the standard, 3% estimate relied on by EU and U.S. regulators.

589. Monsanto was worried about the potential that the study would "blow Roundup risk evaluations. (getting a much higher dermal penetration than we've ever seen before." (MONGLY03738295) Therefore, they decided to stop any further work with TNO to generate new rat skin dermal penetration data.

590. To my knowledge, the results of the TNO rat skin penetration study showing 5% to 10% dermal penetration were not submitted by Monsanto to the U.S. EPA, as required under the Section 6(a)(2) "adverse effects" reporting requirement in FIFRA.

591. Nor, to my knowledge and based on the records I have reviewed, was the TNO data shared with any other regulatory agency. If the company did transmit a 6(a)(2) submission to EPA with these data, or provide it to other regulators, Monsanto will surely correct the record in deposition and/or at trial.

592. In addition, Monsanto continued for years to argue in all regulatory submissions, peer-reviewed journal publications (some with an accurate listing of authorship, others ghost-written), and in the media that the 3% estimate of glyphosate-dermal penetration in the case of Roundup products formulated with POEA ***overstated*** actual penetration and risks, even after the company knew that the opposite was almost certainly the case.

593. Accordingly, for many years, Monsanto consciously perpetuated possibly unsafe uses of RangerPro, Roundup ProConcentrate, and other Roundup products in three ways.

594. First, the company knowingly mislead regulators, and users of RangerPro and Roundup ProConcentrate, including Dewayne Johnson, by failing to disclose to regulators that an erroneously low dermal absorption estimate was included in worker-safety risk assessments.

595. Second, Monsanto knew that people applying Roundup products with backpack

sprayers were subject to much higher dermal exposure levels when the person applying the herbicide walks roughly in the same direction as the wind, or when the herbicide is applied in an upward direction (e.g., when tall vegetation, like trees).

596. In light of such common knowledge about the risk of applicator exposure to spray drift when various Roundup brands are applied by hand held or backpack sprayers, Monsanto employees in Europe had considered the addition of a new label provision requiring applicators, on windy days, to walk perpendicular to the direction of the wind. To my knowledge, this simple, low-cost, worker-risk-mitigation measure has still not been included on Roundup product labels in Europe or the U.S.

597. Third, Monsanto refused to add to its RangerPro and Roundup ProConcentrate labels the more restrictive and cautious worker-safety provisions that EPA called for in the 1986 glyphosate Registration Standard, nor has the company added similar provisions designed to bring about a comparable degree of risk reduction.

598. The failure of Monsanto to assist regulators in producing progressively more accurate, real world worker-safety risk assessments is a clear and consequential breach of the company's pledge to adhere to the best science available in the manufacture and marketing of its herbicides.

599. In addition, Monsanto's failure to propose, and/or agree to incrementally more restrictive worker-safety provisions, especially in known, high-exposure application scenarios, enabled and perpetuated unsafe Roundup application episodes, including many of the legal applications made by Dewayne Johnson in 2012-2014.

600. For these reasons, I conclude that Monsanto's egregious lack of concern for product stewardship and the safety of certain Roundup users substantially increased Mr.

Johnson's many exposures to the glyphosate and surfactants in the formulated herbicides he applied, and hence Mr. Johnson's risk of contracting NHL.

B. Cultivate Relationships with "Friendly" Scientists and Officials in EPA

601. Monsanto invested considerable effort in establishing open channels of communication with selected scientists and decision makers in EPA. Frequent interactions helped Monsanto understand how receptive a given person in EPA would likely be, if asked to move toward Monsanto's view of a given study or issue, or at least give Monsanto a "head's up" about forthcoming agency decisions or actions.

602. My review of the record convinces me that Monsanto had established unusually close relationships with some key officials and scientists in the EPA's Office of Pesticide Programs (OPP) who were involved in either the science reviews or decisions impacting glyphosate-based herbicides. Two examples are discussed herein.

1. Jess Rowland

603. Jess Rowland was the Deputy Director of the OPP Health Effects Division. He was directly involved in managing the EPA's internal assessment of glyphosate's oncogenicity, as well as the EPA's interactions with and response to the IARC review of glyphosate. He also served as a point of contact between EPA and other federal agencies, and managed CARC (Cancer Assessment Review Committee), a key, internal OPP committee that rendered judgement of whether a given pesticide poses cancer risk.

604. In a 2/20/15 email as Monsanto was preparing for the release of the IARC report on glyphosate, William Heydens writes to Dan Jenkins, his Monsanto colleague that works most closely with EPA on registration issues. The topic is "EPA Folks going to IARC" (i.e., attending

the final IARC Working Group meeting in Lyons, France March 10-14, 2015).

605. Heydens reports on the two EPA scientists that "will actually participate in the meeting," and two other EPA representatives that will be attending as observers. He identifies the two observers as "Catherine [Eiden] is a Special Assistant in the Pesticide Re-evaluation Division, and we all know Jess." (MONGLY00986901)

606. The phrase, "we all know Jess," implies a high degree of familiarity among several Monsanto people.

607. In an April 27, 2015 email exchange between Dan Jenkins (registration, EPA interface) and William Heydens (toxicology, safety), Heydens asks Jenkins about approaching EPA and asking them directly "about what area they see as most problematic [in the IARC monograph] or just ask if there is anything that would help them [EPA] defend the situation?"

608. In effect, Heydens is asking Jenkins if there is anything Monsanto can do to support EPA in sticking by the agency's current position that glyphosate is not oncogenic, despite the IARC determination. Jenkins responds: "I think you and I could get on the phone w Jess Rowland and discuss this openly. He'll give us straight talk." (MONGLY03929023)

609. The next day (April 28th), Jess Rowland called Dan Jenkins "out of the blue" and told Jenkins:

> "We have enough to sustain our conclusions [that glyphosate is not oncogenic]. Don't need gene tox or epi. The only thing is the cheminova [another registrant of glyphosate herbicides] study with the sarcoma in mice – we have that study now and its conclusions are irrelevant…I am chair of the CARC and my folks are running this process for glyphosate in reg review." (MONGLY00987756)

610. But Rowland had another message to pass on to Jenkins that day. The Agency for Toxic Substances and Disease Registry (ATSDR), another U.S. government agency responsible for assessing the toxicity of chemicals, was planning to undertake a review of glyphosate. It was

well known in the toxicology community, and in Monsanto, that ATSDR historically reached conclusions similar to IARC. Monsanto was deeply concerned that an ATSDR determination similar to IARC's would raise serious doubts about the EPA's position that glyphosate does not pose cancer risk.

611. In this email, Rowland then asks Jenkins for a contact name at ATSDR, and reports that there is no coordination underway between EPA and ATSDR in terms of ATSDR's pending assessment of glyphosate. Then, according to Jenkins's email, Rowland said: "If I can kill this [the ATSDR review] I should get a medal."

612. I am not aware of another instance in which a senior scientist in the Office of Pesticide Programs made such a blatantly inappropriate statement to a pesticide registrant. In the government agencies for which I have tracked similar regulator-company interactions over the last few decades, an act so blatantly solicitous and inappropriate would have been grounds for dismissal, or worse.

613. Monsanto recognized Rowland's actions and eagerness to help in the company's efforts to downplay the risk of glyphosate-based herbicides. In a September 3, 2015 email to a large group of colleagues, Dan Jenkins wrote that:

> "No questions but Jess Rowland at EPA is quite proud of their recent endocrine conclusions and is also on point regarding their IARC response. Jess will be retiring from EPA in ~5-6 mos and could be useful as we move forward with ongoing glyphosate defense." (MONGLY03351980)

614. Rowland was responsible for an October 2015 evaluation of glyphosate as head of the Cancer Assessment Review Committee (CARC). In conducting this review Rowland apparently violated EPA's own cancer assessment guidelines in concluding that glyphosate was "Not Likely to be Carcinogenic to Humans." In a May 2, 2016 email, Jim Jones, an Assistant Administrator at the EPA, informed Gina McCarthy, the Administrator of the EPA that the

CARC "assessment was not consistent with Agency's guidelines." (EELI_0000037)

615. This Assessment was "inadvertently" released to the public despite its violation of guidelines and "Monsanto saw it and put out a release saying EPA had confirmed glyphosate is not carcinogenic." (EELI_0000037)

2. Jack Housenger

616. As events unfolded in 2015 after the release of the IARC classification, Monsanto's most commonly mentioned rebuttal was that the EPA's Office of Pesticide Programs still classified glyphosate as not likely to pose a human cancer risk. Moreover, EPA had been working for years on its own re-registration of glyphosate. There was intense interest in whether the IARC classification would alter EPA's judgement regarding glyphosate herbicide cancer risk.

617. If EPA did change its position, that would be an extremely grave development, almost sure to seriously curtail Monsanto's "Freedom to Operate," and it would also, in all likelihood, impact the causality phase of ongoing or future litigation.

618. If EPA stuck by its existing determination, it would be helpful to Monsanto in multiple venues, and likely reduce threats to the company's FTO.

619. At the time, Jack Housenger was the Director of the Office of Pesticide Programs, and had been a senior OPP manager for many years.

620. The record (including some text message exchanges) shows a close, deferential, and supportive relationship in communications flowing from Housenger and Monsanto, as well as from Monsanto and Housenger. In short, the communications give rise to the sense that Housenger and Monsanto are on the same "team," pursuing the same goals.

621. In one important sense, they did share a common goal – defending the EPA's scientific judgement that glyphosate herbicides do not pose a risk of cancer to humans, a

judgement directly challenged by IARC's March 2015 classification of glyphosate as a probable human carcinogen. But this EPA-Monsanto comradery obviously depended on EPA sticking to its current judgement regarding glyphosate cancer risk.

622. So, priority number one in Monsanto's interactions with EPA was to assure they did not change their classification of glyphosate herbicide cancer risk, and priority number two was to encourage, if not compel via political pressure, the EPA to be vocal in defense of its position and criticism of IARC.

623. One example of Housenger taking the initiative to help Monsanto occurred in May, 2015, about two months after the release of the IARC report. Monsanto, Jess Rowland of EPA, and apparently Housenger were concerned that a review of glyphosate toxicity by ATSDR might align with IARC's, and undermine EPA's view of the science.

624. After asking Monsanto for help identifying contacts at ATSDR, and calling the ATSDR staff member assigned to carry out the review, Housenger sent a May 20, 2015 email to Patrick Breysse, head of the ATSDR program. Housenger introduced himself as the Director of the EPA Office of Pesticide Programs (OPP), and updated him on the near-complete, comprehensive OPP review. Then he wrote:

> "However, given that our reviews [OPP's and ATSDR's] would be basically done very close in time to one another, there is a question of whether this is a good use of government resources. I's like to talk to you about this and can be reached at the number below." (Public document).

625. Breysse responds nine minutes later: "Can we discuss today or tomorrow".

626. Housenger's email and call with Breysse, the ATSDR Director, was not the only contact he made. In an email sent June 24, 2015 to Dan Jenkins, Monsanto's top, D.C.-based registration official, Housenger writes:

"Dan, here is everyone I talked to

> Henry [Abadin] was the one who ended up saying that they [ATSDR] would put glyphosate on hold holding the OPP risk assessment release [he actually meant "pending" rather than "holding" the OPP risk assessment release]
>
> Hope this helps
>
> Breysse, Patrick N…he's the Director of HCEH/ATSDR
> Stephan, James W (aka Jimmy) he's the acting director of the Division of Community Health Investigation
> Henry Abadin…..he's the branch chief
> Hannah Pohl…..is the person doing the work on glyphosate" MONGLY04028722)

627. This Housenger email to Jenkins reads like a status report from a junior staff person to his/her manager. It reflects a desire to be helpful to Monsanto that is fundamentally at odds with Housenger's role as the senior manager of the EPA's Office of Pesticide Programs.

628. On October 13, 2016, Jay Vroom of CropLife America (Monsanto's lobbying organization) called and emailed Jack Housenger to discuss removing epidemiologist Peter Infante from the glyphosate SAP panel and to invite him to a retreat with Monsanto and other Industry executives at a West Virginia casino and resort. EPA-HQ-2017-000442-0000205.

629. On October 14, 2016, the OPP announces that it was postponing the SAP hearing on glyphosate scheduled for October 18, 2016. On October 19, 2016, the OPP announced that Peter Infante would no longer be on the SAP panel evaluating glyphosate.

630. Jack Housenger attended a CropLife retreat at a Casino and Resort with executives of Monsanto and other pesticide companies in November of 2016, one month before a key SAP Panel Hearing on glyphosate. These executives noted that, "[w]e had some quality time with EPA OPP Office Director Jack Housenger to dig into key issues and operational matters at that vital department of EPA." MONGLY07063555.

C. Scientific Literature and Third Party Voices

631. The record in this case shows that Monsanto worked diligently, and with great success, in influencing the scientific community. It did so by:

- Shaping the published record of science;
- Controlling, to the full extent possible, the information and scientific data accessible to regulators; and
- Influencing, if not controlling, the conclusions drawn by regulators on questions regarding the safety of glyphosate herbicide.

632. Monsanto uses the term "third party experts" or "third party network" to describe scientists it is working with, or has worked with in the past, on glyphosate-science and communication/outreach issues and challenges.

633. The following paragraph contains a partial list of scientists that were, at least at one point of time, either a member of the company's third party network of experts, or were being vetted in anticipation of Monsanto inviting them to become a member.

634. Members, or individuals under consideration for membership, in Monsanto's third part network of experts include: Dr. Bruce Chassy, formerly University of Illinois, now editor of Academic Reviews (runs industry-sponsored journal that publishes Monsanto-friendly pieces, including several ghost-written ones); Dr. K. Chipman; Dr. John DeSesso; Dr. Stuart Dobson, Institute of Terrestrial Ecology, UK (member "Roundup Scientific Committee"); Sir Richard Doll; Dr. John Entine, Genetics Literacy Project (runs industry-funded organization attacking scientists that raise questions over GE crops, pesticides, and glyphosate); Dr. Kevin Folta, University of Florida (advocate of GE crops, active on social media); Dr. C. Harris; Dr. John Geisy, Michigan State University (member RSC); Dr. Malcolm Harrington; Dr. Jack Mandel; Dr. Nikolas Hodges, University of Birmingham, UK; Dr. Rich Irons; Dr. Larry Kier, consultant and former Monsanto official; Dr. David Kirkland, Vrije Universsiteit Brussel, consultant to

Monsanto and co-author of ghost-written papers; Dr. Ron Kleinman, help with IARC response; Dr. Robert Kroes; Dr. James Lamb, former EPA official; Dr. Henry Miller, Hoover Institute, former FDA official (writes pro-GE and pesticide op-eds for Forbes, the Wall Street Journal and other publications); Dr. Pam Mink, Emory University (one paid review of cancer risk, one paid review other risks); Dr. Richard Peterson, University of Wisconsin (member RSC); Dr. G. Portal; Dr. Jerry Rice, former IARC official; Dr. Keith Solomon, Canadian Network of Toxicology Centers and University of Guelph (member RSC); Dr. Tom Sorahan; Dr. Gary Williams, New York Medical College (member RSC, co-author multiple ghost-written papers, presented before regulatory bodies).

635. [redacted] is a Monsanto employee working on outreach/communications efforts. She was asked by Monsanto management for her views in response to this question: "What additional tools and resources would be helpful to your team in responding to issues and communicating about glyphosate?" (MONGLY03398170)

636. In response to this question from headquarters, [redacted] wrote a clear, cogent summary of the role that third party experts, aka third party voices, play in Monsanto's outreach and communication efforts:

> "Additional support in the area of recruitment of third party voices to ensure that we are not the only supporter of Glyphosate in the debate (ideally we should be a catalyst rather than the focal point for a campaign) – could be new academic resources or in some ways more importantly populist voices that recognize the practical benefits and can make a simple common sense case for the product; ***we need real media traction for positive messages and third parties are key in making this a reality***." (Emphasis added; MONGLY03398170)

1. Response to a Key Epidemiological Study

637. Whenever a scientific paper, report from an organization, a piece in high-impact media, or other widely publicized event occurred or appeared that challenged Monsanto's view

of glyphosate safety, the company called upon its third-party network to challenge the validity of the new information, label it as poor science, biased or driven by activists, or just not relevant, given "glyphosate's 40+ history of safe use."

638. Several examples of how Monsanto used third party voices to promote its PR and science messaging are addressed in this section, and other examples are described elsewhere in this report.

639. In 1999 Hardell and Eriksson published in the journal *Cancer* an epidemiological study done in Sweden focused on the connection between pesticide use and Non-Hodgkin lymphoma (NHL) (Hardell, L., Eriksson, M. (1999). A Case-Control Study of non-Hodgkin Lymphoma and Exposure to Pesticides, *Cancer* 85:1353-1360).

640. These scientists reported statistically significant associations between exposure to all pesticides and NHL (Odds Ratio [OR]=1.6), use of any fungicide (OR=3.7), and 4-chloro-2-methyl phenoxyacetic acid [MCPA] (2.7). (Odds Ratios over 1.0 indicate heightened risk, and any statistically significant value for a chemical over 2.0 typically raises considerable alarm. Following commonly accepted conventions, an OR is regarded as "statistically significant" if the 95% confidence interval does not include a value less than or equal to 1.0).

641. The odds ratio for an association between use of glyphosate and NHL was 2.3, with a 95% confidence interval of 0.4 to 13.0. Hence, this association is not regarded as statistically significant because the lower-bound of the confidence interval is less than 1.0. This wide confidence interval was caused by the low number of people with NHL in the study that reported use of glyphosate (there were only 4 individuals who reported use of glyphosate among the 404 individuals with NHL in the study, and 3 individuals among the 741 controls).

642. In an additional analysis, the authors attempted to correct for confounding

between reported use of glyphosate and MCPA. The resulting OR for glyphosate was 5.8, with a 95% confidence interval of 0.6 to 54.0.

643. While the number of glyphosate-linked cases of NHL was small in this study, leading to the wide confidence intervals noted above, the odds ratios were markedly elevated, pointing to the need for a more powerful study with larger numbers of people exposed vs. unexposed, with and without disease symptoms.

644. Two senior Monsanto scientists – John Acquavella and Donna Farmer – wrote a detailed internal review of the Hardell study, dated April 14, 1999. (MONGLY00555372). It included their estimation of an ~0.30 p-value for the reported association between use of glyphosate and NHL. This means there is about a 30% chance the elevated odds ratio is brought about by chance, and about a 70% probability it is real.

645. Aquavella, his Monsanto colleague Dr. Donna Farmer, and Mark Cullen, a Monsanto consultant, co-authored a letter to the editor of the journal *Cancer* on the Hardell-Eriksson study. The letter, along with a response from Hardell and Eriksson, was published in the August 15, 1999 issue (Vol. 86, No. 4, pages 729-730).

646. The Aquavella-Farmer-Cullen letter made many of the same basic points, often nearly word for word, as in the detailed review of the Hardel-Eriksson study done by Acquavelle in April.

647. The Hardell-Eriksson response dismissed the basis of the letter's major criticisms, and added an important, new quantitative result.

648. Hardel and Eriksson wrote in their response that they had conducted a second case-control study focused on a rare form of NHL called hairy cell leukemia. The results of the hairy cell leukemia study were briefly mentioned in the original Hardell-Eriksson paper, and led

to an odds ratio of 3.1, with a 95% confidence interval of 0.8-12.0. Hence, while suggestive, the association was not statistically significant.

649. But in their *Cancer* response to the Aquavelle-Farmer-Cullen letter, Hardell and Eriksson reported the results of a pooled assessment of the association between use of glyphosate and both NHL and hairy cell leukemia. In this analysis, there were 8 exposed cases of NHL and 8 exposed controls, leading to an odds ratio of 3.04 and a now, statistically significant 95% confidence interval of 1.08-8.52.

650. After the results of the Hardell-Eriksson study were published, Monsanto convened an internal meeting on June 29, 1999 to discuss their scientific outreach goals. In response to the Hardell-Eriksson study showing a link between glyphosate and NHL, the minutes note "Network formation underway in Europe, the will do US. Raising awareness about "H" study (claims about G and cancer, small scale, poor study, poor science.). **Goal, be sure bad Epi conclusions do not spread." (**MONGLY00904905)

651. In September 2003, another study was published showing an association between glyphosate and NHL. In De Roos et al. (2005) the authors reported a statistically significant odds ratio of 2.1 for glyphosate and NHL ("Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study," *Environmental Health Perspectives* Vol 113(1): pages 49-54).

652. In a September 2, 2003 email John Acquavella of Monsanto writes to his colleagues "Strangely, glyphosate looks to be one of the pesticides most associated with NHL in this analysis." MONGLY00896655. He further notes "I'm afraid this could add more fuel to the fire for Hardell et al." and states "[i]t looks like NHL and other lymphopoietic cancers continue to be the main cancer epidemiology issues both for glyphosate and alachlor."

653. In October 2008, another study was published showing an association between glyphosate and NHL. In Eriksson el al. (2008) the authors reported a significant odds ratio of 2.02 for exposure to glyphosate ("Pesticide exposure as a risk factor for non-Hodgkin lymphoma including histopathologcal subgroup analysis," *Int. J. Cancer* Vol 123: pages 1657-1663) (MONGLY01179185. The authors conclude that their new study "considerably strengthened" the association between Roundup and NHL reported in the earlier, Hardell-Eriksson study.

654. Donna Farmer of Monsanto was forwarded an email containing an article reporting the study results and recommending that consumers "Avoid carcinogenic herbicides in foods by supporting organic agriculture, and on lawns by using non-toxic land care strategies that rely on soil health, not toxic herbicides." MONGLY01179185. Farmer responds, by stating "We have been aware of this paper for awhile and knew it would only be a matter of time before the activists pick it up..." and asks "... how do we combat this?" (MONGLY01179185)

655. In all of the extensive back-and-forth among Monsanto scientists and corporate officials over this series of epidemiological studies showing that use of Roundup heightens the risk of NHL, there is not a single mention of steps Monsanto could take to improve product safety (e.g., by phasing out the POEA surfactants) or reduce exposures by adding more complete worker safety requirements on their product labels.

656. It is important to emphasize that it is Monsanto's responsibility to take such steps, and add new language on labels, when it recognizes a need to do so and ways to make their products safer. Across the pesticide industry, the majority of proactive steps taken that increase margins of safety in specific pesticide uses and products are initiated by companies, not the EPA.

2. Monsanto Response to Positive Genotoxicity Studies

657. In the 1990s, it became increasingly clear to Monsanto that the current regulatory

status of glyphosate was in jeopardy, worldwide, because of papers published in the peer-reviewed journals reporting genotoxic impacts. Several such papers also explored or speculated on the possible mechanisms leading to observed, adverse impacts on cell and organism viability.

658. Monsanto was deeply concerned by the growing focus in the scientific community on the genotoxic impacts, and possible mechanisms, following exposures to formulated, glyphosate-based herbicides. The company understood that solid evidence of genotoxicity following exposure to glyphosate-based herbicides would be a "game changer" for the regulatory treatment of glyphosate. (E.g., Heydens previously quoted statement that the genotoxicity of Roundup formulations "are obviously another issue" compared to questions over the genotoxicity of 100% pure glyphosate).

659. Moreover, during this same time period, Monsanto was aggressively pursuing hundreds of new tolerances and labels around the world for use of Roundup as a pre-harvest desiccant to accelerate harvest operations in dozens of crops, as well as post-emergence applications of Roundup on genetically engineered (GE), so-called "Roundup Ready" corn, soybeans, and cotton.

660. Monsanto knew that these newly sought and evolving desiccant and GE crop uses of Roundup would create huge growth potential for Roundup sales in the agricultural sector, but the company was also aware that these particular new uses, by their very nature, would lead to sizable increases in estimates of dietary exposure by regulatory authorities. (In general for most crops, the later a pesticide is applied in the growth cycle of a crop, the higher the residues likely to remain in the crop at harvest. Post-emergent, GE-crop uses of glyphosate could be made within ~two months of harvest, instead of before crop germination, and crop desiccation uses are typically made just a few days to two weeks prior to harvest).

661. Monsanto knew there would be major increases in glyphosate plus AMPA residues in several major food crops, and that these residues would require much higher tolerances, which in turn would force regulators to update dietary exposure and risk assessments, and revisit past judgements that overall exposures to glyphosate and its major metabolite, AMPA, do not pose unacceptable levels of risk to humans.

662. Any new, credible adverse human-health data on glyphosate-based herbicides would have almost certainly made it more difficult, if not impossible, for Monsanto to gain approval of the much-higher tolerances that had to be approved prior to the EPA, and other regulators, granting new registrations for desiccant and GE-crop uses of Roundup.

663. This is why Monsanto worked so hard throughout the 1990s on two critical fronts: (1) resisting any new regulatory requirements for genotoxicity testing of glyphosate-based herbicides, and discounting or burying any published studies reporting genotoxic effects, and (2) reversing EPA's judgement that the 1983 Bio/dynamics mouse oncogenicity study was positive in male mice for renal tubule adenomas.

664. As noted earlier, one of Monsanto's core tactics to discount published evidence of genotoxic impacts following exposure to glyphosate-based herbicides was to commission independent, academic scientists to publish "glyphosate-friendly" reviews of existing genotox literature on glyphosate. A "glyphosate-friendly" genotoxicity review is one that generally strives to dismiss any positive evidence in the literature by focusing on study limitations, while also highlighting the results in negative studies, with little or no attention to their limitations.

665. The two strategies, when deployed together, amount to cherry-picking science, and is a tactic that Monsanto used routinely and with considerable success. Among other things, it helped perpetuate the folklore that people, including Dewayne Johnson, don't have to worry if

they come into contact with it because Roundup is safe enough to drink.

666. Three reviews of genotoxicity studies were commissioned and paid for by Monsanto: Williams et al. (2000); Williams et al. 2012; and, Kier and Kirkland, 2013. Each is discussed in the section on ghost-written studies.

667. A review of Monsanto's role in these company-commissioned reviews of the genotoxicity of glyphosate and/or glyphosate-based herbicides demonstrates the remarkable degree to which Monsanto's strategy of engaging "friendly" scientists was successful.

668. Monsanto's deployment of this strategy was "successful" in two ways vital to the interests of the company.

669. First, the strategy delayed the solidification of consensus in the independent scientific community that exposures to glyphosate-based herbicides was causing, and/or could be causing adverse impacts on a wide variety of organisms, including people, through genotoxic mechanisms.

670. It accomplished this goal, in part, by authoring scathing, negative reviews that delayed or blocked the publication of several studies reporting positive genotoxicity studies that had been submitted to peer reviewed journals.

671. Second, the strategy perpetuated the "glyphosate is not genotoxic" conclusion reached by regulatory agencies worldwide, which in turn facilitated Monsanto efforts to downplay glyphosate's oncogenic potential.

3. Monsanto Asks Dr. Parry to Assess Glyphosate Genotoxicity

672. In the 1990s several positive genotoxicity studies were published including:

- Lioi et al., (1998, Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures in vitro, *Mutation Research* 403: 13-20);
- Lioi et al., (1998, Cytogenic damage and induction of pro-oxidant sate in human lymphocytes exposed in vitro to glyphosate, vinclozolin, atrazine, and DPX-

E9636, *Environ. Mol. Mutagenesis* 32: 39-46);

- Bolognesi et al (1997, Genotoxic activity of glyphosate and its technical formulation Roundup, *J. Agric Food Chem* 45: 1957-1962); and
- Clements et al (1997).

673. These recently published studies conflicted with Monsanto's testing and the long-standing regulatory conclusion that glyphosate, and glyphosate-based herbicides are not genotoxic.

674. In addition to several other efforts, the company decided to reach out to a well-known and respected expert in genotoxicity, Dr. James Parry, a professor in the School of Biological Sciences, University of Wales Swansea, in the UK.

675. To gauge how helpful Dr. Parry might be (i.e. whether he would be reliably "glyphosate-friendly") before committing to a more open-ended consulting agreement, Monsanto decided to give him a short-term assignment that entailed reviewing a set of recently published genotoxicity papers. A series of Monsanto emails were sent on May 16-18, 1999 discussing Parry's role and the hoped for outcome. (MONGLY01825649)

676. The emails discussed Parry's fee (600 pounds a day), and estimated that the requested review would take 10 days (total cost of 6,000 pounds).

677. In a letter dated August 18, 1999, Dr. Parry transmitted his evaluation report to [redacted], a Monsanto toxicologist.

678. After reviewing a set of published, genotoxicity studies, along with the results of several of Monsanto's own studies, he offered 19 conclusions on the genotoxicity of glyphosate and/or formulated glyphosate-based herbicides.

679. Based on Dr. Parry's review of the studies: (1) six of his 19 conclusions were that certain types of studies showed no evidence of genotoxicity; (2) 6.5 studies/types of studies were positive for evidence of genotoxicity; and (3) 6.5 were equivocal and would need to be refined

and/or repeated. (Parry's conclusion number 5 notes one positive study, and three negative or equivocal ones in a category of genotoxicity assays; hence, the split score).

680. Parry then states: "I conclude that glyphosate is a potential clastogenic in vitro." He was unable to draw a conclusion on the clastogenicity of formulated glyphosate-based herbicides because of a lack of studies. And that "glyphosate mixtures may be capable of inducing oxidative damage *in vivo*."

681. It is important to note that Parry's two conclusions, reached in 1999, were basically the same as the primary reasons that the International Agency for Research on Cancer, in its March 2015 monograph on glyphosate, classified the evidence on genotoxicity/Mode of Action as "strong."

682. In addition to his written report, Dr. Parry provided Monsanto with a detailed list of recommended research activities to clear up lingering questions over the genotoxicity of glyphosate herbicides, the mechanisms giving rise to genotoxicity, and relevance of these mechanisms to the evaluation of glyphosate's other health effects, and especially oncogenicity. (MONGLY01314264)

683. In his final, summary statement in the research recommendations document, Parry writes: "My overall view is that if the reported genotoxicity of glyphosate and glyphosate formulations can be shown to be due to the production of oxidative damage then a case could be made that any genetic damage would be thresholded. Such genetic damage would only be biologically relevant under conditions of compromised antioxidant status."

684. Clearly, in this final paragraph, Parry was delivering to Monsanto a "good news-bad news" message. The "bad news" is glyphosate is likely genotoxic via induction of oxidation damage in cells, and likely other modes of action. The "good news" is that Monsanto might be

able to convince regulators that one or more of these mechanisms might be subject to threshold effects, leading to the possibility that Monsanto could show that the effects are not likely under real-world exposure scenarios.

685. But Parry's added assertion that oxidative damage from exposure to glyphosate herbicides would only be a problem for people "of compromised antioxidant status" is significant.

686. Undoubtedly, Monsanto scientists should have known at the time that most people in developed nations consume a diet seriously deficient in total antioxidant activity, and that most countries and international scientific bodies were recommending about a doubling in the daily servings of fresh or lightly cooked fruits and vegetables in order to increase total antioxidant intake via the diet.

687. Two Monsanto scientists shared their reviews of the Parry report with colleagues. Stephen Wratten wrote an email entitled "Comments on Parry write-up" to [redacted] and Donna Farmer. It starts by saying: "I was somewhat disappointed…The style and rather casual lack of completeness and preciseness would make it hard to circulate this around to anyone as supporting information."

688. Wratten acknowledges that Parry's conclusion -- glyphosate and formulated glyphosate herbicides are likely genotoxic via an oxidative stress mechanism -- will be hard to disseminate and characterize as "supporting information" for Monsanto's long-held belief, and contention, that glyphosate is not genotoxic.

689. In the next several days in early July 1999, Monsanto officials discuss internally whether to:

- Commission the new genotoxicity research studies Parry recommended;
- Ask someone else to interface with Parry to rough out the edges of his

conclusions; or

- End the effort to cultivate Parry as a "glyphosate-friendly" expert.

690. The final decision came about two months later. In a September 16, 1999 email from [redacted] (Monsanto person communicating with Parry) to Heydens and Farmer, [redacted] asked for "your opinions and then have a discussion on the action to take?" (MONGLY03734971)

691. Heydens responds to [redacted] and Farmer later the same day, and writes:

> "However, let's step back and look at what we are really trying to achieve here. We want to find/develop someone who is comfortable with the genotox profile of glyphosate/Roundup and who can be influential with regulators and Scientific Outreach operations when gentox issues arise. My read is that Parry is not currently such a person, and it would take quite some time and $$$/studies to get him there. We simply aren't going to do the studies Parry suggests." (MONGLY03734971)

692. Then, in this same email, Heydens states that Monsanto should accelerate the search for other genotoxicity experts who would be more "comfortable" with glyphosate's genotoxicity profile (and hence be glyphosate-friendly). The reason – "We have not made much progress and ***are currently very vulnerable in this area***. We have time to fix that, but only if we make this a big priority now." (Emphasis added)

693. In my judgement, this decision was predicated on three points of general agreement among the Monsanto scientists exchanging emails on the purpose and process of engaging Parry, and discussing among themselves the substance of Parry's report: (1) Parry would not change his mind regarding the genotoxicity of glyphosate herbicides until the studies he recommended were done and assessed; (2) it would be costly to commission and tricky to conduct the studies Parry recommended in a way that would assure all the bioassays were negative for genotoxicity; and (3) if done, the studies would likely contribute further evidence in support of the genotoxicity of at least some glyphosate-based herbicides via an oxidative stress

mechanism, and possibly other mechanisms, and hence would, in the end, not change Parry's mind.

694. For years, Monsanto continued to discuss internally Parry's recommendations for more refined genotoxicity testing. There was a February 15, 2001 phone meeting in which Dr. Parry and two Monsanto scientists participated ([redacted]). Internal reports and emails describe the meeting, which "started off in a tense atmosphere because Parry was irritated by the language used in the mutagenicity section of the Williams et al. paper." (MONGLY02626553)

695. In this and other Monsanto-Parry communications, Parry bristled at over-the-top criticisms of other scientists in papers published by teams convened and paid by Monsanto, like the Williams et al. (2000) paper noted above.

696. In a February 12, 2001 email from [redacted], a Monsanto toxicologist, to his colleagues Larry Kier, Donna Farmer, and William Heydens, [redacted] addresses Parry's recommendation to do additional in vitro micronucleus assays on Roundup surfactants. First, he says "let's include talk about laundry detergents, hand soap, dishwashing detergents…" that contain similar surfactant chemicals, to shift attention away from "AG products."

697. On the prospect of another company asking Monsanto for permission to test the genotoxicity of Roundup formulations, [redacted] says: "I know how I would react – with serious concern."

698. In explaining why he would be concerned, [redacted] lists five reasons or arguments that could be advanced to scientists or regulators. First, the surfactants in home cleaning products pose greater risk that ag products. Second, a positive study on a Roundup formulation might trigger the notion that glyphosate might be, or is also genotoxic. Third, pure glyphosate is not

genotoxic, based on data generated mostly by Monsanto. Fourth, some tests on certain formulations and surfactants have been negative (not, of course, mentioning those that have been positive).

699. His fifth reason is identified as a "fall back position," presumably if the above four arguments fail to satisfy some individuals (e.g. Parry) or regulatory agencies.

> "…we can agree with some testing on either surfactant solutions (would suppliers agree with us?) or with ***glyphosate formulations which don't exist anymore on the market*** (e.g. MON 35050) [Roundup "classic"]." [Emphasis added).

700. Why would [redacted] acquiesce to the testing of a Roundup formulation no longer on the market, if the company's goal was to understand and avoid exposing people now buying and spraying Roundup herbicides from possible risk?

701. This 2/12/2001 email demonstrates that Monsanto was avoiding testing its current Roundup formulations, because if they were adequately tested for genotoxicity, the studies would likely confirm Dr. Parry's core conclusion that at least some formulated Roundup products are indeed genotoxic.

702. This email also shows that when pushed hard to conduct new studies to address some lingering concern, Monsanto's response is to tap into its considerable scientific experience and talent to devise a ***seemingly*** responsive set of actions or studies that might, at worst, raise risk concerns about a product no longer on the market. This strategy would help assure that regulators will have little, or no interest in the findings. Such a "fall back" position will, at the very least, protect the brand and Monsanto's "Freedom to Operate" (FTO).

703. On December 23, 2008, the journal *Chemical Research and Toxicology* published online a study by Benachour-Seralini entitled "Glyphosate Formulations Induce Apoptosis and Necrosis in Human Umbilical, Embryonic, and Placental Cells" (Vol 22(1): 97-105;

http://pubs.acs.org/doi/abs/10.1021/tx800218n).

704. On January 5, 2009, [redacted], a Monsanto information specialist, sent an email to over a dozen senior Monsanto scientists alerting them to the online release of this study. In her email to Monsanto colleagues, she writes: "As you know RU [Roundup] is under pressure in France particularly and the team needs talking points very quickly. We would need an issue alert and response to the paper." (MONGLY00987424)

705. Two days later, one of the recipients of the [redacted] alert, Donna Farmer, replies to several of her colleagues: "As usual, the main objective of Seralini in this type of study is to force us (and the regulators) to set long term studies with formulations and not only the active..."

706. Monsanto failed to provide the Parry Report to the EPA as required under 40 CFR § 159.158. This section of FIFRA spells out the information that must be submitted by registrants:

> (a) General. Information which is reportable under this part must be submitted if the registrant possesses or receives the information, and the information is relevant to the assessment of the risks or benefits of one or more specific pesticide registrations currently or formerly held by the registrant. Information relevant to the assessment of the risks or benefits also includes conclusion(s) or opinion(s) rendered by a person who meets any of the following:
> (1) Who was employed or retained (directly or indirectly) by the registrant, and was likely to receive such information.
> (2) From whom the registrant requested the opinion(s) or conclusion(s) in question.
> (3) Who is a qualified expert as described in § 159.153(b).

D. Monsanto Reliance on Ghost-writing

707. As used in this report, the term "ghost-writing" refers to three types of contributions to a written document by a person not listed as the author, or among the co-authors of a document: (1) producing the first and original draft of a document, or section(s) of a document; (2) revising a document, or its section(s), in a way that adds to or alters the substantive content of the document; and (3) providing information and text, either as original

writing or text derived from an existing document, that is used by a listed author or co-author, or document editor, to alter the content of a document and/or respond to comments made during peer review.

708. Each of the above three types of ghost-writing are unethical and unacceptable in the scientific and regulatory communities.

709. As part of Monsanto's effort to discredit the Seralini paper and force its retraction, Monsanto and its network of third-party experts, including Dr. Bruce Chassy, referenced the Committee on Publication Ethics (COPE) "Ethical Guidelines for Peer Reviewers (Irene Hames on behalf of COPE Council, March 2013, v.1, www.publicationethics.org), and shared it with Wally Hayes, editor of *Food and Chemical Toxicology*, the journal that published the Seralini study.

710. The COPE guidelines include that authors and/or reviewers must "declare all potential conflicts of interest" and "recognize that impersonation of another individual during the review process is considered serious misconduct."

711. In multiple instances, Monsanto authors and reviewers failed to disclose obvious, serious conflicts of interest in their interactions with journal editors. Multiple reviews were submitted by one Monsanto scientist that were ghost-written, in whole or part, by others "impersonating" the reviewer-of-record.

712. A 2005 editorial entitled "Ghost Writing Initiated by Commercial Interests" appeared in the *Journal of General Internal Medicine* (Vol. 20:549). It begins by saying:

> "The integrity of the published record of scientific research depends not only on the validity of the science but also on honesty in authorship…The scientific record is distorted if the primary purpose of an article is to persuade readers in favor a special interest, rather than to inform and educate, and this purpose is concealed."

713. Monsanto routinely and regularly ghost-wrote scientific papers published in peer-

reviewed journals, reports, statements submitted to regulatory bodies, op-eds, letters to the editor, promotional material, testimonials, and many other forms of written communications.

714. Ghost-writing, especially of the sort regularly conducted by Monsanto, is grounds for immediate rejection of a submitted manuscript in accord with the disclosure policies of nearly all reputable, peer reviewed journals.

715. If ghost-writing were discovered and proven after a paper passes peer-review and is published, ***all*** reputable journals will demand a full, published explanation and disclosure of the role of those who provided ghost-written material, and ***most*** reputable journals would retract the paper.

716. The record in this case involves dozens of examples of ghost-writing by Monsanto employees. Only a sampling of significant cases are addressed herein.

1. Acquavella Calls Monsanto Out for Unethical Behavior

717. A clear example arose in the wake of the efforts by Monsanto to produce peer-reviewed papers and make presentations at scientific meetings critical of the IARC Working Group's classification of glyphosate as a Group 2A "probable human carcinogen."

718. William Heydens was organizing a group of Monsanto third-part experts and consultants for the "Expert Panel Review of the Carcinogenic Potential of the Herbicide Glyphosate," to be held at the 2015 SRA Annual Meeting. (MONGLY01030787)

719. Via a November 3, 2015 email, he circulated the panel makeup to John Acquavella and Larry Kier, individuals who had been involved in writing, and/or ghost-writing the papers published in the special glyphosate issue of *Critical Reviews of Toxicology* published in 2016.

720. John Acquavella replied about an hour later that his name should be in the author

list, to which Heydens replies: "I thought we discussed previously that…we would not be able to use you or Larry as Panelists/authors because of your prior employment at Monsanto."

721. Just over an hour later, Acquavella responds to Heydens: "I didn't realize that Bill. Also, I don't think that will be okay with my panelists. We call that ghost writing and it is unethical." (MONGLY01030787)

722. Heydens replied to Acquavella, writing: "We will have to pick this up tomorrow." The next day at 9:25 a.m., Heyden emails Acquavella, copying Donna Farmer, the Monsanto scientist managing Acquavella's consulting work. Heydens proposed a call later in the day. Acquavella responds and sets 11:30 a.m. Arizona time for the call. And then he adds:

> "You guys know me. I can't be a part of deceptive authorship on a presentation or publication. Please note the ICME guidelines below [which he attached to his email] that everyone goes by to determine what is honest/ethical regarding authorship." (MONGLY01030787)

2. Gary Williams et al 2000 Paper

723. In 2000, the peer-reviewed journal *Regulatory Toxicology and Pharmacology* published a paper entitled "Safety Evaluation and Risk Assessment of the Herbicide Roundup and Its Active Ingredient Glyphosate, for Humans" (Williams, GM, Kroes, R, Munroe, AC, Volume 3, pages 117-165).

724. In a Powerpoint presentation done on December 10, 2010 by David Saltmiras, a Monsanto toxicologist, this Williams et al (2000) paper was called "an invaluable asset" for "Monsanto responses to agencies…Scientific affairs rebuttals…Regulatory reviews." Later in the same slide, Saltmiras states that "More current external expert publications are now needed to support our FTO and Registration Reviews," and poses a question that had come up before in Gingerich's speculation about an EPA Scientific Advisory Panel meeting (see paragraphs x-y): "Will <u>weight</u> of evidence be measured by <u>number</u> of publications or quality of the science??"

(emphasis in original, MONGLY02067858)

725. The paper emerged from a Monsanto commissioned and paid for project undertaken by the consulting firm then known as Intertek Cantox (http://www.intertek.com/scientific-regulatory-consultancy/).

726. Cantox commissioned and paid for Dr. Williams and Dr. Kroes to write a review of the human safety of glyphosate and Roundup herbicides, and a Cantox employee Dr. Ian Monroe served as a third, listed co-author.

727. Dr. Gary Williams was a professor in the Department of Pathology, New York medical Center, Valhalla, New York. He had been a consultant to Monsanto in the past and was well-known and trusted within the company.

728. Dr. Robert Kroes worked for ROTOX, University of Utrecht, The Netherlands, and had worked with several Monsanto scientists stationed in Europe.

729. Dr. Ian Munro was an employee of Cantox Health Sciences International, the consulting firm hired by Monsanto to produce several peer-reviewed journal articles on glyphosate-based herbicides, in addition to Williams et al..

730. The Williams et al. (2000) paper is unusual in its breathe and detail. It covers 48 pages in the journal and strives to accomplish two goals.

731. First, it provides a summary of a significant, but strategically selective, portion of the toxicology test results from Monsanto-commissioned studies done to fulfill regulatory data requirements. In short, it restates Monsanto's findings and conclusions, and spin, from company-commissioned studies as submitted to regulatory authorities worldwide.

732. Second, the paper discusses scientific findings relevant to the risk characterization and risk assessment of exposures to glyphosate and glyphosate-based herbicides. It directs

special focus on papers in the peer-reviewed literature that the company regarded as inconsistent with its conclusions with respect to glyphosate oncogenicity and the genotoxicity of formulated glyphosate-based herbicides.

733. The paper's "Purpose and Scope" section states:

> "Certain sectors of the scientific and nonscientific communities have commented on the safety and benefits of pesticide use. With this in mind, parts of this assessment address specific concerns that have been raised by special interest groups. This review will focus on technical glyphosate acid; its major breakdown product aminomethylphisphonic acid (AMPA); its Roundup formulations; and the polyethoxylated tallow amine surfactant (POEA)."

734. There is no financial disclosure statement in the paper.

735. To determine if a financial disclosure statement had been added, the journal's website was visited November 25, 2017, and a search was conducted for the Williams et al paper. The search results were to this link:

http://www.sciencedirect.com/science/article/pii/S0273230099913715

736. The paper is now available for online purchase via the url in paragraph 361. The abstract is available for no charge, and lists the three authors and their affiliations, but no information is offered on who paid for the study, or the substantial role of Monsanto in writing the paper.

737. The paper's Acknowledgement statement reads in full:

> "The authors acknowledge the assistance of individuals who participated in the preparation of this document. First, we are grateful to those who gathered and made available the large amount of information used to write the manuscript for this document. Second, we thank the toxicologists and other scientists at Monsanto who made significant contributions to the development of exposure assessments and through many other discussions. The authors were given complete access to toxicological information contained in the great number of laboratory studies and archival material at Monsanto in St. Louis, Missouri, and elsewhere. Key personnel at Monsanto who provided scientific support were William F. Heydens, Donna R. Farmer, Marian S. Bleeke, Stephen J. Wratten, and Katherine H. Carr. We also acknowledge the participation and assistance of Douglass W. Bryant and Cantox Health Sciences International for scientific and logistical

support in the preparation of the final manuscript."

738. The second point in the Acknowledgment statement credits "toxicologists and other scientists at Monsanto who made significant contributions to the development of exposure assessments and through many other discussions."

739. "Significant contributions to the development of exposure assessments" refers to methodological and/or data and statistical work done by Monsanto on exposure assessment, but clearly does not encompass ghost-writing of the sections of the paper on exposure assessment.

740. The acknowledgement that Monsanto toxicologists and other scientists "made significant contributions through…many other discussions" does not disclose, or even hint at ghost-writing.

741. On the role of five "key personnel" at Monsanto, the authors state that their participation and assistance entailed "scientific support," a phrase that most scientists would interpret to mean Monsanto provided access to data and other scientific information generated by Monsanto.

742. Accordingly, this Acknowledgement statement is false, incomplete, and misleading, because it fails to disclose the multiple, substantial instances of ghost-writing in the paper as published.

743. William Heydens admitted in a 2015 email that Monsanto ghostwrote Williams (2000) when discussing plans to ghostwrite an updated publication stating "...we ghost-write the Exposure Tox & Genetox sections...we would be keeping the cost down by us doing the writing and they would just edit & sign their names so to speak. Recall that is how we handled Williams Kroes & Munro, 2000." (MONGLY00977264)

744. In addition to Dr. Heydens admitting that he ghostwrote the article, Monsanto also

documented the writing process for the Williams article showing that Heydens was responsible for drafting the manuscript. (MONGLY02598454)

Steps:

1. **Prepare Rough Outline of Manuscripts**

- WHO: Monsanto Scientists (leads - Heydens, McKee, Wratten)

3. **Write Draft Manuscripts**

- WHO:
  - Mammalian Tox: lead - Heydens

745. Heydens efforts were extensive, as he noted "I have sprouted several new gray hairs during the writing of this thing..." (MONGLY0186926)

746. On June 18, 1999 at 3:18 pm, Douglas Bryant, a Cantox employee, sent a "progress report" on "Roundup documents [papers in preparation by Cantox]" in an email to his client and principle Monsanto contact, Lisa Drake. He copied two people: (1) William Heydens, the senior Monsanto corporate official overseeing the Cantox project and similar "science outreach" efforts, and (2) Cantox colleague and paper co-author Ian Munro.

747. On the subject of the Williams et al. paper on glyphosate health effects, Bryant reports on the status of various reviews, including by co-author Kroes and Dick Peterson. He writes: "Bill Heydens, Donna Farmer, Kathy Carr and all those at Monsanto have been helping get the document through QA."

748. If doing so simply entailed catching and fixing errors, such input would be consistent with the acknowledged role in the paper played by Monsanto scientists and toxicologists.

749. Bryant then outlines the final steps in the process prior to submission of the paper to the journal: Bill Heydens completes the QA changes; sends edited and corrected version back to Cantox to incorporate final comments by the internal-to-Monsanto and Cantox reviewers (e.g. Peterson), and then the paper will be sent to the journal.

750. Twenty-seven minutes after the Bryant email was sent, Heydens sent this reply to

Bryant and the other recipients of the original email. It was addressed to "All," and states:

> "A clarification – there is one step missing – I will review the final manuscript with the reviewers comments incorporated (in revision mode so I can find them easily) before it is sent to the publisher. I will commit to conducting this review very quickly. Assuming the reviewers don't throw any surprises (I'm especially thinking of Peterson), I can turn this back around with a very minimal investment of time."

751. Three days later, on June 21, 1999, Heydens sends a two-line email to his colleague Donna Farmer. The first line simply says "FYI," and is obviously referring to his forward of the Bryant email exchange of June 18th discussed above. The second line of his short email to Donna Farmer states: "And Dougie [referring clearly to Bryant] thinks I would actually leave the final editing to him unsupervised…"

752. This short quip to Farmer speaks volumes about the degree to which Monsanto controlled the content of the Williams et al (2000) paper, and no doubt many other glyphosate-related papers and communications that Monsanto has ghost-written to one degree or another over the past 40 years.

753. The degree of Monsanto control over the content of the Williams et al. paper is clear in a September 15, 1999 email from Heydens to his Monsanto colleagues Donna Farmer and Stephen Wratten.

754. By September 15th, nearly-three months after the June 18, 1999 Bryant email exchange, there had been multiple calls, exchanges of written material, and meetings between Bryant and Cantox, and Monsanto regarding the content and finalization of the Williams et al paper. (MONGLY00905085)

755. The September 15th email from Bryant to Heydens copies Lisa Drake and Katherine Carr of Monsanto, but not any of the co-authors. It states that: (1) Bryant is sending a revised draft of the paper to the three co-authors Williams, Kroes, and Munro today; (2) the draft

manuscript includes "all the changes that were discussed today and during calls last week. Please check it over to be sure that I have been thorough"; each co-author is asked "to complete his review and respond so journal submission (Food and Chemical Toxicology) can be finalized for September 30, 1999"; and, thanks everyone "for all your effort (undoubtedly there will be more)…"

756. Later that same day, September 15, 1999, Heydens sends another short, cryptic email to Donna Farmer and Stephen Wratten. This time he writes (exactly as in email): "FYI – in case you want to see how it ended up (hopefully, that is! – I'll strangle Kroes or Williams if they ask for any re-writes!!) Bill"

757. By "it," Heydens is referring to the pre-submission, near-final draft of the Williams et al paper.

758. An honest submission of this paper to a peer-reviewed journal would have listed several senior Monsanto scientists as the co-authors.

759. It is not clear in the record whether Munro made any substantive contributions to the paper. In a July 30, 1999 email from Heydens to Munro, Heydens writes: "Everyone at Monsanto has agreed with adding you as an author – please do so." (MONGLY01869261)

3. Williams et al 2012

760. In 2012, Monsanto commissioned another team to produce an updated review of recent studies assessing the differential cellular toxicity of glyphosate and formulated Roundup herbicides. This paper appeared in the *Journal of Toxicology and Environmental Health, Part B Critical Reviews* (15(1): pages 39-96). The lead author was AL Williams (not Gary Williams), and RE Watson and JM DeSesso were listed as co-authors.

761. Monsanto employee Donna Farmer made significant contributions to the

manuscript, but was not listed as an author. In an email sending her workup of the manuscript to DeSesso, Farmer states, "[a]ttached is the first 46 pages. I added a section in genotox from the Gasnier study ...see a attached a critique we did that I took that from. Am working on a section for Gasiner in the mechanistic section. Also we cut and pasted in summaries of the POEA surfactant studies. Attached are more detailed summaries - see Knapp." MONGLY00919381

762. In the draft manuscript attached to the email Donna Farmer's name is edited out as an author. (MONGLY00919400)

Developmental and Reproductive Outcomes in Humans and Animals after Glyphosate Exposure:
A Critical Analysis of the Available Literature

Amy Lavin Williams[1, 2]
Rebecca E. Watson[1, 3]
Donna R. Farmer[4]
John M. DeSesso[1, 2, 5*]

763. The co-authors conducted a detailed review of dozens of studies, and concluded:

> "An evaluation of this database found no consistent effects of glyphosate exposure on reproductive health or the developing offspring. Furthermore, no plausible mechanisms of action for such effects were elucidated. Although toxicity was observed in studies that used glyphosate-based formulations, the data strongly suggest that such effects were due to surfactants present in the formulations and not the direct result of glyphosate exposure."

764. The 2012 review was critical of a set of five genotoxicity studies carried out by a team of French scientist led by Dr. R. Belle.

765. In an effort to explain the substantial difference in the conclusions expressed by Williams et al. (2012), in contrast to several published studies, a Letter to the Editor by Belle et al. (2012, Toxicity of Roundup and Glyphosate, Vol 15: pages 233-237) states:

> "The authors [of Williams et al (2012] do not take into account in their interpretation of our results the very poor cell membrane permeability of pure glyphosate."

766. In concluding their hard-hitting letter, Belle et al. write:

> "Although we notice that Monsanto, the manufacturer of Roundup, financed their work, we would have expected strong scientific arguments against our results or alternative findings that would evidence the contrary. This is not the case, and, to our knowledge, our experiments, first published in 2002 and brought to Monsanto's knowledge as early as 1999, have not been demonstrated to be incorrect or biased."

4. Kier and Kirkland 2013 Paper

767. In 2013, the journal *Critical Reviews in Toxicology* published a peer-reviewed paper entitled "Review of genotoxicity studies of glyphosate and glyphosate-based formulations" (Vol 43(4)). Two authors were listed -- Monsanto consultant and former employee, Larry Kier, and Dr. David Kirkland, a professor and Monsanto consultant.

768. The abstract of the 2013 paper reports that it updates an earlier review of studies on the genotoxicity of glyphosate and formulated glyphosate-based herbicides. This earlier review was the Monsanto commissioned and ghost-written paper Williams et al. (2000) discussed earlier.

769. The "Monsanto Manuscript Clearance Form" for the 2013 Kier-Kirkland publication is dated 2/29/2012, and lists two authors: "David Saltmiras, Larry Kier (consultant)." Under "Lead Author's Comments," Saltmiras (presumably) writes: "This work falls under the scope of the EU Glyphosate Task Force and will be a valuable resource in future product defense against claims that glyphosate is mutagenic or genotoxic." (MONGLY02117600)

770. When published, the authors are listed as Kier and Kirkland. Saltmiras's name is deleted. Accordingly, the 2013 genotoxicity review paper is a partially ghost-written update of a partially ghost-written 2000 review.

771. In the published version of the Lier-Kirkland 2013 paper, the "Declaration of Interest" states:

> "Larry Kier and David Kirkland were paid consultants of the Glyphosate Task Force for the preparation of this review. The

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

772. Clearly, this "Declaration of Interest" is only partially truthful. Kier and Kirkland did not write the paper; a third author, David Saltmiras, had contributed substantially to the paper, but is not listed as a co-author (but his help is noted in the Acknowledgements).

773. The authors did not have sole responsibility for the content, and Monsanto, through its consultants Kier and Kirkland, and employee Saltmiras, was largely responsible for the content, not the Glyphosate Task Force. (MONGLY02145924-30)

5. *Critical Reviews of Toxicology* Special Issue on Glyphosate Risks

774. One of the most egregious examples of ghost-writing in the record of this case is the special issue put out by *Critical Reviews of Toxicology* (*CRT*). This special issue was conceived and commissioned by Monsanto when the company learned that the International Agency for Research on Cancer (IARC) would soon issue a monograph discussing the potential of glyphosate-based herbicides to cause cancer.

775. In short, the contents of this entire special issue of *CRT* was a Monsanto-controlled, and largely Monsanto-written rebuttal of the evidence cited by IARC in support of its "probable human carcinogen" classification.

776. There are dozens of emails and other documents in the case record memorializing the role Monsanto played in the conceptualization, writing, and publication of the papers in the special issue of *CRT*.

777. Many of the communications are between Monsanto scientists and individuals working for the Canadian consulting firm Intertek. This firm was hired by Monsanto to put together the papers that would appear in the special issue of *CRT*.

778. It is important to note that the consulting firm Intertek is basically the same company that Monsanto hired in 1998 to manage the process of putting together the also-ghost-written Williams et al (2000) review of glyphosate toxicity. Back then, the consulting firm's name was CanTox Intertek.

779. Intertek served as the primary mechanism through which ghost-written material from Monsanto was incorporated in the drafts of the papers that were subsequently reviewed, edited, augmented, and approved by the listed, non-Monsanto co-authors.

780. In addition, Intertek also served as the primary point of contact with the editor of the journal *CRT*. This arrangement shielded the journal from evidence of Monsanto's direct role, not just an occasional ghost-writer of parts of some of the papers, but as the primary author of several of them, and an important contributor to all of them.

781. MONGLY00998684 and other documents record how Monsanto drove the selection of the papers to be included in the special issue.

782. MONGLY00998682 transmits William Heydens edits on the "Summary Report" paper for the *CRT* special issue back to Ashley Roberts, Senior VP of the Food and Nutrition Group at Intertek. Roberts served as the principle point of contact between Monsanto and Intertek, and between Intertek and paper co-authors.

783. Throughout the review process, Roberts also was the primary point of contact between the paper co-authors and the journal *CRT*.

6. The Many Forms of Ghost-Writing – Monsanto Style

784. The above cited examples of ghost-writing involve unattributed contributions to papers in peer-reviewed scientific journals with explicit, usually clear conflict of interest and disclosure rules that clearly prohibit ghost-writing.

785. But Monsanto deployed the same basic ghost-writing tactics in several other types of written communication. A few of many examples in the record are briefly described below.

786. On August 19, 2008, Dr. Charles Healy, a senior Monsanto scientist, received an email request from the Editor of the journal *Cell Biology and Toxicology* to review a glyphosate genotoxicity paper entitled "Cytotoxicity of herbicide Roundup and its active ingredient, glyphosate in rats." (MONGLY02286842)

787. He accepted the assignment, and contacted his Monsanto colleagues David Saltmiras and Donna Farmer later in the same day. He asked them to conduct the review, explaining:

> "You two would be the reviewers in fact and I would then collate your comments and be the reviewer of record."

788. In such a circumstance, it would have been entirely routine for Healy to write back to the Editor and ask for permission to conduct the review with assistance from two Monsanto colleagues who have deep expertise on the subject matter of the paper.

789. The Editor would have almost certainly approved Healy's request, and thanked him in advance for taking on the assignment.

790. But Healy's decision to rely on ghost-writing in the case of this review is evidence of a deep-set cultural inclination within the company to rely on ghost-written material, even when there was no real reason to do so, nor anything to gain as a result.

791. The ghost-written Healy et al. review of the paper is nearly five pages, single-spaced, and is about the same length of the paper when it was published about a year later. The

Healy et al. review is brutal, rating the paper a 5 on a scale of 1 to 100 (100 top rating) and unacceptable for publication.

792. On September 9, 2008, an email from the journal is sent to Healy stating: "I have had completely opposite reviews on this paper. I would be very grateful for your comments before giving the authors a decision." Later the same day, Healy forwarded this message to Saltmiras and Farmer, and adds: "Looks like ours will be the deciding vote as to whether the glyphosate paper is published."

793. A little over a year later, a revised version of the paper reviewed by Healy et al. appeared in the journal *Environmental Toxicology and Pharmacology* (Vol 28:379-385). The author is Nahla S. El-Shenawy.

794. Rising concerns over Roundup herbicide human health effects in Latin America led to a Toxicology Expert Panel meeting in October 2012. David Saltmiras was charged with putting together an invited, expert panel for the meeting. A seminar on the history and activities of the EU Glyphosate Expert Advisory Panel was among the presentations Saltmiras was organizing.

795. In an August 13, 2012 email, Saltmiras shares with colleagues that he will invite Sir Colin Berry or Jack Mandel to do the seminar, and adds that "I will likely prepare the presentation and send to him to change/adapt as he sees fit."

796. David Saltmiras engaged in an email discussion on January 26, 2013 with Monsanto-consultant and former employee Larry Kier over whether Saltmiras should be added as a co-author of Kier and Kirkland (2013), since he wrote a significant portion of the paper. Saltmiras tells Kier that he had been strongly encouraged by "Senior Monsanto management" to author some peer reviewed publications, and that this Kier and Kirkland paper "is the fifth such

Glyphosate related manuscript I have been involved with over the past few years without co-authorship."

797. [redacted]

798. As part of his 2015 performance evaluation, Saltmiras summarized his glyphosate-related activities, which included "ghost wrote cancer review paper Greim et al. (2015), coord Kier (2015) update to K&K, pushed for Sorahan (2015)." (MONGLY017223742)

D. Attacks on Scientists or Organizations Producing Adverse Data on Glyphosate

1. Intimidation of IARC Working Group Members

799. Dr. Consolato Maria Segi, a professor at the University of Alberta, Canada, was a member of the IARC Working Group that carried out the assessment of the oncogenicity of glyphosate.

800. After the release of IARC Monograph 112 and announcement of the 2A classification, Dr. Sergi received a letter dated October 31, 2016 from a U.S. based law firm, Hollingsworth LLP. This firm had been hired by Monsanto to carry out various activities in response to the IARC decision. Apparently, several other, if not all of the other IARC Working Group members received a similar letter.

801. According to Dr. Sergi's response dated November 4, 2016, the law firm's letter

requested "disclosure of files used in connection with the preparation of the IARC Monograph Volume 112." Prior to responding, she consulted with colleagues on the Working Group and IRAC.

802. She replied that the files belonged to IARC, and the result of their deliberations were explained in detail in the monograph. She then wrote:

> "I found your letter ***intimidating*** and ***noxious*** even though transparency is important…It is impolitic to mention possible consequences without identifying the correct background. I find your approach reprehensive and lacking of common courtesy even by today's standards. As a graduate of a British educational system, I consider your letter ***pernicious***, because it maliciously seeks to instill some anxiety and apprehension in an independent group of experts…Please avoid contacting me or any of my colleagues in the future regarding this issue." (Emphasis in original; Heydens Exhibit 3-54)

2. Seralini Team

803. On September 19, 2012, a team of French scientists led by Gilles-Eric Seralini published a paper entitled "Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize" in the journal *Food and Chemical Toxicology* (Vol 50: 4221-4231).

804. The paper reported the results of a two-year rat study. Both formulated Roundup herbicide and GE-corn, fed separately and together, were found to trigger a variety of pathologies including cancer, damage to the pituitary gland, liver, and kidneys, and premature death.

805. The kidney emerged as a particularly vulnerable organ, given that 76% of the impacted parameters were associated with kidney deficiencies.

806. The abstract ends with this statement:

> "These results can be explained by the non-linear endocrine-disrupting effects of Roundup, but also by the overexpression of the transgene in the GMO and its metabolic consequences."

807. The Seralini study was the first, independent two-year rat feeding study designed

to sort out the individual and combined impacts of long-term exposure to a GE corn (NK603) and formulated Roundup herbicide. Previously, Seralini and colleagues had conducted several genotoxicity experiments comparing the toxicity of glyphosate and formulated Roundup in cell assay systems.

808. The paper's findings received extensive media coverage in the U.S. and Europe, and posed a significant threat to Monsanto's commercial interests, as well as a major challenge for regulators who had approved both Roundup and GE corn.

809. The next day, September 20th, David Saltmiras sent an email to Sir Colin Barry and Andrew Cockburn, a consultant working for Monsanto. It marks the beginning of a campaign that would last years, with the goal of discrediting the Seralini paper and team.

810. In the email, Saltmiras calls the paper "junk science," questions what happened with the journal's peer review process, and states: "I also suspect this paper may be in our own best interests – the last rites for Seralini's few remaining shreds of scientific credibility." (MONGLY01096620)

811. Regardless of the merits and faults of the paper, the rapidity and scope of negative commentary, beginning on the day the paper was released, was virtually unprecedented.

812. A week after the paper's release, a Monsanto-funded, retired academic in the U.S., Dr. Bruce Chassy, emailed the journal editor Wallace Hayes calling for the paper to be retracted, in order to save the reputation of the journal. (MONGLY00900629)

813. After Hayes responds and says he will process Chassy's email as a letter to the editor, and give the Seralini team an opportunity to reply in accord with standard journal policy, Chassy quickly replies and writes that his initial email "was a heartfelt expression by a caring colleague who is deeply concerned…My intent was to urge you to roll back the clock, retract the

paper, and restart the review process." Then, Chassy alleges that "The paper in question has not been peer reviewed," a claim which he no doubt knew was false.

814. In the coming weeks and months, Monsanto encourages and helps orchestrate a series of progressively more critical commentaries, that soon include allegations of scientific fraud by the Seralini team.

815. A remarkable exchange of emails between senior Monsanto officials and scientists occurs on September 26, 2012. Saltmiras starts the email chain at 11:50 a.m., which is sent to seven colleagues, including Eric Sachs, Bill Heydens, Bruce Hammond, and Daniel Goldstein.

816. In the email, he reports on a call he had earlier that morning with the journal editor, Wallace (Wally) Hayes. Saltmiras writes:

> "He [Hayes] expressed concern that to date he has only received links to blogs, web postings, media releases, etc. and no formal letters to the Editor…Therefore, he urgently needs rational, objective and authoritative formal letters to the Editor….I believe he would like such letters TODAY!" (Emphasis in original, MONGLY02063095-96)

817. Among "Actions" Saltmiras lists in his email, he reports that he has emailed the EU Glyphosate Task Force (GTF) Toxicology Working Group about the GTF submitting a letter; that Eric Sachs (Monsanto's head of Regulatory Policy & Scientific Affairs) will follow-up with "his third party scientific experts…and request they consider formal letters to the Editor." Last, Saltmiras asks for his colleague's "thoughts on promptly moving forward."

818. Eric Sachs responds 13 minutes later, reporting that Bruce Chassy will soon submit his letter to the journal, and "notify other scientists that have sent letters [to media outlets or Monsanto] to do the same. He understands the urgency."

819. Fifteen minutes later, Heydens replies to the group: "And I very strongly believe we must go ahead and put together a Monsanto letter to the editor…"

820. At 12:22 p.m., four minutes after Heydens email, Eric Sachs writes to the group: "I remain adamant that Monsanto must not be put in the position of providing the critical analysis that leads the editors to retract the paper." (MONGLY02063096)

821. Heydens replies privately to just Sachs 10 minutes later:

> "This [Sachs' recommended role for Monsanto] makes no sense to me at all. We have defended our science every step of the way since our 1st encounter with him [Seralini]. That fact remains that the external sector has not given us what we need, and the editor is telling us it is the 11th hour…"

822. Then Sachs replies just to Heydens 16 minutes later:

> "I am not challenging that Monsanto should defend our science – we absolutely should and have. There is a difference between defending science and participating in a formal process to retract a publication that challenges the safety of our products. We should not provide ammunition for Seralini, GM critics and the media to charge that Monsanto used its might to get this paper retracted. The information we provided clearly establishes the deficiencies in the study as reported and makes a strong case that the paper should not have passed peer review. We have done our part. It is time now for the public sector and especially our network of experts to do theirs." (MONGLY02063095-96)

823. In this exchange, Sachs argues that Monsanto must not be perceived as orchestrating and supporting a campaign that is designed to force the journal to retract the Seralini paper, but that is essentially what they did, beginning with the sharing of Monsanto-written criticisms of the Seralini study, before its public release, to a number of its third-party experts who were quoted in various media stories, and/or wrote blogs, commentaries, and letters to the editor.

824. Two days later, in an email from Daniel Goldstein to Sachs on the effort to encourage letters to the editor, Goldstein writes to Sachs: "We are being asked to keep internal correspondence down on this subject." (MONGLY00936725)

825. In early October, Goldstein shared notes from conference calls with Monsanto scientists and registration specialists in Asia/Pacific the Americas/Europe/Africa with dozens of

colleagues regarding the fallout from the Seralini study. It includes "A list of pending actions in St. Louis is provided below." (MOMGLY00978885-90)

826. These actions and "Key Points" cover Monsanto efforts to support the retraction campaign; studies that Monsanto should consider undertaking to have a basis to challenge the findings in the Seralini paper; and, rebuttal arguments and related talking points to share with regulators trying to determine whether and/or how to react to the Seralini paper's explosive findings.

827. Then Goldstein writes: "c. And finally – the one [new study that Monsanto should consider doing] you have all been waiting for: 2 year rat/chronic studies of pesticide formulations on crop."

828. The Monsanto letter to the Editor of *Food and Chemical Toxicology* appeared ***[date].*** It spanned six pages of text in the journal; the original Seralini paper was 11 pages, of which about 4.5 pages were tables, figures, and photos. The Monsanto letter was signed by three Monsanto scientists: Bruce Hammond, Daniel Goldstein, and David Saltmiras.

829. Remarkably, the authors of the letter write "The authors declare that there are no conflicts of interest" in the section of the letter labeled "Conflict of Interest," when in fact it is hard to imagine how three authors could be more directly conflicted.

830. On November 19, 2013, *Food and Chemical Toxicology Editor* Wallace Hayes wrote Seralini a letter informing him his paper would be retracted. The letter included the retraction statement that Hayes was going to publish. It recounts the controversy, the letters to the editor, "and even allegations of fraud."

831. Then, Hayes writes:

> "Unequivocally, the Editor-in-Chief found no evidence of fraud or intentional misrepresentation of the data…Ultimately, the results presented (while not incorrect) are

inconclusive, and therefore do not reach the threshold of publication in *Food and Chemical Toxicology*."

832. The retraction of a scientific paper for reporting inconclusive results is extremely rare, and if such a test for conclusiveness of results were adhered to consistently, the number of published papers would be dramatically reduced.

833. The real reasons for the retraction of the Seralini paper, in my opinion, were the economic threat the paper's findings posed to two of Monsanto's most profitable products (GE corn, Roundup), and the orchestrated retraction campaign carried out by Monsanto's network of third party experts. "Inconclusive results" was, in short, a lame excuse, but apparently the best that Wally Hayes could come up with.

E. The IARC Bombshell

834. The International Agency for Research on Cancer (IARC) released a summary of its Working Group report on glyphosate and glyphosate-based herbicides via a short report published in the May 2015 issue of *The Lancet Oncology*, a highly regarded medical journal. The full Working Group monograph was published on January 26, 2917 (http://monographs.iarc.fr/ENG/Monographs/vol112/mono112.pdf).

835. The key, concluding section of the full monograph discussing the basis for the Working Group's classification decision states:

"6.3 Overall evaluation

Glyphosate is *probably carcinogenic to humans (Group 2A).*

6.4 Rationale

In making this overall evaluation, the Working Group noted that the mechanistic and other relevant data support the classification of glyphosate in Group 2A.

In addition to limited evidence for the carcinogenicity of glyphosate in humans and sufficient evidence for the carcinogenicity of glyphosate in experimental animals, there is strong evidence that glyphosate can operate through two key characteristics of known human carcinogens, and that these can be operative in humans. Specifically:

• There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals.

One study in several communities in individuals exposed to glyphosate-based formulations also found chromosomal damage in blood cells; in this study, markers of chromosomal damage (micronucleus formation) were significantly greater after exposure than before exposure in the same individuals.

• There is strong evidence that glyphosate, glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals, and in studies in humans in vitro. This mechanism has been challenged experimentally by administering antioxidants, which abrogated the effects of glyphosate on oxidative stress. Studies in aquatic species provide additional evidence for glyphosate-induced oxidative stress."

1. Placing the IARC Classification in Perspective

836. Monsanto had hoped that the IARC Working Group would classify glyphosate and glyphosate-based herbicides in Group 4 ("The agent is probably not carcinogenic to humans"), or at least in Group 3 ("The agent is not classifiable as to its carcinogenicity to humans").

837. But since Monsanto scientist Tom Sorahan had been among the invited, industry observers at the public meetings of the Working Group, the company was aware of the Working Group's likely judgements in the key areas that drive IARC determinations – animal testing, human epidemiology, and genotoxicity/possible mechanism(s) of action.

838. Given that the IARC classification system is clearly explained and is driven by the strength of evidence these three areas, Monsanto had a reasonably firm basis for projecting

that the ultimate Working Group classification decision, would be either a 2B classification ("possible human carcinogen") or a 2A classification ("probable human carcinogen") was possible, if not the most likely outcome. A memo prepared in advance of the meeting stated "We should assume and prepare for the outcome of a 2B rating (possible human carcinogen); a 2A rating (probable human carcinogen) is possible but less likely." MONGLY02913526

839. In the spring of 2015, I was among many scientists awaiting the IARC decision on glyphosate and the Working Group's report. When I learned of the Group 2A, "probable human carcinogen" classification, I was very surprised, since I had expected a Group 2B classification.

840. I read with interest the membership of the Working Group, which was chaired by Dr. Aaron Blair. I had met Dr. Blair in 1982 or 1983, when he was invited to give Congressional testimony on behalf of the National Cancer Institute (Blair's employer) on cancer-causing pesticides to the Department Operations, Research, and Foreign Agriculture Subcommittee (DORFA), of the House Committee on Agriculture. From 1981-1983, I served as the staff director of the DORFA Subcommittee.

841. Over the years, I remained in touch with Dr. Blair, sought his advice on scientific matters, and considered him a professional colleague. To me, the Working Group's 2A classification decision was unexpected, and bound to trigger a strong response from Monsanto, other glyphosate-based herbicide registrants, and farmers choosing to grow GE crops reliant on Roundup herbicides. It would also have significant regulatory ramifications.

842. To better understand the thinking of the Working Group, I called Dr. Blair and had a phone conversation with him on or about March 22, 2015. He outlined the factors leading to the Working Group's decision, and said both the Working Group and IARC had anticipated

the strong reactions that had already started to appear in media stories and various blogs.

843. In response to a question I asked about how strong the support was in the Working Group for the 2A classification, Dr. Blair told me that as the Working Group approached a final decision, the most extended debate was not between a 2A ("probable") or 2B ("possible") human carcinogen classification, but actually between a Group 1, "The agent is carcinogenic to humans" and a Group 2A classification ("The agent is probably carcinogenic to humans").

844. Again, this was shocking information.

845. I suspected that the focus of the internal debate within the Working Group would eventually become public knowledge, and when it did, it would place the Working Group's 2A decision in a substantially different light.

846. The fact that the Working Group almost classified glyphosate as a Group 1 carcinogen did become public knowledge as a result of an Andrew Cockburn story in the September 2015 issue of *Harpers Magazine.* The story was entitled "Weed Whackers – Monsanto, glyphosate, and the war on invasive species" (https://harpers.org/archive/2015/09/weed-whackers/).

847. Cockburn's story labels the IARC classification "a massive speed bump" undercutting Monsanto's 'mantra…all labeled uses of glyphosate are safe for human health'…"

848. To gain perspective on the IARC Working Group's assessment of the science, Cockburn interviewed Aaron Blair. The germane passage in Cockburn's story reads:

> "According to Blair, there were good grounds to declare that glyphosate definitely causes cancer [i.e., to classify it as a Group 1, *proven* human carcinogen]. This did not happen, he said, because 'the epidemiologic data was a little noisy.' In other words, while several studies suggested a link, another study, of farmers in Iowa and North Carolina, did not. Blair pointed out that there had been a similar inconsistency in human studies of benzene, now universally acknowledged as a carcinogen. In any case, this solitary glitch in the data

caused the group to list glyphosate as a probable (instead of a definite) cause of cancer."

2. Monsanto's Preparation for the IARC Report and Classification

849. In mid-September 2014, Donna Farmer, a senior Monsanto toxicologist, learned of the forthcoming IARC review of the oncogenicity of glyphosate and glyphosate-based herbicide, and began developing a plan to respond to the forthcoming report. (MONGLY01207339)

850. A month later, William Heydens sent an email to Monsanto colleagues including [redacted], Farmer, [redacted], Koch, and Saltmiras, in which he asked: "…wouldn't an adverse IARC evaluation have the real potential to impact the results of the Annex 1 renewal [re-registration of glyphosate in the EU]." Then, he also notes:

> "And while we have vulnerability in the area of epidemiology, we also have potential vulnerabilities in the other areas that IARC will consider, namely, exposure, genotox, and mode of action." (MONGLY00989918)

851. In November 2014, a consulting agreement was completed between former Monsanto epidemiologist John Acquavella and Monsanto at $400 per hour, with Donna Farmer as the principle point of contact. (MONGLY01224009)

852. A December 17, 2014 email from Kimberley Link in Monsanto's communications division to Daniel Goldstein discusses the need to identify third-part voices. It reports that Monsanto has hired Potomac Communications to place favorable op-eds, targeting the Washington Post and USA Today, and a potential plan to approach officials in the American Academy of Pediatrics to find someone to serve as "high profile author." (MONGLY01021656)

853. A document dated 2/15/15 describes "Glyphosate Key Points Following IARC Decision," and was developed by a Heydens-Farmer-Saltmiras led team preparing for the release of the IARC decision. In the event that IARC assigns glyphosate-based herbicides "an

unfavorable 2B classification," the company set forth a plan that would hopefully generate an "orchestrated outcry" after the March 3-10, 2015 IARC working group meeting when, presumably, the final classification decision would be made.

854. The plan set forth seven "Key Industry Points" critical of the feared, 2B classification. (MONGLY01021709-11) Seven more talking points for "Academics" are outlined, and include:

- "IARC has done a disservice by creating baseless fears with a cancer rating for glyphosate, and the confusing classification is certainly open to distortion by alarmists";
- The IARC decision "was predictable and political"; and
- "Government regulators remain reassuring about the potential risks."

855. On February 19, 2015 William Heydens sent an email to Donna Farmer, copied to Koch, Saltmiras, and Hodge-Bell, on the subject "RE: IARC Planning." The email describes "the next two most important things that we need to do…" These were a meta-analysis of epidemiology studies, and a re-assessment of Agricultural Health Study data that established a weak link between use of a glyphosate-based herbicide and multiple myeloma. (MONGLY00977267)

856. Heydens goes on to describe possible approaches to generate peer-reviewed journal articles counteracting the IARC classification. He writes that:

> "If we went full-bore, involving experts in all major areas (Epi, Tox, Genotox, MOA [Mechanism of Action], Exposure – not sure who we'd get), we could be pushing $250k or maybe even more. A less expensive/more palatable approach might be to involve experts only for areas of contention, epidemiology and possibly MOA…and we ghost-write the Exposure Tox & Genotox sections. An option would be to add Greim and Kier or Kirkland to have their names on the publication, but we would be keeping the cost down by us doing the writing and they would just edit & sign their names so to speak. Recall that is how we handled Williams Kroes & Munro, 2000." (MONGLY00977267

857. The "option" laid out in Heydens email is essentially what Monsanto did in the course of developing the papers that were published September 28, 2016 in a special, glyphosate-

safety issue of the journal *Critical Reviews of Toxicology*.

858. In a detailed, internal document dated February 23, 2015, Monsanto describes its multi-faceted plan for responding to the IARC decision due to be announced in about two weeks. It provides background on IARC, and states, for example,

> "IARC has a history of questionable and politically charged rulings on the carcinogenic properties of products such as cell phones, coffee and caffeine. We should assume and prepare for the outcome of a 2B rating (*possible* human carcinogen); a 2A rating (*probable* human carcinogen) is possible but less likely." (MONGLY02913526)

859. Attachment A to this document sets forth the "Objectives for Preparedness & Engagement" in Monsanto's response to the IARC decision. The two-bulleted items read:

- "Protect the reputation and FTO of Roundup by communicating the safety of glyphosate"; and
- "Provide cover for regulatory agencies to continue making re-registration decisions based on science."

860. Under "Strategies/Tactics" to achieve the above stated objectives, the Attachment A document states, under the heading "Post-IARC": "4. Orchestrate Outcry with IARC Decision ~ March 10, 2015." (MONGLY02913530)

861. The introductory section of the full, 2/13/15 document states that: "Regulatory is not aware of a situation where a regulatory body took a different position than IARC." (MONGLY02913526)

862. The "Key Deliverables" section outlines 24 items and actions, organized by milestone date (pre-IARC decision; week of Feb. 23-27; Post-Decision/Posting, etc). These include:

- Engage Henry Miller, "Inoculate/establish public perspective on IARC reviews" (Miller produced a hard-hitting Forbes piece the day of the release of the IARC decision);
- Blog posts;
- Outreach to EPA/IARC participants;
- Contact journals to inquire about press releases, for "amplification of scientific

studies (a Saltmiras task, which went badly awry);
- "Inform/Engage Industry Associations", with the objective "Lead voice in 'who is IARC' plus 2B outrage"; and
- Post-release of decision, "Outreach to key stakeholders," including grower groups, in order to "Neutralize impact of decision/gain support.

863. A March 17, 2015 email is sent from Eric Sachs, head of Monsanto's public affairs and outreach efforts, to Henry Miller, a long-term, glyphosate-friendly member of Monsanto's third-party network. In it, Sachs forwards to Miller a Monsanto/Potomac Communications-written draft of Miller's op-ed for Forbes.

864. Five days earlier, Sachs had emailed Miller to ask him if he would be willing to write more on the IARC decision, to which Miller replied: "I would be if I could start from a high-quality draft." (MONGLY02063615)

3. Monsanto Selects Donna Farmer to be a Key IARC-Response Spokesperson

865. On February 25, 2015, Donna Farmer received an email from Kimberley Link informing her that "you have been selected as one of the primary spokespersons for the company to defend glyphosate." (MONGLY01210309)

866. Michael Koch, a senior official and part of Monsanto's communications team, emails Farmer seven minutes later to "discuss" this new role for Farmer in the IARC response, and writes that "In the short term I think you are the right 'fix'."

867. A flurry of emails then address how to rapidly gear up the third-party expert response, in support of Monsanto's critical reaction to the expected IARC 2B classification of glyphosate (MONGLY01021648)

868. The communications team asks Dan Goldstein several times to identify experts that are vetted, and prepared to say and write messages aligned with Monsanto's position. Such third-party experts would work with Farmer, and are needed so that the communications team

and Potomac Communications can move ahead with writing and placement of favorably, largely ghost-written op-eds.

869. Goldstein replies in a remarkable email sent 2/23/15:

> "I realize that a non-paid individual would be preferred – but I do not know anyone who has kept up with this in their 'spare time' as a toxicologist and ***one needs to be mighty prepared if one wishes to feel comfortable arguing with IARC***." (Emphasis added)

870. Goldstein estimates that a new expert would need "a good 10 hours of work in this, at $200 per hour" to accomplish the task.

871. On February 23, 2015, Kelly Clauss, another person working on Monsanto's IARC outreach and media response, emails Goldstein with a list of experts to engage in the response effort, and for work with Potomac Communications. Five epidemiologists are identified, and were listed in the email in order of "most to least familiar with published studies and data [the focus of IARC's work]." The scientists identified in her ordered list are:

- [redacted], University of Birmingham (was an invited observer at the IARC meeting);
- Pam Mink, Emory University (did one review on glyphosate-cancer studies, one on non-cancer issues, both paid for by Monsanto);
- John Acquavella, former Monsanto employee, now retired and consulting with Monsanto;
- Elizabeth Delzell, University of Alabama-Birmingham; and
- Nalini Sathiakumar, University of Alabama-Birmingham (works with Delzell).

872. [redacted] replies to the list, and writes that "[redacted] knows glyphosate but his contract, FCPA etc have expired so that would take 6 weeks to sort out."

873. A few days later, on February 26th, Donna Farmer responds to the now lengthy email chain on the Subject "RE: URGENT: Draft email for experts to help with IARC." She begins her response to Goldstein and the communications team (Carlo Lord, Kelly Clauss and Kimberley Link) with this sentence: "Help me understand why these folks were selected and who is Potomac?"

874. On February 27, 2015, now less than two weeks before the IARC decision, Carla Lord responds to Farmer and others on the email chain, with a remarkably clear explanation of the plan outlined earlier in the IARC response document:

> "Donna,
>
> Thanks and I'm sorry. I didn't realize until now that you were not on the original email string (included below). Potomac is a media house that is writing op-eds and letters to editors in response to negative press surrounding glyphosate. These would be 'authored' by those on the list then placed by Potomac in media where needed. Potomac writers would do the heavy lift with the expert authors as final editor. We know these items in the media need to be from those outside the industry." (MONGLY01021648)

875. On March 14, 2015, four says after the end of the Working Group meeting and six days before the March 20th release of the embargo on the decision and publication of the results of the IARC review in *The Lancet Oncology*, Donna Farmer reported that a Monsanto colleague was on a CropLife Americas (CLA) call (pesticide industry trade association), and that an EPA representative, Jess Rowlands, announced the IARC decision to classify glyphosate as a Group 2A carcinogen. (MONGLY00977253)

876. Farmer's 3/14/2015 email was sent to [redacted], Monsanto's invited observer at the meeting, and other Monsanto colleagues including [redacted], [redacted], and William Heydens. These individuals were most directly involved with the IARC meeting. In the email, Farmer restates several of the plans and talking points in the IARC response plan document. She closes it by writing: "We know it must have been a challenging week for all of you to try to keep the assessments based on sound science…"

877. [redacted], the invited observer at the IARC Working Group meeting that represented Monsanto, replies to Farmer and others on the email chain:

> "I do know of instances where observers at IARC felt they had been treated rudely or brusquely at Monograph meetings. That was not the case for me at Vol. 122 [the one containing the glyphosate review and classification]. I found the Chair, sub-chairs and

invited experts to be very friendly and prepared to respond to all comments I made…In my opinion the meeting followed the IARC guidelines. [redacted], the Director of the Monographs programme, has an intimate knowledge of the IARC rules and insists they were followed."

4. "Why Do More?"

878. In the weeks and months after the release of the IARC decision, the nature and scope of Monsanto's "response" activities expand. There is a discernable sense of urgency.

879. Another Monsanto internal document circulated in April 2015 with the title "IARC Follow Up." Unlike all pre-decision planning documents, Monsanto is now dealing with the very serious Group 2A "probable human carcinogen" classification. The goals, activities, and work products is this document include:

- "Invalidate relevance of IARC";
- "Protect regulatory FTO [Freedom to Operate]";
- "Litigation prevention/defense";
- "Protect Sales Globally"; and
- "Compilation of 3rd Party Statements in defense of glyphosate." (MONGLY03316369-71)

880. About the same time, John Acquavella sends an email to Donna Farmer. In it, he discusses IARCs assessment and final judgements on the epidemiology data. He writes:

> "IARC's classification of the epidemiology evidence follows directly from their definition of 'limited' [evidence]. There is not really much to quarrel about with respect to the epidemiology classification." (AcquavellaPROD00010215)

881. A draft Powerpoint entitled "Proposal for Post-IARC Meeting Scientific Projects" dated May 11, 2015, is circulated internally in preparation for a meeting. It begins by asking "**Why do more**?" in large letters, and then lists these reasons:

- "Severe stigma attached to Group 2A Classification";
- Aaron Blair continues to defend work & exaggerate number of studies w/association while ignoring AHS";
- "In response to our critique, can expect IARC to beef-up monograph as much as possible";
- ASTDR;

- Prop 65 [California State law requiring labeling of oncogenic products]; and
- Litigation support. (MONGLY01228577)

882. Several new projects and scientific papers are outlined, nearly all to be authored by third-party experts. But in order to increase credibility and lower costs, "Majority of writing can be done by Monsanto."

5. Producing the CRT Special Issue on Glyphosate Toxicity

883. Most of the internal documents and emails setting forth possible post-IARC actions include discussion of the need for new, Monsanto-commissioned and controlled peer-reviewed papers providing Monsanto's critique of the basis of IARC's decision, and/or critical reviews of the findings and conclusions advanced by other scientists not adequately aligned with Monsanto's positions and messaging.

884. From the fall of 2014, about six-months before the release of the IARC decision, to mid-2015 (about 4 months after the release of the decision), these discussions led to a plan to convene a "Glyphosate Expert Panel Review" of the scientific basis for IARC's classification of glyphosate as a probable human carcinogen (Group 2A).

885. The "Expert Panel" idea was eventually adopted, funds were committed, and the plan implemented, starting in late-June 2015. The panel would meet, discuss the issues, and produce a set of papers suitable for publication.

886. A detailed proposal describing several options for moving forward was presented to the "Glyphosate Strategy Team Meeting" on June 18, 2015. (Acquavella Exhibit 10-27; MONGLY03500777)

887. "**Approach A**" would entail an Expert Panel that "consists primarily of people we have worked with already…they have some/much knowledge…[and this approach would have] Lowest cost (est. $200-250k), but also lowest credibility/impact."

888. "**Approach B**" would be to add "a few 'big name' scientists & possibly some who have not worked for Monsanto before (more credibility)… hire a firm (Intertek, formerly CanTox) to manage the meeting…Cost estimate - $350-400k."

889. "**Approach C**" takes another step toward "credibility/impact" and would include hiring a well-respected risk assessment firm (presumably Intertek did not fall in this category based on Monsanto's assessment), in order to:

> "set up a totally independent review: they choose scientists, conduct meeting, write the report…Most credibility/impact but we have virtually no control…Cost estimate - $375-450k."

890. **Approach B** was the recommended path forward advanced during the meeting, and the one adopted. In fleshing out the plan, the document states: "Monsanto provides draft report which Experts edit & then publish…Use journal with quick review time…Negotiate for expedited review with journal editor."

891. A "Backup Slide" provides an even more detailed "Summary of Overall Process" and individual actions/steps include:

- "Review IARC Monograph to identify all areas that need to be addressed";
- "Prepare initial draft document";
- "Edit draft manuscript to capture meeting discussion/conclusions";
- "Send draft manuscript to Experts for their review";
- "Send manuscript to journal for review";
- "Revise manuscript per comments from journal"; and
- "Re-submit [papers] & get final approval from journal."

892. In other words, in Approach B, Monsanto would control every step of the process, from producing an initial draft of the report/papers, to managing the revision of the draft in response to the meeting of the experts, making and/or approving final edits prior to submission to a journal, and managing/approving any changes made in response to peer-review comments.

893. This "Backup" slide failed to include two other key responsibilities Monsanto

clearly reserved to itself – (1) deciding which names would appear on each published paper, and (2) deciding on what information would be provided to the expert panel and teams of co-authors.

894. The first task – deciding the list of co-authors on various papers -- ended up creating many problems and challenges for Monsanto and its scientific staff, its hired third-party experts/co-authors, and the journal to which Monsanto-controlled papers were submitted for publication.

895. A February 8, 2016 exchange between Monsanto consultant and *CRT* paper co-author John Acquavella and Intertek's Ashley Roberts focuses on the difficulty Intertek, Monsanto, and the third-party expert co-authors were having in reaching a consensus on who would be the listed as the author or co-authors on summary paper in the *CRT* special issue.

896. Both Acquavella and Roberts wanted the entire expert panel to sign the summary report. But Acquavella tells Roberts that:

> "I've had some initial correspondence from the panelists about the summary article and the consensus is that they will not be authors on an article that has inflammatory comments about IARC. Assuming those inflammatory comments were carried over from the animal carcinogenicity and genotoxicity articles, I'm sure the epi panelists would not want to be associated with those articles either. To achieve the complete authorship goal, an extensive revision of the summary article is necessary."

897. Roberts forwards Acquavella's email to Heydens, and writes: "Hi Bill, Please take a look at the latest from the epi group!!!! Can you call me once you have digested this."

898. Heydens replies the next day:

> "Ashley,
>
> OK, I have gone through the entire document and indicated what I think should stay, what can go, and in a couple of spots did a little editing." (Heydens Exhibit 3-20)

899. The second responsibility generally reserved to Monsanto, and specifically claimed in the case of the Intertek/*CRT* paper-preparation process was deciding what scientific

materials to provide to the experts and co-authors. While Monsanto could not control access to published studies by its expert panel members, it had total control over what parts of its proprietary testing results would be supplied to expert panel members.

900. This is evident in an August 6, 2015 email from Ashley Roberts to Donna Farmer in which he asks: "Please could you let me know in a sentence what we will be providing to the Animal Bioassay Expert group." (MONGLY01183933)

901. By the "we" in the phrase above, "what we will be providing," he really means what information will Donna Farmer/Monsanto provide to her/Intertek, so she/Intertek can then provide the information to the expert panel.

902. The discovery record in this case shows clearly that violation of widely accepted ethical norms in scientific publishing was a routine, accepted part of the culture at Monsanto. Over several decades, such actions were conceived and implemented in the interest of heightening the "credibility/impact" of scientific papers the company commissioned and controlled.

6. Content of the *CRT* Special Issue on Glyphosate Safety

903. The 2015-2016 Intertek expert panel review of the IARC decision and monograph resulted in the publication of five papers, and a Foreword by the journal editor, Roger McClellan (all open access, i.e. accessible for free at http://www.tandfonline.com/toc/itxc20/46/sup1?nav=tocList). The papers included:

- Gary Williams et al., overview paper on the carcinogenic potential of glyphosate and the IARC assessment;
- Keith Solomon, assessment of exposure studies;
- Acquavella et al. on epidemiological studies;
- Gary Williams et al. on rodent bioassays; and
- Brusick et al. on weight of evidence evaluation of glyphosate, formulated glyphosate herbicides, and AMPA (major glyphosate metabolite).

904. Roger McClellan was acutely aware of the scrutiny his journal's special issue on glyphosate safety would receive. On multiple occasions, he stressed in exchanges with Ashley Roberts, the employee of Intertek that managed the process of developing the papers, the importance of clarity and full transparency in the Acknowledgements and Declaration of interest sections of the papers.

905. In a June 19, 2016 email to Roberts, McClellan writes:

> "I am still concerned about the tone in some places. Why antagonize the reader? I am still not clear as to the process used by all of the Panels. These reports are essentially a rebuttal of the IARC process and conclusions. There appears to be a reluctance to be absolutely clear in presenting exactly what IARC concluded, the panels conclusions and how they differ. Am I missing something?" (MONGLY02360733-34)

906. Six days later, Roberts replies from vacation. He states that "I am getting a lot of pressure to publish the papers for a lot of reasons as you can imagine." He then asks for the specific changes McClellan wants in the Acknowledgements and Declaration of interest (DOI) statements.

907. Just 90 minutes later, McClellan responds to Roberts. He spells out the changes he wants in the Acknowledgements (thank the reviewers for extensive comments received). He also says that "The Acknowledgements section should also identify any other reviewers of the paper and any editorial assistance." (MONGLY02360732)

908. In reference to the DOI, McClellan writes that it should:

> "…make clear how individuals were engaged, i.e. by Intertek. If you can say without consultation with Monsanto that would be great. If there was any review of the reports by Monsanto or their legal representatives that needs to be disclosed."

909. Each of the papers has a similar "Declaration of Interest" statement. The "Declaration of interest" statement in the Brusick et al paper is quoted below:

> "The employment affiliation of the authors is as shown on the cover page. However, it should be recognized that each individual participated in the review process and

> preparation of this paper as an independent professional and not as a representative of their employer….[Past and current relationship of each co-author to Monsanto is then listed]"
>
> "The Expert Panel Members recruitment and evaluation of the data were organized and conducted by Intertek Scientific & Regulatory Consultancy…"
>
> "Funding for this evaluation was provided by Monsanto Company which is a primary producer of glyphosate and products containing this active ingredient. Neither any Monsanto company employees nor any attorney reviewed any of the Expert Panel's manuscripts prior to submission to the journal."

910. The major differences across the DOI statements arise from differences in the current and past affiliations of each co-author with Monsanto. The Acquavella et al. paper contains a different version of the statement regarding Monsanto's role in the review of the papers; the Acquavella et al. DOI states "The authors had sole responsibility for the content of the paper, and the interpretations and opinions expressed in the paper are those of the authors."

911. The first paragraph in the above quoted DOI is presumably truthful, the second paragraph is not truthful, and the second sentence in the third paragraph is not truthful.

912. Via direct interactions with Roberts of Intertek, it is clear that Monsanto reviewed, and approved of the content of the papers prior to submission, and again after the papers were revised in response to peer review comments.

913. The expert panel evaluation, and the composition of the panel itself, was controlled by Monsanto. Indeed, a July 1, 2015 email from William Heydens (Monsanto's lead in the scientific response to IARC) to Ashley Roberts, the man running the Monsanto project for Intertek, Heydens tells Roberts "we" (Monsanto) are adding two additional scientists, and that: "We just learned this morning that we can't have you send out 'invitations' until the names have been approved by our legal group." (MONGLY00992949-51)

914. Heydens places the word "invitation" in quotes because the Intertek contact/invite is not really the invitation, since the scientists had all previously been contacted by Monsanto

and had all agreed to serve.

915. The record shows clearly that Monsanto was heavily involved in most stages of paper preparation, from deciding on the information that would be provided to the co-author teams by Intertek; producing drafts of the papers, or sections of papers provided to the teams; deciding on whose name(s) would appear on the papers; interacting with the teams on how to address tricky, key issues, and especially clear-cut evidence of risk from glyphosate exposures in well-designed, published studies; responding to review comments; and, the final stages of editing.

916. Heydens, in particular, played a direct, hands-on role in all stages of the process.

917. An August 28, 2015 email to Donna Famer and other Monsanto colleagues from Heydens circulates for comment his first draft of the Intertek Expert Panel report on the carcinogenic potential of glyphosate (Acquavella Exhibit 10-30; MONGLY02844211)

918. In the draft Heydens circulated, "William Heydens" does not appear as a co-author, nor does his name appear on any of the papers as published. In failing to truthfully acknowledge authorship, and declaring in the conflict of interest disclosures that Monsanto employees played no role in the review of the papers, Monsanto violated well known ethical norms governing scientific publishing, including the policies of the journal *Critical Reviews in Toxicology*.

919. Heydens was influential, if not responsible for many critical decisions about how strongly to make positive statements regarding the safety of glyphosate and Roundup herbicides, and how sharply to criticize the IARC report and the studies in the peer-reviewed scientific literature that the IARC working group relied upon in reaching its "probable human carcinogen" classification.

920. For example, Heydens sharply disagreed with some panel-members, and ex-employee Acquavella over how sharply to be critical of IARC and its classification decision. Examples of such disagreements are evident throughout Heydens' track-changes comments and editing of Acquavella's edits to the draft of the summary panel report. (MONGLY01000680-01000709)

7. Political and Other Activities Post-IARC

921. The breadth of Monsanto's activities in response to the IARC classification of glyphosate herbicide as a probable human carcinogen is striking. A June 5, 2015 update on "US Government Outreach – WHO IARC Classification on Glyphosate" outlines dozens of ongoing and proposed actions and goals. Under "**THE STRATEGY**", the document states:

> "One strategy for addressing widespread confusion in the wake of the IARC classification has been to seek clarification from the World Health Organization (WHO) which would provide the proper context of the classification for governments and regulators around the world to have greater confidence defending their science based regulatory decisions." (MONGLY02953363)

922. The document reports on multiple briefings given to U.S. government agencies, including a Donna Farmer briefing of Dr. Mitchell Wolfe, the Deputy Assistant Secretary for Global Heath, in the of Department of Health and Human Services (HHS), to which "we came prepared with a robust set of technical materials for the Secretary's background…".

923. In the briefing for the HHS Deputy Secretary Dr. Wolfe, he was told about ATSDR (Agency for Toxic Substances and Disease Registry), an agency under HHS of which he was reportedly unaware. Monsanto then told Wolfe about the ongoing ATSDR review of glyphosate, and made the case that such a review was unnecessary and that the EPA bears the primary responsibility for "determination of pesticide safety."

924. Then Monsanto briefed Wolfe on "A common element between IARC and

ATSDR…Christopher Portier Ph.D…[who] was Director of ATSDR and co-chair of the IARC Advisory Group."

925. Dr. Portier's views on glyphosate oncogenicity were no doubt discussed, as was the fact that Dr. Portier "was an invited specialist representing the Environmental Defense Fund."

926. According to Monsanto's recounting of the meeting "Dr. Wolfe said he would follow up on what was going on with ATSDR and he was encouraged to have discussions with the EPA staff, as well."

927. Last, Monsanto asked for Wolfe's and HHS's "assistance in securing a WHO clarification. We emphasized that we were not seeking changes to IARC, the classification or the IARC process."

928. In fact, Monsanto had already initiated, and is still carrying out campaigns to punish IARC for its classification through, among other things (details below):

- Lobbying members of Congress to challenge U.S. government funding for IARC, via U.S. government support for the WHO;
- Calling for Congress to hold hearings;
- Mounting a campaign to force IARC to release drafts of its glyphosate review document and notes from Working Group deliberations;
- Working with a Washington Post reporter purportedly doing a hit piece; and
- Mounting multi-faceted outreach and third-party expert criticisms of the IARC process, the people who participated in it, the conclusion it reached, and its accountability.

929. Accordingly, the statement in Monsanto's account of the Wolfe-HHS briefing that "…we were not seeking changes to IARC, the classification or the IARC process" was clearly not truthful.

Blocking the ATSDR Review of Glyphosate

930. Another important Monsanto action-item, post-IARC, was stopping an ongoing

ATSRD review of glyphosate safety. Monsanto regarded the ATSDR review as a clear threat because the agency is "IARC-like," very conservative, and has often disagreed with EPA in the past.

931. An ATSDR review that supported IARC's conclusions and classifications was to be avoided. (MONGLY03342947)

932. Since Monsanto suspected that ATSDR would agree with IARC on the science, the only way to avoid a huge setback in Monsanto's ongoing campaign to isolate and marginalize IARC would be to stop ATSDR from issuing the results of its review.

933. In pursuit of their ATSDR goal, Monsanto:

- Sought and carried out meetings, briefings, and webinars with ATSDR to communicate its assessment of the issues, explain why it felt the ATSDR review was unneeded, and the scientific flaws in the IARC review;
- Received significant help from two senior OPP/EPA officials – Jess Rowland and the OPP Director, Jack Housenger;
- Sought assistance and support from the Deputy Assistant Secretary for Global Health in HHS (the agency home of ATSDR);
- Asked Monsanto's home-state Senators to contact HHS and reinforce the urgency of quick HHS action to intercede with ATSDR, given information Monsanto had obtained suggesting the ATSDR report might be released in only a few weeks;
- Lobbied Congresswoman Lynn Jenkins to submit questions regarding the ASTDR glyphosate review to the Secretary of HHS at the conclusion of a hearing before the House Ways and Means Committee on health care reform (MONGLY03064699); and
- Recruited individuals to write letters to Congressmen complaining that the ATSDR review was duplicative and a waste of taxpayer money, so that the letter(s) could be used to trigger media coverage of the campaign to stop the ATSDR study. (MONGLY03342947)

E. Allied Organizations, Front Groups, and the Media

934. Monsanto engages with a wide diversity of organizations in the course of promoting its business and industry objectives. These include pesticide industry trade associations, the most important of which is CropLife America, which is part of CropLife

International. (CropLife America was formerly called the National Agricultural Chemicals Association, or NACA).

935. Monsanto and other pesticide manufacturers use CropLife to align the industry on issues, organize and carry out initiatives that are responsive to industry-wide issues, lobby the U.S. Congress and federal agencies, and conduct a wide array of media and PR activities.

936. Monsanto also works with all major farm commodity groups (corn growers, cotton growers etc), and general farm organizations like the Farm Bureau and Future Farmers of America. It provides financial and content support to most agriculture and food-relevant scientific and professional society meetings.

937. The company is working simultaneously with several PR, communications, and issue management companies on specific projects.

938. In some cases, Monsanto's financial support is welcomed and acknowledged, while in other cases it is not. In the later case, Monsanto works out a scheme to route its funding through one or a few organizations, in order to hide the source of the funding (Monsanto) from the person or entity receiving the funding, as well as from the general public.

939. While comprehensive statistics are not publically available, I suspect that a substantial portion of Monsanto's funding for scientific organizations, science-related activities, and individual scientists is provided through circuitous channels that avoid the need for recipients to openly acknowledge the company's funding support.

940. Such practices are not unique to Monsanto, but I am not aware of another company in the pesticide industry that invests so heavily, creatively, and aggressively in its third-party network of scientists and the activities of scientific organizations.

1. CropLife America and CropLife International

941. CropLife America routinely carries out special projects and activities, with funding provided by member companies, or sometimes one or a few company members. In some cases, such funding comes from routine membership dues, in other cases, CropLife requests and/or is offered targeted support for a special project. Many such projects are done under contract by consulting firms or academics with ties to the industry.

942. Such arrangements often assure that funding from a given company passes through at least two entities before reaching the person or entity carrying out an activity. As a result, it becomes difficult, if not impossible for members of the public to know exactly who actually paid for a given activity or project, nor the basic motivation leading to the project or activity.

943. A good example unfolded in the fall of 2015. Several pesticide manufacturers were concerned by the way OPP/EPA was using epidemiological studies done by scientists not working for, or representing the pesticide industry. Several such studies had been published in peer-reviewed journals, and had become a part of the science-base reviewed by EPA in the pesticide risk assessment process.

944. Three companies were acutely aware of the risk posed to one of their major products: Dow AgroSciences over epidemiological studies showing a link between chlorpyrifos insecticide use and neurodevelopment in infants and children; Syngenta over the link between atrazine exposures via drinking water and breast cancer; and, Monsanto over the cancer risks posed by glyphosate.

945. A decision was made by the companies to commission a scientific critique of how OPP/EPA had utilized the results of epidemiology studies. On behalf of the companies, CropLife America requested a proposal from a closely aligned consulting firm, Exponent. Exponent

provided a detailed proposal to CropLife outlining such a study, at a projected cost across three major tasks of $70,000-$100,000. (MONGLY02134326)

946. Task 1a in the proposal describes four case studies focused on glyphosate, organophosphate insecticides (and especially Dow's chlorpyrifos), and Syngenta's atrazine.

947. On January 4, 2016 Exponent released the 89-page report commissioned via the September contract. It was entitled "Human Epidemiology Data Incorporated Into Regulatory Risk Assessment: Retrospective Analysis." (MONGLY03409329-03409423)

948. After the release of the IARC classification, CropLife International developed and implemented a multi-prong response on behalf of the industry. Key activities included:

- "Generating influencer commentary on IARC…to challenge the credibility of IARC…working with the issue management consultancy v-Fluence to generate proactive news/commentary articles…all articles have been pushed widely on social media channels through a wide network of industry commentators";
- "High level outreach to WHO";
- "Building credible 3rd part support…(in particular toxicologists and academics)"; and
- "Coordinating industry alignment."

2. Engaging PR Firms

949. Over the years, Monsanto used a variety of PR and communication firms to assist in the defense of glyphosate herbicides. These firms were typically tasked with actions that would be difficult and/or tainted if undertaken by Monsanto staff.

950. There is nothing unusual about pesticide manufacturers or other companies engaging such firms in support of outreach, policy, regulatory, and political goals. But the scope and nature of the activities pursued by Monsanto via such firms stands out as uniquely broad and aggressive.

951. Monsanto commissioned Potomac Communications to place not just one or a few supportive op-eds and letters to the editor in response to the IARC decision, but dozens.

952. In May 2015, Monsanto received a detailed document from the PR firm FleishmanHillard (FH). This firm had conducted multiple projects for Monsanto in the past. The current proposal focused on triggering expressions of support for the EPA's re-registration of glyphosate in the political, farm, academic, and gardening communities. (MONGLY03550020-24)

953. FH recommended targeting two audiences: "those who live and work in congressional districts with significant agricultural glyphosate use and whose elected representative sit on committees relevant to EPA"; and second, "those who live in suburbs that lean conservative politically." FH then adds:

> "Please note that this general consumer approach is intended as a supplement to a stakeholder outreach campaign targeting farmers, agricultural trade associations and other agricultural audiences…Finally, please note that the below campaign elements represent efforts that FH would conduct above and beyond the scope of ongoing support for the [Monsanto-funded] Cultivating Trust campaign."

954. The scope of the newly proposed "Re-registration Campaign" is impressive. Seven "markets" would be included (suburban Dallas and/or Houston, Atlanta, Davenport/Iowa City; Detroit, Indianapolis, Memphis Minneapolis/St. Paul; St. Louis); a table describes each area, noting key politicians or reasons why the area was selected.

955. Within each area, a set of FH-paid "community organizers" (COs) would be assigned a specific set of tasks and goals. Each "would target 750-1,000 consumer signatures/comments or letters and 15-25 'high quality' letters …per month of the [glyphosate re-registration] comment period (either 60-90 days)."

956. The proposal then spells out what FH would do to prepare/support the COs in achieving their target goals. In addition, FH "would manage a paid digital campaign on Facebook, using sponsored content targeted at a relevant audience…with the aim of driving them

to Monsanto's comment generation website."

957. The estimated budget for the proposed 3-4 months of activity was $355,000-$400,000.

3. Shaping the Agenda and Supporting Scientific Meetings

958. There are several instances in the record of this case documenting why and how Monsanto played a role in shaping the focus of a scientific meeting to include discussion of glyphosate risk issues, as well as some instances where Monsanto also provided the funding needed for a meeting to occur.

959. In a March 10, 2016 email, Dan Goldstein, Monsanto's "Lead, Medical Sciences and Outreach," contacts a colleague, Allister Vale, a consulting clinical pharmacologists and Director of the National Poisons Information System (Birmingham Unit), in the U.K.

960. Dr. Vale is active in several organizations that convene meetings of medical toxicologists, a group that Monsanto is striving to engage in the ongoing reaction to IARC and debate over glyphosate safety.

961. In his "preliminary inquiry," Goldstein asks Vale if she would work with Sir Colin Berry to "reincarnate" an expert panel, this time composed of European medical toxicologists. (MONGLY0256574-75) He writes that: "Cost (including Honoria) will be picked up by Monsanto via an appropriate granting mechanism which allows for a proper degree of academic independence."

962. Vale and Goldstein meet briefly later in the month at a meeting of the Society of Toxicology (SOT). They discuss the idea raised by Goldstein in the March 10 email, and agree to get back in touch after the meeting.

963. Vale sends Goldstein a March 24, 2016 email apologizing for her limited time

during the SOT meeting and stating:

> "The issues you raise in regard to glyphosate are of course of considerable professional interest to me…we have proposed a symposium for next year's SOT which will include a discussion of the carcinogenicity of glyphosate."

964. Goldstein responds the next day, and provides much more detail, and points out that "the situation around glyphosate continues to be, frankly, bizarre." He goes on to note "serious process issues surrounding this IARC assessment. Then he writes:

> "Our only goal at this point is to create a large number of medical toxicologists who know about glyphosate products. You have hit on the key problem of course – direct involvement of Monsanto is not going to be acceptable to experts in the EU."

965. Goldstein then returns to the issue of funding for a meeting. He writes:

> "I assume that the cost will be considerable….Funding can perhaps come from the Glyphosate Consortium which is conducting the EU re-registration or via ECETOX or CEFIC, for example, and be routed via SOT or one or more academic institutions. At that point, we can be 'hands off' altogether."

966. So, under the Goldstein proposal, Monsanto would provide funding to the Glyphosate Consortium, the Consortium would contract with one or more academic institutions, and/or route funding to the SOT, which would then make invitations and cover the costs of participants and presenters. As Goldstein notes in his email, there would be an "appropriate degree" of separation between Monsanto funds and the people receiving them.

967. Vale responds two weeks later, in general agreeing that an indirect funding mechanism could be found. But she then reminds Goldstein, "However, to make this work, neither I nor they could be in receipt of direct funding from Monsanto or the [industry-funded] Glyphosate Consortium."

968. This correspondence is important not because of the impact of one meeting, or even whether the meeting took place. It is important because it documents clearly the techniques Monsanto deploys to engineer meetings, papers, events, and other activities where the company

will have a well-controlled forum, or a mechanism to communicate its view of some set of issues to a possibly influential audience.

969. Goldstein ends his March 25th email to Vale with a statement referring to the government-employed medical toxicologists that Monsanto is trying to reach out to: "As important resources for their respective national agencies, we are of course hopeful that they can support ***a balanced and scientific approach in the EU***." (Emphasis added).

970. Of course, such an approach would have to be aligned with Monsanto's positions on issues, and certainly not IARC's on the issue of glyphosate oncogenicity.

VII. Protecting "Freedom to Operate" and Scientific Deceit Characterize Monsanto's Assessments of and Response to Glyphosate-Related Risks

971. Pesticide companies bear an obligation vested in various laws and regulations, and common corporate decency, to assure that the products they bring to market are safe and will reliably produce the benefits for which they are registered, i.e. control of weeds as in the case of glyphosate.

972. The term "product stewardship" is used within the industry and regulatory agencies to describe and encompass the actions pesticide manufacturers should take on an ongoing basis in the interest of product stewardship, before and after a new use of a pesticide is approved.

973. In the pesticide arena, the sciences supporting both human-health risk assessments and environmental-impact assessments are dynamics and imperfect, and heavily dependent on location- and even application-specific data, which is almost never available. So, in companies and regulatory agencies alike, many assumptions and a considerable degree of judgement is essential in deciding upon the science that must be conducted prior to seeking, and approving a new use of a pesticides.

974. Where to draw the line between presumably safe and possibly risky pesticide uses is also fraught with scientific, social, and political challenges, uncertainty and tension.

975. The same is true after approval, as companies and regulators strive to refine and agree on the nature and magnitude of risks after a pesticide is approved and has been applied for a period of time.

976. But in general, Monsanto claims that they base all their product development, testing, commercialization, and regulatory actions on the best available science. Such science is

often produced and communicated by pesticide registrants in the hope of altering the outcome of risk assessments conducted by regulators, especially when existing estimates of risk point to potential problems (e.g., a risk that exceeds the EPA's "level of concern").

977. The crux of most protracted and contested regulatory confrontations over the last half-century has been debate over what the "best" or "soundest" science shows relative to the balance of pesticide risks and benefits.

978. This is surely the case with glyphosate and Roundup herbicides.

A. Mission One – Protect Freedom to Operate (FTO)

979. Tensions often arise between the commercial interests of a pesticide manufacturer and what the latest and best science suggests is the most responsible way to manufacture and sell a given pesticide.

980. In Monsanto, protecting the Freedom to Operate in the manufacture and sale of glyphosate-brand herbicide was the dominate objective across the whole company. Science was valuable, and supported, only when and to the extent it was expected to support glyphosate FTO.

981. Monsanto's John Acquavelle makes the case for one such investment in science as part of a proposal for a new, industry-funded, multi-pesticide non-Hodgkin lymphoma epidemiology study.

982. The goal of the study, among other things, would be to respond to the positive glyphosate-NHL results in the Hardell-Eriksson, and the forthcoming epidemiological study results from the National Cancer Institute's "Agricultural Health Study:

> "There are a number of reasons why industry should consider this proposal seriously. First, allegations that pesticides cause cancer are important to the business and regulatory climate for pesticide manufacturers and, indeed, companies have a product stewardship obligation to ensure that their products can be used safely." (MONGLY00894005)

983. Monsanto did not follow Acquavella's advise and has never conducted an

epidemiological study to evaluate the relationship between NHL and Roundup formulations.

1. Section 6(a)(2) of FIFRA

984. Section 6(a) (2) of FIFRA, discussed earlier, is a provision in federal law intended to vest clear responsibility on pesticide registrants to report to the EPA any information, data, or new insights regarding pesticide risks that are gained by the registrant, regardless of the source of the information.

985. The June 1986 Registration Standard for glyphosate contains this passage: "Registrants [at this time for glyphosate, only Monsanto] are reminded that FIFRA sec. 6(a)(2) requires them to submit factual information concerning possible unreasonable adverse effects of a pesticide at any time that they become aware of such information…including interim or preliminary results of studies, if those results suggest a possible adverse effect on man or the environment. This requirement continues as long as your products are registered by the Agency." (page 3)

986. Dozens of instances arise in the 40+ year record of glyphosate in which Monsanto chose not to disclose information that might suggest a new or heightened risk from use of glyphosate-based herbicide. Some information not disclosed under Section 6(a)(2) arose from the company's inhouse research or commissioned studies, while other information was learned from the experience of users of the company's products.

2. Responding to FQPA Challenges

987. Passage of the Food Quality Protection Act (FQPA) in 1996 changed the basic standard and rules governing the setting of food-additive tolerances for pesticide known to be oncogenic, including glyphosate beginning in 1983. Implementation of the FQPA required EPA to deal with dozens of science and risk assessment policy issues over several years, some of

which had potential impacts on a number of Monsanto products, including glyphosate.

988. Monsanto established an "FQPA Core Team to engage with EPA as it developed FQPA policies and procedures, and to alert colleagues of possible implications for the labels and tolerances sanctioning use of specific Monsanto pesticide products." (MONGLY03750989)

989. Abby Li [FND/1735] was a member of this FQPA Core Team. She sent a November 20, 1999 email to several Monsanto management team and senior officials regarding the activities of the FQPA Core Team. After listing the six members of the FQPA Core Team, the email stated:

> "This [membership] is a good mix of people that allows us to have external influence as well as ensure that we have practical understanding of the full impact to our products. I'd like to make sure we push hardest on those issues that are threatening our business." (MONGLY03750989)

990. Two days earlier, on November 18, 1999, Abby Li sent an email to 10 Monsanto colleagues regarding a scoping session on the evolving OPP policies governing aggregate risk assessment under the FQPA. (The FQPA directed the EPA to take account of exposures to a given pesticide from water, food, occupational, atmospheric, and any other routes of exposure; such total estimates of exposure from all routes are called "aggregate exposure" in the context of FQPA implementation).

991. The email begins: "Dear people who might be interested in the FQPA,…" The last paragraph addresses the membership of the FQPA Core Team and key areas of expertise that need to be represented. Then, Abby Li writes: "A key goal is to understand how our products are impacted so we know what issues Monsanto should fight the hardest on." (MONGLY03750990)

992. The implication is clear. The number one goal driving Monsanto's assessment of evolving EPA science policies and regulatory procedures is minimizing the impact on FTO and sale of Monsanto products.

993. In the records I have reviewed, I have not encountered a single example of a person working for Monsanto who reacted to a new pesticide law or regulatory requirement by assessing where and how compliance might make the company's products inherently safer, or reduce the frequency of high-exposures application scenarios, like some of those experienced by Dewayne Johnson.

B. Overstating Roundup Benefits and Understating Possible Risks

994. In the portion of the discovery record in this case that I have reviewed, there are dozens of examples where Monsanto employees, consultants, third party network scientists, and PR firms prepare and share written materials that overstate the certainty of some things (e.g., get up and shout glyphosate is non-toxic"), and downplay the significance of other known facts (e.g., glyphosate-based herbicides are genotoxic in some tests).

995. No doubt the total number of such episodes that could be identified after a comprehensive review of the whole record would be in the hundreds.

996. In an episode described in detail earlier, Monsanto officials substantially mischaracterized statements made by third-party experts that Monsanto had brought to an EPA Scientific Advisory Panel meeting.

997. The inaccurate statements were contained in a letter from Monsanto's senior U.S. registration specialist, to EPA after the SAP meeting. The letter asserted that Monsanto's invited guests testified at the SAP meeting that a repeat of the controversial Bio/dynamics mouse study was not warranted, when none of the invited experts made such a statement.

998. Only a small group of other examples are discussed below.

1. Attempts to Influence the IARC Review

999. Monsanto knew that the IARC review of glyphosate herbicide carcinogenicity

was coming in the spring of 2015. In 2014, they initiated a number of activities in the hope of influencing the decision reached by the IARC Working Group assessing glyphosate carcinogenicity.

1000. IARC procedures and policies are clearly stated and well known. For example, see the 2015 published paper "IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans" (Donna Farmer Exhibit I-44; or access online https://ehp.niehs.nih.gov/wp-content/uploads/123/6/ehp.1409149.alt.pdf).

1001. IARC Working Groups review and rely only on the results, insights, and information in scientific papers published in peer-reviewed journals. Unpublished studies conducted by companies, or papers in the publication process, but not accepted, are not considered.

1002. This is why Monsanto wanted two papers published before the end of the IARC review process, so that both would be among those in the peer-reviewed literature, and hence eligible for consideration by the IARC Working Group.

1003. Both papers had been in preparation for some time, and included a paper by Kier on genotoxicity and one by Greim et al. on the results of rodent bioassays.

2. Kier (2015) Sets a Record for Speedy Publication

1004. Monsanto commissioned and paid for a review article focused on genotoxicity biomonitoring studies.

1005. The goals for the paper were to first, influence the outcome of the IARC assessment, assuming the timing of the paper's publication allowed, and second, to have a current, peer-reviewed paper offering Monsanto's assessment of positive, genotoxicity studies available for use as Monsanto worked to discredit the legitimacy and science-base of the IARC

classification decision.

1006. Larry Kier, then a consultant to Monsanto and a former, long-term employee, wrote the paper, which was submitted to Roger McClellan, Editor of the journal *Critical Reviews in Toxicology* (*CRT*). This journal had been used several times by Monsanto to, in effect, spin and/or recycle in a peer-reviewed science journal the company's proprietary, internal studies, findings, and assessments of glyphosate risk issues, including those that had been previously submitted to regulators.

1007. The 2015 *CRT* paper by Kier was entitled "Review of genotoxicity biomonitoring studies of glyphosate-based formulations" (Vol 45(3): pages 209-218; accessed 12/10/17 at http://www.tandfonline.com/doi/pdf/10.3109/10408444.2015.1010194?needAccess=true).

1008. The paper's "History" declaration states that the initial paper was submitted to *CRT* on January 7, 2015, and was revised by the author and submitted back to *CRT* on January 17, 2015. It was accepted for publication by the journal the next day, January 18th, and published online February 16, 2015, or about one month before the March 3-10, 2015 final meeting of the IARC Working Group conducting the glyphosate assessment.

1009. Accordingly, 11 days transpired from the date of the original submission to the receipt and acceptance of the Kier paper. This meant that the peer review process, the editor's assessment of the reviewer comments, the author's revisions in response to peer-review comments, submission back to the journal, the editor's consideration of the author's response to reviewer comments, and decision to accept and publish all occurred in 11 days!

1010. I have published about three-dozen peer-reviewed papers. Between several months to over a year transpired between initial submission and acceptance of each of them, a time-frame that is typical of most papers, and most peer-reviewed science journals.

1011. Over the last 30+ years at the request of journals, I have served over 100 times as a peer-reviewer of papers submitted for possible publication. It generally takes a few weeks to two months for me to free up sufficient time to complete and submit such reviews.

1012. Not a single paper of mine, or paper that I reviewed, progressed through the publishing process in 11 days. Indeed, I doubt that many, ***if any***, papers in the history of scientific publishing in a well-respected journal have matched this record for "timely" publication.

1013. Clearly, there had to have been an extraordinary set of circumstances driving the pace of the publication process for the Kier (2015) *CRT* paper. Based on the record, the two most important special circumstances were the close and long-term relationship between this journal and Monsanto, and second, Monsanto's openly-stated need for the paper to be published before the final meeting in March of the IARC, glyphosate Working Group.

1014. But for this to happen, the company had to find a friendly journal willing to conduct the peer-review process in world-record time. They did in *CRT*.

3. "Inappropriate Absolutes" Used to Promote Kier (2015)

1015. On February 19th, a few days after the Kier (2015) *CRT* paper was published online, an email exchange occurred between the paper author, Larry Kier, the journal editor Roger McClellan, and Monsanto's David Saltmiras.

1016. This exchange focused on the content of promotion material on the Kier paper that Saltmiras had sent to the journal editor, along with a request that McClellan and the publisher take steps to raise the visibility of the paper. (MONGLY01087311-17)

1017. This email chain starts on 2/19/17 with an email from David Saltmiras to *CRT* editor McClellan that begins "Roger – FYI on press releases." This email was not cc'd to the

lead authors of the papers (Greim and Kier).

1018. The Saltmiras email to McClellan then lists the full citation to the papers by Greim et al. (2015) and Kier (2015) that are being published at the same time in *CRT*, a summary of each paper, the paper abstracts, and "Sound bytes for social media."

1019. A few hours later in response to the suggestion from Saltmiras, McClellan sent an email to Charles Whalley, a senior manager at the publishing company Taylor and Francis (T and F). This is the publishing company that puts out McClellan's journal, *CRT*. The email begins:

> "I spoke with David Saltmiras today concerning the two Glyphosate papers that will be the lead papers in the next issue of Critical Reviews in Toxicology with regard to F and F [referring to T and F, the first "F" in the original text is a typo] putting out any publicity on these two papers. The email below includes complete citations for the papers, abstracts and some information developed by Monsanto Company on the papers."

1020. The McClellan email goes on to state the relevance of the Kier (2015) paper to the ongoing IARC glyphosate review, and then writes:

> "As a bottom line the two papers [Greim et al. and Kier] published on line in *CRT* are likely to attract some attention in the scientific and regulatory community and, possibly, by lay media."

1021. McClellan then asks about Taylor and Francis policies regarding the publisher's promotion of just-released papers, and asserts that the two papers "would be excellent candidates" for such a promotional effort by the publisher.

1022. As a courtesy, McClellan had also sent a copy of his seemingly innocuous, 2/19/17 email to David Saltmiras and Larry Kier. Just under a half-hour later, Kier responded by email to *CRT* Editor McClellan. He begins: "I'm a little cautious about high levels of publicity for the biomonitoring review and have concerns about some of the suggested publicity material." (MONGLY01087312)

1023. Kier then writes: "I don't know who wrote the 'Summary' for my paper and certainly don't want to offend them but it is not the way I would have worded it and I would personally not want this used to characterize my paper."

1024. The differences between the "Summary" of Kier's paper sent to McClellan by Saltmiras, and presumably written by him, and the revised "Summary" Kier wrote and included in his email to McClellan are subtle, but significant.

1025. The key passages from the Saltmiras-submitted "Summary" of Kier's paper read: "The author concluded that there are no direct risks to human DNA under normal exposure conditions" and "these results confirm previous conclusions that glyphosate-based herbicides do not damage DNA in humans following real world exposures."

1026. The comparable passages that Kier wrote for a revised "Summary" of his paper read: (1) "The author concluded that these studies [on genotoxicity] do not indicate significant genotoxic risks to humans from glyphosate-based herbicides under normal exposure conditions"; and (2) "These findings are consistent with an earlier review of an extensive number of laboratory studies that indicated little likelihood of significant genotoxic risk or reaction with DNA under normal exposure conditions."

1027. The Saltmiras version of sentence (1) is unequivocal – "there are no direct risks to human DNA." Kier's rewrite of (1) includes an important change. Instead of "no risk," Kier writes that there is an absence of "significant genotoxic risks," implying there might be some risk.

1028. In key passage (2) quoted above, the Saltmiras version states that glyphosate-based herbicides "do not damage DNA in humans." Kier's rewrite says that there is "little likelihood of significant genotoxic risk or reaction with DNA under normal exposure

conditions."

1029. This version contains two, and perhaps three caveats. First, there is "little likelihood," but hence some chance of "significant genotoxic risk or reaction." Second, Kier again leaves the door open for less than "significant" genotoxic risk or reaction.

1030. In the same email to McClellan, Kier then turns his attention to the "Sound bytes for social media" in the Saltmiras email to McClellan sent earlier the same day. The sound bytes state that glyphosate-based herbicides "do not damage cellular DNA…" and are "not associated with DNA damage in human cells." About these statements, Kier writes:

> "I also don't think the 'Sound bytes for social media' are accurately worded. They are way too absolute for my taste and place undue emphasis on the strength of the biomonitoring data. Unfortunately, I can't readily suggest alternatives that fit nicely into the 'sound byte' format."

1031. Nine minutes later at 5:12 p.m., after receiving the above described and unusual email from Kier, *CRT* Editor McClellan responds to Kier, sending a copy to Saltmiras. He writes:

> "Larry:
>
> What I forwarded to T and F (Charles Whalley) is what I received from David Saltmiras. I assumed you were in the loop on what had been developed at Monsanto. I suggest you get in touch ASAP with David."

1032. Around noon the next day, Larry Kier does email David Saltmiras. His message is terse and to the point, and quoted in full below:

> "David,
>
> I think I might have misunderstood something in our earlier conversation today but apparently the Summary and Sound bytes were from Monsanto.
>
> Please consider the bcc: comments I sent earlier to Roger. While I definitely support glyphosate and GBF's [glyphosate-based formulations] I really don't want to have ***inappropriate absolutes*** representing this [Kier, 2015] review." (Emphasis added; MONGLY01087311)

4. Advertising

1033. In June 1988, a member of the medical school faculty at the University of Iowa saw an advertisement for Roundup herbicide on TV, depicting a bean bar application of the herbicide. The person in the advertisement was wearing gym shoes, a short sleeve shirt, and long pants. He called the EPA to raise concern over the safety of such a method of application under the conditions depicted in the advertisement.

1034. Edwin Tinsworth, then Director of the OPP Registration Division, wrote a July 26, 1988 letter to Dr. Timothy Long, then Roundup's Registration Manager, stating that: "We are concerned that advertisements for Roundup (running through July in Iowa and perhaps other soybean growing areas) show the product being applied in a manner inconsistent with protective clothing requirements…and we request that you cease running these spots."

1035. In a certified letter dated April 7, 1992 to Monsanto, Leo Alderman of the Toxics and Pesticides Branch in EPA Region VII challenges misleading claims made in Monsanto advertising literature promoting Roundup sales. These statements included "Roundup doesn't stay in the soil, won't leach to nearby plants and breaks down into natural substances…Nothing kills weeds better, or easier, than Roundup…Biodegrable."

1036. He instructs Monsanto that "such statements should be removed from all literature advertising the product…" Alderman directs Monsanto to cease distributing all advertising material with such claims and that the Monsanto send him/EPA copies of the revised advertising material within 30 days.

C. Tactics Used to Bury or Obscure Issues Perceived to Raise Risk and Regulatory Threats to Future Sales

1. Positive Evidence of Carcinogenicity

1037. Given the facts of this case, one of the most compelling and germane statements by a senior Monsanto scientist on the topic of glyphosate's carcinogenicity comes from Donna Farmer.

1038. In alerting an overseas spokesperson for Monsanto about what can be said to the media on the question of glyphosate health risks, she writes "…you cannot say that Roundup is not a carcinogen…we have not done the necessary testing on the formulation to make that statement." She goes on to acknowledge that "The testing on the formulations are not anywhere near the level of the active ingredient." (MONGLY00922457-8)

1039. Instead, she advises the spokesperson to respond to questions about glyphosate safety by saying: "When Roundup herbicides are used according to label directions, no unreasonable adverse effects to people, wildlife, and the environment are expected." (MONGLY092259)

2. Counteracting Positive Epidemiology Study Findings

1040. In 2000, Dr. John Acquavella, a Monsanto epidemiologist, attended a meeting of the International Society for Environmental Epidemiology (ISEE) in Buffalo New York. (MONGLY02628625). Two papers focusing on pesticide-cancer linkages were presented by scientists working for Health Canada.

1041. Dr. Helen Mcduffee was the lead scientist at the Center for Agricultural Medicine at the University of Saskatchewan, and carried out the Health Canada-funded case-control study of 517 individuals with non-Hodgkin lymphoma (NHL) and 1,506 controls. The paper presented at the ISSE reported a statistically significant odds ratio of 2.1 (95% CI 1.2-3.6) for individuals with NHL who sprayed Roundup more than 2 days per year.

1042. Following Dr. McDuffee's presentation, Acquavella sought her out for further

discussion of her work, and in the hope of establishing a dialogue. He characterized her as "a reasonable person" who does not have "preconceived notions about glyphosate."

1043. In Acquavella's memo to senior colleagues responsible for health assessments of Roundup, the following agreements and next steps were outlined:

- McDuffee would share her paper on these results when it is ready for submission;
- She was asked, and agreed to attend a meeting where her work would be presented to an industry audience; and
- She was given a copy of the Monsanto-commissioned CANTOC review of glyphosate and Roundup toxicity, and told about the ongoing Monsanto Farm Family Exposure Study (FFES).

1044. A second study by a member of Dr. McDuffee's team, Pahwa Punam, was presented via a poster at the ISEE meeting. This presentation focused on regional differences in the association between Roundup use and NHL, and Hodgkin's disease (HD).

1045. "Of interest to us," according to Acquavella, was the significant association between glyphosate/Roundup and HD in the Canadian province British Columbia. In that province, there was a markedly elevated, statistically significant odds ratio of 4.0 (CI 1.4-11.3), in contrast to no such association in the other Canadian provinces.

1046. Acquavella asked Punam if she had any explanations for the very different, and worrisome result in British Columbia. According to Acquavella, "she speculated that the variation might be explained by the heavier use or the tendency to use higher exposure application equipment in specific provinces."

1047. Acquavella then reports that if "we [Monsanto] get inquiries" regarding the Roundup-HD association, "we can point out that the variation [across provinces] in the findings is inconsistent with a causal relationship with glyphosate."

1048. Then, Acquavella addresses "Follow-up Plans," which include:

- Developing a "collegial relationship" with Dr. McDuffee;

- Sharing information on the FFES;
- Adding McDuffee "in our plans to develop a scientific outreach network in Canada; and
- Inviting McDuffee to present her data at a Monsanto-sponsored scientific outreach meeting in Canada later in the year.

1049. Such follow-up actions, according to Acquavella, could be important strategically in light of Health Canada's continued investment in agricultural epidemiology and the ongoing networking between Health Canada and the [U.S.] NCI [National Cancer Institute]." In addition, the above meetings "would allow her to consider her findings in light of the available glyphosate toxicology/exposure information…"

1050. Clearly, Acquavella was concerned that a positive epidemiological study sponsored by the Canadian government linking glyphosate/Roundup to NHL and HD would carry weight, and possibly reinforce similar associations identified in other studies, including, perhaps, those emerging from the ongoing NCI Agricultural Health Study.

1051. His follow-up actions included providing McDuffee with the Cantox review, and likely the Williams et al (2000) review of glyphosate/Roundup toxicity, both of which were commissioned by Monsanto, co-authored by proven, glyphosate-friendly members of the company's Scientific Outreach team, and substantially ghost-written by Monsanto scientists.

1052. He does not mention providing her with any of the published, positive genotoxicity studies, nor Dr. Parry's report.

1053. These follow-up actions are a good example of the way Monsanto establishes a relationship with independent scientists in order to discover, first, whether a scientist is already glyphosate-friendly, and if so, whether he/she would be willing to be a public spokesperson in defense of glyphosate/Roundup safety.

1054. In cases where a scientist has reported, and/or appears ready to publish and

discuss in public findings that are not favorable to glyphosate-based herbicides, Monsanto strives to alter the scientist's interpretation and/or explanation of a study's findings in a way that minimizes the potential damage to Monsanto's unequivocal claim that "Roundup is safe," a message Monsanto wants people to get up and shout.

1055. Via this sort of follow-up actions, the company also makes it clear that the work of a scientist like McDuffee will be examined closely and any limitation or possible confounding factor will, in all likelihood, be used to discredit the study's design, methodologies, and findings, if and when the study is published, discussed publicly, or especially, if it becomes available to regulators.

1056. There is no universally accepted way to distinguish between legitimate give-and-take between scientists, and intimidation. However, Monsanto has a well-deserved reputation for engaging in aggressive and systematic defense of its products, and especially glyphosate/Roundup. Such actions have undoubtedly discouraged some scientists from publishing results from studies that have limitations, like small sample sizes or potential recall bias.

1057. In other cases, scientists may state their findings and conclusions in a more equivocal way than they otherwise would, in the hope of not triggering overt and covert actions by Monsanto to discredit the research, or the researcher.

3. Dermal Absorption

1058. The rate of dermal absorption when a person's skin is exposed to a glyphosate-based herbicide like Roundup is a key variable in estimating applicator exposure and risk.

1059. In the hope of maximizing Roundup sales and minimizing regulatory warnings and/or restrictions, Monsanto has worked to convince regulators that the dermal absorption rate

for glyphosate and Roundup herbicide is very low, as a percentage of the amount of glyphosate or Roundup that initially comes into contact with a person's skin.

1060. Low dermal-absorption rates for any pesticide, other things being equal, will result in less worrisome warning symbols on labels, less strict limits on the conditions of use, and/or fewer and less onerous requirements for personal protective clothing and equipment for those mixing and loading Roundup, or applying the herbicide.

1061. In EPA's 1986 glyphosate Registration Standard and the 1993 Re-registration Eligibility Document (RED), the agency incorporated an estimated 3% dermal absorption rate for glyphosate in its estimates of applicator exposures and risk. This estimate, in turn, was based on studies conducted by Monsanto and submitted to the agency in the past.

1062. As the diversity of Roundup uses expanded in the consumer market in the U.S. and worldwide, regulators became more concerned about the dermal route of exposure, especially in the case of people engaged professionally in weed control on a farm, in an horticultural or industrial setting, or in parks, around schools, or golf courses, among other places.

1063. To prevent the EPA from imposing additional restrictions, or requiring higher-level warnings on Roundup labels, Monsanto continued to conduct dermal absorption studies periodically, in the hope of eventually convincing the EPA, and/or other regulators, to lower the standard estimate of dermal absorption to below 3%.

1064. Glyphosate-based herbicides were going through the European re-registration process in the late 1990s into the 2000s. The German regulatory authority had been assigned the task of serving as the rapporteur through the process on behalf of the EU. German regulators had asked registrants of glyphosate-based herbicides to repeat some old dermal absorption studies

that did not meet current European regulatory standards, a request that Monsanto agreed to carry out. (MONGLY03737015)

1065. An email exchange occurred in April 2002 between Monsanto employees in Europe working on the new data required by German regulators, and senior Monsanto personnel in St. Louis (Heydens, Healy, Farmer, [redacted], Wratten, among others).

1066. [redacted], a Brussels-based Monsanto employee, reported that Monsanto had agreed to conduct a new *in vitro* dermal penetration study with rat skin, work that had begun with a contract laboratory called TNO.

1067. An email chain was started on March 29, 2002 by [redacted] on the topic of the newly requested dermal absorption study. It described preliminary findings reported to Monsanto by TNO, steps taken in response, and addressed the need for a conference call to agree on "next steps."

1068. In an April 2, 2002 email from William Heydens to his colleague Charles Healy about the "new issues and topics for the conf call of Tuesday, 2 April," Heydens wrote: "My primary concern is with glyphosate in terms of the potential for this work to blow Roundup risk evaluations (getting a much higher dermal penetration than we've ever seen before." (Text as it appears in email). (MONGLY03738295)

1069. By "this work," Heydens was clearly referring to the new rat skin dermal penetration study. His concern that such a study might "blow Roundup risk evaluations" arose from the fact that a higher dermal absorption rate would invariably increase estimated risks, and possibly by enough to raise serious new concerns among regulators and restrict glyphosate's FTO.

1070. In an April 4, 2002, email, [redacted] reports to the group that, as a result of the

preliminary TNO results reported to Monsanto, "we came to the conclusion that the penetration of glyphosate would have been [probably] greater than the 3% already imposed by the German authorities. We decided thus to **STOP** the study (effective today)." (Emphasis in original; MONGLY03737015)

1071. Donna Farmer replied to this email later the same day, asking for clarification, leading to an email the next day from [redacted], a Monsanto scientist more directly involved with the scope and focus of recent and ongoing work on dermal absorption.

1072. [redacted] wrote in his April 5, 2002 email response to Farmer, and all others on the April 2 email chain, "We dropped the programme for glyphosate because a further study was not likely to help us meet the project objective...", which was to make the case for reducing below 3% the glyphosate dermal absorption rate used by regulators.

1073. This decision was triggered by preliminary results from TNO showing that the dermal absorption rate for the glyphosate in formulated Roundup herbicide (MON 35012) through rat skin is 5% to 10%, compared to less than 1.5% for pure glyphosate. (MONGLY03738296)

1074. According to [redacted], this surprisingly large difference between the dermal absorption rate of pure glyphosate (~1.5%), compared to formulated Roundup (5% to 10%), "confirm our expectation that surfactant concentration affects dermal absorption."

1075. So, the early data from TNO suggested that a properly conducted set of dermal absorption studies on Roundup herbicides would actually lead to a substantial increase in the then-current 3% estimate of dermal absorption.

1076. This new data was obviously not helpful, given Monsanto's stated objective in conducting new, improved dermal absorption studies (reducing the 3% estimate of dermal

absorption used by regulators).

1077. Moreover, the sharp contrast between the absorption rate for pure glyphosate, as opposed to the absorption data for the glyphosate in formulated Roundup with surfactants, highlighted a critical risk assessment and regulatory issue that Monsanto had worked diligently since the late 1970s to suppress and ignore – the very different risk profile stemming from exposure to the glyphosate in formulated Roundup products, in contrast to studies quantify the risk of exposure to pure glyphosate.

1078. This episode is one of dozens in the record showing that Monsanto's primary interest in conducting tests on glyphosate and/or Roundup was to defend current registrations and/or convince regulators to approve new uses, rather than to understand more accurately actual risk levels.

1079. Monsanto was simply not interested in providing regulators new data that would provide a sounder base of information to quantify risk levels, so that high-risk application scenarios can be identified and addressed.

1080. Nor was Monsanto willing to use better information on worker risk levels to devise label instructions that warn applicators about high-risk application methods and circumstances, like using a backpack sprayer on a windy day, and commonsense measures to reduce exposures, like walking perpendicular to the wind when spraying on windy days.

1081. In all likelihood, this episode involving the TNO study of dermal penetration is an example of Monsanto's many failures to comply with the so-called adverse effects reporting requirement in federal pesticide law (FIFRA Section 6(a)(2)).

1082. This provision in FIFRA places a clear obligation on pesticide registrants to report to the EPA on a timely basis any information the company comes into the possession of that

suggests the existence of new risks, or higher risks than previously recognized and addressed by the EPA.

1083. The TNO data suggesting that the actual dermal absorption rate for glyphosate in formulated Roundup should be 5% to 10%, instead of 3%, is exactly the type of important, new information that Section 6(a)(2) in FIFRA requires registrants submit to the EPA.

1084. I conclude that the failure to share the results of the preliminary TNO rat skin dermal penetration study was a likely violation of Section 6(a)(2), recognizing that Monsanto may have submitted the data in compliance with Section 6(a)(2).

1085. If Monsanto did make such a disclosure to the EPA of the TNO glyphosate dermal absorption data, the company will surely challenge my opinion and correct the record, by sharing with the court the documents confirming that such a transmission of data was made in accord with Section 6(a)(2) requirements.

4. Nitrosamine Contaminants in Roundup Herbicide

1086. In a July 14, 1977 "Recommendation" in response to a Monsanto request for an extension of an existing Experimental Use Permit (EUP) that would sanction use of 705 gallons of Roundup in 1978, EPA notes that the Toxicology Branch has previously raised concern over the 0.2 to 0.4 ppm of N-nitrosoglyphosate (NNG) in formulated, Roundup herbicide (MONGLY00223253).

1087. The "Recommendation" was to not approve the EUP extension because the petitioner, Monsanto, "…has made no assessment of possible hazards…" to applicators and those handling the herbicide.

1088. Accordingly, since 1977, EPA concerns over the NNG content of Roundup herbicides were among the health and safety issues in play between EPA and Monsanto.

1089. Several new toxicology studies were submitted by Monsanto to EPA in the 1977-1980 period in support of pending temporary tolerance petitions and EUPs, including some specifically in response to the agency's concern over NNG.

1090. An October 4, 1977 memo from the Toxicology and Residue Chemistry Branch evaluated four new studies, only one of which was judged "satisfactory" (an oral LD-50 study using rats) (MONGLY00223244).

1091. The October 7, 1977 memo ends with the statement "However, we have not recommended, and do not intend to recommend, for either permanent tolerances or registrations, based on these data." This is one of several EPA memos raising concerns with the quality and completeness of the data submitted by Monsanto in support of both tolerances and registrations.

1092. In 1978, Monsanto submitted to EPA an internal study assessing the metabolism of NNG in rats. This report discusses the possibility that glyphosate can interact with nitrite in the diet to form cancer-causing nitrosamines. (MONGLY00922461)

1093. Several years later in 2004, a Canadian agricultural scientist wrote Monsanto about this concern, and asked if the company had any new data or insights they could share on this possible source of cancer risk.

1094. The response from Monsanto was that such a concern is unwarranted because "…glyphosate has been carefully monitored for years by regulatory agencies around the world, and, consistently it is not detected in drinking water sources."

1095. While there were limited reports of glyphosate in drinking water in 2004, just a few years later there would be several.

1096. Over the last decade, scientists in Europe, South America, and the U.S. have reported steadily rising levels of glyphosate in drinking water resources. In heavily farmed areas where Roundup Ready crops are widely planted and Roundup is heavily used, glyphosate detections in drinking water are now common.

Charles Benbrook

12/21/17

Exhibit 4

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

-vs- Case No. CGC-16-550128

MONSANTO COMPANY,

Defendant.

CONFIDENTIAL VIDEOTAPED DEPOSITION OF

DR. CHARLES M. BENBROOK

9:04 a.m. to 7:45 p.m.

February 8, 2018

Orange, Virginia

Job No. 137478

REPORTED BY: Rhonda D. Tuck, RPR, CRR

Confidential Videotaped Deposition of DR. CHARLES M. BENBROOK, taken and transcribed on behalf of the Defendant, by and before Rhonda D. Tuck, RPR, CRR, Notary Public in and for the Commonwealth of Virginia at large, pursuant to the Rules of Civil Procedures for the State of California, and by Notice to Take Depositions; commencing at 9:04 a.m., February 8, 2018, at The Round Hill Inn, 750 Round Hill Drive, Orange, Virginia.

APPEARANCES OF COUNSEL:

THE MILLER FIRM
The Sherman Building
108 Railroad Avenue
Orange, Virginia 22960
BY: TIMOTHY LITZENBURG, ESQUIRE
JEFFREY TRAVERS, ESQUIRE
Counsel for the Plaintiff

APPEARANCES OF COUNSEL CONT'D:

ANDRUS WAGSTAFF
19 Belmont Street
South Easton, Massachusetts 02375
BY: KATHRYN FORGIE, ESQUIRE
Counsel for the Plaintiff

HOLLINGSWORTH
1350 I Street, N.W.
Washington, DC 20005
BY: WILLIAM COPLE, III, ESQUIRE
GRANT HOLLINGSWORTH, ESQUIRE
Counsel for the Defendant

APPEARANCES OF COUNSEL CONT'D:

WINSTON & STRAWN
35 W. Wacker Drive
Chicago, Illinois 60601
BY: SARAH KRAJEWSKI, ESQUIRE
Counsel for the Defendant

ALSO PRESENT:
Matthew Henry - Videographer

I N D E X

WITNESS: DR. CHARLES M. BENBROOK

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Examination by Mr. Litzenburg.....573

Q. Chemistry?

A. No, sir.

Q. Is there any physical science in which you have received education that has recognized you with a degree?

A. No.

Q. What about the field of regulation, specifically the U.S. Environmental Protection Agency? Are you trained and certified by any organization as someone who has expertise in EPA regulations?

MR. LITZENBURG: Form.

THE WITNESS: I don't know of any organization that does that. If one had existed, I perhaps might seek such certification, since my -- throughout my entire career I've worked on federal pesticide legislation, regulation issues, but I don't know of any such certification.

BY MR. COPLE:

Q. Well, let's just --

A. So I have none.

Q. Well, let's just talk about what you just said for a brief moment: Throughout your career that you've worked on pesticide legislation and

DR. CHARLES M. BENBROOK

COMMONWEALTH OF VIRGINIA AT LARGE, to wit:

I, Rhonda D. Tuck, RPR, CRR, Notary Public in and for the Commonwealth of Virginia at Large, and whose commission expires on May 31, 2020, do certify that the aforementioned appeared before me, was sworn by me, and was thereupon examined by counsel; and that the foregoing is a true, correct, and full transcript of the testimony adduced.

I further certify that I am neither related to nor associated with any counsel or party to this proceeding, nor otherwise interested in the event thereof.

Given under my hand and notarial seal at Charlottesville, Virginia, this 12th day of February, 2018.

_____

Rhonda D. Tuck, RPR, CRR

Notary Public Registration No. 224847

Commonwealth of Virginia at Large

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF SAN FRANCISCO

DEWAYNE JOHNSON,

Plaintiff,

-vs- Case No. CGC-16-550128

MONSANTO COMPANY,

Defendant.

CONFIDENTIAL VIDEOTAPED DEPOSITION OF

DR. CHARLES M. BENBROOK

9:13 a.m. to 3:28 p.m.

February 9, 2018

Orange, Virginia

Job No. 137479

REPORTED BY: Rhonda D. Tuck, RPR, CRR

in your expert report, correct?

A. It's a -- it is a TNO report. I don't know which one it is. I don't know the full number of reports that TNO provided to the agency. I do know what the Monsanto scientists who commissioned this work -- what they said to their colleagues and reported about the -- a rat dermal absorption study that they had commissioned TNO to undertake.

Q. Did you review any of the TNO reports on dermal testing?

A. I was unable to locate any of these in the record. They may be in the discovery record, but I didn't see them. And since they've got a Bates number, they're clearly a part of the record. So no, I did not have an opportunity to review this skin penetration or skin permeability study.

Q. You -- on Page 111 of your report, that's Exhibit 4.

A. Okay.

Q. In Paragraph Number 588, your report says that "to address revolving worker risk concerns among European regulators, Monsanto commissioned a dermal penetration study in rats. It was conducted by then a contract lab, TNO. The results of the rat study using Roundup formulations suggests that 5 to

they have. I felt that it was important to at least include in my expert report that the identity and levels of impurities in glyphosate-based herbicides has been an issue under review since actually the late '70s. There's been some data generated. Monsanto actually has done studies on this NNG. I simply note that that is part of the scientific evaluation of risk that's associated with glyphosate-based herbicides.

I'm not aware of any conclusions that the agency has reached that these impurities contributed to any of the indication of oncogenetic response or genotoxic response in any of the studies that have been done by Monsanto and submitted to the agency or published in the peer-reviewed literature.

However, it will I think remain an issue that the EPA and other regulatory authorities continue to track and monitor.

BY MR. COPLE:

Q. EPA has not determined that the level of impurities in glyphosate formulations is an issue of toxicological concern, right?

MR. LITZENBURG: He's asked the same

question and you've answered it six times. You're welcome to stand on your answer or --

THE WITNESS: Yeah.

MR. LITZENBURG: -- answer the same way over and over again.

THE WITNESS: I agree with that. Yes. The answer is yes.

BY MR. COPLE:

Q. Now, let's take a brief look at your report, Paragraph Numbers -- on Page 115, and it continues to Page 116, and it starts at 608 talking about a Jess Rowland from EPA. Then it goes to 609, continues to talk about Mr. Rowland, 610, and the same thing on the next page. It continues to talk about him in Paragraph Number 611, 612, 613, 614, and I think that's where it stops.

Now, do you know Mr. Jess Rowland?

A. No.

Q. And Mr. -- and these paragraphs, discussing emails inside Monsanto about various potential communications with Mr. Rowland, Mr. Rowland was not a party to those documents that you reviewed, right?

A. He was to some of them. Some of the emails in the record are between Jess Rowland and

COMMONWEALTH OF VIRGINIA AT LARGE, to wit:

I, Rhonda D. Tuck, RPR, CRR, Notary Public in and for the Commonwealth of Virginia at Large, and whose commission expires on May 31, 2020, do certify that the aforementioned appeared before me, was sworn by me, and was thereupon examined by counsel; and that the foregoing is a true, correct, and full transcript of the testimony adduced.

I further certify that I am neither related to nor associated with any counsel or party to this proceeding, nor otherwise interested in the event thereof.

Given under my hand and notarial seal at Charlottesville, Virginia, this 12th day of February, 2018.

_____

Rhonda D. Tuck, RPR, CRR

Notary Public Registration No. 224847

Commonwealth of Virginia at Large

Exhibit 5

TNO-rapport / TNO report

V 4478

In vitro percutaneous absorption study with [^{14}C]glyphosate using viable rat skin membranes

Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek / Netherlands Organisation for Applied Scientific Research

Confidential - Produced Subject to Protective Order MONGLY01285806

TNO Nutrition and Food Research

Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek/Netherlands Organisation for Applied Scientific research

Location Zeist
Utrechtseweg 48
P.O. Box 360
3700 AJ Zeist
The Netherlands

www.tno.nl

T +31 30 694 41 44
F +31 30 695 72 24

TNO report

V 4478

In vitro percutaneous absorption study with [^{14}C]glyphosate using viable rat skin membranes

Date	29 July 2003
Authors	Drs. J.A. van Burgsteden
At request of	Monsanto Europe S.A. Tervuren Avenue 270-272 B-1150 Brussels Belgium
TNO Project number	010.45110
TNO Study number	4478
Sponsor Study code	-
Status report	Final report
Previous version	Draft report, 27 March 2003
Number of pages	41
Number of tables	4
Number of appendices	6

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TN-2002-011



Confidential - Produced Subject to Protective Order MONGLY01285807

Summary

1. The herbicide glyphosate in the formulations MON 35012 and MON 0139 70% was examined for *in vitro* percutaneous absorption through viable rat skin membranes. Both the concentrated formulation and the field dilution were tested (6.249 and 0.080 mg glyphosate per cm^2, respectively for MON 35012 and 6.343 and 0.080 mg glyphosate per cm^2, respectively for MON 0139 70%). After 8 h of exposure, the test substance was removed from the application site, and samples of the receptor fluid were collected for an additional 40 h.

2. Fourty-eight hours after application of concentrated MON 35012, 10.3 % of the dose glyphosate had penetrated through rat skin membranes. When MON 35012 was applied as field dilution, the relative penetration of glyphosate was 2.6 % after 48 h. For MON 0139 70% these values were 0.52 % for the concentrate and 1.4 % for the field dilution. The mean flux constants were 35.6 $\mu g.cm^{-2}.h^{-1}$ (MON 35012 concentrate), 0.127 $\mu g.cm^{-2}.h^{-1}$ (MON 35012 field dilution), 2.33 $\mu g.cm^{-2}.h^{-1}$ (MON 0139 70% concentrate) and 0.100 $\mu g.cm^{-2}.h^{-1}$ (MON 0139 70% field dilution). The mean Kp values were 0.089×10^{-3} cm/h (MON 35012 concentrate), 0.025×10^{-3} cm/h (MON 35012 field dilution), 0.006×10^{-3} cm/h (MON 0139 70% concentrate) and 0.019×10^{-3} cm/h (MON 0139 70% field dilution).

3. At the end of the 8-h exposure period, an average of 111.7 % (MON 35012 concentrate), 44.8 % (MON 35012 field dilution), 120.8 % (MON 0139 70% concentrate) and 78.3 % (MON 0139 70% field dilution) of the applied dose of glyphosate could still be removed from the application site with cotton swabs. At the end of the study (48 h after application of the test compound), an average of 4.7 % (MON 35012 concentrate), 23.1 % (MON 35012 field dilution), 1.6 % (MON 0139 70% concentrate) and 2.3 % (MON 0139 70% field dilution) of the applied dose of glyphosate was still present in the skin membranes. At the end of the study (48 hours after application of the test compound), the mass balance was found to be very variable: 132.4 %, 73.4 %, 122.7 % and 82.6 % for MON 35012 concentrate, MON 35012 field dilution, MON 0139 70% concentrate and MON 0139 70% field dilution, respectively.

4. The results of the autoradiography show too much variation to draw any conclusions. In general, the results of the histomorphology indicate that exposure to the MON 35012 and MON 0139 70% concentrated formulations causes damages to the epidermis and stratum corneum. Localisation of the test compound and the reference compound was found mainly in the epidermis and stratum corneum.

5. Testosterone was used as a reference compound in this study. The penetration data were in good agreement to the historical data of our laboratory.

6. In conclusion, an 8-hour exposure resulted in a penetration of *ca.* 10 % (MON 35012 concentrate), *ca.* 2.6 % (MON 35012 field dilution), *ca.* 0.5 % (MON 0139 70% concentrate) and *ca.* 1.4 % (MON 0139 70% field dilution) over a period of 48 h in viable rat skin membranes. Due to the high variation in dermal penetration within the test groups and the poor recoveries, the data presented in this report are not acceptable for regulatory use and risk assessment. The study should be regarded as a sighting study rather than a definitive study.

Exhibit 6

IN THE CIRCUIT COURT OF CAMDEN COUNTY

STATE OF MISSOURI

PHYLLIS KENNEDY,)
)
Plaintiff,)
)
vs.) Case No. 16M-CC00001
)
MONSANTO COMPANY,)
)
Defendant.)
_____)

VIDEOTAPED DEPOSITION OF KIRK J. AZEVEDO, D.C.

CAMBRIA, CALIFORNIA

WEDNESDAY, JUNE 8, 2016

8:58 A.M. - 12:25 P.M.

REPORTED BY MELISSA PLOOY, CSR #13068

THE VIDEOTAPED DEPOSITION OF KIRK J. AZEVEDO, D.C., WAS TAKEN AT EL COLIBRI HOTEL & SPA, 5620 MOONSTONE BEACH DRIVE, CAMBRIA, CALIFORNIA, BEFORE MELISSA PLOOY, A CERTIFIED SHORTHAND REPORTER IN AND FOR THE STATE OF CALIFORNIA, ON WEDNESDAY, JUNE 8, 2016, COMMENCING AT THE HOUR OF 8:58 A.M.

APPEARANCES OF COUNSEL

FOR PLAINTIFF:
THE MILLER FIRM, LLC
BY: TIMOTHY LITZENBURG, ESQ.
108 RAILROAD AVENUE
ORANGE, VIRGINIA 22960
(540) 672-4224
TLITZENBURG@MILLERFIRMLLC.COM

FOR DEFENDANT:
HOLLINGSWORTH, LLP
BY: ERIC G. LASKER, ESQ.
1350 I STREET, N.W.
WASHINGTON, DC 20005
(202) 898-5800
ELASKER@HOLLINGSWORTHLLP.COM

- and -

JENNIFER S. KINGSTON, ESQ. (APPEARED TELEPHONICALLY)
MONSANTO COMPANY
800 NORTH LINDBERG BOULEVARD
ST. LOUIS, MISSOURI 63167
(314) 694-3083

ALSO PRESENT: DEBORAH ALVINO, VIDEOGRAPHER

THE VIDEOGRAPHER: We are now on the record. My name is Deborah Alvino and I'm a certified legal video specialist for Golkow Technologies. Today's date is June 8th, 2016, and the time is 8:58 a.m. This video deposition is being held in Cambria, California, in the matter of Phyllis Kennedy, Plaintiff, versus Monsanto Company, Defendant, in the Circuit Court of Camden County, State of Missouri. The deponent is Kirk Azevedo, D.C.

Counsel, please identify yourselves.

MR. LITZENBURG: Timothy Litzenburg for the plaintiffs.

MR. LASKER: Eric Lasker for Monsanto, with Jennifer Kingston from Monsanto on the telephone.

THE VIDEOGRAPHER: The court reporter is Melissa Plooy and she will now swear in the witness.

KIRK J. AZEVEDO, D.C.,

having been first duly sworn,

was examined and testified as follows:

EXAMINATION

BY MR. LITZENBURG:

Q. Good morning, Dr. Azevedo. Is that a comfortable --

MR. LASKER: Objection. Form, foundation, lack of foundation.

BY MR. LITZENBURG:

Q. Let me ask you this: Were you privy during your time at Monsanto to the sales strategy of the company in this area? Is that something you discussed?

A. I know at least some of it. Not all of it. I know there's different levels and different structures; however, at the time, you know, with this team-based protocol, it was really, you know, a great system where we had ability to access information all over the world and to communicate with people internally, and otherwise, within Monsanto to get information. And so it was a great communication system.

So if I, you know, wanted some ideas, I could call someone up, but I wasn't privy to all the sales ideas and all of the post-patent market strategy. I just knew some of those.

Q. But you worked primarily in sales throughout this time?

A. Yes. A local market manager, yeah.

Q. So not to belabor it, but -- well, let me ask this: During this time period in 1996 to 1998, was Roundup pretty -- cotton, for example, was that in development or was that on the market?

A. Different price point, yes.

Q. Were there other products at the time you were there that Monsanto made, glyphosate products, that didn't contain the word "Roundup"?

A. Yes. You know, one of which is like Rodeo. Rodeo was used mostly around aquatic areas and it had different types of, once again, less or no surfactant in it that could be dangerous to those -- the organisms that are living inside an aquatic environment.

There might have been other products, too, that were glyphosate-based, but the main one was Roundup itself, and so that's what I stewarded the most.

Q. Based on your experience with the company, and if you know, did the EPA test these Roundup products themselves or did they rely on, say, Monsanto to do the testing?

MR. LASKER: Objection to form, lacks foundation.

THE WITNESS: I don't know.

MR. LITZENBURG: Okay.

THE WITNESS: I don't know that.

BY MR. LITZENBURG:

Q. What was your impression at the -- let me start again.

When you worked at Monsanto, did you develop an

Q. Okay. But when you were speaking to somebody, if they would have a question about the product, you'd refer them to the label; is that fair?

A. Yeah, if I were to -- had that question asked of me. But really, I -- this stuff and the culture of agriculture at the time, it's safe. You know, people use it all the time, and it really wasn't a question that came up, the safety of Roundup.

Q. I'm going to mark, as Exhibit 2 -- I'll wait for you to mark it.

(Plaintiff's Exhibit 2 was marked for identification.)

BY MR. LASKER:

Q. And for the record -- that's yours.

For the record, Exhibit 2 is a document from the USDA, U.S. Department of Agriculture, APHIS, a division, A-P-H-I-S, which stands for Animal and Plant Health Inspection Service, and this is Approval of Monsanto Company Request, brand 04-086-01p, Seeking a Determination of Non-regulated Status for Glyphosate-Tolerant Cotton Event MON, M-O-N, 88913, Finding of No Significant Impact, dated December 2004.

Now, you are familiar, generally, with the fact that Monsanto's Roundup Ready cotton has been approved by the U.S. Department of Agriculture, correct?

the cotton plant because there was so much material to get just that Bt toxin to study the cotton-produced Bt toxin that we ended up just studying the bacterially-produced toxin for toxicological studies.

Q. Let me just interrupt you and make sure the record is clear here.

When you say "when we did these toxicological studies" --

A. That would be Monsanto. Yeah.

Q. You didn't conduct any --

A. No, I didn't. I'm just kind of going back in time.

Q. Right. And you've not conducted any studies with respect to any of the issues you raised?

A. No. Yeah, of course. Yeah. Not me. It's Monsanto and other universities and so forth.

Q. And you talked earlier about your research and I think you said your research was reading PubMed. That's a --

A. That's one of the main areas, medically, we look at. It's one of the more respected areas to find things that are not just subjective, but we look at double-blind clinical trials. That's the gold standard, you know, and try to look at these things and even reviews and so forth and using this as a resource to

REPORTER'S CERTIFICATE

STATE OF CALIFORNIA) SS.

I, MELISSA PLOOY, Certified Shorthand Reporter, licensed in the State of California, holding CSR License No. 13068, do hereby certify:

That prior to being examined, the witness named in the foregoing proceeding was by me sworn to testify the truth; the whole truth and nothing but the truth;

That said deposition was verbatim-reported by me by the use of computer shorthand at the time and place therein stated and thereafter transcribed into writing under my direction.

I further certify that I am not of counsel nor attorney for or related to the parties hereto, nor am I in any way interested in the outcome of this action.

In compliance with Section 8016 of the Business and Professions Code, I certify under penalty of perjury that I am a Certified Shorthand Reporter with License No. 13068 in full force and effect.

WITNESS my hand this _____ day of _____, _____.

_____

MELISSA PLOOY, CSR#13068

Exhibit 7

SUPERIOR COURT OF THE STATE OF CALIFORNIA

FOR THE COUNTY OF SAN FRANCISCO

CASE NO.: CGC-16-550128

DEWAYNE JOHNSON,

Plaintiff,

vs.

MONSANTO COMPANY,

Defendant.

_____/

CONFIDENTIAL

Continued Videotaped Deposition of WILLIAM SAWYER, PH.D., taken at 1451 Middle Gulf Drive, Sanibel, Florida, commencing at 8:09 a.m. - 5:57 p.m., Tuesday, February 27, 2018, before Tracie Thompson, RMR, CRR, CLR, Registered Merit Reporter, Certified Realtime Reporter, Certified LiveNote Reporter.

JOB No. 2820385

PAGES 265 - 557

A Correct.
Q This is an estimate that you were calculating based upon the background exposure levels of glyphosate in the general population, right?
A Yes, based on the US EPA DEEM model, which I referenced a moment ago.
Q And am I correct that these background levels from dietary consumption are generic? In other words, you didn't calculate Mr. Johnson's actual consumption, right?
A No. It's actually from the Acquavella study.
Q And you didn't do any calculation of Mr. Johnson's actual consumption of glyphosate, did you?
A Any what?
Q Calculation of Mr. Johnson's actual dietary consumption of glyphosate.
A No.
Q And you discussed yesterday that there are multiple manufacturers of glyphosate, right?
A That's my understanding.
Q There's no way to tell in the case of dietary consumption which glyphosate -- manufacturer's glyphosate is on any particular piece

Q And obviously DeWayne Johnson eats food, correct?

A I'm sorry?

Q Obviously DeWayne Johnson eats food, correct? That was a poor question. I'll strike that question.

DeWayne Johnson would have been exposed to glyphosate through his diet, correct?

MR. DHINDSA: Objection. Leading.

THE WITNESS: Yes, I can't ascertain what percent of his diet was glyphosate treated or GMO glyphosate food, but certainly some.

BY MR. TRAVERS:

Q And you didn't include that in your exposure assessment for DeWayne Johnson, as you testified earlier, correct?

MR. DHINDSA: Objection.

THE WITNESS: Correct.

BY MR. TRAVERS:

Q So would you say that -- so you would be underestimating DeWayne Johnson's risk in your report, right?

MR. DHINDSA: Objection. Leading.

THE WITNESS: Well, certainly additive to his occupational exposure.

CERTIFICATE OF REPORTER

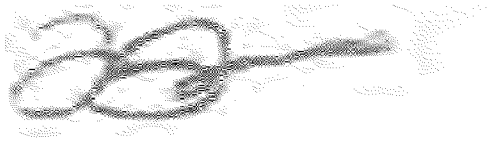
STATE OF FLORIDA

COUNTY OF LEE

I, TRACIE THOMPSON, Registered Merit Reporter, do hereby certify that I was authorized to and did stenographically report the foregoing videotape deposition of WILLIAM SAWYER, PH.D.; pages 269 through 558; that a review of the transcript was requested; and that the transcript is a true record of my stenographic notes.

I FURTHER CERTIFY that I am not a relative, employee, attorney, or counsel of any of the parties, nor am I a relative or employee of any of the parties' attorneys or counsel connected with the action, nor am I financially interested in the action.

Dated this 28th day of February, 2018.



Tracie Thompson

Notary Public

State of Florida

My Commission No. GG 175178

Expires: March 1, 2022

Exhibit 8

Toxicology Consultants & Assessment Specialists, **LLC**

TCAS

6450 Pine Avenue, Sanibel, FL 33957
29 Fennell Street, Skaneateles, NY 13152
(239) 472-2436 [FL] (315) 685-2345 [NY] (800) 308-0080
E-mail: drsawyer@experttoxicologist.com & Website: experttoxicologist.com

Toxic Exposures · Environmental Testing · Risk Assessment · Forensic Toxicology · Causation Evaluation

Toxicological Assessment of Dewayne Johnson and Toxicological Risk Assessment of Glyphosate and Roundup® and Ranger PRO® Formulations

William R. Sawyer, Ph.D., D-ABFM
Toxicologist

December 21, 2017

Prepared for

Michael J. Miller, Esq.
Jeffrey A. Travers, Esq.
Timothy Litzenburg, Esq.

The Miller Firm, LLC
108 Railroad Avenue
Orange, VA 22960

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Executive Summary

- **History:** Available from Monsanto since 1974, glyphosate is a non-selective herbicide used on both food crops (either prior to planting or just prior to harvesting) and non-food crops. Since that time, use of glyphosate (the active ingredient in Roundup®) has greatly expanded and is now used in conjunction with genetically modified organisms (GMOs) present in agriculture, forestry, industrial rights-of-way and residential applications worldwide. The IARC (International Agency for Research on Cancer) recently classified glyphosate as a *"probable human carcinogen."*

- **Complaint:** Filed by Mr. Dewayne Johnson, the complaint alleges that he has been repeatedly exposed to glyphosate contained within Monsanto Roundup® formulations and Ranger PRO® in his workplace without adequate warning of its carcinogenicity. Mr. Johnson states that his exposures initiated in June of 2012 through the summer of 2015. He was diagnosed with T-cell lymphoma[1] in August of 2014 while he continued to use the products and his condition worsened. He applied Roundup a minimum of 20-40 days per year, but deposition testimony reports a higher application frequency.[2] Each application lasted several hours. His exposures also included some severe acute exposures including the soaking of his upper body with glyphosate.

- **Exposure:** Toxicologists generally focus on three primary routes of exposure: ingestion, inhalation and dermal absorption. This toxicological assessment is primarily concerned with dermal absorption of glyphosate. Aspects of absorption are explored in some detail.

- **Absorption Characteristics:** Dermal contact can occur during mixing, loading and application as well as accidental equipment failures such as hose disconnections or re-entry after application. Monsanto has attempted to claim (unsuccessfully) that dermal penetration through human skin is lower than in rat skin. It is not. Additionally, there is evidence of omissions in Monsanto-sponsored dermal absorption study data

---

[1] Final diagnosis was that of a CD4 folliculotropic and syringotropic mycosis fungoides with granulomatous features. It should be noted that mycosis fungoides is not related to mushrooms or is the disease a fungal infection, but rather, a form of non-Hodgkin's lymphoma (NHL).

[2] Mr. Johnson's deposition testimony details a substantially higher frequency of glyphosate use.

which purport to reduce the apparent percentage of glyphosate absorbed thus bringing the value below the minimum required for regulatory approval.

- **Absorption Factors:** Additives within Roundup® formulations increase glyphosate dermal absorption. These include (a) "co-formulants" (ingredients other than glyphosate) such as surfactants (compounds which lower surface tension) and humectants (to inhibit moisture loss) and (b) adjuvants (chemicals which modify the effect of other agents). Other factors affecting absorption include skin damage such as lesions, cracks and other irregularities, lack of personal protective gear, etc. Co-formulants are of particular concern as they can be more toxic than glyphosate itself.

- **Pharmacokinetics:** This refers to the amount and the rate at which a substance is directly absorbed, distributed and metabolized by the body and how much is excreted. While normally an objective measurement, there are examples cited herein showing that the percent absorbed versus excreted is higher than that purported by the manufacturer. Additionally, Monsanto (knowingly or unknowingly) has regularly misstated glyphosate dermal absorption recovery in its communications. These are regarded as pertinent issues with respect to credibility and weight of evidence.

- **Industrial Secrecy:** IARC relied solely on ***independent research*** to render its conclusion. Monsanto-sponsored studies played little or no part in the IARC classification ruling. Similarly, this toxicological assessment has primary relied upon independent studies though Monsanto-sponsored studies were also assessed, noting inconsistencies and consistencies where appropriate.

- **Regulatory Considerations:** Regulatory rulings play a role no more or less important in a toxicological assessment than any other objective evidence. It is noteworthy that there is presently disagreement within the U.S. EPA itself with respect to some of the issues raised in this assessment. Although the State of California listed glyphosate as a carcinogen on July 7, 2017, *this toxicological assessment does not assume any position of advocacy*. The opinions expressed herein are based on objective, reliable evidence without deviation from the assessment methodology.

- **Carcinogenic Studies:** This assessment takes into account numerous studies and cancer bioassays in animals as well as chronic dietary studies and carcinogenicity

studies in rats and mice. The results of each study were assessed on their merits and their review occupies a considerable portion of this report.

- **Human Epidemiological Studies:** Due to the volume of epidemiological studies as well as the need for a fully qualified epidemiological assessment, I will be deferring any detailed epidemiological opinions in this matter to Christopher J. Portier, Ph.D., Director of the National Center for Environmental Health and Director of the Agency for Toxic Substances and Disease Registry (ATSDR); Beate Ritz, M.D., Ph.D., Professor of Epidemiology at the University of California, Los Angeles (UCLA) Fielding School of Public Health and former chair of the UCLA Epidemiology Department; and Alfred I. Neugut, M.D., Ph.D., Professor of Cancer Research and Professor of Medicine and Epidemiology at Columbia University.

- **Animal Carcinogenicity Studies:** The toxicological methodology for carcinogenic assessment is specific and was applied consistently herein as standard risk assessment criteria. This includes dose-response data, extrapolation methods, potential for genotoxicity and other considerations. Extensive footnotes have been inserted throughout.

- **Animal and Human studies:** It is my opinion to reasonable toxicological certainty that correct application of the U.S. EPA methodology results in a finding from the available animal studies, as referenced herein, that glyphosate is probably carcinogenic. Additionally, the prevailing objective human epidemiological evidence (as summarized in this assessment and as documented within the epidemiological expert reports and noted in numerous citations) supports the contention that glyphosate is a human carcinogen in doses applied in real world applications. Additionally, adjuvant formulations and various mixtures of glyphosate have greater potential for carcinogenic health risks primarily due to increased dermal absorption.

- **Cancer Risk:** Cancer risk is the outcome of pragmatic application of the assessment methodology per U.S. EPA guidelines. The calculated cancer risk ranges from a low of **9.8×10^{-5}** (lowest dietary exposure) to a high **of 6.1×10^{-4}** (for applicators) based on applicator dose measurements. A full mathematical analysis is presented on page 107. Appendix A shows how the cancer slope factor was derived using U.S. EPA modeling software designed for this purpose.

- **Toxicological Conclusions:** Mr. Dewayne Johnson was diagnosed with mycosis fungoides (an infrequently encountered, rare T-cell lymphoma) approximately 2.25 years following his frequent mixing and application duties applying glyphosate herbicides for the Benicia Unified School District. Mycosis fungoides is a rare malignancy encountered in only 5.6 persons per million. Mr. Johnson's absorbed dose of glyphosate was within the range of that encountered within the generally accepted toxicological and epidemiological literature among hydraulic applicators. Review of Mr. Johnson's medical records, deposition testimony and history fails to reveal any family history, genetic predisposition, prior occupational chemical exposures or lifestyle risk factors that increased his likelihood of developing this lymphoma other than his exposure to glyphosate.

  Based on the documented and inherent properties of glyphosate to produce lymphoma in animal studies as well as the results of statistically significant human epidemiological studies, I am certain to reasonable toxicological certainty that Mr. Johnson's glyphosate exposures induced or significantly contributed to the onset of his T-cell lymphoma.

Part A: Dewayne Johnson Medical History

Background

Mr. Dewayne Johnson was born on January 20, 1972, (current age 45) in Vallejo, California, where he currently lives. He is African-American. His weight as of 2014 was noted as 162 pounds. He has no known allergies. Other than a possible hernia repair in the past, there is no other surgical history noted.

His family history is significant for a 70 year old mother with cardiovascular disease. His father died at age 80 with Alzheimer's disease and cardiovascular disease. His siblings are healthy although one has Crone's disease. His three children, ages 8-21, are reportedly all healthy.

Of particular interest, his family history is uniformly negative for lymphoma, leukemia, skin cancers, dermatitis, allergies and/or asthma.

Mr. Johnson occasionally consumes alcohol. He is a short-term smoker who began smoking in 2004 and quit in March 2006, although there are some records that record him as a "never" smoker. He has never used illicit drugs or been in the military.

Medical Chronology

The following physicians are noted in the Chronological Medical Records (Table 1).

- Kim, Youn-Hee, MD – Cutaneous T-Cell Lymphoma clinic at Stanford
- Ofodile, Onaopemipo, MD - Dermatologist at Permanente Medical Group
- Thach-Guaim, Truoung, MD – Oncologist at Permanente Medical Group
- Tsai, Eunice, MD – Cutaneous lymphoma specialist at Kaiser

Table 1

Dewayne Johnson: Chronological Medical Records

Date	Physician	Complaint/Symptoms	Diagnosis
9/26/13	Regional Medical Center of San Jose	Motor vehicle accident (MVA) with left knee injury (abrasions); left side chest pain (possibly abrasions due to seatbelt)	Left shoulder abrasion, right shoulder contusion and left knee abrasion. No other pathology noted. Discharged. It was determined on 8/21/15 after a medical chart review that none of his symptoms after this date were related to this MVA. (pg. 896/1233)
4/30/14		Estimated date of exposure to Ranger Pro® chemical	Treated with prednisone and "*a cream*."
6/23/14	LaClinica (Urgent Care)	Presents with rash; affected areas are scattered on body including scalp, neck, arms, elbows, hands, chest, back, trunk, abdomen, groin, buttocks, legs, knees. Described as scaly.	Diagnosed with tinea corporis; prescribed terbinafine, prednisone 10 mg, cephalexin 500 mg.

Date	Physician	Complaint/Symptoms	Diagnosis
7/23/14	Permanente Medical Group	Noted use of pesticide Ranger Pro® for 2 years at work. Pesticide exposure on left side of face. Did not develop any skin irritation at that time. However, developed skin rash to body (trunk, both arms and legs, not face) about 1 month after incident with itching. (Date of incident noted as 4/30/14 – three months prior to this date.[3])	Atopic dermatitis, eczema. Physician writes "*it is my opinion that the patient's current medical condition, more likely than not, was not caused or aggravated by factors of employment based on MSDS of the pesticide, timing and clinical irritations*."
7/29/14	Permanente Medical Group	Finger caught between a motor and cage on sprayer[4] at work; smashed by cage. Stated "*a few pounds of pressure got me at once*." Pain and swelling	Crush injury of left hand/laceration; prescribed ibuprofen.
8/1/14		Presents for rash (scattered) lasting several months which started on his legs. No recent medications or travel. Describes affected areas as stinging. Aggravating factors include sweating. Relieving factors include oral steroids/ not relieved by antifungal cream.	Notes scalp with hyper-pigmented patches; trunk, arms, legs, buttocks with diffusely scattered annular erythematous scaly patches. Biopsy of right thigh collected. Consideration of psoriasis v. pityriasis rosea v. syphilis?

[3] Sought additional treatment on this date because rash seemed worse upon re-exposure.

[4] Sprayer reportedly on the back of his truck.

Date	Physician	Complaint/Symptoms	Diagnosis
8/4/14	University of California at San Francisco (UCSF)	Pathology report	Right thigh biopsy "*epidermotropic T cell lymphoma with an unusual immunophenotype, IHC CD3+, CD7+, CD56+/- (gamma/delta stain) and negative for CD4, CD8, CD30 and Beta F1 (usually + in alpha/beta T cells), FISH negative for EBV m RNA. Coupling the results of these stains with the findings on H&E section, this specimen appears to represent a cytotoxic and epidermotropic T cell lymphoma. Furthermore, the GM3 and partial CD56 positivity point to a gamma/delta T cell lymphoma. Gamma/delta T cells typically behave in an aggressive fashion. Nevertheless, there are rare case reports of both GM3 and CD56 positivity in mycosis fungoides so cannot be excluded*."
8/18/14	Solano Dermatology .	Presents with widespread non-pruritic papulosquamous eruption of several months duration, minimally relieved by oral steroids.	"*Unusual cutaneous lymphoma*." Biopsy consistent with gamma/delta T cell lymphoma. Referred to UCSF cutaneous lymphoma clinic
8/26/14	UCSF Dermatology	Initial consultation for evaluation of diffuse papulosquamous rash concerning for cutaneous lymphoma	History of Present Illness states that Mr. Johnson first noticed a skin rash on chest/trunk and face in the fall of 2013 which he initially thought was due to his detergent; however changing to a hypoallergenic detergent did not have a significant effect. Noted waxing and waning of rash. "*Three months ago started to note the rash spreading through body and becoming significantly more scaly with itch and occasional stinging sensation*."

Date	Physician	Complaint/Symptoms	Diagnosis
9/30/14	University of California at SF (UCSF)	Undergoing workup	Widespread papulosquamous eruption for over the past year which has become more pronounced in the last 3 months. Biopsy consistent with CTCL that is GM3+ and Beta F1 negative. Pathology differential includes mycosis fungoides mycosis fungoides) with an unusual and cytotoxic immunophenotype versus a relatively indolent variant of gamma/delta T cell lymphoma vs. peripheral T cell lymphoma not otherwise specified. Would favor mycosis fungoides as the diagnosis although most CTCL, including mycosis fungoides, generally are composed of alpha/beta T cells.
10/1/14	Permanente Medical Group	Melanoma – Noticed first lesion on right medial knee six months ago and now spread over body. Feels that lesions are changing form and starting to itch.	"*Skin cancer all over; was seen at UCF; has had multiple skin biopsies*." No palpable lymphadenopathy. Unclear etiology though concerning given spread over last 6 months.
10/3/14	Permanente Medical Group	Consultation. Physical exam notes that skin is 80% covered; lymphatics - tiny 5-8 mm in upper neck, palpable lymphadenopathy[5] Blood sent for T cell receptor gene rearrangement to Stanford. Results were positive, TCR gamma	T cell lymphoma. Noted as a one year history of progressive skin lesions, initially flat and red but older lesions are plaque-like with hyperkeratosis. Some improvement with Prednisone. Continuing work up to subtype. Requested that Sezary cells be ruled out. Also seen by Dr. Ofodile, dermatologist for full skin examination. Notable for diffuse erythematous scaly thin plaques scattered extensively. No nodules or ulcerations appreciated. Scattered small shotty LAD[6] on cervical nodes bilaterally. Notes atypical immunophenotype, further workup pending to rule out systemic involvement. Will begin with skin specific treatment with topical corticosteroids and light therapy. Prescribed triamcinolone acetonide 0.1% topical ointment.

[5] Clinical chemistry for ALT noted as 50, Reference range 0-36 U/L' alkaline phosphatase high at 197, Reference range 37-117 U/L

[6] Lymphadenopathy.

Date	Physician	Complaint/Symptoms	Diagnosis
10/3/14	Vallejo Medical Center regional lab	Peripheral blood collected on this date tested for flow cytometry	No malignant population of T cells identified by immunophenotyping. Comment: T cells are a mixture of CD4 and CD8 positive cells with adequate ratio. There is no CD3 positive/CD4 negative/CD8 negative T cell population identified. Gamma/Delta T cells account for approximately 3% of lymphocytes and 1% of total events. They are within normal range. For this case, flow cytometry may not be sensitive to detect a small population of abnormal T cells. Non lymphoid blasts account for less than 0.5% of total events.
10/5/14		CT of neck	Adenopathy in the neck, axilla and groin, (Mildly enlarged lymph nodes.), Possible soft tissue mass noted in the area of the left palatine tonsil. Patient denies pain, bleeding, dysphagia, dysphonia, cigarettes
10/8/14	Permanente Medical Group		Mammographic right breast mass (right axillary abnormal lymph node).

Date	Physician	Complaint/Symptoms	Diagnosis
10/9/14[7]		Biopsy of right axilla after findings on CT scan dated 10/5/14 Pathology reports: CD3, CD20, CD56, CD4, CD 8 as positive on immunohistochemistry (pg. 144/1233)	Biopsy reveals enlarged 2.6 x 1.6 cm lymph node with cortical thickening measuring up to 1 cm. Dermatopathic lymphadenitis, negative for malignancy; no clinical concern for breast cancer Pathology report: "*Do not find support for CTCL in the current material. Flow cytometry was negative for malignancy population (FL014-5908). Additionally the immunostains do not support a T cell lymphoma. The possibility of an underlying lymphoma exits; however, there is no support in the current material.*" "*Lymph node biopsy – patients with mycosis fungoides and extensive skin involvement may have enlarged lymph nodes demonstrating histologic findings of dermatopathic lymphadenitis, showing sinus histiocytosis, an abundance of pigment-laden microphages and a small number of atypical lymphocytes.*"[8]
10/14/14	Permanente Medical Group		Notes that Mr. Johnson is a 42 year old with stage IIA CTCL.
10/15/14	Dr. Ofodile, dermatology	Mr. Johnson reports using triamcinolone infrequently, reports getting new red bumps on legs looks like "*spider bites*"	Mycosis fungoides, Stage 2; Notes that topical treatment with corticosteroids and phototherapy is appropriate for stage IIA disease. Will start PUVA (psoralen and ultraviolet A) therapy.
10/21/14	Permanente Medical Group		Lymph node biopsy does not support USCF working diagnosis.
10/22/14		Discussion with UCSF dermatopathologist/oncologist	"*Treat with cutaneous therapy such as PUVA. Do not over treat even if peripheral blood T cells come back positive*" which she doubts. (pg. 171/1233)

[7] A note from this date states that tissue immunophenotyping has been completed and "the immunophenotyping panel was developed and its performance characteristics were determined and deemed acceptably by Kaiser Permanente Regional Laboratory. These tests have not been cleared or approved by the US FDA." (pg. 139/1233)

[8] Page 144 of 1233.

Date	Physician	Complaint/Symptoms	Diagnosis
10/27/14	Dr. Ofodile, dermatology	New small bumps, the size of BB pellets on skin, not symptomatic	Scheduled for appointment on 11/3 at which time the primary encounter diagnosis was mycosis fungoides, Stage 2. Medication changed to clobetasol 0.05% topical ointment
11/3/14		First treatment of light therapy; widespread erythematous scaly patches and plaques on entire body; scattered new papules on extremities.	Entire body treated; initial dose in J: 0.3, initial duration of treatment time = 0.31. Doses/duration varied with subsequent PUVA treatments. Pathology reveals disease progression with increased large cells and tumor stage disease. Baseline labs needed to initiate bexarotene
12/12/14	Dr. Ofodile, dermatology	Follow-up	Exam notable for firm, pink papules on forearms; post inflammatory hyper-pigmented patches on trunk, scattered annular, erythematous plaques on scalp and face. Improvement of patch stage disease with phototherapy although newly developed firm papules are less responsive to phototherapy.

Date	Physician	Complaint/Symptoms	Diagnosis
12/23/14	Permanente Medical Group	42 year old male here for evaluation of possible mycosis fungoides. Over a year ago, had raised lesion on right thigh, red but not associated with significant itching. Initially thought related to job as pest inspector for public schools, W/C evaluation directed to dermatology, referred to UCSF. Biopsies revealed epidermotropic T-cell lymphoma, Differential diagnosis - mycosis fungoides with an unusual and cytotoxic immunophenotype (CD4-, CD8-, CD3+, CD7+, CD30-, CD56+/- gamma/delta+, TIA-1+), a relatively indolent variant of gamma/delta T cell lymphoma and peripheral T cell lymphoma, NOS. He was started on UVB therapy with improvement of skin patches. Axillary lymph node biopsy 10/9/14 revealed dermatopathic lymphadenitis. Developed new types of lesions recently. Biopsy was done at USCF. (Page 300/1233)	Mycosis fungoides, possibly CD8 epidermotropic aggressive variant, consider adding methotrexate or bexarotene to UVB. Consider referral to Stanford Clinic. Punch biopsy left arm- some CD30 expression. Repeat biopsy for confirmation (UCSF). Differential diagnosis mycosis fungoides vs. CD30 lymphoprolierative disorder (lyp or large cell transformed mycosis fungoides) v. other tumor. UCSF dermatopathology states repeat testing shows diagnosis of epidermotropic T cell lymphoma with cytotoxicity with one section showing a deep infiltrate with large lymphocytes (right forearm/left chest) Infiltrate is suggestive of lymphomatoid papulosis. Seen many cases of mycosis fungoides with developing concurrent lymphomatoid papulosis. If these clinical lesions resolve in 4-6 weeks, suggestive of lymphomatoid papulosis (pg. 319-324/1233)
1/3/15		CT Scan of entire body (page 8/8, Kaiser Permanente Dermatology.pdf)	Scattered areas of mild skin thickening associated with mild uptake probably related to cutaneous lymphoma. Neck nodes, axillary nodes and inguinal nodes less conspicuous. Nodes appear nonspecific but are favored to be reactive rather than malignant in nature.
1/9/15	Eunice Tsai, MD		PEWT/CT scan confirms no internal organ disease so mycosis fungoides is only on skin. Biopsy confirmed mycosis fungoides but a slightly more aggressive variation. Starting methotrexate 2.5 mg with reduced UV dose during PUVA therapy. On 1/30/15, notes to be off methotrexate (1 week course) and treatment increased again.

Date	Physician	Complaint/Symptoms	Diagnosis
1/29/15	Jeffrey Gao, MD	Mr. Johnson has been working full time as a maintenance worker. Noted to be "*spraying herbicide*[9] *using a back pack sprayer with full Tyvek suite, full hood and respiratory protection; spill from leaky tank on left shoulder area with minimal burning at time,*" total exposure was about 15 minutes. Washed area with soap and water several times, no more skin irritation	No redness, swelling; new skin lesion in his left shoulder area, no skin wound. Herbicide noted to be Ranger Pro® by Monsanto. Patient returned to full work duty and released from care with no permanent impairment. Causation: "*The stated mechanism is consistent with my clinical exam findings and no information has been presented that would indicate a cause other than the alleged employment event/exposure*."
2/9/15			Returning to methotrexate and continuing phototherapy.
3/4/15	Stanford Cancer Center	Biopsies taken - Right thigh lesion with significant pain despite oral antibiotics. Not purulent.	Invasive keratinizing squamous cell carcinoma of thigh, well-differentiated (pg. 476/1233); (Surgical excision on 3/30/15) Additional biopsies consistent with Mycosis fungoides exhibiting epidermotropism and syringotropism
3/14/15	Permanente Medical Group	Right foot pain. Noted to be working 40 hours per week at this time.	Foot notable for scaly erythematous patches and plaques scattered diffusely on bilateral feet. Inflamed callus vs. mycosis fungoides,I Not caused by aggravated by factors of employment
3/17/15		Letter to Dr. Ofodile, dermatologist, from Mr. Johnson	"*I'm getting to the point where I feel a little foolish spraying and applying chemicals – do you feel it's safe to do the kind of work that I am doing with the kind of skin condition that I have?"*
3/18/15	Stanford	Final pathology report	Final diagnosis is a CD4 folliculotropic and syringotropic mycosis fungoides with granulomatous features. Given recent squamous cell carcinoma, patient may not be a good candidate for electron beam radiation or further phototherapy.

[9] Noted to be a backpack sprayer. "Noticed dampness on my back – I thought it was sweat and kept spraying but back became more wet. Noted leakage from sprayer." (pgs. 402/1233)

Date	Physician	Complaint/Symptoms	Diagnosis
4/29/15	Permanente Medical Group	Plaque on frontal scalp cultured with MSSA over 1 month ago and treated with doxy; failed to completely heal, now larger in size, painful, oozing	Biopsy taken. Result: superficial and deep perivascular interstitial and periadnexal mixed inflammatory-cell infiltrate with occasional epidermal T lymphocytes. Per pathologist, "*Bulk of features, particularly in dermis, are in keeping with a fundamentally inflammatory process. However, there are CD4 T lymphocytes in the epidermis some appear hyperchromatic and convoluted. This may represent the patient's underlying mycosis fungoides. However, features in the dermis are not sufficient to compel me to a diagnosis of tumor or plaque stager mycosis fungoides*." (pg. 605/1233)
5/11/15	Dr. Ofodile, dermatology	Progress note	Bexarotene v. brentuximab vedotin (BV) via a clinical trial at Stanford. If skin biopsy reveals >10% CD30 cells, will be eligible to receive BV. Mr. Johnson opted for oral bexarotene 225 mg/day/no enrollment in clinical trial
6/30/15	Permanente Medical Group	Fracture of left hand	Placed on modified duty at school district
7/16/15	Permanente Medical Group	Peripheral blood analysis	Mildly increased CD4+/CD26- T cell population.
8/4/15	Permanente Medical Group	Whole body PET/CT scan	Scattered areas of skin thickening and mild FDG uptake likely representing the patient's known cutaneous lymphoma. Compared to prior PET/CT, many lesions appear less prominent demonstrating a decrease in size and intensity of uptake. At least two new areas of skin uptake involving the right upper thigh and left medial calf representing new areas of disease. Previously noted cervical, axillary and inguinal nodes appear relatively stable in size demonstrating stable to mildly decreased FDG uptake.

Date	Physician	Complaint/Symptoms	Diagnosis
9/3/15	Permanente Medical Group	Follow-up	Skin appears progressive; getting new thicker plaques with some ulcerations. On 525 mg of bexarotene (Targretin) (max dose) daily since 8/20/15. Two skin punches to rule out large cell transformation revealed mycosis fungoides with large cell transformation on left upper arm while left medial calf revealed mycosis fungoides, patch stage.
9/17/15	Permanente Medical Group	Progression of disease despite maximum dose of bexarotene	Consider initiation of Bentuximab with oncology. This drug has high risk of neuropathies[10] – consult for evaluation of baseline neuropathy revealed no symptoms of neuropathy.
11/4/15	Richard, Hoppe, MD, Stanford	Cancer staging summary	Stage IIB (TC, N0, M0)/consent for total electron beam therapy received
11/10/15	Permanente Medical Group		Began total body electron bean radiation therapy (TBEBT) 1.5 weeks ago at Stanford with 5 treatments received at this time. Tolerating well with noticeable flattening of facial lesions/Interferon injections. After total treatment of 3 more weeks, 80% improvement in mycosis fungoides; some scaly patches on back. Stopped interferon due to difficulty tolerating. (Completed treatment 11/20/15)
1/6/16		Noted to be working full duty	
1/20/16	Permanente Medical Group	Sore area on left shin, eroded, swollen, no purulent drainage	Prescribed nitrogen mustard topically; diagnosed as recurrent mycosis fungoides after total electron beam radiation; will contact Stanford to see if more TBEBT is needed.
2/4/16	Permanente Medical Group	Peripheral blood collection	Percentage of CD4+/CD26 negative T cells is slightly increased. Possible Sezary syndrome (a different T-cell lymphoma).
2/25/16		Total skin electron beam therapy, dose 36 gy	Started repeat course at Stanford; boosted by Actimmune (Completed 2nd course April 2016)

[10] 20% incidence of peripheral motor neuropathy; 50% incidence of peripheral sensory neuropathy

Date	Physician	Complaint/Symptoms	Diagnosis
3/4/16	Permanente Medical Group		Some evidence that the lymphoma is in his blood as there was an increase count of CD4+/CD26 cells on his serum flow cytometry. Suggest intravenous systemic therapy.(Pg.1189/1233)
7/8/16		Evaluation of subcutaneous nodule	DDX includes cellulitis and early abscess. Alternatively, infiltrative neoplasm, although less likely, cannot be excluded. (Resolved as of 7/14/16)
10/28/16	Thach-Guaim Truong, MD, Oncology	Follow-up	Mycosis fungoides with large cell transformation, stage IIB; Fully active, able to carry on all pre-disease performance w/o restriction
12/9/16	Thach-Guaim Truong, MD	Follow-up	Chemotherapy-induced peripheral neuropathy; hold brentuximab
1/12/17		PET/CT scan of entire body	Mild residual disease involving bilateral axillary and inguinal lymph nodes as well as multiple skin lesions of bilateral lower extremities; mild increased uptake of the gall bladder, new increased uptake of posterior nasopharyngeal wall
4/18/17		PET/CT scan of entire body	Compared to 1/12/17, mild interval increase in axillary and inguinal lymph node uptake and a significant interval increase in the number, size and intensity of skin lesions suggesting interval progression of disease.
6/1/17	Thach-Guaim Truong, MD	Severe, open sores that won't close	Oncologist states Mr. Johnson is resistant to treatment
6/22/17	Permanente Medical Group	Letter from Dr. Truong, Oncology	Mr. Johnson carries a diagnosis of progressed mycosis fungoides with large cell transformation for which he is undergoing active chemotherapy. Median survival after diagnosis for this type of lymphoma is typically 1.5 years.
6/29/17		Peripheral blood collection; CT scan of entire body	Increased percentage of CD4+/CD26- T cells. CT scan reveals significant interval progression of skin disease since 4/18/17; probable malignant cervical node, bilaterally axillary, bilateral pelvic and bilateral inguinal nodes; probable marrow involvement of mycosis fungoides.

Employment History

Table 2 provides summarized employment information. Subsequent sections describe Mr. Johnson's employment activities and bearing upon this current matter in greater detail, particularly in the summarized deposition(s).

Mr. Johnson estimated that he averaged 48 hours of work per week (average of eight hours overtime per week) for the Benicia Unified School District (BUSD). Mr. Johnson's job duties included setting animal traps and relocating nuisance animals, preparing and applying the herbicides Roundup® and Ranger Pro® Weed Killer. His formal medical records report his spraying between 20-40 pesticide applications yearly, but deposition testimony reports far higher application frequency than these numbers.

Mr. Johnson has also applied Dolomark® baseball line chalk, performed landscaping, gardening, cleaning and managed irrigation systems. He also used Henry's Wet Patch Cement® to patch roofs. He reports that he wears personal protective equipment (PPE) and a Tyvek suit when in contact with ant sprays, fertilizer, etc.[11]

[11] Solono Dermatology records, page 35 of 56.

Table 2

Dewayne Johnson: Summarized Employment History

Time Period[12]	Employment/Job Description
2005-2007	Waterproof worker in San Francisco (sealed windows and caulked, glazing)[13]
2008-2010	Employment with temp company in Napa, California
Early 2000s	Vallejo Unified School District[14] (approximately 9 years)
2007-2010	Caretaker for his grandmother
(unspecified)	Vacaville Unified School District[15]
2010-2012	Wine warehouse worker for Allied (stacked pallets or boxed wine)
June 2011	Began as a part-time utility worker and then later a maintenance department grounds man for the Benicia Unified School District in California[16]

[12] Per Mr. Johnson, He is "*not really good with that type of stuff, dates*." Thus, the dates shown in the table are estimated from the available records.

[13] On this job, he was exposed to silicone and 100% isopropyl alcohol which was used to clean areas before silicone was applied to seams to waterproof structures. Although he did not use a mask when working with silicone, he was required to use a full-face canister mask when working with the alcohol.

[14] At this position, he was exposed to bleach and other basic learning chemicals such as Comet or Ajax. He testified that he used a mask and gloves when cleaning.

[15] Same type of duties and exposures as above.

[16] Per Mr. Johnson's workmen's compensation deposition on October 28, 2015, he began as a part-time worker (25 hours) and after 1-2 years became full time as a utility worker. He performed general maintenance including gardening, pruning trees, cleaning gutters, and spraying pesticides (Ranger Pro® and Roundup®), etc., especially in the summer. He specifically noted that as of October 2015, he had sprayed every summer of his employ with the exception of the first year. He also became the Integrated Pest Manager (IPM) in September 2012 for the school and as such was responsible to keep documentation of the different pesticide applications performed on the school grounds.

Deposition of Dewayne Johnson: December 8, 2017

The following notes were derived from the available deposition record to provide exposure data and historical context. As the deposition transcript is very long, content is split into related sections to facilitate comprehension of key points.

Acute Exposure Characterizations

- Mr. Johnson testified that his first major exposure was at the Mary Farmer school location in the Benicia Unified School District. This was the exposure from leakage of the 50 gallon tank[17] (as described in his October, 2015 deposition). "*The hose came [dis-attached] from the back of the truck and it was just juice everywhere, flying out the back of the truck. So that's when I had to hop in because the switches are in the back. There's no safety switch there ... I reach in the back there and turn it off and that's when I got it on the back of my neck and the back of my head and everywhere and on my face.*"[18]
- Mr. Johnson testified that there were noticeable and visible consequences of his initial exposure. He stated, "*When I got ahold of that liquid on my skin that day, it got red, it got irritated. I finished the day off. It was seven hours. Maybe six hours. We spray two hours in the morning. So after that, I just waited until I could work and went home and showered and changed clothes like nothing ever happened. We didn't have an eye wash or shower station. That came a few months later after my exposure*." He later testified that upon returning to the main facility (about 15-20 minutes after his exposure), he wiped down with soap and wet paper towels from the sink and then continued with his day (wearing the contaminated clothing). He did not see a physician or call a poison control center.
- Mr. Johnson did not provide a precise date for his initial exposure; however, later in the deposition at 2:28:22 he states that it was in 2012. At this time, he did not yet have his Qualified Applicator Certificate (QAC).

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[17] Mr. Johnson testified that he asked for a cutoff switch to be installed on the 50 gallon tank after his initial exposure, but this was never done. Consequently, he began using the backpacks more than the tank.

[18] At 12:37, he stated. "Cause it got down to my neck and got down to about the tip of my shoulder. I was able to rinse a lot of that off. I don't know if I'm wiping it in or I'm taking it off. ..But I'm using what I had at the time."

- Mr. Johnson told the acting supervisor for the day ("John"), about his initial exposure. No incident report was written because "*we had been trained that the glyphosate was okay enough for us to drink. So we didn't really worry like, you got it on your skin; you're going to die tomorrow*."
- Mr. Johnson stated that that a woman from Horizon Company (from which the district purchased herbicides) had informed them during a two hour training session that "*glyphosate was okay enough for us to drink.*" This woman said that if he was exposed to the glyphosate on his skin, he should shower off or go to the sink and rinse out.
- During his second major exposure in 2015 (as described in his workman's compensation deposition), "*I went home at that time. I got exposed from the backpack. I said I'm leaving right now. I left, went home and showered and even came back*." He was wearing his Tyvek suit at the time but it soaked through and his clothes were again "*saturated,*" especially the lower back area and around his waist. Again, he is unsure of precise dates but this happened after his mycosis fungoides diagnosis. Mr. Johnson stated that no report was filed because "*we didn't have that in place*." However, he did tell his supervisor ("Roy").
- On the day of his second major exposure, Mr. Johnson presented to Dr. Gao regarding the leaking backpack exposure as a W/C claim. Dr. Gao's notes state that Mr. Johnson had been wearing a full Tyvek suit and hood as well as respirator protection. Dr. Gao's notes state that the spill was on his shoulder area with a total exposure time of about 15 minutes. However, Mr. Johnson stated that Dr. Gao "*assumed*" the 15 minute exposure time and it was actually closer to 45 minutes before he returned to his home and showered.

Chronic Exposure Characterizations

- The term "drift exposure" refers to airborne aerosol coming into contact with the applicator. Mr. Johnson testified that he experienced drift exposure "*all the time*." There was no way to control the drift even by spraying on calm days or changing out nozzles size to increase droplet size. He wore goggles and a sweatshirt-type hoodie which he would pull close around his face when working. Though he wore no facemask, he testified that once he had all that on, the only part of his face exposed was the tip of his nose and his cheeks as well as a bit of his forehead.

- With regard to the number of times he sprayed, Mr. Johnson testified that "*we would go out during the spray months (June, July, August). We could go out four weeks in a month. I would say 12 times in a month. Because we only do 3-4 days in a row. We have to keep this stuff in the morning so we only had two hours. So we might get 2-3 days to do the same site. Other guys would be using the backpacks and I'd be using the power sprayer connected to the truck*." During the other nine months, he might spray around some trees or along a fence line.
- Mr. Johnson also recounted being splashed on the side of his head one time as well. But "*my face has never been as bad as the rest of my body.*"
- Mr. Johnson testified that he always wore PPE including a Tyvek suit which appears to have been merely water-resistant, allowing penetration of drift of the applied liquid herbicide. "*If I poured the water bottle on the Tyvek suit, it went straight through to your skin. It's just the way that suit worked*." He also wore boots and goggles. He wore paper masks when applying Ranger Pro; however, after his diagnosis, he began using a respirator.
- During prior jobs (he was working several different jobs at the same time at one point), he always wore a Tyvek suit or used PPE. He used a new Tyvek suit each day.
- Mr. Johnson performed his own diluting and mixing of the Ranger Pro with water. He kept his "*recipe*" ("*a little book that they give you*") in his pocket. The dilution proportions were based on what was being sprayed (type of weed)[19] and how much footage was to be sprayed per the Ranger Pro pamphlet. "*I know I used five gallons to 10 ounces with it."* He also kept the MSDS in the glove box of his work truck in case it was needed by EMS. He said could smell the Roundup as soon as the bottle was opened.

[19] He states that if you were spraying "something serious like ivy or pampas grass, you have a higher ratio of liquid pesticide that you add into the water."

Medical Symptoms and Treatment

- As of the date of deposition, Mr. Johnson is experiencing "*serious, very chronic pain*" and has started seeing a pain management physician within the last two weeks. He had been taking up to 15 Aleve per day for pain prior to that.
- Mr. Johnson described the "*mother lesion*" or "*mother mark*" which was the first mark he noticed on the inside of his right knee. He told the physician that the only thing he could have been exposed to was the pesticides he applied at work. He believes he first noticed a skin rash on his chest, trunk and face in the fall of 2013.
- Prior to his diagnosis of mycosis fungoides, Mr. Johnson had never been diagnosed with any other cancer, immune system deficiency or the AIDS virus. "*I have never had any medical problems before this problem started.*" This includes any skin irritation, eruption or boils (with the exception of chicken pox). He has no family history of cancer of any kind nor is there a family history of an immune deficiency or an autoimmune disease.
- After diagnosis with mycosis fungoides (August-September 2014), Mr. Johnson continued to apply Ranger Pro up until approximately late 2015. He stopped working for the school district as Integrated Pest Manager (IPM) in the summer of 2016 when Dr. Kim put him on permanent disability.
- None of Mr. Johnson's physicians have told him that Ranger Pro causes mycosis fungoides. "*They won't say.*" This includes Dr. Kim who is a specialist in cutaneous T-cell lymphoma. "*They say it could be the sun, exposure to chemicals, it could be a lot of things*."
- Mr. Johnson believes that Dr. Pincus, from UCSF, told him that his cancer was "*kind of unexplainable. Could lean towards definitely T-cell lymphoma but with signs of different cancers…*" However, the attorney for Monsanto (Mr. Cople) told Mr. Johnson that Dr. Pincus responded "*under oath that she does not have an opinion on whether occupational exposures to such things as herbicides can cause mycosis fungoides*."
- Mr. Johnson saw Dr. Fishman on June 26, 2017. Dr. Fishman reviewed Mr. Johnson's employment responsibilities as IPM. Mr. Johnson told Dr. Fishman that he sprayed 3-4 times per week and it could vary from 20 to 50 gallons or more; specifically, at the high school it could have been a hundred gallons. In his report, Dr. Fishman states that he doesn't understand how Mr. Johnson was exposed to Ranger

Pro in 2012 given the PPE he was wearing. He defers his opinion on this to an environmental hygienist.

- Dr. Fishman also notes a medical record from July 23, 2014, in which it is stated by Dr. Chanson that "*it is my opinion that patient's current medical condition more likely than not was not caused or aggravated by factors of employment. I base this opinion on MSDS of the pesticide, timing and clinical presentations*."
- However, Dr. Fishman also notes in his report that males are twice as likely as females to develop mycosis fungoides and African Americans are also twice as likely to develop it. (Mr. Johnson is African American.) Dr. Fishman wrote in his report that "*at the present time, I am concluding through reasonable medical probability that the applicant's mycosis fungoides is non-industrial etiology without identifiable industrial factors….The only factors impacting an onset of mycosis fungoides for this case are male gender and African American."*
- Mr. Johnson's skin condition improved with Valchlor (nitrogen mustard cream); however, Mr. Johnson testified that he believed he was steered away from this treatment due to high cost and possible adverse effects. *("She didn't want me to use the Valchlor, and I think it's because it can give you worse cancer and it's so expensive. It's ten thousand dollars an order.")* Records later note that the lymphoma is now in his blood. Intravenous systemic therapy (chemotherapy) was recommended which he is now undertaking under the direction of Dr. Truong. At that time he was told that his prognosis is for 3 to 5 years life expectancy.
- Mr. Johnson also describes recently experiencing a metallic taste in his mouth.

Background and Employment-Related Information

- Mr. Johnson is unsure of dates but appears from testimony that he was hired by Benicia Unified School District in California in June 2011 as a mail carrier, then became a custodian followed by work as a maintenance man. He did not begin using Ranger Pro until approximately June 2012 when he became the IPM. He did not become certified until sometime later, however, as required by the State of California. "…*We kind of jumped the gun and we got the spraying and the stuff going before we*

got the license. They wanted me to have that license – it's a legal requirement for Ranger Pro if you are over the gallon mark."[20]

- Mr. Johnson stated that he had never been exposed to Ranger Pro or Roundup or any other product containing glyphosate until he started as IPM at Benicia in June 2012. As IPM, Mr. Johnson was to start a program to stop the use of Ranger Pro and use more natural, non-chemical methods for weed control. It appears that did not happen during his employment tenure.
- As IPM, Mr. Johnson prepared the Benicia Unified School District Pesticide Application Tracking sheets which indicated the dates of spraying, the site and amount of product as well as the number of times applied and what was being treated (such as a baseball diamond or a right of way). He estimates that half of his employment time was spent spraying or related tasks and the other half was spent on paperwork.
- They were using "*a lot*" of Roundup at the school district (described as "*regular stuff you can purchase at Home Depot"*) but Mr. Johnson testified that Roundup is for smaller spaces while Ranger Pro is the industrial version. "*We started out using Roundup[21] which wasn't doing the ticket for the large amounts we needed. We started using Ranger Pro because it's supposed to be the industrial version of Roundup and comes in a gallon, a small can like Roundup or in big 50 gallon buckets*." They purchased these herbicides from Horizon Company.
- Additionally, Roundup would not always work on some of the more difficult weeds. "*It was my decision to say, this is not working. Roundup is not concentrated enough. I should just keep putting more Roundup...so Ranger Pro is less concentration and you got more area from the ratio you could mix up with Ranger Pro and can get a lot more done*." He further stated that the Ranger Pro worked "*really good*."
- The Ranger Pro label directs the applicator to take off contaminated clothes which Mr. Johnson did immediately following his second major exposure.
- Mr. Johnson also used pesticides for insect control on the school grounds; i.e, Wasp Zone or Wasp Freeze. "*One time, I got a little glob of that on me and I went and washed that stuff off right away because it was just on my arms*."

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[20] Apparently was allowed by the school district as his supervisor, Roy, stated that Mr. Johnson would be spraying under him as Roy had a certified applicator license.

[21] Testified that he used Roundup for approximately two months before switching to Ranger Pro.

- Mr. Johnson was very familiar with the labels on the Roundup/Ranger Pro products and he never saw anything on the labels stating that the products could cause cancer. Rather, "*I was told more than one time it was safe enough to drink*."

Supplemental Information

- Mr. Johnson testified that Attorney Litzenburg informed him in 2015 that, "*the State of California declared that glyphosate was a chemical known to them to cause cancer and that no signs have been put up in the last two years because Monsanto has been suing the state to prevent it from happening*."
- After receiving his cancer diagnosis, Mr. Johnson continued to use Ranger Pro. However, he contacted Monsanto approximately eight months later to find out if the Roundup or Ranger Pro might have something to do with his cancer. "*I told her that I have been exposed to chemicals and I was wondering if this Ranger Pro might be the one and she asked what symptoms I was having."* The woman he talked to "*had a whole spiel for me. She had a whole thing like she understood and what she needed to do*." "*She said, we really don't have those symptoms along with this product but if you want I can have somebody call you back*." No one ever called him back even after the World Health Organization (WHO) determined that glyphosate caused cancer including lymphoma. Per Monsanto's record of this call, "*The symptoms are not an expected response from this product*."
- Mr. Johnson smoked from 2004 to 2006. He limited his smoking to one "Black & Mild" cigar per day ("Black & Mild" is a short cigar with a plastic tip made from pipe tobacco.) He smoked no cigarettes or pipe nor did he use chewing tobacco or snuff.
- Apparently, the original complaint in this matter states that Mr. Johnson lived on a commercial sod farm earlier in his life. Mr. Johnson denies this. *("I've never lived on a sod farm. I don't know where that came from.")*
- While performing custodian duties, Mr. Johnson also waxed floors and cleaned bathrooms. He used bleach and possibly Peroxide 300 (he is not sure of the exact product name). He has <u>not</u> worked with <u>benzene, chlorinated solvents</u> or any other herbicides other than Roundup and Ranger Pro.
- Mr. Johnson used Henry's Wet Patch in Benicia to repair leaks in a classroom roof. After kneeling in the Wet Patch on his knee (wearing only jeans and a work shirt), he was diagnosed with squamous cell carcinoma (SCC) on that knee. However, Mr.

Johnson testified that Dr. Ofodile, a dermatologist, told him that the SCC was related to mycosis fungoides as per Stanford.

- Mr. Johnson performed miscellaneous painting jobs while working at Benicia. He also occasionally filled trucks with diesel fuel (outdoors) and also used Turf Patch.
- Mr. Johnson used Dolomark (limestone; calcium-magnesium carbonate) to line the softball, baseball and football fields. He wore only chemical proof gloves and boots and regular jeans (no Tyvek suits) when applying the limestone substance.
- The original workman's compensation matter in January 2015 was due to pain in Mr. Johnson's shoulder and chest muscles unrelated to his mycosis fungoides. Mr. Johnson is now pursuing a workman's compensation case for the mycosis fungoides as he claims that he was exposed to Ranger Pro as part of his job responsibilities working for the school district.

Workman's Compensation Deposition (dated October 28, 2015)

This deposition summary provides further information related to Mr. Johnson's exposure to Roundup® and Ranger Pro®.

- As grounds man and Integrated Pest Manager (IPM) at the Benicia School District, Mr. Johnson was spraying sites at five different school locations at different times. He usually would spray no more than 4-5 hours per day. He would not spray all five sites in one day because opportunity was dependent on the number of people "*milling around*" and the amount of time available to do the work.
- Mr. Johnson became certified for this position as he was not allowed to spray certain pesticides without a license. According to him, his license was issued in April 2015. He further noted that he only sprayed Ranger Pro® and Roundup® prior to receiving his license.
- As IPM, he also performed more maintenance work with an increased workload. In this position, "*I was exposed to a lot of different chemicals*." These chemicals included Henry's Roofing Patch® and Dolomark® (chalk used to mark baseball

fields). Dolomark® contained limestone[22] and during the baseball season, he would line up to 4 fields up to 3 times per week – each field would take one hour. Occasionally, he would apply the chalk on the track for field events.

- When first using Dolomark®, he did not know that one was supposed to wear a mask when using it.[23] "*But I found out from the paper bag you read on the side that you should be using a mask, gloves. And I found out that it's a pretty serious dust that you shouldn't be messing around with*." (pg. 26)
- Ever since that time, "*I wear gloves and PPE, a mask and gloves, to the point of laughter*"[24] as he also came in contact with bug spray, wild animals, feces, etc. He also noted that he found out that separate boots were needed for spraying. He even noted that separate spray trucks and work trucks were suggested because the spray truck would be full of pesticide residue.
- "*I have sprayed gallons, thousands of gallons of this*." (pg. 98)
- He had not been exposed to chemicals while at his home as he has never owned a home. He recalled no chemical exposures while working as a handyman.
- Mr. Johnson discussed two significant exposures to Ranger Pro® and Roundup®. The first exposure occurred when he was using a large, 50 gallon tank sprayer that was mounted in the back of a truck. The sprayer was built by school district employees from spare parts. On this particular day, he was spraying from the top and spraying downhill. He was using a 200-300 foot hose. The hose became caught in a crack of the sidewalk and then became detached. The machine continued to run and spray pesticide at the point where the hose had detached (he estimates a total of 10-20 gallons sprayed). Mr. Johnson "*had to get in there* (back of the truck to shut down the machine/no cutoff switch), *pesticide got all over me. It got down in my shirt, everywhere*." (pg. 75) He further stated that the pesticide got on the top of his head, down the side of his face and into the Tyvek suit on his chest and shoulders

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[22] On page 97-98, he testified that he reached in one of the canisters of chalk until an older man told him that it was lime and he shouldn't be "*sticking his hand in that*."

[23] He testified that for about 1/3 of the time he used Dolomark®, he did not utilize a mask. He describes the mask as a regular dust mask. He also used gloves.

[24] Noted that when he first started using PPE, he would reuse his suit but now only uses them once before destroying them.

and even down into his gloves. (Pg. 92) However, there was no burning or itching associated with his exposure.

Mr. Johnson testified that he finished the working day but did not take a shower until he got home later that day after leaving work at 2:30 pm.[25] He estimated that the exposure happened approximately at 8:30 am that day. (No date given for this exposure but ***prior*** to his lymphoma diagnosis.) (Pg. 85)

- He further testified that no incident report was written up for this.
- The machine held 50 gallons of water and a percentage of pesticide was added to the water depending on what plant was being targeted.[26] "*Ivy or pampas grass has a higher ratio of pesticide in the water*" than what would be used for annuals. "*You might have a five percent mix, you might have a ten percent mix*." (pg. 86)
- He also described further exposures on his face and hands due to drift from the machine whenever he used it. "*I had no control over the drift. This machine was built by the supervisor. There was no way to regulate your pressure*." (pg. 78).
- Although he wore a Tyvek jumpsuit, boots, mask and goggles, the suit was not sealed and there was an opening at the arms, legs and neck. "*All my face… ears, neck, all that is exposed*." (pg. 80)
- The second exposure happened less than a year before this deposition. He took a backpack out to spray and "*you kind of get sweaty out there working and a little damp sometimes. So I didn't really worry. And then my back started to feel wet and that's when I came back to the office and realized that I had a back full of pesticide*." He went to Kaiser and was checked out. He specifically noted that he already had the skin condition at this time. He testified that he was told his skin condition was related to his family's history, but no such history exists. "*I don't have anybody in my family that has had anything like what I have on my skin*." (pg. 34)
- Mr. Johnson testified that when being trained on pesticide application "*the teachers teach that it's just like water. That glyphosate glycine is just like water and you can*

[25] He did try to clean up with water and paper towels at work and removed his Tyvek suit.

[26] On page 90, he states that he had been spraying for annuals during this exposure and was spraying at a rate as required in the Ranger Pro® manual.

almost drink it. It's that safe of a pesticide that you can drink it. That's the way they pushed Ranger Pro®…" (pg. 89)

- His physicians have not given him a cause for his cutaneous T-cell lymphoma and "*that it is skin cancer*." They have told him that he doesn't fit the risk factors "*usually older white males who have been exposed to chemicals such as Agent Orange or arsenic, people that spend a lot of time in the sun or in tanning beds*."
- He testified that after the first exposure (a few months later), he noticed the "*mother mark*" on his right knee that would not go away and it became painful. He began finding more and more marks on his skin and especially on his left shoulder where he had to reach in and turn off the spray machine. (Pg. 93) He noted that it was there when he had his MVA in September 2013.
- Mr. Johnson mixed his own pesticides. He describes mixing as "*one of the most dangerous times because you have just raw chemical and just water. But it's actually one of the safest times because you have control of what's happening*." (pg. 134)
- He described having "*different pains*" that he doesn't understand like the "*pain in the chest and like the pain on the skin here and there. When I sweat, I get burning*." Also, "*burning in my chest. The chest pain is usually a really sharp, burning pain. Sometimes it can feel almost like fire in your chest*." (pg.117)
- As of the date of this deposition, he was still working for the school district. "*So I go to work and I suck it up and I do what I've got to do*." He currently (as of date of deposition) is responsible for all the maintenance work, grounds, etc. at the middle and elementary school "*and I'm just guessing that they still expect me to be an IPM*." (pg. 125)
- He also stated that over the last three months, his symptoms have worsened. He feels overwhelmed and stressed because no one has any answers for him.

Evaluation of Stuart Shear, MD, Dermatologist Dated September 5, 2016

Per the History of Present Illness, Mr. Johnson presented to Dr. Shear for a medical evaluation in dermatology.

Mr. Johnson noted that in November 2013, he spent three hours kneeling on Henry's Wet Patch Cement® with his right knee. In October 2014, almost one year later, an excision for a squamous cell carcinoma was performed on this knee. Dr. Shear states that this "*was caused with medical probability by exposure to Henry Wet Patch Cement®.*"

In June 2014,[27] Mr. Johnson first noticed a skin rash on his scalp, face, neck, trunk and extremities. A month later, his physician diagnosed the rash as atopic dermatitis. A biopsy on August 1, 2014, however, revealed that Mr. Johnson had epidermotrophic T cell lymphoma. He was treated with Valchlor (0.16% nitrogen mustard) and Targretin (oral bexarotene) and was scheduled to begin participation in a Stanford clinical trial (mid-September 2014) using an experimental drug.[28]

Dr. Shear states that Mr. Johnson has cutaneous T cell lymphoma (CTCL) which is proven by the biopsy report. Per Dr. Shear, clinical findings are classic. "*As far as causation, it has certainly been present in evidenced-based literature that the HLV/cr virus and the Epstein bar virus can cause cutaneous t-cell lymphoma. In terms of apportionment, is 100% due to his employment with Benicia Unified School District. However, it is medically probable that a patient whose skin has been exposed to Roundup® weed killer during 20-40 applications yearly from June 2011-June 2014 (3 years), that the cause was Roundup® weed killer which has evidence-based medical literature referenced as a causative agent of cutaneous t-cell lymphoma.*"

At that time Dr. Shear gave Mr. Johnson a 3% impairment of the whole person. Additionally, "*Mr. Johnson has a class 2 impairment intermittently present with no limitations in performance of daily living and requiring no intermittent treatment*."[29]

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[27] Other records state first notice of rash was in fall of 2013 (see Table 1, 8/26/14).

[28] Appears that he did not begin participation due to non-compliance with medications.

[29] Per the AMA Guide to the Evaluation of Permanent Impairment, page 178, table 8-2.

Part B: Introduction to Glyphosate

Glyphosate (Roundup® and Ranger PRO®) History and Use

Glyphosate is the active ingredient in various herbicide formulations known as Roundup®. The Monsanto Company discovered the herbicide activity of glyphosate in 1970 and initiated sales and distribution for weed control in 1974. Glyphosate is not selective and is used on food and non-food crops. Over the subsequent four decades, glyphosate use as an herbicide has greatly expanded. It is used in agriculture, forestry, industrial rights-of-way and in residential applications worldwide.

Glyphosate's use in agriculture has been further expanded by the development of genetically modified plants that are tolerant to glyphosate treatment (Roundup-Ready®).[30] This has significantly increased the use of glyphosate on these crops for weed control with no concern for crop injury.[31] As a result, genetically modified crops contain far more glyphosate residue than conventional crops.

The introduction of glyphosate-resistant (GR) crops in 1996 and the expiration of the glyphosate patent have resulted in its ubiquitous use today, characterized by a 15-fold global increase since the mid 1990's.[32] According to glyphosate pesticide registration, in 1993 approximately 13 to 20 million acres of land had been treated with 18.7 million pounds of glyphosate and used mostly on hay/pasture, soybeans and corn.[33] According to the U.S. Geological Survey, in 2014, 300 million pounds of glyphosate were used on agricultural land in the U.S. Since 1974 in the U.S., over 3.5 billion pounds of glyphosate have been applied.[34]

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[30] Williams, G. et al., Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pg. 117-165.

[31] Duke, S. S., Encyclopedia of Agrochemicals, 2003, John Wiley & Sons.

[32] Benbrook, C.M., "Trends in glyphosate herbicide use in the United States and globally," 2016, Environmental Sciences Europe. 28:3.

[33] U.S. EPA, "Registration eligibility decision-facts: Glyphosate," 1993 United States Environmental Protection Agency, Prevention, Pesticides and Toxic Substances (7508W), EPA-738-F-93-011.

[34] Benbrook, C.M., "Trends in glyphosate herbicide use in the United States and globally," 2016, Environmental Sciences Europe. 28:3.

Modes of Action and Safety Considerations

Glyphosate can be applied both as a ground spray and as an aerial spray. It is used to modify plant growth, speed up the ripening of fruit, applied as a ground spray for peanuts and an aerial spray for sugarcane.[35] Glyphosate is also sprayed directly on wheat just prior to harvest, a rather peculiar practice called "browning or desiccating."

Glyphosate is absorbed by the leaves and stems of the plant and readily translocated throughout. It destroys the plant by reducing the production of certain aromatic amino acids that form the proteins critical for plant growth and development.[36] Specifically, glyphosate disrupts the shikimate acid pathway[37] by inhibiting the activity of a key enzyme (EPSP synthase) that is needed to form the essential amino acids.[38,39,40] This shikimate acid pathway is a crucial process in all higher order plants. Thus, glyphosate will kill most plants. Glyphosate-resistant crops use an alternative EPSP enzyme and are, therefore, specifically engineered to withstand extremely high levels of glyphosate without perishing. This metabolic process is also a crucial one in many microorganisms, but it is not utilized *directly* by animals or humans.

Throughout the years, Monsanto has advertised and promoted the safety of their Roundup® products by claiming that the active ingredient, glyphosate, works by targeting an enzyme found in plants, but not in people or pets. However, recent evidence suggests that glyphosate may disrupt the essential shikimate process in bacteria, particularly the beneficial bacteria of the human intestinal tract.

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[35] Id.

[36] Jaworski, E. G., "Mode of action of N-phosphonomethylglycine. Inhibition of aromatic amino acid biosynthesis," 1972, J. Agric. Food Chem. 20 (6), pg. 1195-1198.

[37] Williams, G. et al., "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pg. 117 - 165.

[38] Boocock, M. R., "Kinetics of 5-enolpyruvylshikimate-3-phosphate synthase inhibition by glyphosate," 1983, FEBS Letters 154, pg. 127-133.

[39] Hollander, H., & Amrhein, N., "The site of the inhibition of the shikimate pathway by glyphosate," 1980, Plant Physiol 66(5), pg. 823-829.

[40] Schönbrunn, E. et al., "Interaction of the herbicide glyphosate with its target enzyme 5-enolpyruvylshikimate 3-phosphate synthase in atomic detail," 2001, Proc Natl Acad Sci USA Feb 13; 98(4), pg. 1376–1380.

Additionally, glyphosate has been shown to sporadically cause potent inhibitions in the xenobiotic-metabolizing enzyme, CYP2C9[41], which is responsible for the biotransformation, metabolism and elimination of various toxic compounds from the body.[42] A recent review by Samsel and Seneff (2013) hypothesized that glyphosate's known ability to disrupt the intestinal bacteria flora and to suppress a family of enzymes that play an important role in detoxifying harmful chemicals could be contributing to a rise in modern human diseases worldwide.[43] Glyphosate has also been demonstrated to be genotoxic and carcinogenic as discussed below in detail.

Glyphosate (Roundup®) Formulations: Chemical and Physical Information

Glyphosate is the declared active ingredient (DAI) in Monsanto's Roundup® herbicide products; however, it is only one ingredient in the formulation and is not typically applied in its isolated form. Other substances, referred to as co-formulants, are added in order to modify the physicochemical properties, thereby improving the efficacy of the glyphosate-based formulation.[44,45,46] Examples of co-formulants are spreaders, compatibility agents, anti-foaming agents, drift retardants and surfactants. The specific identities and the amounts of co-formulants in the herbicide formulations have largely been kept confidential because they are considered by the manufacturers to be proprietary data. Often, co-formulants are declared as "inert" as they do not act directly on the intended target, i.e., the weed. Moreover, they historically have not been included

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[41] Abass, K., Turpeinen, M., and Pelkonen, O. "An evaluation of the cytochrome P450 inhibition potential of selected pesticides in human hepatic microsomes," 2009, Journal of Environmental Science and Health Part B, 44(6).

[42] Gueguen, Y. et al., "Cytochromes P450: xenobiotic metabolism, regulation and clinical importance," 2006, Ann Biol Clin (Paris) 64, pg. 535-548.

[43] Samsel, A..and Seneff, S, "Glyphosate's suppression of cytochrome P450 enzymes and amino acid biosynthesis by the gut microbiome: Pathways to modern diseases," 2013, Entropy (15), pg. 1416-1463.

[44] Defarge, N. E., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels," 2013, Int J Environ Res Public Health. 13(3), pg. 264.

[45] Nobels, I. et al., "Toxicity ranking and toxic mode of action evaluation of commonly used agricultural adjuvants on the basis of bacterial gene expression profiles," 2013, PLoS ONE 6, pg. 264.

[46] Haefs R. et al., "Studies on a new group of biodegradable surfactants for glyphosate," 2002, Pest Manag. Sci. 58, pg. 825–833.

in either toxicity tests of pesticides on mammals for the establishment of their acceptable daily intake (ADI) or in animal carcinogenicity studies.

Most glyphosate-based formulations (GBFs) contain the same three primary ingredients: (1) glyphosate salt, (2) co-formulants (e.g. surfactants) and (3) inert ingredients (e.g., "water").[47] Formulations differ from one another by the specific salt included in the formulation and the amount and type of surfactants, other co-formulants and inert ingredients. The ingredients can be examined individually; however, one must be mindful that the sum of these ingredients may have very different properties than the individual ingredients alone. This is especially important when investigating the absorption of a GBF herbicide into non-target organisms.

The salt of glyphosate in a GBF is comprised of an organic base combined with glyphosate. Glyphosate [*N*-(phosphonomethyl) glycine] is amphoteric (can act as either an acid or a base) and is practically insoluble in organic solvents.[48] Glyphosate as a weak acid has a hydrogen ion held to a phosphorous group by a weak electrostatic charge. By replacing this hydrogen ion with a different cation (organic base), herbicide manufacturers are able to make a more water-soluble glyphosate salt. Isopropylamine (IPA) is the organic base that is most commonly used in Roundup formulated products.[49,50] This cation is also bound by a weak electrostatic charge and may not stay with the glyphosate acid; once it is added to water by the applicator, it can be easily replaced by other positively charged ions from the water.[51] Thus, the glyphosate that is working in the plant is usually not associated with the original salt.[52] The specific salt used in the formulation may not significantly impact herbicide performance but rather is selected to ensure that

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[47] [redacted], Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake," 2001, (Tab 15; see also MONGLY01839476 for draft of this document.)

[48] Williams, G. et al., "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pg. 117 - 165.

[49] Id.

[50] [redacted], Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake," 2001, (Tab 15; see also MONGLY01839476 for draft of this document.)

[51] Interactions between glyphosate and calcium salts found in water are the primary reason for adding AMS to the spray tank. (http://www.weeds.iastate.edu/mgmt/2001/glyphosateformulations.htm)

[52] [redacted], Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake," 2001, (Tab 15; see also MONGLY01839476 for draft of this document.)

the formulated product handles well, is compatible with other products that might be included and will not cause adverse crop responses. The glyphosate concentration in the final formulation will depend on the salt used as each salt has a different molecular weight. A lighter salt will result in a higher glyphosate concentration.[53]

Throughout the years, several salt types have been used to formulate glyphosate products including isopropylamine (IPA), ammonium, sodium and potassium glyphosate salts.[54] (See Table 3 below.) Glyphosate isopropylamine salt is the one most commonly used in Roundup® formulated products[55] and most commonly used in all glyphosate-based products.[56]

Table 3
Properties of Glyphosate and Common Salts of Glyphosate in Roundup®[57]

Herbicidal Agent	Solubility in water (g/L)	MW (g/mol)	Molecular Formula
Glyphosate acid	**pH 1.9:** 10.5 **pH 7.0:** 157	169.07	$C_3H_8NO_5P$ or $HOOCCH_2NHCH_2PO(OH)_2$
Glyphosate Potassium salt	900[a]	207.16	$C_3H_7KNO_5P$
Glyphosate Ammonium salt	300[a]	186.11	$C_3H_{11}N_2O_5P$
Glyphosate Sodium salt	500[a]	191.06	$C_3H_7NNaO_5P$
Glyphosate Isopropylamine salt (IPA)	**pH 7.0:** 900 **pH 4.1:** 786	228.19	$C_6H_{17}N_2O_5P$ or C_3H_9N - $C_3H_8NO_5P$

[a] From *"Managing Glyphosate. Performance of different salts and adjuvants."* Grants Research and Development Corporation. GRDC Project code ICN00016.

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[53] The active ingredient concentration in a GBF is specified as a glyphosate equivalent or an acid equivalent (a.i.) referring to the free form of the acid. This allows for comparability between formulations.

[54] [redacted], Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake." 2011, (Tab 15; see also MONGLY01839476 for draft of this document.)

[55] Giesey, J. P., Dobson, S., & Solomon, K. R., "Ecotoxicological risk assessment for Roundup herbicide," 2000, Rev. Environ. Contam. Toxicol. 167, pg. 35-120.

[56] U.S. EPA, "Registration eligibility decision-Facts: Glyphosate," 1993, United States Environmental Protection Agency, Prevention, Pesticides and Toxic Substances (7508W), EPA-738-F-93-011.

[57] http://npic.orst.edu/factsheets/archive/glyphotech.html

In addition to the organic base and, therefore, the salt used, the other major difference between glyphosate-based formulations is the inclusion of co-formulants. Some co-formulants are "pre-loaded" or included by the manufacturer in the GBF while others, called adjuvants, are added by the end user to modify the herbicide to the particular situation in which it is being used.[58] Adjuvants are not added to the GBF by the manufacturer mainly because different types of crops may require different types of adjuvant, e.g., certain crops are sensitive to oils, some are difficult to wet. Thus, an herbicide manufacturer avoids limiting the application of a given herbicide to only one crop or situation.

As an example of adjuvant use, the addition of ammonium sulfate (AMS) and water conditioners have been shown to significantly improve weed control with glyphosate. Water in some regions contains excessive amounts of salts including calcium, magnesium, iron and sodium, and these salts bind to glyphosate and reduce its absorption and solubility. The sulfate component of AMS is negatively charged and will bind to positively charged salts so that they cannot reduce the activity of glyphosate. Other commonly used adjuvants include emulsifiers, dispersants, stabilizing agents, compatibility agents, buffering agents, anti-foam agents, spreader-stickers, drift retardants and surfactants.

Some GBFs may contain a greater percentage of co-formulants than glyphosate salt. These are listed simply as *"Other Ingredients"* on the label. For example, the label on Roundup Original Max herbicide, which contains a proprietary surfactant, reads

[58] The terms "co-formulants" and "adjuvants" are sometimes used interchangeably in the literature. A fact sheet form Cornell University states, "A pesticide adjuvant is broadly defined as any substance added to the spray tank, separate from the pesticide formulation that will improve the performance of the pesticide. Sometimes adjuvants are more narrowly defined as a substance added to a pesticide mixture to improve its physical qualities and, hence, its effectiveness." http://psep.cce.cornell.edu/facts-slides-self/facts/gen-peapp-adjuvants.aspx

ACTIVE INGREDIENT	
Glyphosate N (phosphonomethyl)glycine, in the form of its potassium salt	48.7%
OTHER INGREDIENTS	51.3%
	100%

The most commonly pre-loaded co-formulants used in herbicides are surfactants. Surfactants are complex chemicals that facilitate and accentuate the emulsifying, dispersing, spreading, wetting or other surface modifying properties of aqueous solutions. For example, waxes on plant leaves are lipophilic and chemically non-polar and thus repel water while herbicides such as glyphosate are highly hydrophilic and chemically polar.

Adding surfactants will significantly increase how well glyphosate spreads on and enters leaf surfaces. A surfactant can also reduce the amount of glyphosate washed off of plants by rain. Surfactants in herbicides vary greatly in their nature and concentration and are added to increase the absorption rate of the acid into the plant's leaf and stem tissue. Sometimes a combination of surfactants is used in one glyphosate formulation. The most prevalently used surfactants in herbicides contain POEA (PolyOxyEthylene alkylAmine).

The co-formulants in a GBF individually, or in combination with each other, have a profound toxicological effect on a non-target organism. Some of these co-formulants may synergistically attenuate the negative effects of glyphosate, or as in the case of surfactants which can increase dermal absorption, may simply increase glyphosate's systemic exposure. Surfactants, as well as other co-formulants, are particularly important with respect to a risk assessment and are, therefore, discussed in detail later in this report.

Roundup is offered in dry or aqueous formulations at various concentrations. Glyphosate is commonly formulated with water at 2.13 M (356 g/L free acid) or as an isopropylamine salt 480 g/L.[59] The ethoxylated tallowamine (POEA) surfactant in Roundup Classic is

[59] Williams, G. et al., "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pg. 117 - 165.

designated by Monsanto as *MON 0818*[60] with a concentration that is typically reported as approximately 15% of the formulation weight to volume or 150 g/L.[61,62,63,64]

Toxicological Considerations of Exposure and Dose

In assessing exposure, toxicologists examine how humans come into contact with chemicals, the amounts of the chemical that enters the body (absorbed dose) as a result of contact and how these amounts change over time (pharmacokinetics). The goal of the exposure assessment is to quantify the amounts over various time periods. The quantitative expression of those amounts is referred to as dose. Thus, dose is the measurement needed to quantify a chemical's risk of toxicity. Therefore, the initial goal of any exposure assessment is first to objectively establish dose.

Glyphosate Exposure

The ubiquitous use of Roundup® imposes a tremendous increase in the potential for human exposure, not only to the active ingredient (glyphosate) but to other chemicals (or "co-formulants") as well. This section reviews the dose measurement methods.

Systemic Dose

When a person is exposed to a chemical such as glyphosate, the dose physically contacting the body is referred to as the "*exposure dose*." This is different from the

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[60] Monsanto response to the concern of the Slovenian authorities on the composition of the Plant Protection Product MON 79376 (360 g/ 1 glyphosate) and the surfactant MON 59117 (CAS n ° 68478-96-6). MONGLY02817577

[61] Id.

[62] Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

[63] Giesey, J. P., Dobson, S., & Solomon, K. R., "Ecotoxicological risk assessment for Roundup herbicide," 2000, Rev. Environ. Contam. Toxicol. 167, pg. 35-120.

[64] Defarge, N. E., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels, 2016, Int J Environ Res Public Health, Vol. 13(3): 264.

"*systemic dose*" which enters the bloodstream and reaches various organs within the body.

Systemic dose is typically only a portion of the exposure dose and is identified through pharmacokinetic (PK) or chemical disposition studies that can trace the fate of a chemical after it enters the body. Pharmacokinetic studies investigate the amount of a chemical absorbed by the body, how the chemical is distributed throughout the body to specific tissues, how the chemical is metabolized and finally, how a compound is excreted from the body. This is commonly known as ADME (absorption, distribution, metabolism and excretion). This data is applied in conjunction with epidemiological and occupational exposure studies that have included biomonitoring and dosimetry for use in the human health risk assessment process. Thus, pharmacokinetic studies provide the necessary link between estimates of exposure, toxicity studies and estimates of human risk. It is, therefore, imperative that these studies are designed, conducted and interpreted accurately.

Routes of Exposure

The route of exposure controls how a chemical gets absorbed into the body. The primary routes by which potential toxins become absorbed into a person's system are dermal absorption, ingestion and inhalation.

Ingestion

Ingestion of herbicides may be intentional, as in suicides/poisonings, or unintentional through the consumption of residue-laden foods. In the current matter of assessing exposure in operator use, intentional ingestion is not considered since it will contribute negligibly to the overall exposure.

Inhalation

Since the vapor pressure of glyphosate is very low ($9.8x10^{-8}$ mm Hg or $1.31X10^{-2}$ mPa at 25°C),[65] inhalation during mixing and preparation of an herbicide is typically not a significant contributor to exposure unless an aerosol is produced. Thus, inhalation during spray application of the herbicide can be a factor. Such exposure depends mainly on

[65] National Toxicology Program, U.S. Department of Health and Human Services.

droplet size of the spray and the equipment used for spraying. Different nozzle types (often modified by farmers to increase discharge) will generate different volumetric droplet size distributions. Lesmes-Fabian, et al., found that for the standard discharge nozzle as used in their study, approximately 5% of the total volume of droplets was smaller than 100 µm.[66] In dry climates, droplets less than 100 µm are subject to evaporation and are respirable.

Dermal Absorption

For occupational users such as farmers, the key determinant of a person's exposure is how the herbicide is actually handled and/or applied.[67] This dermal exposure will occur throughout the mixing, loading and application of herbicides as well as through re-entry (i.e., handling stems, leaves or soil after herbicide treatment).

Studies have found that workers performing the common farm task of "thinning" are more exposed to pesticides than (for example) workers who are harvesting or pruning.[68,69] One study[70] found a higher level of pesticides in the house and vehicle dust of the thinning workers. Additionally, their children revealed higher urinary pesticide metabolite concentrations which showed evidence of a "take-home pesticide pathway."[71] The same

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[66] Lesmes-Fabian, C., Garcia-Santos, G., Leuenberger, F., Nuyttens, D., & Binder, C. R, "Dermal exposure assessment of pesticide use: The case of sprayers in potato farms in the Colombian highlands," 2012, Science of the Total Environment, 430, pg. 202-208.

[67] Curwin, B.D. et al., "Urinary and hand wipe pesticide levels among farmers and non-farmers in Iowa," 2005, Journal of Exposure Analysis and Environmental Epidemiology, Vol. 15, pg. 500–508.

[68] de Cock, J. et al., "Determinants of exposure to captan in fruit growing," 1998, Am Ind Hyg Assoc J 59, 1998a, pp. 166–172 and 1998b, pg. 158-165.

[69] Simcox, N.J. et al., "Farmworker exposure to organophosphorus pesticide residues during apple thinning in central Washington State," 1999, Am Ind Hyg Assoc J 60, pg. 752–761.

[70] Coronado, GD, Thompson, B, Strong, L, Griffith, WC, and Islas, I., "Agricultural task and exposure to organophosphate pesticides among farm workers," 2004, Environ Health Perspect 112, pg.142–147.

[71] The take-home pesticide pathway is the pathway that children and spouses of agricultural workers are exposed through. (Hyland, C. and Ouahiba Laribi, Q., "Review of take-home pesticide exposure pathway in children living in agricultural areas," 2017, Environmental Research. Volume 156, pg. 559–570.)

study showed that workers in apple or pear crops had higher pesticide metabolite concentrations than those who worked in peach, cherry or grape crops.[72]

Mechanisms of Absorption

Farmers, forestry workers and landscapers are primarily exposed to herbicide chemicals through dermal contact during mixing, loading or application of the glyphosate formulation as well as through re-entry. Therefore, with respect to occupational exposure, the skin is the predominant route by which glyphosate enters the human body.

The Dermal Barrier

Human skin is a complex organ consisting essentially of two layers: a thin, outermost layer called the *epidermis* and a much thicker under-layer called the *dermis*. It is the outer layer of the epidermis, called the *stratum corneum* (SC) that provides the primary protective barrier function of the skin. This barrier is largely responsible for resisting the entry of foreign agents into the human body.

The stratum corneum is primarily composed of non-living cells, or corneocytes, in a brick and mortar type system of lipid matrix. Corneocytes are terminally differentiated keratinocytes that have migrated from the epidermis to the skin's surface. The composition of the stratum corneum lipid matrix is dominated by three lipid classes: (1) cholesterol, (2) free fatty acids and (3) ceramides which are waxy lipid molecules. These lipids adopt a highly ordered, three dimensional structure of stacked, densely packed lipid layers[73] as shown in Figure 1.

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[72] Coronado, GD, et al., "Organophosphate pesticide exposure and work in pome fruit: Evidence for the take-home pesticide pathway," 2006, Environ Health Perspect 114 (7), pg. 999-1006.

[73] van Smeden, J. and Bouwstra, J.A., "Stratum corneum lipids: Their role for the skin barrier function in healthy subjects and atopic dermatitis patients," 2016, Curr Prob. Dermatol 49, pg. 8-26.

Figure 1
Epidermal Layers of Human Skin

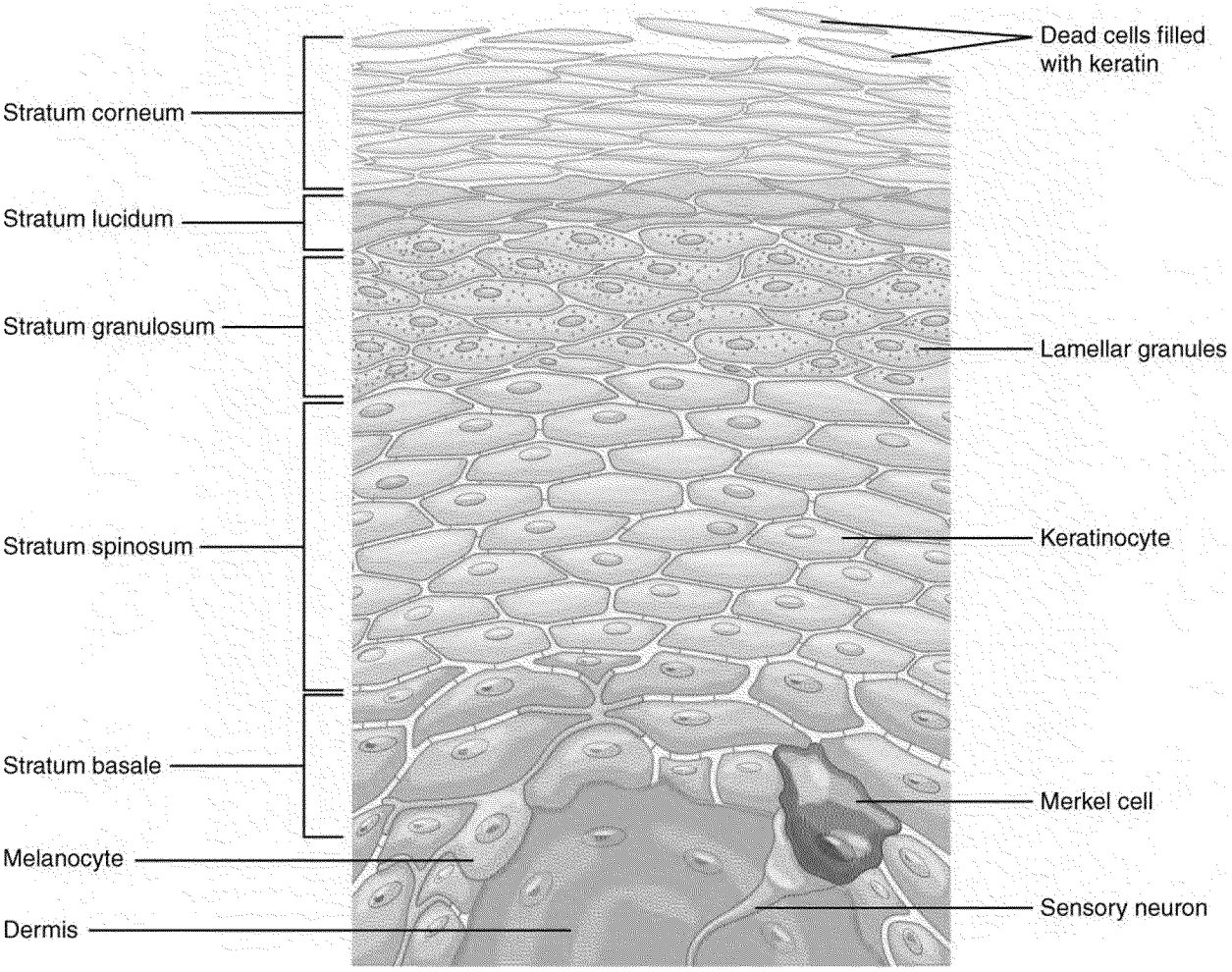


Image courtesy of Wiki Journal of Medicine

Percutaneous Absorption of Glyphosate

A chemical can enter the stratum corneum directly through the corneocyte cells, through channels between the cells or through follicles, pores and glands. Due to its structure, the stratum corneum is highly lipophilic (lipid loving) and hydrophobic (tending to repel water). Thus, lipid-soluble chemicals are able to penetrate this layer into the circulatory system much more efficiently than water-soluble chemicals.

Since glyphosate is a small hydrophilic molecule, it travels easily thru the channels and follicles; however, it cannot easily pass through lipid layers. The stratum corneum is, therefore, the rate-limiting barrier in the absorption of a hydrophilic agent such as glyphosate. How quickly glyphosate passes through this outer layer determines the overall absorption rate of the chemical into the body.

Once glyphosate has been absorbed into the stratum corneum, it may pass through into the viable epidermis and then into the dermis where it is transported systemically by the dermal blood supply or lymphatics and circulated to other areas of the body. This passive diffusion process is governed by Fick's law which states that the rate of absorption or flux (J) of any substance across a barrier is proportional to its concentration difference across that barrier.

The stratum corneum is resistant to penetration of weak acids but is much less effective against organic acids and some inorganic chemicals. Organic and alkaline chemicals can soften the keratin cells in the skin and pass through this layer to the dermis where they are able to enter systemic circulation.

The thickness of the skin, as well as its lipophilicity, varies with location on the body. Areas of the body such as the forearms, which may be particularly hairy, are most easily penetrated by chemicals since they can enter the small ducts containing the hair shafts. Chemicals can also enter through cuts, punctures or scrapes of the skin since these are breaks in the protective layer. Due to the nature of their occupation, the skin of farmers (particularly their hands) typically have a higher percentage of fine cracks and breaks than that of the average person.

Percutaneous Absorption Models

The term *"percutaneous"* refers to any action involving penetration of the skin. Accurate determination of the rate at which agents penetrate the skin is critical for assessing the dose and potential risk from exposure. Dermal penetration is generally considered to occur by passive diffusion (Fick's law); however, in living organisms, biotransformation of a substance within the deeper viable regions of the skin (via metabolism) can also occur prior to systemic absorption.

The amount of a chemical that is absorbed through the skin is dependent on the properties of both the chemical and the skin. The most significant properties impacting the absorption of a chemical are its water and lipid solubility, molecular weight, degree of ionization and polarity.[74] The most important properties of the skin are the number (density) of follicles, the thickness of the stratum corneum and the sebum composition as well as the distance of capillaries to the surface of the skin.

Dermal penetration studies are conducted to measure the absorption or penetration of a substance through the skin barrier and into the skin and determine whether it has the potential to be absorbed into the systemic circulation. A wide range of experimental protocols exist for the determination of percutaneous absorption; the protocol used in any particular experiment will depend on the penetrant being studied.

Penetration studies may be conducted *in vivo* (in whole living animals) or *in vitro (*outside of a living organism). In assessing the risk of human exposure to glyphosate, the aim of a dermal absorption study is to measure the amount of glyphosate that passes into and through human skin and into systemic circulation.

Due to greater differences between rodents and humans verses primates and humans, *in vivo* human studies would provide the most accurate dermal penetration models. However, inasmuch as such studies would be both impractical and unethical, animals such as rats, mice, and monkeys are used for *in vivo* studies of the absorption of glyphosate.

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[74] Van Ravenzwaay, B. and Leibold, E., "A comparison between in vitro rat and human and in vivo rat skin absorption studies, 2004, Toxicol. In Vitro. 18(2), pg. 219-25.

***In Vivo* Measurement Methods**

In vivo dermal absorption measurement methods include two methods: (1) the indirect method of surface disappearance and surface recovery whereby the dermal absorption is inferred and (2) direct methods of determining dermal absorption which includes measuring glyphosate in the blood, excreta (urine or feces) or stratum corneum or by estimating through biological or pharmacological responses.[75]

Zendzian, 2000,[76] published a method for measuring glyphosate in excreta and in carcasses as well as the quantity remaining in the skin after washing. The Zendzian study states that the United States Environmental Agency's Office of Pesticide Programs (OPP) has developed a standard protocol for evaluating the dermal penetration of pesticides in the rat. This protocol was formalized in 1994 as a guideline for dermal absorption studies of pesticides.

As of the year 2000, in excess of 263 studies on the dermal absorption of over 160 pesticide chemicals had been submitted to OPP as part of the pesticide registration and risk assessment processes. From this standard protocol, it is possible to describe, quantitatively with dose and time, the entrance of a chemical into and penetration through the mammalian epidermis into the systemic circulation as well as the chemical's concentration in blood, the body and its excretion in urine and feces.

***In Vitro* Measurement Methods**

Since *in vivo* studies are complex and expensive, *in vitro* methods are more widely used as a screening method for dermal penetration estimates. *In vitro* experiments involve the use of a diffusion cell, wherein two chambers, donor and receptor, are separated by a membrane (human or animal skin). There are many variations, but all diffusion cells involve the penetrant passively diffusing from the donor chamber into the receptor chamber where it can be measured.

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[75] U.S. EPA, "Dermal exposure assessment: A summary of EPA approaches," September 2007. United States Environmental Protection Agency, National Center for Environmental Assessment Office of Research and Development, EPA/600/R-07/040F

[76] Zendzian, R.P., "Dermal absorption of pesticides in the rat," 2000, AIHAJ, Vol. 61(4), pg. 473-83.

In 2007, the U.S. EPA published "Dermal Exposure Assessment: A Summary of EPA Approaches" which provides a dermal exposure assessment methodology for treated surfaces.[77] The U.S. EPA and other regulatory agencies accept a wide diversity of *in vitro* protocols, but they caution comparing these studies due to differences such as cell type (i.e. static or flow through), the membrane selected, composition of the receptor fluid and the dosing method (infinite or finite).

Other Measurement Models and Methods

In a static diffusion cell, also known as a Franz cell,[78] the penetrant diffuses from the donor chamber through the membrane into a "static" receptor chamber of a fixed volume which is continually stirred. In a flow through cell or Bronaugh[79] cell, *in vivo* conditions are simulated by using a constantly flowing receptor fluid that mimics *in vivo* blood flow beneath the skin membrane. The skin membrane is bathed below by a flowing solution maintained at 37 degrees C.

When studying the absorption of glyphosate, the membrane separating the chambers is typically human (from cadavers), rat or monkey skin and may be full thickness or dermatomed (sliced). Dermatomed skin, wherein only the epidermis is used after it has been separated from the dermis, is commonly used because full-thickness skin can be cumbersome in the diffusion apparatus. Since glyphosate is hydrophilic, the main barrier to its diffusion across the skin resides in the stratum corneum and, therefore, the absence of the dermal tissue is generally not of concern.[80] Ideally, when fresh skin is used, the receptor fluid should allow skin metabolic activity.

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[77] U.S. EPA, "Dermal exposure assessment: A summary of EPA approaches," September 2007. United States Environmental Protection Agency, National Center for Environmental Assessment Office of Research and Development, EPA/600/R-07/040F

[78] Franz TJ., "Percutaneous absorption. On the relevance of in vitro data," 1975, J Invest Dermatol. 64, pg. 190–5.

[79] Bronaugh, R., H. Hood, M. Kraeling, and J. Yourick, "Determination of percutaneous absorption by *In Vitro* techniques," 1999, pg. 229-233 in Percutaneous Absorption, 3rd ed., R.L. Bronaugh and H.I. Maibach, eds. New York: Marcel Dekker, Inc.

[80] Williams, A.., "Transdermal and dermal drug delivery: From theory to clinical practice," 2003, London, Pharmaceutical Press.

Dosing Techniques and Measurement Considerations

The loading, or dosing, of the donor chamber in all diffusion cells is accomplished in one of two ways: infinite dosing or finite dosing. In the infinite dosing, or flux, technique, a high concentration of glyphosate is installed into the donor chamber (so its concentration does not decrease) while the concentration is measured in the receptor chamber over time until steady state is reached. This allows for the calculation of a permeability coefficient.

A finite dose technique allows the herbicide to be tested under conditions similar to those found *in vivo*. The donor chamber is loaded with a known amount of herbicide which is depleted due to penetration during the course of the experiment. The concentration of the herbicide in the receptor fluid is measured to determine the percent of the original dose that penetrated the skin per unit area of skin over a period of time.

Loading conditions can greatly impact calculation of *percent absorption*. As the applied dose becomes greater than the absorbable amount, the excess does not contribute to absorption but it does diminish the observed *percent of dose* that is absorbed.[81] Therefore, when comparing *in vitro* results of percent absorption, all the dosing conditions should be maintained as finite dose applications rather than flux.[82]

Rat skin is generally, but not always, more permeable than human skin. In a review of 79 studies which measured absorption of 110 chemicals, four chemicals were found that are less permeable through rat skin than human skin.[83] Van Ravenzwaay also found that in comparing human *in vitro* skin with *in vivo* rat skin, the penetration of 3 of 12 chemicals

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[81] Frasch, H.F. et al., "Analysis of finite dose dermal absorption data: Implications for dermal exposure assessment," 2014, J Expo Sci Environ Epidemiol, 24(1), pg. 65–73.

[82] Guidance Notes on Dermal Absorption, OECD Environment, Health and Safety Publications, Series on Testing and Assessment No. 156. ENV/JM/MONO(2011)36.

[83] Jung, E, and Maibach, H., "Animal models for percutaneous absorption," 2014, in Shah, V., Maibach, H., and Jenner, J. eds. Topical Drug Bioavailability, Bioequivalence, and Penetration, 2nd ed. New York: Springer, pg. 21-40.

was greater through human skin than thru rat skin. This held true at 4, 8 and 10 hours after dosing.[84]

A recent study has also questioned the reliability of converting percutaneous absorption data from rats to humans due to the mentioned differences in species as they studied the absorption of hazardous substances.[85]

In Vitro Dermal Absorption of Herbicides through Rat versus Human Skin

The use of rat skin in percutaneous absorption models is premised on the theory that rat skin is generally more permeable than human skin; however, there have been some cases which have reported that rat skin is less permeable.[86] Monsanto attempted to demonstrate (and failed) that the dermal penetration of Propachlor® (2-chloro-N-isopropyl-N-phenylacetamide) through human skin was lower than in rat skin. Instead, the study revealed:

- Concentrate formulation: The percent penetration with human skin **is equal to** the percent penetration with rat skin.
- Spray dilution: The percent penetration with human skin **is greater than** the percent dermal penetration with rat skin ($p<0.05$).
- Microautoradiographies clearly revealed stores of Propachlor in the epidermis of human skin.[87]

Monsanto In Vitro Absorption Study of Glyphosate

In February 2010, Dermal Technology Laboratory Ltd., UK, completed their Monsanto-commissioned lab study entitled *"In vitro absorption of glyphosate through human*

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[84] Van Ravenzwaay, B. and Leibold, E., "A comparison between *in vitro* rat and human and *in vivo* rat skin absorption studies," 2004, Toxicol In Vitro., Vol.18(2), pg. 219-25.

[85] Korinth G, Goen T, Schaller KH, & Drexler H., "Discrepancies between different rat models for the assessment of percutaneous penetration of hazardous substances," 2007a, Archives of Toxicology 81, pg. 833-840.

[86] Hotchkiss, SA, et al., "Percutaneous absorption of 4,4'-methylene-bis (2-chloroaniline) and 4,4'-methylenedianiline through rate and human skin in vitro," March, 1993, Toxicology In Vitro, Volume 7(2), pg. 141-148.

[87] Monsanto email (Tab 21) from [redacted] on 3/29/2002 to [redacted], et al.

epidermis" (MON 79545) wherein they investigated the absorption and distribution of glyphosate in three different herbicide formulations. For all three formulations, they concluded that the dermal absorption of glyphosate from exposure to the herbicide would be minimal at less than 1%. However, there are problems with this study that contribute to its inconsistency with other studies and, as a consequence, warrant its exclusion.

Finite dosing of 10 µL/cm^2 was used on a surface of 2.54 cm^2; this was left unoccluded for an exposure period of 24 hours with no interim wash. A static-type glass diffusion cell was used with dermatomed human skin. Each formulation was applied in three doses: one concentrated dose and two diluted doses. Thus, the amount of glyphosate in the 25.4 µL volume applied depended on the dilution. The absorption process was followed by taking samples of the receptor fluid (physiological saline) at recorded intervals throughout the exposure period.

There appears to be a problem with respect to their definition of the absorbed dose:

> **"The absorbed dose is considered to be the glyphosate detected in the receptor fluid**, while the biologically available proportion of the dose is regarded as the sum of absorbed dose and the amount recovered from the epidermis after tape stripping. Material removed from the surface of the epidermis by the washing procedure is regarded as unabsorbed. **Glyphosate recovered from the epidermis at the end of the exposure is also considered to be unabsorbed, although it is recognized that a proportion of this material may be absorbed beyond the duration of the exposure investigated in this study.** In vivo, the majority of the dose in the epidermis, especially that recovered from the stratum corneum (i.e. that found on the tape strips), would eventually be lost by desquamation."(Ramsey et al, 1992)

- The laboratory **did not include** the glyphosate recovered from the tape stripping as they claimed that it was not biologically available.
- They also **did not include** the amount of glyphosate recovered from the epidermis (available for eventual absorption).
- Additionally, since the duration of exposure in this study was only 24 hours, the glyphosate present within the epidermis at the conclusion of that period should have been reported as absorbed or, at a minimum, absorbable beyond the 24-hour limit. However, **this was not done.** Instead, the remaining glyphosate in the epidermis was simply considered to be *"unabsorbed."*

Review of the raw data specific to "Cell 18" revealed that the remaining epidermis contained 7.78 µg of glyphosate which was not included. If it had been included, the total absorbed **would have been approximately 3%.** Thus, the "*In vitro* absorption of glyphosate through human epidermis" study presents itself as a pre-destined design failure. It is completely inconsistent with other Monsanto *in vitro* and *in vivo* studies and should be excluded.

The term "Triple Pack" refers to the use of three types of dermal absorption data from: 1) *in vivo* rat; 2) *in vitro* rat and 3) *in vitro* human dermal absorption studies.[88] This approach is used to refine the estimation of dermal absorption by correcting for differences between *in vitro* and *in vivo* absorption rates in rats as well as for species differences between rats and humans.[89] This approach is based on the premise that the absorption difference between humans and rats will show in the same proportion in both *in vitro* and *in vivo* test, which may not be true. It should also be noted that the "Triple Pack" approach should be used to estimate a dermal absorption value only when the three studies are conducted under the same experimental conditions.[90]

More accurate measurement models generally include animal or primate *in vivo* measurements since *in vitro* human cadaver skin does not have an intact physiologic and metabolic system present to accommodate active blood capillary transport gradients or metabolism as do the *in vivo* models. Studies have shown there are species differences in the absorption of different chemicals: measurements in rats, rabbits or pigs may or may not reflect human absorption.[91] A more accurate model includes dermal absorption across primate (monkey) skin. Often, though not always, *in vivo* monkey skin most accurately resembles percutaneous absorption across human skin.

Numerous studies have been published using skin from different animal models. However, the knowledge that there is a significant difference in absorption when it comes

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[88] U.S. EPA OPP Memorandum June 2, 2010. "Review of Triple Pack dermal absorption studies for Maxim Quattro."

[89] Id.

[90] "Guidance notes on dermal absorption," OECD Environment, Health and Safety Publications, Series on Testing and Assessment No. 156. ENV/JM/MONO(2011) 36.

[91] Rozman, KK and Klaassen CD., "Absorption, distribution and excretion of toxicants," in Cassarett & Doull's Toxicology, The Basic Science of Poisons. 5th edition. 1996. McGraw-Hill.

to different animal species and humans has led to the necessity of a thorough interpretation when adapting data from animal studies that are to be used in relation to humans. Interpretation of the data to refine dermal absorption values can vary between regulatory authorities.[92,93]

Dermal Absorption and Pharmacokinetic Studies of Glyphosate

Models Used to Measure Glyphosate Dermal Absorption

There are two primary models which have been used to measure glyphosate dermal absorption: (1) the Maibach studies of 1983 and (2) the Wester et al., studies of 1991. Both of these studies were funded by Monsanto. This section reviews these two studies and assesses the findings in light of present-day objective science.

Maibach Study (1983)

Full Title: *Maibach, H.I. (1983) (a) Elimination of ^{14}C-glyphosate in Rhesus monkeys following a single parenteral dose, (b) Percutaneous absorption of 14C-glyphosate in Roundup formulation in Rhesus monkeys following a single topical dose. Unpublished report No. MA-81-349, dated 1 April 1983, from University of California, School of Medicine; San Francisco, California, USA. Submitted to WHO by Monsanto Int. Services SA, Brussels, Belgium.*

The purpose of this Monsanto-funded primate study was to determine the *in vivo* dermal penetration of glyphosate through Rhesus monkey skin. The study consisted of two parts:

- Part (a): ^{14}C-Glyphosate (MON 0139; isopropylamine salt) was administered to four Rhesus monkeys through intramuscular (IM) injection. Maibach found that, on average, 89.9% of the injected dose was excreted in the urine. He did not, however, measure the amount of glyphosate eliminated in the feces. Maibach

[92] "Guidance notes on dermal absorption," OECD Environment, Health and Safety Publications, Series on Testing and Assessment No. 156. ENV/JM/MONO(2011)36.

[93] U.S. EPA OPP Memorandum June 2, 2010. "Review of Triple Pack dermal absorption studies for Maxim Quattro."

reported two distinct phases of urinary excretion: (1) 0-24 hours $t_{1/2}$ = 6.9 hrs; (2) 1-7 days $t_{1/2}$ = 35.1 hrs, concluding that "*systemic doses of glyphosate in MON 039 are rapidly eliminated in monkeys, predominantly via the urine*."

- Part (b): ^{14}C-Glyphosate (MON 0139; isopropylamine salt) was dermally applied to Rhesus monkeys at a concentration of 1.13 mg/cm^2. The IM data from Part (a) was used to quantify the dermal penetration obtained in this part of the experiment.

There are problems with the findings of this study as explained below.

Since the majority of ^{14}C-Glyphosate administered by IM injection was excreted rapidly thru the urine, Maibach erroneously assumed that 89.9% of the dermal dose would be eliminated in the urine as well. He used this correction factor for incomplete urinary excretion (89.9%) to determine that 1.8% of the applied dermal dose penetrated the skin. This conclusion was errant for several reasons:

1) Two different routes of exposure (IM verses dermal);
2) Two different paths of excretion (urinary and fecal);
3) Failed to measure the ^{14}C-Glyphosate excreted in the feces.

Additionally, a further error was made by assuming the unrecovered glyphosate was permanently bound in the skin. The skin-washing procedure removed 14.2% (standard deviation of 3.5%) of the applied ^{14}C-label on the glyphosate. Therefore, only 16% (14.2 + 1.8) of the dermally-applied glyphosate was recovered. "*The total percent recovery … was low, i.e., 16.0%. Although a definitive explanation cannot be offered for the low recovery, previous experience suggests that much of the test material may in some way bind to or in the skin and cannot be removed by washing. This bound material is not apparently available for systemic absorption.*"[94]

[94] Maibach, H.I., "(a) Elimination of 14C-glyphosate in Rhesus monkeys following a single parenteral dose, (b) Percutaneous absorption of 14C-glyphosate in Roundup formulation in Rhesus monkeys following a single topical dose," 1983, Unpublished report No. MA-81-349, from University of California, School of Medicine, San Francisco, California, USA. Submitted to WHO by Monsanto Int. Services SA, Brussels, Belgium.

The key point is that this explanation is inconsistent with generally-accepted guidelines. For example, OECD guidelines[95] cite an adequate mean recovery is in the range of 100 ± 10%. (OECD, 2004). If the test material did indeed bind to or in the skin, then it could have been available for absorption and, according to guidelines given by OECD, would have to be included in the amount absorbed.[96]

In 1985, the U.S. EPA classified the Maibach, 1983, study as unacceptable since the majority of the dose could not be accounted for. Currently, most authorized agencies calculate by "*absorbed amount + amount remaining in the treated area tissue + (when necessary) amount remaining in the skin tissue after a washing process*" when calculating the absorption amount.[97]

In communications regarding the Maibach study, Richard Dirks, Ph.D., Senior Product Toxicologist at Monsanto, wrote (April 11, 1983):

> *"The total percent recovery (percent label removed by washing plus total percent label contained in urine) was low, i.e., 16.0%. A definitive explanation for the low recovery is not provided in the report, but the author does state that previous experience would suggest that much of the test material may in some way bind to or in the skin and cannot be removed by washing. In support of this, it has been reported (Vickers, 1963) that a "chemical reservoir" is formed in the skin after drug application which is eventually shed without penetration. Thus, it is concluded that the bound material is not apparently available for systemic absorption."* [98]

Dr. Dirks erroneously concluded (not in keeping with prescribed methodology) that *"… the bound material is not apparently available for systemic absorption."* The OECD guidelines state that the amount of substance not found in the donor chamber should be

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[95] Guidelines require that at least 90% of the dose be accounted for compared to just 16% in the Maibach study.

[96] OECD/OCDE 427, "Guidelines for the testing of chemicals. Skin absorption *In vivo* Method," Adopted: 13 April 2004.

[97] Jaehwan, S., "Comparison of international guidelines of dermal absorption tests used in Pesticides Exposure Assessment for Operators," 2014, Toxicol Res 4, pg. 251-260.

[98] MONGLY01330783

considered absorbed and, therefore, potentially available in the systemic circulation. This also accounts for the amount of substance deposited in the skin.[99]

Subsequent experiments have demonstrated that absorption of chemicals temporarily deposited in the skin can continue for up to 24 hours after exposure has ended. Thus temporary skin deposition will potentially underestimate the true absorption if assessed in blood or urine immediately following exposure (within 24 hours).[100]

Wester, et al., Study (1991)

Full Title: *Wester, R. et al., "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination,"1991, Fundamental and Applied Toxicology 16, pp. 725-732.*

This Monsanto-funded study included human *in vitro* testing as well as an *in vivo* primate (monkey) testing. The test material was a Roundup® formulation supplied by Monsanto; it is not stated what glyphosate salt was used in the formulation. The exact formulation was not disclosed, but no surfactants or other adjuvants were listed as ingredients.

In vitro human skin absorption: A finite dose technique was used with human plasma as the receptor fluid in a flow-through diffusion cell. Dosing concentrations ranged from 2.6 µg/cm^2 to 154.0 µg/cm^2 with exposure times of 30 minutes, 4 hours, 8 hours and 16 hours. The greatest absorption (2.2 ± 0.5 %) occurred at the lowest glyphosate dose concentration (2.6 µg/cm^2) after 8 hours of exposure. This was more than twice that which was absorbed at any of the other dose concentrations after 8 hours.

The data in this study is highly variable, i.e., it shows no discernable pattern with respect to the dose and time of exposure other than that the highest percentage of absorption occurred at the lowest dermal dose. The standard deviation of the mean was greater than the mean for 12 of the 20 means reported. No overall accountability (mass balance) was provided for this part of the study; no data was provided with respect to how much

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[99] OECD, "Guidance document for the conduct of skin absorption studies," 2004a, Paris. 28, pg.1-31.

[100] "Dermal absorption of pesticides – evaluation of variability and prevention," 2009, Danish Environmental Protection Agency. Pesticides Research No. 124, 13.1.

glyphosate was lost. Thus, it was not possible to compare the percentage lost to that of the *in vivo* dermal study shown below.

In vivo rhesus monkeys IV doses: Three Rhesus monkeys were intravenously dosed with 93 µg glyphosate and three were dosed with 9 µg glyphosate. The study found that in the six monkeys, 95% - 99% of the IV administered dose was recovered in the urine. Overall accountability was greater than 96% of the administered doses. Wester, et al., used these results to make the assumption that all *dermally*-absorbed glyphosate would similarly be excreted in the urine. This assumption is invalid according to their data reported in the next part of the study as shown below.

In vivo rhesus monkeys dermal dosing**:** Eight monkeys were dermally dosed with one of two doses (as summarized in Table 4).

Table 4
Disposition of Glyphosate Following Topical Administration to Rhesus Monkeys[101]

Disposition Site	Percentage of applied dose*	
	Dose C = 5400 µg/20 cm^2	Dose D = 500 µg/20 cm^2
Urine	2.2 ± 1.5	0.8 ± 0.6
Feces	0.7 ± 0.5	3.6 ± 1.6
Urine + Feces	**2.9 ± 2.0**	**4.4 ± 2.2**
Surface Washes	73.5 ± 6.0	77.1 ± 9.2
Contaminated Solids	0.05 ± 0.1	0.3 ± 0.1
Total	**76.5 ± 6.7**	**81.8 ± 6.9**

Topical administration in 4 Rhesus monkeys per dose: *each value is the mean ± SD for 4 monkeys.

The above data reveals several critical findings:

1) The low topical dose was excreted primarily in the feces. In the monkeys administered Dose D, 3.6 % of the dermally-applied dose was recovered in the feces whereas only 0.8 % was recovered in the urine (***total dermal absorption of 4.4%***).

[101] Wester, R. et al., "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination, 1991, Fundamental and Applied Toxicology 16, pg. 725-732.

From this data, it is apparent that **urine recovery does not accurately represent the amount of glyphosate that was dermally absorbed**. In this case, 4.5 times more glyphosate was found in the feces than in the urine.

2) This study finding is deeply troubling since epidemiology studies rely on urine concentrations to quantify the systemic dose of glyphosate exposure through dermal absorption. The lower dose (Dose D) at 500 µg/20 cm^2 corresponds to real world exposures in farmers and applicators. Thus, the exposure studies prepared by Monsanto that have relied on urinary excretion are in error by a factor of 4.5 times the current calculated values. From the data in this study, the total systemic dose from dermal exposure can be calculated:

$$GLY_{systemic} = GLY_{urine} + Gly_{feces}$$
$$= GLY_{urine} + 4.5 \times Gly_{urine}$$
$$GLY_{systemic} = 5.5 \times Gly_{urine}$$

The actual systemic dose in the human epidemiological exposure studies could have been accurately quantified by including the relative amount of glyphosate that would have been excreted in the feces **but which was not measured**.

3) The dose of 5,400 µg/20 cm^2 is too large to accurately represent the dose/absorption relationship. As previously explained, dosing conditions can have enormous effects on percent absorption. The excessive dosing in this case is approaching infinite dosing and the excess does not contribute to absorption, but it does diminish the calculated percent of dose absorbed.[102] U.S. EPA guidelines for dermal testing recommend a maximum practical dose on the order of 1 mg/cm^2; larger doses can exceed saturation of the absorption process.[103] The resulting error herein is an **artificially reduced percent absorption**; this high saturation dose resulting in 2.9% absorption is not relevant when looking at percent absorption.

4) The effect of glyphosate on skin has been shown to depend on the relative concentration of glyphosate. Dermal cells exposed to low levels of glyphosate have been shown to induce a stiffening of the cytoskeleton (the cell's internal structural

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[102] Frasch, H.F. et al., "Analysis of finite dose dermal absorption data: Implications for dermal exposure assessment," 2014, J Expo Sci Environ Epidemiol, Vol. 24(1), pg. 65–73.

[103] U.S. EPA OPPTS 870.7600, "Health effects test guidelines dermal penetration," August 1998, pg. 4.

support) while higher levels of glyphosate cause gross changes in cell shape.[104] As **realistic exposure levels were not used**, the findings are automatically suspect.

5) Only 81.8 % of the applied "Dose D" was recovered. The authors claimed that the remaining 18.2 % was "lost" since it was not detected. If any of the missing 18.2% remained in the monkey in tissue or fluid that was not tested, the amount absorbed would have been underestimated. The lost material is beyond the acceptable limit according to OECD guidelines of mass balance. If all of the missing 18.2 % is assumed to have remained in the monkey and is included the amount absorbed, the total % of applied dose absorbed becomes 22.6%. Either way, a casual and unverifiable "claim" that 18.2% of the dose was "lost" can scarcely be regarded as objective and should be added to the amount absorbed (4.4%) to provide an upper limit value of 22.6%.

6) The impact of surfactants on absorption is still not considered in this study.

From Wester, et al., it is reasonable to conclude that dermal absorption at "Dose D" reasonably estimates a ***dermal absorption dose ranging from 4.4% to 22.6%***. More importantly, the epidemiological exposure studies ***underestimate the systemic dose*** from dermal absorption ***by a factor of 4.5*** due to the failure to consider hepato/fecal elimination at the lower dose levels.

Studies, Reviews & Articles Impacted by Wester and Maibach Studies

Inasmuch as there are obvious and significant flaws in the two Monsanto-sponsored studies, it is important to understand the impact these have had on other studies, reviews and published articles (some of which were authored by Monsanto consultants).

1. *Williams, GM, Kroes, R., and Munro, IC, "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology. Vol. 31, pp. 117–165.*

[104] Heu, C. et al., "Glyphosate-induced stiffening of HaCaT keratinocytes, a peak force tapping study on living cells," 2012, Journal of Structural Biology, 178, pg. 1-7.

The Williams, et al., risk assessment article opined that the dermal penetration of glyphosate is very low based on results from studies in Rhesus monkeys and *in vitro* studies with human cadaver samples. With respect to the Wester studies, Williams failed to acknowledge the documented fecal elimination route and only relied on urinary excretion. Additionally, Williams, et al., failed to note the difference in fecal verses urinary excretion dependent upon dose level including the extraordinarily high dose level of pure product on the skin of primates within the Wester studies.

The Williams, et al., review stated,[105] "*Maibach (1983) studied the in vivo dermal absorption of glyphosate when undiluted Roundup herbicide was applied to the skin of monkeys. Penetration was slow as only 0.4 and 1.8% of the applied dose was absorbed over 24 hours and 7 days, respectively. A second study in Rhesus monkeys investigated the absorption of diluted glyphosate (1:29) to simulate a spray solution (Wester, et al., 1991). Dermal penetration was found to be 0.8 and 2.2% at low and high dose (500 or 5,400 mg/cm^2, respectively). Wester, et al. (1991) also reported that the in vitro percutaneous absorption of glyphosate through human skin was no more than 2% when applied for up to 16 hours either as concentrated Roundup or as a diluted spray solution.*"

2. *Niemann, Lars, et al., "A critical review of glyphosate findings in human urine samples and comparison with the exposure of operators and consumers," 2015, Journal für Verbraucherschutz und Lebensmittelsicherheit, Vol 10, Issue 1, pp 3-12.*

   The basic assumption in Niemann, et al., is that dermally absorbed glyphosate is eliminated nearly entirely through urine and that "*measuring of urine levels could be a powerful tool for human biomonitoring*." The study fails to reference or acknowledge the Wester and Maibach studies and does not consider dermally absorbed glyphosate at low, steady state rates of absorption being metabolized and excreted primarily through the feces.

   Niemann, et al., states, *"For active substances in plant protection products (PPP) with well-defined urinary elimination, no potential for accumulation and virtually no metabolism, measuring of urine levels could be a powerful tool for human biomonitoring. Such data may provide reliable estimates of actual internal human*

[105] Williams, pg. 123-124.

exposure that can be compared to appropriate reference values such as the 'acceptable daily intake (ADI)' or the 'acceptable operator exposure level (AOEL)'."

Based on the Wester (1991) study, the evidence of "*well defined urinary elimination*" has been compromised. Such an assumption is misleading and potentially dangerous with respect to the human health risk assessment and comparisons to current ADI or the AOEL regulatory levels. Studies cited by Niemann, et al., include non-dermal dose assessments such as male SD rates receiving oral dosing (Brewster et al 1991)[106], oral dosing in feed (Chan & Mahler 1992)[107] and IV and oral doses in rats (Anadon, et al., 2009).[108] None of the cited studies involve dermal dosing and **do not** establish "*well defined urinary elimination*" which is simply assumed. Furthermore, the Brewster study found that urine and feces were equally important routes of elimination and after 7 days the total body burden (~1%) of the dose administered was mostly in bone. Since dermal glyphosate exposure is the primary route of exposure contributing to systemic exposure in agricultural users, the assumption that distribution, metabolism, and excretion are identical by IV and dermal routes of exposure leads to **egregious errors** in systemic dose calculations.

3. *Acquavella, J. et al., "Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study,"2004, Env. Health Perspect 112, pp. 321–326.*

   In an internal Monsanto document entitled, "*Glyphosate Stewardship, Epidemiology, and the Farm Family Exposure Study,*" the Monsanto scientists report the impetus for this study:

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[106] Brewster, D.W., Warren, J., and Hopkins, W.E., "Metabolism of glyphosate in Sprague-Dawley rats: Tissue distribution, identification, and quantitation of glyphosate-derived materials following a single oral dose," July 1991, Fundamental and Applied Toxicology, Volume 17, Issue 1, pg. 43-51.

[107] Chan, P. and Mahler, J., "Glyphosate (CAS No. 1071-83-6) administered in dosed feed to F344/N rats and B6C3F1 mice," 1992, U.S. Department of Health and Human Services. NTP Technical Reports Series No. 16. NIH Publication 92-3135.

[108] Anadón, A. et al., "Toxicokinetics of glyphosate and its metabolite aminomethyl phosphonic acid in rats," 2009, Toxicol Lett 190(1), pg. 91-95.

> *"We have been working to maintain glyphosate's favorable reputation through a strategy that anticipates challenges and puts appropriate initiatives in place. One of those initiatives is a unique research program called the Farm Family Exposure Study (FFES)."*[109]

The report further states

> *"The FFES was developed to fill two data gaps. First, there is a (PPE) information about applicator pesticide exposure under "real world" conditions. Second, there is little empirical exposure information for farm children although children's health is a driving force in environmental regulation and a focus of epidemiologic research."*[110]

This biomonitoring study evaluated urinary glyphosate concentrations for forty-eight farm families (farmers, spouses and their children) the day before, the day of and three days after a glyphosate application. The authors used the urinary concentrations to estimate systemic doses which they then compared to the U.S. EPA reference dose of 2 mg/kg/day.

The main assumption cited in their analytic method is "*Pharmacokinetic research indicates that absorbed glyphosate is excreted unchanged, predominantly in urine (Williams 2000).*"[111] Unfortunately, **glyphosate is not excreted predominately through the urine in primates**, especially at low doses, as demonstrated by the Wester, 1991, study.

The authors used the 95% urinary recovery that Wester reported using IV dosing to correct their data for complete pharmacokinetic recovery. This correction factor is not applicable to this data since the farmers and their family members were presumably exposed dermally and not through IV dosing.

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[109] "Glyphosate Stewardship, Epidemiology, and the Farm Family Exposure Study," MONGLY00905651

[110] Id, MONGLY00905652

[111] Acquavella, J., et al., "Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study," 2004, Environ Health Perspect, 112, pg. 321–326.

Monsanto also points out the limited degree of accuracy of their urinary glyphosate measurements in the Acquavella, et al, 2004, biomonitoring study:

> *"Monsanto's analytic chemistry expertise was essential to the FFES. However,* ***our current method is outdated****. It requires relatively large volumes of urine (100 ml, versus 5 ml for the 2,4-D and chlorpyrifos methods) and produces less precise results than methods for other FFES chemicals.* ***Given the likelihood that human health allegations will continue to surface for glyphosate****, it seems advisable to invest in modernizing the analytic method to increase analytic flexibility and precision."*[112]

4. *Solomon, K., "Glyphosate in the general population and in applicators: a critical review of studies on exposure," 2016, Critical Reviews in Toxicology, 46(1), pp. 21-27.*

   In the Solomon, 2016, review, it is again assumed that "*the systemic dose of glyphosate can be estimated from the total amount of glyphosate excreted in the urine over the four or five days following and including the day of application."* A "*correction for incomplete excretion*" of 95% is made "*based on observations in TK*[113] *studies in monkeys which showed that 95% of total systemic dose was excreted via urine* (Wester, et al., 1991), *divided by 0.95."*[114] Solomon does not consider dermally absorbed glyphosate at low, steady state rates of absorption being metabolized and excreted primarily through the feces.

5. *Monsanto's Spanish "OPEX" biomonitoring study entitled, "MON 78294: An Applicator Exposure Study Conducted in Spain," Autumn 2005.*

   This study was conducted in order to estimate a systemic dose for occupational users of glyphosate and determine whether certain uses of the product resulted in unacceptable levels of dermal penetration. Monsanto submitted the results of the studies to the Spanish regulatory authorities as part of the process to register the

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[112] "Glyphosate Stewardship, Epidemiology, and the Farm Family Exposure Study", MONGLY00905655

[113] TK is an abbreviation for toxicokinetic and is used here as a synonym for pharmacokinetic

[114] Solomon, K., "Glyphosate in the general population and in applicators: a critical review of studies on exposures," 2016, Critical Reviews in Toxicology, 46(1), pg. 21-27.

herbicide product for use. A report was prepared for submission to the U.S. EPA, but it is unclear if it was ever submitted.

In their determination of the systemic dose, they extrapolated the Wester, et al., 1991, study results to their biomonitoring data. As in the other examples discussed above, doing so invalidated their values of the estimated systemic dose.

Regulatory Guidance on Dermal Absorption and Recovery

Either knowingly or unknowingly, Monsanto regularly misstates or understates glyphosate dermal absorption recovery and factors in its communications. It is not the purpose of this toxicological risk assessment to draw conclusions about the intent of such misstatements. However, it is helpful to understand the position of regulatory agencies on these points and to briefly review some key guidelines pertinent to this issue.

OECD: 18-Aug-2011 GUIDANCE NOTES ON DERMAL ABSORPTION Series on Testing and Assessment No. 156

The current default approach taken by nearly all regulatory agencies is to determine the dermal absorption value by adding the absorbed dose and the chemical remaining in the skin, following washing. This is appropriate for both *in vivo* and *in vitro* studies unless compelling evidence demonstrates that some portion of the residue in the skin is unlikely to be absorbed. OECD TG 427 and 428 (OECD 2004a and 2004b) require a mean mass balance recovery of the test substance of between 90–110%. The OECD GD28 (OECD 2004c) contains the same recommendation with a caveat that for volatile test substances and unlabeled test substances, a range of 80–120% is acceptable. However, with the *in vivo* study design, recoveries outside this range may be acceptable but must be justified.

The criteria to justify mean mass balance recovery values outside the acceptance range can be summarized by the following examples:

1. **Recovery values exceed the recommended range**: If the recoveries exceed the accepted maximum range, the data generated should not be normalized because that would result in potentially underestimated absorption values. If these absorption values are not acceptable when a risk assessment is conducted, then the study should be repeated to address any bias resulting from excessive recoveries.
2. **Recovery values below the recommended range**: Low recoveries raise the concern that the value for absorbed dose could be lower than that which would be achieved from a study where the recoveries were within the guideline range. The reason for low recovery may be attributable to the following factors: (a) incomplete application of dose, (b) loss to the experimental equipment, (c) incomplete extraction from matrices (or incomplete collection of exhaled CO_2), (d) evaporation, (e) unlabeled test preparations, metabolism or degradation or (f) insufficiently high analytical LODs/LOQs, in particular where non-labelling analytical methods are applied.

Errors and Omissions in Monsanto Communications

During the glyphosate registration process in Spain, the Spanish Ministry of Health advised Monsanto of errors in their "OPEX" study. Faced with denial of Spanish product registration, Monsanto employees attempted to redirect attention away from deficiencies with respect to pharmacokinetics of glyphosate. The following excerpts summarize some of the Monsanto communications.

A. Communication of [redacted] (11-4-2008): Subject: Pk (Pharmacokinetics) recovery Wester, et al.

> *"The IV data gives in vivo disposition of a systemic available dose. This dose could be the result of aggregate systemic exposure (meaning a systemic dose after combined oral, dermal, inhalation exposure). The total accountability of this experiment is high >96% - ~100% and we know exactly the amount that was systemically available. The recovery factor for urine is therefore relevant and reliable."* [115]

Unfortunately, the dose was not an "*aggregate systemic exposure"* as stated, but the result of an IV "push" injection. **This is clearly stated in the study.** One cannot conclude that the recovery factor from IV dosing is "*relevant and reliable"* to dermal dosing. It is critical to note that IV administration presents a **tremendously high acute dose** to the liver. Saturation of the liver as an elimination pathway to the feces would result in spill over to the urinary excretion elimination pathway. Giving the same (IV) dose quantity over a slow drip period of 24 hours would not expose the liver to potential saturation. The email conversation further states:

> *"The in vivo dermal absorption experiment yielded variable results (table 4) and much lower total accountability 77-82% which is normal for this kind of experiment. The authors take the outcome of the IV-experiment to justify the use of the urinary excretion results from the topical experiment **only** as an estimate for dermal uptake: 'Since all of the IV administered doses were excreted in urine, the percutaneous absorption of glyphosate is estimated to be 0.8-2.2% of the applied dose' (p728-729). They did not take the feces into account based on the iv-study."* [116]

[115] MONGLY02155831

[116] Id.

Either knowingly or unknowingly, Monsanto employee [redacted] failed to take hepatic excretion through the feces into account and appears to have relied solely on the IV study to make a point favorable to his company's product. This omission produced **acutely high blood levels** not comparable to those achieved through slow, steady-state dermal absorption. Additionally, the erroneous urinary recovery assumption that Monsanto used to correct the systemic dose is in **grave error by a factor of 4.5x** and, therefore, is in no way a good "*estimate.*"

B. Communication of [redacted] (11-4-2008, response to [redacted]): Subject: Pk recovery, Wester, et al.

> *"Many thanks for your help which I will try to defend as Monsanto position, but the authorities will decide next week. That: means they are now doing the homework- if our proposed safety evaluation for CAYENNE formulation is compatible with the Acceptable Operating Exposure Level (AOEL) for glyphosate. I imagine we do not have other studies on the urine/feces excretion after topical applications of glyphosate to support our position.* ***As it is critical that we have our product accepted in this coming meeting****, I would like to complete my defense with a paragraph like this one:*
>
> *"Although we believe that the intravenous dose is accepted by toxicology peer reviewers as the best indicator to simulate the systemic presence of glyphosate, in case the Spanish authorities consider that the excretion through the urine should be taken from the* ***variable data*** *reported in the topical administration (urine/urine + feces = 75.86% or 18.18%), the average excretion in the urine of 47.02% would mean that our final exposure values should be multiplied by 2.13, resulting in exposure levels which are well below the AOEL. of 0.2 mg/kg/day."* [117]

The communication above of [redacted] states that Monsanto believes the IV model is the best indicator as to how systemically administered glyphosate is metabolized and excreted. Specifically, the memo states that the IV dose "*…is the best indicator to simulate the systemic presence of glyphosate."* This statement is inaccurate since it is the **dermal systemic dose** that is of primary interest to both toxicologists and regulatory authorities. There are no reports of applicators intravenously injecting themselves with glyphosate. In the absence of actual primate

[117] MONGLY02155830

dermal absorption data, the IV model should have been compared to animal models with urinary and fecal measurements conducted.

However, it is not acceptable in toxicology to replace real *in vivo* data with a "model" unless the actual dermal dosing data was faulty. There is no evidence to support this.

Based on the [redacted] communication, it appears that Monsanto fabricated a "variable data" problem by incorrectly interpreting the results for the purpose of securing regulatory approval of their product. The issue of high variability is being abused in order to dismiss the primate dermal absorption test results. Monsanto appears to have dismissed the primate data by failing to disclose why the "variable data" was excessive.

The variability of the data (i.e., the percentage of urinary versus fecal elimination) varied due to absorption saturation at the high dose as described previously and, therefore, only the low dose is relevant since it is closer to real-world exposure scenarios. Consequently, **the exposure values should be multiplied by 5.5, not 2.13**. It is perhaps noteworthy that [redacted] stated that it is "*critical*" to have the product accepted at the upcoming meeting. Thus, his solution appears to be one of manipulating the data by claiming there was a "variable data" problem.

C. Communication of [redacted] (11-5-2008, response to All): Subject: Pk recovery, Wester, et al.

> *"Even though we can absorb additional 'uncertainty factors' in our risk assessment based on our biomonitoring results, I feel uncomfortable with this discussion. This approach by Spain sets a precedent and* ***contradicts the fact that we always claimed to fully understand the glyphosate pharmacokinetics****. The Wester IV experiment suggests that almost the entire 'systemically' available dose was excreted in urine. The low dose topical in vivo experiment suggests that almost the entire dose (82%) that was absorbed through the skin was excreted in feces (3.6% feces versus 0.8% in urine). We should have a robust and well-documented explanation for this and stick to our original risk assessment or develop additional data to fully understand this matter and adjust our systemic dose calculations accordingly."* [118]

[118] id

Clearly, there is internal concern that deficiencies in Monsanto-published values and methods may be subject to criticism and further, that Monsanto itself is not fully conversant with the facts and/or that their risk assessment methodology may be insufficient to meet regulatory approval requirements.

D. Communication of David Saltmiras (11-4-2008, response to [redacted]): Subject: Pk recovery, Wester, et al.

> *"Joel, Donna & I have discussed your approach and you are correct. How much below the AOEL are your calculations?* [redacted] *- by our rough calculations* [redacted]*'s approach is approximately 50x below the AOEL of 0.2 mg/kg/day, Even if we applied the 90th percentile for the passive dosimetry numbers we would be below the AOEL."* [119]

The preceding two internal Monsanto memos serve as an admission that the pharmacokinetics assumed to be correct using the IV methodology **are contradicted by the primate dermal absorption studies**. [redacted] states, "*This approach by Spain sets a precedent and contradicts the fact that we always claimed to fully understand the glyphosate pharmacokinetics.*" Thus, Monsanto's claim of fully understanding the pharmacokinetics of glyphosate has been contradicted. He cites the discrepancy in the Wester study and the need to further investigate in order to fully understand the pharmacokinetics and thereby "adjust" their systemic dose calculations.

E. Response communication of Joel Kronenberg (11-10-2008, response to All): Subject: Pk recovery, Wester, et al.

> *"To fully address this issue would likely require a repeat of the monkey dermal and intravenous studies. We no longer own the custom-designed monkey chairs that prevented exfoliated abdominal skin from contaminating the excreta. Additionally, it is not clear whether similar chairs are used anymore by any researcher or if they would even be allowed. Thus, conducting a new series of monkey studies may not be easy nor inexpensive. Furthermore, it is not clear to me that such a study is necessary and would be* ***totally without risk****. Should we arrange a conference call to discuss this?"* [120]

[119] MONGLY02155829

[120] MONGLY02155826

Ethical quandaries with respect to fearing that a valid pharmacokinetic study might pose a risk to regulatory approval of a commercial product are beyond the scope of this toxicological assessment. However, such implications clearly do exist in this communication and must be considered with respect to veracity and credibility.

F. Communication of [redacted] (11-10-2008, response to team): Subject: Pk recovery, Wester, et al.

> *"To me, all this discussion continues to show that we still need solid data for ADME (Absorption, Distribution, Metabolism and Excretion) arising from dermal exposure.*

> 1. *Our dermal absorption endpoint is based on the literature and, as I recall, we failed to get the original data to support the results.*
> 2. *The movement of glyphosate in the blood flow from dermal contact is different to that through oral or intravenous exposure. The little data we have suggests that the excretion is significantly more through the feces than the urine.*
> 3. *Dermal exposure is the greatest risk of exposure for operators. Therefore, we need to be secure on the ADME of such exposure.*
> 4. *The WHO and EU reviews focus on the IV and oral but not the dermal. My position is, therefore, unchanged. We need to address this properly in the Annex II dossier and, therefore, should be considering a study.*[121]

In this instance, [redacted] of Monsanto appears to have objectively assessed the data and admits that "*The movement of glyphosate in the blood flow from dermal contact is different to that through oral or intravenous exposure*."

[121] MONGLY02155827

Communication of [redacted] (11-12-2008, response to Joel Kronenberg):
Subject: Pk recovery, Wester, et al.

> *"Monsanto is a company with recurring discussions (which is good!)... You will remember that we discussed this in length with a lot of people before we initiated the Spanish OPEX study... (please see attached). The outcome was that (1) other animal data confirmed the Wester findings; (2) such a study would* ***be too risky*** *(potential for finding another mammalian metabolite); and (3) we would wait for the evaluation of Spain.*
>
> *Looking forward to this discussion on the 24th of November. I also recall that David has asked 2 external pharmacologists for an opinion on the Wester study. Would that opinion be available by that time?"*[122]

The above communication raises numerous ethical red flags with respect to the statement "*such a study would* ***be too risky*** *(potential for finding another mammalian metabolite.)*" The charge and responsibility of the toxicologist is to determine the ADME (absorption, distribution, metabolism and excretion) as ADME are critical components in the risk assessment process. The goal of the toxicologist is to find "*another mammalian metabolite,"* not to avoid discovery of it.

It is always of great importance to identify all metabolites since certain chemicals have been known to produce toxic metabolites under high dose levels (such as Tylenol) or carcinogenic metabolites (such as benzene). Inasmuch as the author of the Monsanto memo stated that the potential finding of another mammalian metabolite would be "*too risky,*" one must presume a lack of objectivity. *Failing to perform a needed study due to the risk of finding an adverse result that could negatively impact marketing goals represents an unacceptable practice in the field of toxicology.*

Monsanto Communications Summary

Reviewing Monsanto's communications in an inculpatory context is an unfortunate necessity. The preceding Monsanto messages revolve around complex human health factors having a direct and immediate bearing on the purpose of this toxicological assessment. This premise is supported by clear evidence of admissions of deficiencies and a tendency for commercial considerations to outweigh the risk of negative

[122] MONGLY02155826

consequences. Indeed, it seems the erroneous scientific conclusions presented in these messages can serve no other conceivable purpose. In the absence of impartial oversight, such conclusions obscure the underlying science.

The generally-accepted, peer-reviewed basis of scientific information is highly relevant in the context of reliability of Monsanto's health risk assessments.

Factors Intensifying Dermal Absorption of Glyphosate

Beyond the underestimation of dermal absorption by Monsanto, there are additives within Roundup® formulations that further increase dermal absorption of glyphosate. There are numerous factors governing the rate and degree of glyphosate dermal absorption, both intrinsically and potentially. These include (a) "co-formulants" (ingredients other than the active ingredient such as detergents or anti-foam agents), (b) surfactants (compounds which lower surface tension), (c) humectants (to inhibit moisture loss), (d) adjuvants (chemicals which modify the effect of other agents), (e) absorption enhancement due to skin damage, lesions, cracks and other irregularities, (f) lack of personal protective gear and (g) other factors such as penetration enhancers and skin creams. This section reviews and assesses these factors as toxicological considerations.

Generally speaking, with the exception of substances of a proprietary nature or which have not been disclosed by Monsanto, most of the considerations mentioned above tend to intensify absorption rather than reduce it. The following sections review each factor individually given the limited information available at this time.

Co-Formulants

The exact identities and amounts of the co-formulants in GBF herbicides are usually unknown as they are kept as confidential trade secrets. In many countries (including the U.S.), manufacturers are only required to identify the declared active ingredient (DCI), *i.e.* glyphosate. The co-formulants (*i.e.* all ingredients other than the DCI) have rarely been identified and have often been declared as "inert ingredients."[123]

[123] Defarge, N. et al., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels," 2016, Int J Environ Res Public Health, Vol. 26;13(3), pii: E264.

Herbicide manufacturers frequently take advantage of regulatory agency definitions of "inert ingredients." Despite their name, inert ingredients may be biologically or chemically active and are labeled inert only because of their function in the formulated product. For example, an herbicide ingredient can be considered "inert" if it has no direct effect on the intended target, *i.e.* the weed. In herbicides, the ingredients added to enhance absorption, increase ionization, prevent foaming or reduce drifting are characterized by the manufacturer as "inert ingredients" since they do not directly kill the weeds. However, *they are not necessarily without toxicity to animals or humans.*

Independent studies of complete herbicide formulations are not generally possible as specific herbicide formulations are protected. Manufacturers of co-formulants have been historically unwilling to provide them to scientists who wish to assess toxicity. Consequently, most co-formulants have evaded scientific scrutiny and regulation.

In a confidential draft report dated July, 2001, entitled, "Clustering glyphosate formulations with regard to the testing for dermal uptake," Monsanto scientist [redacted] promoted the need for formula-specific studies. Mr. [redacted] stated:

> *"Glyphosate has a whole series of different formulations. The differences between those formulations are based on:*
> - *The different salt types used to formulate the active ingredient*
> - *The use of different surfactants*
> - *The active ingredient/surfactant ratio*
> - *The concentrations of active ingredient and surfactants*
> - *The presence or absence of other inert ingredients such as anti-foam agents.*

He also added:

> *Until today Monsanto has conducted formulation specific dermal uptake research only on the formulation Roundup (MON2139). It is clear that because of the compositional differences, the dermal uptake data for Roundup can't be extrapolated as such towards the wide range of formulations. Every ingredient in a formulation can have a specific influence of dermal uptake.* ***Scientific experimental evidence is necessary****."*

Detergents in herbicides act as mediators which change the absorption by increasing bioavailability[124] or by affecting the skin barrier function.[125,126] Brand and Mueller (2002) showed dermal penetration of commercially formulated compounds was significantly greater ($p < 0.05$) than that of pure compounds at the same concentration.[127]

Surfactants

Like co-formulants, the exact identities and amounts of surfactants in GBF herbicides are usually unknown as they are kept as confidential trade secrets. The most predominately used type of surfactant in GBFs are polyoxyethylene alkylamine (POEA) surfactants.[128,129]

POEA is an acronym, not a specific chemical, which encompasses a wide range of alkyl-amine ethoxylate compounds. Within the group of POEA surfactants, the chemistry is complex and varied. Ethoxylated tallowamine has been the traditional surfactant component and the most well-known 'inert' ingredient contained in the original Roundup® formulation and many others. It is a POEA non-ionic surfactant consisting of beef tallow fatty acid-derived alkyl chains converted to primary amines and ethoxylated with between 10 to 20 ethylene oxide (EO) units.[130] It is often mixed with polyethylene glycol, or other surfactants, plus other materials to facilitate manufacturing and

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[124]Sartorelli, et al, 1997.

[125]Treffel, P. & Gabrad, B., "Skin penetration and sun protection factor of ultraviolet filters from two vehicle," 1996, Pharmaceut Res, Vol. 13, pg. 770-774.

[126]Tupker, R. et al., "Susceptibility to irritants: role of barrier function, skin dryness and history of atopic dermatitis," 1990, *BJD.* Volume 123, Issue 2, pg. 199–205.

[127]Brand, R.M. & Mueller, C., "Transdermal penetration of atrazine, alachlor, and trifluralin: effect of formulation,"2002, Toxicol Sci., Vol. 68(1), pg. 18-23.

[128]Williams, G., et al., "Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans," 2000, Regulatory Toxicology and Pharmacology, Vol.31, pg. 117 - 165.

[129] Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

[130] From an internal Monsanto report, Surfactant Issue Analysis, Issue: Increasing public attention to the POEA (Polyoxyethlene alkylamine) surfactant component of glyphosate formulations in connection with claims of adverse impact to aquatic life (recently, amphibians) and human health (in vitro (cell culture) toxicity tests). MONGLY01700591

formulation stability.[131] Roundup's surfactants include 1,4-dioxane (a probable human carcinogen) as an impurity at about 0.03%.[132]

POEA significantly increases penetration in plant cells as well as in animal cells. Richard, et al., found that **the addition of surfactants "greatly facilitated" the penetration of glyphosate through animal cell membranes**.[133]

It is helpful to understand that, due to corporate secrecy and proprietary concealment, POEA was first recognized as a common ingredient in herbicides in the 1980's when physicians in Japan reported that morbidity and deaths of patients who drank Roundup® were due to POEA, not glyphosate.[134] POEA is an eye irritant, toxic to aquatic organisms, penetrates cell membranes and disrupts their structure and function. Diamond and Durkin made the following observations regarding surfactants in glyphosate based formulations:

1. **Multiple Formulations**: The formulations are chemical mixtures and must be considered as mixtures in toxicity assessments. In this context, an assessment of the specific surfactants in any of the formulations or generalizations about the toxicology of surfactants as a group may not apply to the formulations. This consideration places extreme importance on data regarding the toxicity of the formulations themselves. **The lack of such data will render any predictions about the effects of the formulations on glyphosate highly uncertain**.[135]

2. **Unknown Interactions:** Surfactants can be expected to interact with and perturb the structure, physical properties and function of membranes.[136]

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[131] Id.

[132] Monsanto, 1990 in Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

[133] Richard, S. et. al., "Differential effects of glyphosate and Roundup on human placental cells and aromatase," 2005, Environmental Health Perspectives.

[134] Sawada, Y., Nagai, Y., Ueyama, M., and Yamarnoto, I., "Probable toxicity of surface active agent in commercial herbicide containing glyphosate," 1988, Lancet 1 (8580), pg. 29.

[135] Diamond, G., Durkin, P., "Effects of surfactants on the toxicity of glyphosate with specific reference to RODEO," 1997, Syracuse Research Corporation, SERA TR 97-206-1b.

[136] Id.

3. **Objective Evidence is Lacking:** For specific mechanisms of interactions between glyphosate and surfactants.[137]

4. **Multiplicity of Potential Reactions:** The structural characteristics of extreme hydrophilicity and hydrophobicity of surfactants may result in very different interactions with hydrophobic and hydrophilic herbicides. Thus, the relatively water-soluble isopropylamine salt of glyphosate may interact differently with surfactants than the less water-soluble parent compound or other more insoluble herbicides.[138]

Indirect Disclosures of Surfactant and Co-Formulant Toxicity

In 2013, Mesnage, et al., published their study of nine herbicides containing glyphosate including five different formulations of Roundup. After studying the chemicals' patterns using mass spectrometry, Mesnage and his colleagues determined the identity of co-formulants in Roundup® and performed toxicity analyses. They were able to deduce the chemical structure of additives in six of the nine formulations and also show that **each of these supposedly inert ingredients was more toxic than glyphosate alone**.[139]

Subsequently, other studies have examined the toxicity of these co-formulants and measured significant enhancement of toxicity. While there occasionally may be performance differences between glyphosate products, these differences are more likely to be caused by the differences in surfactants formulated with the product.

Defarge, et al., 2016, study showed that each of the five co-formulants affected the function of both the mitochondria in human placental cells and aromatase, an enzyme that affects sexual development. Not only did these chemicals, **which are not named on herbicide labels**, affect biological functions, they did so at levels far below the concentrations used in commercially available products. In fact, POEA, an "inert"

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[137] Id.

[138] Id

[139] Mesnage, R., Bernay, B., and Séralini, G.E., "Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity," 2013, Toxicology 313(2-3), pg. 122-8.

ingredient, was between 1,200 and 2,000 times more toxic to cells than glyphosate, the "active" ingredient. They also reported that six glyphosate formulations similarly decreased aromatase activity in human placental cells at concentrations much lower than glyphosate alone [140]

Examples of Surfactant and Co-Formulant Toxicity

There is a general agreement and consensus that co-formulants can be more toxic for animals than glyphosate itself.[141] For example, cytotoxicity of the commercial formulation Roundup® to human peripheral mononuclear cells was 30-fold higher (LC_{50} = 56 mg/L) than for the active ingredient (LC_{50}=1640 mg/L). Several *in vitro* and *in vivo* studies with parallel testing of glyphosate active ingredient and Roundup® showed that only the commercial formulation was genotoxic. [142]

Registration data in New Zealand revealed Roundup® contained POEA.[143] Other formulations may contain much higher levels, even as high as 60 - 80%, as in the formulation Genamin.[144] In studies using hepatic (HepG2), embryonic (HEK293) and placental (JEG3) cell lines to compare ten formulations of glyphosate, the most toxic formulations were those that contained POEA. **This surfactant induced necrosis and disrupted the structure and function of cell membranes** with negative dose-dependent effects on cellular respiration and membrane integrity between 1 and 3 mg/L.[145]

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[140] Defarge, N. et al., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels," 2016, Int. J. Environ. Res. Public Health 13, pg. 264.

[141] Defarge, N. et al., "Co-formulants in glyphosate-based herbicides disrupt aromatase activity in human cells below toxic levels," 2016, Int. J. Environ. Res. Public Health 13, pg. 264.

[142] Bolognesi, et al., "Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate," 2009, Journal of Toxicology and Environmental Health Part A, 72, pg. 986—997.

[143] Watts MA, "The poisoning of New Zealand,"1994, AIT Press, Auckland. From Pesticide Action Network (PAN). http://pan-international.org/wp-content/uploads/Glyphosate-monograph.pdf

[144] Mesnage, R. et al., "Ethoxylated adjuvants of glyphosate-based herbicides are active principles of human cell toxicity," 2013.

[145] Id.

POEA potentiates the effect of glyphosate, facilitating its penetration of cell membranes and bioaccumulation in cells.[146] The bio-concentration factor for glyphosate is also increased in the presence of POEA in the aquatic environment.[147]

Regulatory Considerations Based on Surfactant and Co-Formulant Toxicity

In the absence of clear, unambiguous information pertaining to a commercial product's chemical composition, some countries take a hardline approach to regulation. For example, due to toxicity concerns, Germany removed glyphosate products containing POEA from their market in 2014[148] and the European Union banned them in 2016.[149] The New Zealand Environmental Protection Agency (NZ EPA) has current approvals for 91 formulations of glyphosate of which 69 contain POEA. The New Zealand EPA refuses to name them "*because the composition of the formulations is commercial-in-confidence information.*"[150]

This situation is typical of many countries. The decree that banned the use of glyphosate formulations containing POEA in Italy named 55 formulations, including well-known names such as Roundup®, Rodeo® and Touchdown® and brands from Cheminova,

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[146] Richard, S. et al., "Differential effects of glyphosate and Roundup on human placental cells and aromatase," 2005, Environ Health Perspect 113(6), pg. 716-20.

[147] Annett R, Habibi HR, Hontela A., "Impact of glyphosate and glyphosate-based herbicides on the freshwater environment," 2014, J Appl Toxicol 34(5), pg. 458-479.

[148] Farrer P, & Falck M., "Toxic glyphosate herbicides fly under the EU's regulatory radar," 2014, Pesticides News 96, pg. 1-4.

[149] EC. 2016. Glyphosate. European Commission - Fact Sheet FAQs: Glyphosate. Brussels. June 29th. http://europa.eu/rapid/pressrelease_MEMO-16-2012_en.htm

[150] NZ Parliament. 2016. Written questions 10151, 10153, 10154. Steffan Browning to the Minister for the Environment. New Zealand Parliament Paremata Aotearoa, Wellington. https://www.parliament.nz/en/pb/order-paper-questions/ written-questions/?criteria.Keyword=glyphosate&criteria. Timeframe=&criteria.DateFrom=&criteria.DateTo=&criteria. ParliamentNumber=-1&criteria.ParliamentNumber=-1&criteria. MemberOfParliament=&criteria.Portfolio=Environment

Syngenta, Nufarm, Dow AgroSciences, and Arysta as well as Monsanto and some Italian companies.[151]

The key point here is that *experimental studies suggest that the toxicity of POEA is greater than the toxicity of glyphosate alone and commercial formulations alone.* However, safety evaluations performed by Monsanto have largely been performed on pure glyphosate or **without identification of all ingredients**. There is also evidence that glyphosate preparations containing POEA are more toxic than those containing alternative surfactants. Since surfactants contribute to the toxicity of glyphosate formulations, adverse health consequences are not necessarily caused by glyphosate alone, but as a consequence of complex and variable mixtures. Even Monsanto has recognized this in correspondence (as cited in this assessment).

Monsanto TNO Dermal Penetration Study with Co-Formulant Cocoamine

Monsanto's previously reported dermal absorption studies did not include surfactant co-formulants. Monsanto did find evidence of the effects of one surfactant**,** cocoamine, on dermal absorption in their TNO dermal penetration studies. These studies were not submitted to the U.S. EPA or to any European regulatory agency.

TNO Study: Johan van Burgsteden, "In vitro percutaneous absorption study with [14C]-glyphosate using viable rat skin membranes," June 14, 2002, ***Unaudited draft report*** *V4478 (Tab 24).*

Glyphosphate in formulations MON 35012 and MON 0139 (70%) was examined for *in vitro* percutaneous absorption through viable rat skin membranes. Both contain the IPA salt of glyphosate, but MON 35012 also contains the surfactant cocoamine. Both the concentrated formulation and the field dilution were tested as shown below in Table 5. After eight hours of exposure, the test substance was removed from the application site and samples of the receptor fluid were collected for an additional 40 hours.

[151] Pesticide Action Network (PAN). http://pan-international.org/wp-content/uploads/Glyphosate-monograph.pdf

Table 5
Formulations and Doses Tested in TNO Dermal Absorption Studies

Formulation	Ingredients	Dose (mg gly/cm^2)	
		Concentrate	Field dilution
MON 35012	Glyphosate Isopropylamine salt (46% w/w) Surfactant Cocoamine (18% w/w) Water & minor ingredients (35.5% w/w)	6.249	0.080
MON 0139 70%	Isopropylamine salt (62% w/w) Inert ingredients (38% w/w)	6.343	0.080

The investigators in this study used doses outside the range recommendations of the U.S. EPA 1998 Health Effects Test Guidelines for dermal penetration as follows:

> *The maximum practical dose is on the order of 1 mg/cm^2—larger doses tend to fall off the skin or exceed saturation of the absorption process. When only three doses are given, the highest dose should be on the order of 0.1 mg/cm^2.*[152]

There are two doses in this study, the higher dose being 6.2 times larger than the recommended maximum dose. Furthermore, the U.S. EPA Guidelines state that:

> *The maximum dose volume should not exceed 10 µL/cm2. Larger volumes of liquid have been found to flow on the skin and produce uneven distribution on the dosed area.*[153]

In this study, 10 µL of the test samples was applied on a 0.64 cm^2 skin surface area. This is the equivalent of 15.6 µL/cm^2, which is more than one and one half times greater than the recommended maximum (liquid) dose. The excess in both the concentration and the volume of the concentrated doses will contribute to absorption saturation as described by the U.S. EPA:

> *The amount of chemical coverage on the skin surface can influence the amount of dermal absorption. Chemical coverage of the skin surface may be incomplete where only part of the surface is covered or it may be complete where the entire skin surface is covered. In*

[152] U.S. EPA OPPTS 870.7600, "Health Effects Test Guidelines Dermal Penetration," August 1998, pg. 4.

[153] Id.

both cases, only the amount of chemical in contact with the skin surface is available for absorption such that the capacity of the skin to absorb the chemical may be exceeded.[154]

The results of the eight hour exposures are shown in Table 6 below.

Table 6
Percent Absorption of Glyphosate (percent of dose)

	MON 35012 (containing surfactant)		**MON 0319 (70%) (no surfactant)**	
	Penetration within 48 hrs	Mass balance	Penetration within 48 hrs	Mass balance
Dose	**% of dose**		**% of dose**	
Low dose	2.6 ± 1.4 % (2.10 µg/cm^2)	73.4 %	1.4 ± 2.2 % (1.13 µg/cm^2)	82 .6 %
High dose	10.3 ± 4.2 % (646.3 µg/cm^2)	132.4 %	1.3 ± 1.9 % (80.8 µg/cm^2)	128 .2 %

The following key points emerged from the exposure/absorption tests:

- The maximum penetration of **10.3 %** occurred with the higher dose of MON 35012 concentrate which contained the surfactant Cocoamine.
- Even at the lower glyphosate dose of 0.080 mg/cm^2 of MON 35012, the penetration was 2.6 % of the dose **which is greater than Monsanto had previously reported**.
- The mass balance was found to range from 73 % to 132 %. **This variability is very high** as guidelines cite an adequate mean recovery is in the range of 100 ± 10%. (OECD, 2004). This suggests variability in the amount of absorption among the rat skin membrane samples at each dosing.
- In fact, while the mean penetration of the higher dose in MON 35012 was 646.3 µg/cm^2, one membrane absorbed approximately 1,100 µg/cm^2, or about **18 % of the applied dose**. The mean penetration of the lower dose of MON 35012 was 2.10

[154] U.S. EPA OPPTS 870.7600, "Health Effects Test Guidelines Dermal Penetration," August 1998, pg. 3.

µg/cm^2 while the maximum penetration was about 3.5 µg/cm^2 or approximately **4.4 % of the applied dose**.

- At the lower dose, using the worst case scenario, the missing 27% of the dose should be included in the amount absorbed and, therefore, the amount of absorbed glyphosate would be **30% of the applied dose**.

The measured 10.3 % dermal absorption of glyphosate through rat skin in the presence of a surfactant was not received well by Monsanto.

A series of communications among corporate employees followed disclosure of the test results which collectively suggests a keen lack of interest in making their findings known to the outside world. Thus, in a spirit of relevant disclosure and objective assessment, samples of Monsanto internal correspondence appear on the following pages.

In a message from [redacted] (3-29-02) to [redacted], et al: Subject: *"TNO dermal penetration studies: new issues and topics for the conference call of Tuesday, 2 April (8 A.M STL time),"* the following was noted:

> *"As of today we received preliminary surprising results on in vitro dermal penetration of propachlor and glyphosate through rat skin, it is imperative that we work closely together and communicate well on the conduct, the practical difficulties and the results associated with these studies.*
>
> *Glyphosate:*
>
> *- The EU rapporteur for glyphosate used a dermal penetration factor of 3% based on several published in vitro/in vivo dermal penetration studies*
>
> *- We launched human and rat in vitro dermal penetration studies with MON 35012 with and without surfactant*
>
> *- **Preliminary results with rat skin are not acceptable** (see fax); due to very bad reproducibility (sic) that TNO cannot explain, they proposed to repeat the study in parallel with the human skin study. However, we can already conclude that:*
>
> *a. For the concentrate MON 35012, the % in vitro dermal penetration of glyphosate through rat skin is between 5 and 10%*
>
> *b. For the spray dilution of MON 35012, the % in vitro dermal penetration of glyphosate through rat skin will be around 2%*
>
> *c. The dermal penetration of glyphosate itself in the absence of surfactant is lower than 1.5%."*

Rather than attempt to interpret this message, it is perhaps more instructive and revealing to cite a follow-up communication from Mr. William Heydens (4-2-02, to Charles Healy): Subject: *"TNO dermal penetration studies: new issues and topics for the conf call of Tuesday, 2 April (8 A.M STL time)."*

> *"… My primary concern is with the glyphosate in terms of the potential for this work to blow Roundup risk evaluations (**getting a much higher dermal penetration than we've ever seen before**."*

It seems the primary concern among Monsanto employees was for the potential of the test results to upset the product risk evaluations and confound the regulatory approval process. The potential human health issues raised by the product test results were not raised by any participant.

For undisclosed reasons, Monsanto **did not share this study** with the public or the scientific community. Additionally, they also decided not to have it repeated. Some incidental communications on this subject are available for consideration:

[redacted] (4-4-02):

> *"Although we agreed to repeat the in vitro dermal penetration study with rat skins as proposed by TNO, we came to the conclusion that the penetration of glyphosate would have been [probably] greater than the 3% already imposed by the German authorities. We decided thus to **STOP** the study (effective today morning)."*

In view of the concern that the test results might derail the regulatory approval process, the ethical red flags raised by this message are largely self-explanatory.

With further explanation, [redacted] (4-5-02):

> *"…we initiated the studies from a regulatory angle to help meet the requirements for operator exposure, given that the Annex I endpoint for dermal absorption for glyphosate was set at 3%, …the results of the rat skin studies show levels of absorption for glyphosate of a similar order to the Annex I endpoint, also confirm our expectation that surfactant concentration affects the dermal absorption… therefore, from the regulatory angle, there is no point in pursuing the studies further."*

Once again, the focus is strictly on the business aspects of introducing a commercial product. This masterpiece of sophistry effectively proclaims that Monsanto fully expected the results, and this was all part of the plan. Unfortunately, the potential human health issues raised by the product test results were also, once again, ignored.

Humectants

In addition to surfactants, Roundup® formulations also contain humectants which reduce the loss of moisture. As Monsanto notes,[155]

> *"Certain co-formulants like humectants that will make it **highly likely we will get large amounts penetrating the skin**."*

Humectants include chemicals such as ethylene glycol (anti-freeze). Ethylene glycol is included in most Roundup formulations. In addition to increasing dermal absorption, ethylene glycol is a toxic chemical in and of itself.[156] It is uncertain whether Monsanto ever studied the effect of ethylene glycol on glyphosate dermal absorption.[157]

Adjuvants

Adjuvants may be added to glyphosate formulations prior to use to improve their efficacy against weeds by enhancing penetration of glyphosate into the target plant. However, many of these may also increase the toxicity of glyphosate to other species. For example, organosilicone surfactants, described as the most potent of adjuvants and commonly added to glyphosate formulations, are now linked to a decline in honeybees in the U.S.[158] The common adjuvant surfactant TN-20 used in glyphosate formulations caused cell death and mitochondrial damage in rat cells which disrupts the integrity of the cellular barrier to glyphosate and promotes its toxicity.[159] Martini, et al., (2016)

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[155] Monsanto MONGLY06653096

[156] MONGLY01832749 (Toxic to children at 70 cc of Roundup with 5% ethylene glycol.)

[157] MONGLY01745304

[158] Mullin CA, Fine JD, Reynolds RD, Frazier MT, "Toxicological risks of agrochemical spray adjuvants: organosilicone surfactants may not be safe," 2016, Front Public Health, 4:92.

[159] Kim YH, Hong JR, Gil HW, Song HY, Hong SY, "Mixtures of glyphosate and surfactant TN20 accelerate cell death via mitochondrial damage-induced apoptosis and necrosis," 2013, Toxicol In Vitro 27(1), pg.191-197.

demonstrated that adjuvants other than POEA inhibited proliferation and differentiation of mammalian 3T3-L1 fibroblasts to adipocytes.[160]

Enhanced Absorption Due to Skin Damage

Skin, by its nature, is often compromised due to cracking and fissures, by cuts, scrapes, chemical damage, water-submersion, burns, sensitivity reactions, eczema and infections. This is particularly true for outdoor workers. Breaks in the protective lipophilic barrier of the stratum corneum significantly increase absorption of hydrophilic compounds. A compromised protective lipid barrier will allow the hydrophilic glyphosate to pass through into the hydrophilic dermis, thus avoiding slow diffusion through the lipid layer. Percutaneous absorption studies have demonstrated that glyphosate deposition in damaged skin is five times that of healthy skin and penetration through damaged skin is increased 20-fold.[161] The integrity of the skin also effects the distribution of chemicals within the skin compartments which will have implications in the efficacy of hand-washing after herbicide exposure.[162]

With respect to applicators, the acute quantity of glyphosate entering the skin is low. However, with repeated doses, especially coupled with a failure to wash the skin before it can be absorbed, the cumulative dose increases. Studies have documented that glyphosate penetration of skin increases linearly with time. Thus, if the worker is unaware of the exposures, absorption continues.[163]

Glyphosate's Role in Skin Damage

Evidence of glyphosate interference with mitochondrial function is increasingly emerging in the scientific literature. Mitochondria are the powerhouse bodies within cells which are necessary in the programmed cell death needed to form skin. Impairment of mitochondrial

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[160] Martini, C. et al., "Glyphosate-based herbicides with different adjuvants are more potent inhibitors of 3T3-L1 fibroblast proliferation and differentiation to adipocytes than glyphosate alone," 2016, Comparative Clinical Pathology, Volume 25, Issue 3, pg. 607–613.

[161] Nielsen, J. et al., "Defense against dermal exposures is only skin deep: significantly increased penetration through slightly damaged skin," 2007, Arch Dermatol Res, Vol. 299, pg..423-431.

[162] Id.

[163] Kezic, S. & Nielsen, J.B, "Absorption of chemicals through compromised skin," 2009, International Archives of Occupational and Environmental Health, Vol. 82(6), pg. *677-88.*

function reduces the transition of dermal to epidermal cells leading to a decrease in the protective epidermis.[164]

Additional studies by Heu, et al., have demonstrated glyphosate-induced structural changes.[165] In these studies, the control cells show Young's modulus values respectively increasing approximately 4-fold for 6 hours and 3-fold for 18 hours. These increases reflect a significant rise in cell stiffness. Heu, et al., reported that after a gentle cytotoxic treatment (6 h, 15 mM-glyphosate), the topography profile changes. The cells exhibit a flattened membrane and a different distribution of native protrusions. They also show a complex subcellular filamentous network with numerous membrane junction points.[166] Thus, glyphosate itself has an intrinsic propensity to damage skin.

Lack of Personal Protective Equipment (PPE)

The presence of systemic glyphosate in humans has been well documented and previously reported.[167] Acquavella, et al., performed biomonitoring of 48 farmers, their spouses and 79 children (4-18 years) for glyphosate in urine the day before as well as one and three days after glyphosate application (tractor and boom). They reported detectable levels of glyphosate in urine on the day of application in sixty percent of the farmers (geometric mean was 3 ppb, the maximum value was 233 ppb, and the highest estimated systemic dose was 0.004 mg/kg). The maximum value of 233 ug/L was from a farmer whose teenage son also had the highest urinary concentration of 29 ug/L among children. **Farmers who did not use rubber gloves had five times more glyphosate in their urine than those wearing protective gloves**. Various glyphosate-based formulas were used with various surfactants and/or salts. The proportions of participants with detectable urinary glyphosate differed between the two states: 87% detection rate in South Carolina; 36% in Minnesota. The urine concentrations were similarly different: 7.9

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[164] Heu, C., et al., "A step further toward glyphosate-induced epidermal cell death: Involvement of mitochondrial and oxidative mechanisms," 2012, Environmental Toxicology and Pharmacology 34.

[165] Heu C, Berquand A, Elie-Caille C, Nicod L., "Glyphosateinduced stiffening of HaCat keratinocytes, a Peak Force Tapping study in living cells", 2012, J Struc Biol 178, pg. 1-7.

[166] Id.

[167] Acquavella JF, Alexander BH, Mandel JS, Gustin C, Baker B, et al., "Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study," 2004, Environ Health Perspect 112, pg. 321-326.

µg/L on day of application in South Carolina; 1.4 µg/L on day of application in Minnesota. The proportion of applicators wearing rubber gloves in Minnesota (96%) was much greater than that in South Carolina (43%) suggesting that the use of gloves is responsible for the differences seen. It is interesting to note that a similar proportion of glove-wearing applicators was reported by Alavanja, et al., 1999: 39% in North Carolina; 76% in Iowa.

Other Factors Increasing Dermal Absorption

Various skin cream compounds applied to the skin prior to handling pesticides have been demonstrated to alter percutaneous absorption as reported in a study by Brand, et al., (2007).[168] In these studies, four commercially available moisturizing creams were tested with respect to their capacity as transdermal penetration enhancers using the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) as a model compound. Their data demonstrated that pre-treatment with three of the four creams increased the absorption of 2,4-D as evidenced by either an increased cumulative penetration or shorter lag-times. Korinth, et al., (2003) reported that skin barrier creams have been demonstrated to enhance the penetration rates of different industrial solvents. The creams significantly enhanced the penetration rates of solvents from complex mixtures compared with the single solvents.[169]

Ethanol is also well known as a topical penetration enhancer as it is frequently used in transdermal drug delivery systems (patches). Bommannan, et al., (1991)[170] found during *in vivo* studies with human skin that ethanol enters the skin and removes measurable quantities of the lipid barrier material from the stratum corneum. This lipid extraction may lower the skin barrier function and render the membrane more permeable which is the most likely explanation for the effect of ethanol as a skin penetration enhancer. The mechanism by which ethanol facilitates permeation of a solute, such as glyphosate, is

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[168] Brand, R. et al., "Transdermal absorption of the herbicide 2,4-dichlorophenoxyacetic acid is enhanced by both ethanol consumption and sunscreen application," 2007, Food and Chemical Toxicology, Volume 45, Issue 1, pg. 93-97.

[169] Korinth G, Geh S, Schaller KH, Drexler H., "*In vitro* evaluation of the efficacy of skin barrier creams and protective gloves on percutaneous absorption of industrial solvents," 2003, Int Arch Occup Environ Health, Vol. 76(5), pg. 382-6.

[170] Bommannan D, Potts RO, Guy RH, "Examination of the effect of ethanol on human stratum-corneum *in vivo* using infrared-spectroscopy," 1991, J Control Release, Vol. 16, pg. 299–304.

referred to as the "'pull" (or "drag") effect.[171] Hand sanitizer use has become widespread in the U.S. and typical hand sanitizers contain on average of 62% ethanol.

Thus, the use of creams and lotions to treat dry, cracking skin as well as the use of hand sanitizers potentiate the dermal absorption of glyphosate among occupational applicators.

[171] Heard CM, Kung D, Thomas CP, "Skin penetration enhancement of mefenamic acid by ethanol and 1,8-cineole can be explained by the "pull" effect," 2006, Int J Pharm., Vol. 321:167–170.

Part C: Toxicological Assessment of Glyphosate Carcinogenicity

Methodology

For the purposes of toxicological assessment, regulatory rulings play a role no more or less important than any other objective evidence. The generally-accepted, peer-reviewed toxicological literature is not based on unsubstantiated, subjective opinions. A responsible scientific investigation applies a well-established and prescribed risk assessment methodology.

This assessment applies the generally accepted and U.S. EPA-prescribed investigative methodology in assessing the potential carcinogenicity of glyphosate. Expert opinions must always be based on objective, reliable evidence without deviation from the methodology. The strands of evidence are never assumed to stand by themselves in isolation but are viewed as pieces of a larger puzzle. Scientific interpretation of the puzzle forms the basis of the investigative process in which each piece is assessed on its merits. Only in this manner can a scientifically credible assessment be conducted.

Regulatory Considerations

On July 7, 2017, the State of California listed glyphosate as a carcinogen, a chemical "*known to cause cancer*" under the state's Proposition 65 law. The ruling followed a move by the World Health Organization's International Agency for Research on Cancer (IARC) classifying glyphosate as a "*probable human carcinogen*." Monsanto is fighting the state's action but the California Supreme Court denied the company's request to stop the listing from taking effect while litigation is underway. Monsanto's vice president of global strategy announced that *"We will continue to aggressively challenge this improper decision."* Monsanto further alleged that IARC *"ignored crucial scientific data that undermines its conclusion."* To date, Monsanto has produced no objective evidence to directly support its contention.

Glyphosate is currently undergoing registration review as mandated by the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) which requires all registered pesticides to be re-evaluated every 15 years. As part of the review, the U.S. EPA's Office of Pesticide Programs (OPP) released a report dated September 12, 2016, focusing on

the carcinogenic potential of glyphosate.[172] The report included an evaluation of all cancer bioassays submitted under FIFRA.

Evaluation of Carcinogenic Potential Using Animal Models

U.S. EPA's Office of Pesticide Programs (OPP) stated that it has followed the U.S. EPA's "Guidelines for Carcinogen Risk Assessment." Consequently, as part of their evaluation of the results of each cancer bioassay, the OPP performed a Cochran-Armitage test (trend test) which statistically determines if the tumor incidences observed increased as the dosages to the groups of test animals (rodents) increased.[173]

Also undertaken was the Fisher exact test which performs a pairwise comparison of individual dose groups to controls to determine if the proportion of incidents in a dose group is statistically increased over the controls.[174]

The U.S. EPA's 2005 "Guidelines for Carcinogen Risk Assessment"[175] states that "*Trend tests and pairwise comparison tests are the recommended tests for determining whether chance, rather than a treatment-related effect, is a plausible explanation for an apparent increase in tumor incidence.*" The U.S. EPA's guidelines then conclude that "*Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result*."

In addition to the trend test and pairwise comparison test, OPP performed a multiple comparison test as it states in the U.S. EPA's guidelines that "*consideration of multiple comparisons should also be taken into account.*"

Furthermore, for some study results, the OPP compared the incidence proportions to historical control data as the U.S. EPA's guidelines also state that "*Additional insights*

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[172] U.S. EPA Office of Pesticide Programs, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, United States Environmental Protection Agency.

[173] U.S. EPA, "Guidelines for Carcinogen Risk Assessment," 2005, EPA/630/P-03/001F, Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

[174] Id.

[175] Id.

about both statistical and biological significance can come from an examination of historical control data."

Review of OPP Cancer Bioassay Study Results

In the most recent glyphosate cancer bioassay study,[176,177] the CD-1 mice bioassay observed significant results for the Cochran-Armitage trend test and the Fisher exact test. The results revealed 1) a significant positive trend of increased lymphoma incidents with increased doses of glyphosate (with only a 0.7% chance that the trend is wrong) and 2) a significant 10% increase in incidence of lymphoma at the 810 mg/kg/day dose level as compared to the control group in the study which had zero (0) incidences of lymphoma. Per the earlier stated U.S. EPA's carcinogen risk assessment guidelines, "*Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result*." The Wood, et al., 2009b, study had significance in both tests which more than sufficiently met the requirements of the U.S. EPA guidelines showing that the results are valid.

However, the OPP concluded in its evaluation of the Wood, et al., 2009 study that "…*the agency does not consider the increase in malignant lymphoma to be treatment-related*." This was because the OPP did not consider significance in either test as its criteria. The OPP merely mentioned that "*a statistically significant trend was observed*" and made no further reference to the trend in their decision making, thus significantly discounting the importance of the result.

It is both relevant and noteworthy that the rationale behind the OPP's decision was based on two additional conditions imposed by the OPP on the Wood, et al., 2009b, study results These conditions were: 1) a multiple comparison analysis (*Šidák* correction-an additional

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[176] (a) Wood, E., Dunster, J., Watson, P., and Brooks, P., (2009a) "Glyphosate technical: Dietary combined chronic toxicity/Carcinogenicity study in the rat," 2009a, Harlan Laboratories Limited, Page 156 of 227 Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-012. April, 23, 2009. MRID 49957404. From "Glyphosate issue paper: Evaluation of carcinogenic potential," U.S. EPA's Office of Pesticide Programs, September 12, 2016.

[177] (b) Wood, E., Dunster, J., Watson, P., and Brooks, P., "Glyphosate technical: Dietary carcinogenicity study in the mouse," 2009b, Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-011. April, 22, 2009. MRID 49957402. From "Glyphosate issue paper: Evaluation of carcinogenic potential," U.S. EPA's Office of Pesticide Programs September 12, 2016.

statistical analysis which made it harder to find a significant difference) and 2) comparing the significant lymphoma incidents to historical control data.

While the U.S. EPA's 2005 "Carcinogen Risk Assessment Guidelines" do allow for "*consideration*" of multiple comparisons, the guidelines recommend that the results of the analysis be "*taken into account*" and "*should be treated with caution*" and not as criteria for negating its fundamental guidelines for having a significant trend or a significant pairwise comparison. Furthermore, when evaluating the results of the Lankas, 1981, Sprague-Dawley rats bioassay,[178] the OPP determined that there was a significant positive trend ($p = 0.009$) of increased testicular tumors, a significant increased tumor incidence proportion at pairwise comparisons of 12% in the highest dose of 31.49 mg/kg/day as compared to the control at 0% ($p = 0.039$). The OPP applied the multiple comparison correction which confirmed the pairwise comparisons result ($p = 0.013$). The OPP still concluded that "*… tumors in the testes were not treatment-related*" and based this solely on the fact that, according to the OPP, the controls were "*unusually low*" for this type of tumor as compared to historical controls.

In its dismissal of the significance of the Wood, et al*.,* 2009b[179], results, the second issue was the comparison to historical controls. The OPP noted that "*For this strain of mouse, the mean incidence for untreated animals is approximately 4.5% (range: 1.5%-21.7%) based on historical control data from Charles River (59 studies performed from 1987-2000; Giknis and Clifford, 2005), Huntingdon Laboratories (20 studies from 1990-2002) and Son and Gopinath, 2004."* The OPP stated that "*Although the data is not from the performing laboratory, it does indicate that the incidence in concurrent controls in this study was low which can contribute to the pairwise significance observed at the highest dose tested with the raw (unadjusted) p-value."*

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[178] Lankas, G., "A lifetime study of glyphosate in rats," 1981, Report No. 77-2062 prepared by Bio Dynamics, Inc. in U.S. EPA, "Glyphosate issue paper," 2016 and reported in Greim, et al., 2015.

[179] (b) Wood, E., Dunster, J., Watson, P., and Brooks, P., "Glyphosate technical: Dietary carcinogenicity study in the mouse," 2009b, Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-011. April, 22, 2009. MRID 49957402. From "Glyphosate issue paper: Evaluation of carcinogenic potential," U.S. EPA's Office of Pesticide Programs September 12, 2016

The U.S. EPA's 2005 "Carcinogen Risk Assessment Guidelines" allow for insight from historical controls; however, with regards to the use of historical controls, the guidelines state *"Caution should be exercised in simply looking at the ranges of historical responses because the range ignores differences in survival of animals among studies and is related to the number of studies in the database…Generally speaking, 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. Random assignment of animals to groups and proper statistical procedures provide assurance that statistically significant results are unlikely to be due to chance alone."*

Per the guidelines, when historical control data is used, the evaluation should have addressed several issues that affect the comparability of historical and current control data such as genetic drift that would occur in the CD-1 mice strains over time and differences in the protocols followed by different laboratories in performing their pathology examination as these protocols can change between labs and over time. According to the guidelines, "*The most relevant historical data comes from the same laboratory and the same supplier and is gathered within 2 or 3 years of the study under review. Other data should be used only with extreme caution*."

Inexplicably, the OPP **completely ignored the directive** to use "*extreme caution*" as they used data from other laboratories and from studies published more than 22 years before the Wood, et al., 2009b, study (i.e. 1987 compared to 2009).

Additionally, the OPP made no indication that they took into account the potential for genetic drift or differences in laboratory protocols for identifying lesions. Most importantly, the lower range of historical control data reported by the U.S. EPA was 1.5% which is close to the observed control lymphoma incidence of 0%. Further, CD-1 mice in the bioassay by Sugimoto, 1997,[180] had a lymphoma incidence of 0% in its controls and a significantly elevated incidence of 17% at its highest dose.

[180] Sugimoto, K., "Eighteen month oral oncogenicity study in mice," 1997, The Institute of Environmental Toxicology, Tokyo, Japan in "Tier II summaries for glyphosate carcinogenicity studies from Greim, et al., 2015," as Arysta Life Sciences, 1997a.

FIFRA Scientific Advisory Panel Review

The OPP in their report[181] stated that it was soliciting advice from FIFRA's Scientific Advisory Panel with respect to their evaluation and interpretation of the data on glyphosate. The FIFRA Scientific Advisory Panel, the peer-review arm of the U.S. EPA, held a meeting in December, 2016,[182] to consider and review the scientific issues associated with the U.S. EPA's evaluation of the carcinogenic potential of glyphosate (2016).

With regards to Wood, et al., 2009b, the FIFRA Scientific Advisory Panel's memo stated "*In the response of malignant lymphomas in male CD-1 mice in Wood (2009b), it is not clear that the difference in the observed concurrent control group incidence (0%) should be considered unusually low as compared to the cited lower bound among historical controls (1.5%)*."

According to the FIFRA panel meeting minutes and final report, "*Overall, the panel concluded that the U.S. EPA evaluation does not appear to follow the U.S. EPA (2005) Cancer Guidelines in several ways: notably for use of historical control data and statistical testing requirements*." The minutes also stated that the U.S. EPA's use of multiple comparisons after the presence of a significant trend was "*neither consistent with the 2005 "Guidelines for Carcinogen Risk Assessment" nor a conservative approach for public health protection*."

OPP's "Novel" Assessment Method

It is troubling to all objective scientists (including the FIFRA panel) that OPP deviated from the long standing U.S. EPA's evaluation of carcinogenic potential methodology by implementing novel, non-peer-reviewed, extremely stringent "AND" requirements. U.S. EPA rules normally apply as "EITHER" as opposed to "AND" with respect to 1) concluding a significant dose response if one of the pairwise comparisons was significant or 2) the

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[181] U.S. EPA Office of Pesticide Programs, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, United States Environmental Protection Agency.

[182] FIFRA SAP, "A Set of scientific issues being considered by the Environmental Protection Agency regarding: EPA's evaluation of the carcinogenic potential of glyphosate," 2016, FIFRA Scientific Advisory Panel Meeting Minutes and Final Report No. 2017-01.

Cochran-Armitage tests were significant and the observed trend appeared monotonic. In the Wood, 2009b study, **all 3 tests were positive, exceeding the requirements**.

Inexplicably, OPP instituted a peculiar approach for glyphosate only of requiring **all 5 factors to be positive**. Furthermore, OPP attempted to argue that the control data was low (0 lymphomas in the control group) compared to 1.5% in the outdated (22-year-old) data set. Additionally, OPP instituted the highly demanding (Šidák correction analysis) using multiple comparison adjustments to be positive. Thus, the only factor of the 5 which Wood, 2009b, did not pass was the Šidák correction analysis – a purely optional test.

Assessment of OPP Conclusions

OPP's methodology was inappropriate per the FIFRA Scientific Advisory Panel. The OPP decision to dismiss the results of the Wood, et al., 2009b, study was inevitable by virtue of applying administrative criteria inconsistent with established methodology, guidelines and procedures. There is no clear explanation for this.

The upshot is that the OPP decision is not in line with their mission to protect human health. The rationale as published by OPP raises many questions and leaves a vacuum where those with a vested interest in objective science would expect to see guidance from a regulatory body tasked with this outcome. As noted by the Scientific Advisory Panel, "*When one uses conservatism of a test as a criterion, there is no clear stopping point as a more conservative test can always be found.*"

Thus, with respect to the current toxicological risk assessment, strict adherence to long standing, generally-accepted methodology has been applied throughout.

Chronic Studies and Cancer Bioassays in Animals - Oral Studies

Chronic carcinogenicity bioassays are used to simulate lifetime exposures of an individual to a chemical. Carcinogenicity bioassays evaluated in this assessment are from studies submitted for evaluation by regulatory agencies (such as the U.S. EPA). These bioassays tend to follow OECD accepted guidelines and protocols (Test Nos. 451 and 453)[183] and

[183] Greim, H., Saltmiras, D., Mostert, V., Strupp, C., "Evaluation of carcinogenic potential of the herbicide glyphosate drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies, et al.," 2015, Critical Reviews in Toxicology, Vol. 45(3), pg. 185 - 208.

are submitted to the U.S. EPA under 40 CFR Part 158.500. This statute requires chronic carcinogenicity testing studies to be performed on two rodent species for registration of food use pesticides OR if a pesticide is likely to have repeated human exposure over a significant portion of the human lifespan.

Glyphosate's cancer bioassay studies from 1979 to 2009 were evaluated by the U.S. EPA's Office of Pesticide Programs (OPP) and the results presented in their 2016 report entitled "Glyphosate issue paper: Evaluation of carcinogenic potential."[184] A vast majority of the studies reviewed by the OPP overlapped with those also reviewed in Greim, et al., 2015,[185] and summarized in detail in their report "*Tier II summaries for glyphosate carcinogenicity studies*."[186] These two reports were used as sources of data in the current evaluation of glyphosate's carcinogenicity. Of note, all of the cancer bioassays in the OPP evaluation and all but one in Greim, et al., 2015, are unpublished. All of the studies from the U.S. EPA's "Glyphosate Issue Paper" [187] and Greim, et al. (with the exception of Chruscielska, et al., 2000), were dietary studies in which high purity glyphosate was mixed in with laboratory animals' food to yield various doses.

The exception, Chruscielska, et al., (2000), is a drinking water study that evaluated a glyphosate formulation (13.85% glyphosate) and not strictly glyphosate and thus, was not included in this evaluation.[188] Another study from the "Tier II summaries" from Greim, et al., 2015, entitled "Excel 1997" (authored by Bhide, R.) did not provide information on the purity of glyphosate used and also was not included in the current evaluation. It was also found to be unreliable for carcinogenicity evaluation by Greim, et al., 2015, due to deviations from OECD test guidelines. Another mice study by Reyna and Gordon, 1973, only examined ten mice out of 50 for histological changes which is insufficient to make

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[184] U.S. EPA, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs, US Environmental Protection Agency.

[185] Greim, H., Saltmiras, D., Mostert, V., Strupp, C., "Evaluation of carcinogenic potential of the herbicide glyphosate drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies, et al.," 2015, Critical Reviews in Toxicology, Vol. 45(3), pg. 185 – 208.

[186] "Tier II summaries for glyphosate carcinogenicity studies from Greim, et al., 2015 paper," Unpublished data.

[187] U.S. EPA, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs, U.S. Environmental Protection Agency.

[188] Chruscielska, K., et al., "Glyphosate - Evaluation of chronic activity and possible far-reaching effects Part 1. Studies on chronic toxicity," 2000, Pestycydy Vol. 3-4, pg. 11 – 20.

such a determination. To date, there are no chronic inhalation carcinogenicity studies or chronic dermal animal bioassays.

Carcinogenicity in Chronic Dietary Studies

Reliable dietary studies for carcinogenicity are generally long-term studies in which a substance is fed or applied to test animals at controlled rates under a variety of conditions. Measurements of health effects, mortality, changes in body mass and other variables are recorded and incidences of carcinogenicity are carefully noted. Rats and mice are the most common test animals although other animals are also used.

Two-year studies in laboratory rodents remain the primary method by which test articles are identified as having the potential to be hazardous to humans. Typically, two or more species of both sexes are employed to demonstrate the widest possible range of response and variability although some studies limit sex and specie. Studies in rats along with studies in human populations (epidemiology studies) are the best means currently available for identifying potential human hazards. Chemicals recognized by the International Agency for Research on Cancer (IARC) as human carcinogens essentially all cause cancer when adequately tested in at least one species of laboratory animals.

Carcinogenicity Studies in Rats

Burnett, et al., 1979 [189]

In this two year, chronic carcinogenicity study, an aqueous monosodium salt of glyphosate was administered to 90 albino rats (male and female) through oral intubation at doses of 0, 3, 10 or 30 mg/kg/day for 24 months.

The results indicated a **high rate of mortality** in the control group in comparison to the treated groups. There were no treatment-related increases in tumor incidences observed.

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[189] Reported in U.S. EPA's "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016.

Burnett, P., Borders, J., Kush, J., "Report to Monsanto Company: Two year chronic oral toxicity study with CP-76100 in albino rats: IBT No. 8560-08924," (Unpublished study sent to the U.S. EPA on June 24, 1982, under 524-308); prepared by Industrial Bio-Test Laboratories Inc.

The highest dose tested in this study was 30 mg/kg/day which is considered below the maximum tolerable dose to assess the carcinogenic potential of glyphosate.

Lankas, 1981[190]

In this chronic carcinogenicity study, 50 Sprague-Dawley rats (male and female) were fed diets containing 98.7% pure glyphosate at doses of 0, 3, 10 and 31 mg/kg/day for male rats and 0, 3, 11, 34 mg/kg/day for female rats (corresponding to 0, 30, 100 and 300 PPM) for 775 - 776 days for males, and 784 - 785 days for female rats before termination. The study recorded body weights, organ weights, food consumption, hematology, clinical chemistry, urinalysis and survival as well as necropsy and histopathological examination. The results are shown in Table 7 below.

[190] Not published but reported in U.S. EPA, "Glyphosate issue paper," 2016, and reported in Greim, et al., 2015, as Monsanto (1981).

Lankas, G., "A lifetime study of glyphosate in rats," Report No. 77-2062 prepared by Bio Dynamics, Inc., 1981.

Table 7

Incidence of Testicular Interstitial Cell Tumors in Male Sprague-Dawley Rats (Lankas, 1981)[191]

Animal Dose (mg/kg bw/day)	0	3	10	31
(N) number of animals examined	(50)	(50)	(50)	(50)
Tumor incidents	0**,a	3	1	6*,b

* Denotes statistical significance at p= 0.05
** Denotes statistical significance at p= 0.01
a Cochran-Armitage Trend Test (p ≤ 0.01)
b Fisher's Exact Test (p ≤ 0.05)[192]

It was reported that the rats' survival was not impacted by treatment at any dose level. The 31/34 mg/kg/day (M/F) dose was considered to be a maximum tolerable dose to assess carcinogenic potential. However, the results showed a **statistically significant trend of increased incidences of interstitial cell tumors** of the testes (Leydig cell tumor) in male rats. Furthermore, the incidence was statistically elevated in the high-dose males as compared to the control. This was the only incidence of testicular interstitial cell tumor among the rat studies.

Pavkov and Wyand, 1987[193]

Pavkov and Wyand, 1987, is a two year, chronic carcinogenicity study in which glyphosate trimesium salt (sulfosate, 56.2% pure) was administered to male and female Sprague-Dawley rats with 60 rats in the first dose group, 80 rats in the second dose

[191] This table is adapted from U.S. EPA's, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs.

[192] Fisher's Exact Test Results are per the EPA.

[193] Unpublished and reported in U.S. EPA's "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016.

Pavkov, K., Wyand, "Two year chronic toxicity and oncogenicity dietary study with SC-0224 in mice," 1987, Stauffer Chemical Company.

groups and 90 rats in the third dose group. The dose groups were 0, 4.2, 21.2, or 41.8 mg/kg/day for male and 0, 5.4, 27, 55.7 mg/kg/day for female rats for 24 months.

The treatment doses had no effect on survival. There were no treatment-related increases in tumor incidences in this study.

Stout and Ruecker, 1990[194]

This two year, chronic carcinogenicity study fed groups of 60 Sprague-Dawley rats (male and female) diets containing 96.5% pure glyphosate at doses of 0, 89, 362 and 940 mg/kg/day for male rats and 0, 113, 457, 1183 mg/kg/day for female rats (corresponding to 0, 2,000, 8,000 and 20,000 PPM). Ten rats per dose group were sacrificed at an interim of 12 months for examination.

Examination of the rats covered clinical signs, ophthalmic examinations, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, necropsy and histopathological examination. The researchers observed that rats' survival was not impacted by treatment. A significant trend of elevated incidences of hyperplasia was observed in the stomach squamous mucosa cells. (Hyperplasia is the abnormal enlargement of an organ due to an increased replication rate of cells which can progress to become malignant.)[195] There were also significantly elevated trends of benign tumors (adenomas) of the pancreas, liver and thyroid, as shown in Table 8.

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[194] Not published but reported in U.S. EPA, 2016 and reported in Greim, et al., 2015, as Monsanto (1990). Stout, L., Ruecker, P., "Chronic study of glyphosate administered in feed to albino rats," 1990.

[195] NCI, "Definition of hyperplasia," n.d., NCI Dictionary of Cancer Terms, National Cancer Institute. Retrieved from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45956

Table 8
Histopathology Results Observed in Sprague-Dawley Rats (Stout and Ruecker, 1990) [196]

Histopathology		Dose groups (PPM)		0	2000	8000	20000
	Tissue	Dose groups (Male/Female) mg/kg bw/day		(0/0)	(89/113)	(362/457)	(940/1183)
Non-neoplastic lesions	Stomach squamous mucosa	Hyperplasia[a,b]	Males	3/58 (5)	3/58 (5)	5/59 (8)	7/59 (12)
			Females	2/59 (3)	3/60 (5)	9/60 (15)	6/59 (10)
Neoplastic lesions	Pancreatic islet cells	Adenomas	Males	1/43 (2)*	8/45 (18)	5/49 (10)	7/48 (15)*,[c]
	Liver	Adenomas	Males	2/44 (5)*	2/45 (4)	3/49 (6)	7/48 (15)
	Thyroid C-Cells	Adenomas	Males	2/54 (4)	4/55 (7)	8/58 (14)	7/58 (12)
		Carcinomas	Males	0/54 (0)	2/55 (4)	0/58 (0)	1/58 (2)
		Combined	Males	2/54 (4)	6/55 (11)	8/58 (14)	8/58 (14)
		Adenomas	Females	2/57 (4)*	2/60 (3)	6/59 (10)	6/55 (11)
		Carcinomas	Females	0/57 (0)	0/60 (0)	1/59 (2)	0/55 (0)
		Combined	Females	2/57 (4)*	2/60 (3)	7/59 (12)	6/55 (11)

* Denotes statistical significance at p= 0.05
[a] Number of incidents/number of animals examined, excluding those that died or were sacrificed prior to week 55
[b] Percentages of incidents appear in parenthesis
[c] Fisher's Exact Test ($p \leq 0.05$)[197]

The trend analysis for pancreatic tumors was not statistically significant as incidents of pancreatic tumors did not follow a dose response pattern; however, they were statistically elevated in the low and high dose groups as compared to the controls.

In the case of tumors in multiple tissue locations, the National Toxicology Program uses the following criteria for listing a chemical as "Reasonably Anticipated to be a Human Carcinogen." When "*there is sufficient evidence of carcinogenicity from studies in*

[196] This table is adapted from both U.S. EPA's, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, and "Tier II summaries for glyphosate carcinogenicity studies from Greim, et al., paper, 2015." "Fisher's Exact Test" and "Cochran-Armitage Trend test results" were performed by U.S. EPA.

[197] Fisher's Exact Test results are per the U.S. EPA.

experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites or (2) by multiple routes of exposure or (3) to an unusual degree with regard to incidence, site or type of tumor or age at onset." [198]

Consequently, this study is a good indicator that glyphosate is reasonably anticipated to be a human carcinogen.

Atkinson, et al., 1993[199]

This chronic toxicity/carcinogenicity study fed groups of 50 Sprague-Dawley rats (male and female) diets containing 98.9% pure glyphosate at doses of 0, 11, 112, 320 and 1,147 mg/kg/day for male rats and 0, 12, 109, 347 and 1,134 mg/kg/day for female rats for 104 weeks before termination. The treatment doses had no effect on survival. There were no treatment-related increases in tumor incidences in this study.

Suresh, 1996[200]

This two year, chronic carcinogenicity study fed groups of 50 Wister rats (male and female) diets containing 96.8% pure glyphosate at doses of 0, 7.4, 73.9, and 740.6 mg/kg/day for male and female rats (corresponding to 0, 100, 1,000 and 10,000 PPM). Twenty rats per sex were sacrificed at an interim of twelve months for examination.

The rats' survival was not affected by treatment. A high volume of tumor incidences was observed in moribund animals sacrificed after termination of the study as shown in the table below. Tumor incidences appeared elevated above controls in the low and mid doses (hepatocellular carcinoma and intrahepatic bile duct adenoma); these did not exhibit dose-response relationships (as shown in Table 9) and were not statistically significant.

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[198] https://ntp.niehs.nih.gov/pubhealth/roc/criteria/index.html

[199] Not published but reported in U.S. EPA, 2016, and reported in Greim, et al., 2015, as Cheminova (1993).

[200] Not published but reported in U.S. EPA, 2016, and reported in Greim, et al., 2015, as Feinchemie Schwebda (1996).

Table 9
Neoplastic histopathological findings in Wistar Male Rats[201] (Suresh, 1996)

	Animal Dose in PPM	Incidence of Adenoma (%)	Incidence of Carcinoma (%)
Hepatocellular (male rats)	0	24/50 (48%)	21/50 (42%)
	100	22/50 (44%)	28/50 (56%)
	1,000	10/52 (19%)	18/48 (38%)
	10,000	21/41 (51%)	24/50 (48%)
Bile duct (intrahepatic adenomas and cholangiocarcinoma) (male rats)	0	2/50 (4%)	1/50 (2%)
	100	1/50 (1%)	3/50 (6%)
	1,000	0/50 (0)	2/48 (4%)
	10,000	0/50 (0)	3/50 (6%)
Hepatocellular (female rats)	0	18/50 (36%)	10/50 (20%)
	100	18/48 (38%)	15/48 (31%)
	1,000	19/49 (39%)	14/49 (29%)
	10,000	13/50 (26%)	9/50 (18%)
Bile duct (intrahepatic adenomas and cholangiocarcinoma) (female rats)	0	6/50 (12%)	1/50 (2)
	100	11/48 (23%)	0/48 (0)
	1,000	12/48 (25%)	0/50 (0)
	10,000	4/50 (8%)	0/50 (0)

[201] This table was adapted from "Tier II summaries for glyphosate carcinogenicity studies from Greim, et al., 2015, paper."

Entomoto, A. (1997)[202]

This two year chronic toxicity/carcinogenicity study fed groups of 50 Sprague-Dawley rats (male and female) diets containing 94.6 - 97.56% pure glyphosate at doses of 0, 104, 354, and 1,127 mg/kg/day for male rats and 0, 115, 393 and 1,247 mg/kg/day for female rats corresponding to 0, 3000, 10,000 and 30,000 PPM.

Examination of the rats by this study covered clinical signs, ophthalmic examinations, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, necropsy and histopathological examination.

Results on neoplasms were considered to not be treatment-related by the authors and were not reported.

Brammer, 2001[203]

This chronic carcinogenicity study fed groups of 52 Wister rats (male and female) diets containing 97.6% pure glyphosate at doses of 0, 121, 361 and 1,214 mg/kg/day for male rats and 0, 145, 437, 1,498 mg/kg/day for female rats (corresponds to 0, 2000, 6000, and 20,000 PPM) for 24 months before termination.

Examination of the rats by this study covered clinical signs, ophthalmic examinations, body weight, food consumption, hematology, clinical chemistry, urinalysis, organ weights, necropsy and histopathological examination.

A significantly higher survival trend was found in male treated rats (p=0.03) with a significant higher survival found in the highest dosed group of male rats (p =0.02). As shown in Table 10, a statistically significant trend (p= 0.008) was found for liver adenomas in male rats although the middle dose did not show a response. A statistically elevated tumor incidence was also found at the high dose concentration at p= 0.028.

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[202] Not published but reported in U.S. EPA, 2016, and reported in Greim, et al., 2015, as Arysta Life Sciences (1997).

[203] Not published but reported in U.S. EPA, 2016 and in Greim, et al., 2015, as Syngenta (2001).

Table 10
Incidence of Liver Adenomas in Male Wister rats[204] (Brammer, 2001)

Animal Dose (mg/kg/day)	Tumor incidence	Percentage Incidence
0	0/52 [a**]	0
121	2/52	4
361	0/52	0
1,214	5/52[b*]	10

* Denotes statistical significance at p= 0.05
** Denotes statistical significance at p= 0.01
[a] Cochran-Armitage Trend Test ($p \leq 0.01$)
[b] Fisher's Exact Test ($p \leq 0.05$)[205]

Wood, et al., 2009a[206]

This chronic carcinogenicity study fed groups of 51 Wister rats (male and female) diets containing 95.7% pure glyphosate at doses of 0, 95, 316.9 and 1,229.7 mg/kg/day for male and female rats equivalent to 0, 1500, 5000, and 15,000 PPM for 24 months before termination.

A statistically significant trend of elevated incidences of mammary gland tumors (adenocarcinomas) (p=0.042), combined adenomas and carcinoma (p = 0007)) were noted in female rats as shown in Table 11 below. A statistical difference was noted at the high dose when adenoma and carcinoma incidences were combined.

[204] This table is adapted from U.S. EPA, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs. Fisher's Exact Test and Cochran-Armitage Trend test results were performed by the U.S. EPA.

[205] Fisher's Exact Test results are per the U.S. EPA.

[206] Not published but reported in U.S. EPA, 2016, and in Greim, et al., 2015, as Nufram, (2009a).

Table 11
Mammary Gland Tumor Incidences in Female Wister Rats (Wood et al, 2009a)[207]

Animal Dose in mg/kg/day	Incidence of Adenoma (%)	Incidence of Carcinoma (%)	Combined Incidences (%)
0	0/51 (0)	2/51 (4)*,[a]	2/51 (4)**,[b]
95	0/51 (0)	3/51 (6)	3/51 (6)
316.9	0/51 (0)	1/51 (2)	1/51 (2)
1,229.7	2/51 (4)	6/51 (12)	8/51 (16)*,[c]

* Denotes statistical significance at p= 0.05
** Denotes statistical significance at p= 0.01
[a] Cochran-Armitage Trend Test (p ≤ 0.05)
[b] Cochran-Armitage Trend Test (p ≤ 0.01)
[c] Fisher's Exact Test (p ≤ 0.05) [208]

Summary of Rat Carcinogenicity Studies

Three out of six feeding studies with dietary doses within regulatory guidelines (i.e. maximum tolerated dose or MTD)[209] had positive trends and/or significantly elevated tumor incidences. One study, Stout and Ruecker (1990), observed elevated tumor trends in multiple tissue types - pancreas, liver and thyroid. In Stout and Ruecker, hyperplasia, which can be a precursor to cancer, was also found at significantly elevated levels in the stomach squamous mucosa.

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[207] This table is adapted from U.S. EPA, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs. Fisher's Exact Test and Cochran-Armitage Trend test results were performed by U.S. EPA.

[208] Fisher's Exact Test results are per the U.S. EPA.

[209] "Long-term animal studies at or near the maximum tolerated dose level (MTD) are used to ensure an adequate power for the detection of carcinogenic activity," in U.S. EPA, "Guidelines for carcinogen risk assessment," EPA/630/R-00/004, September 1986, page 5.

Other studies found elevated incidences of tumors in the testes (Lankas, 1981), liver (Brammer, 2001) and mammary glands (Wood, et al., 2009a)[210]. Statistically significant doses were observed for testicular, pancreatic, liver and mammary glands. The results are summarized in Table 12 below.

Table 12
Summary of Bioassays for Detecting Carcinogenicity

Study	Doses / Concentration	Test gender / Strain	Tumor Incidences	Comments
Burnett, et al., 1979	0, 3, 10, or 30 mg/kg/day	Male and female / Albino rats	Negative	Dose below regulatory testing guidelines
Lankas, 1981	0, 3, 10 and 31 mg/kg/day	Male / Sprague-Dawley rats	**Positive trend** of elevated testicular interstitial cell tumors. Positive elevated tumor incidence	Dose below regulatory testing guidelines
Pavkov and Wyand, 1987	0, 4.2, 21.2, or 41.8 mg/kg/day	Male and female / Sprague-Dawley rats	Negative	Dose below regulatory testing guidelines
Stout and Ruecker, 1990	0, 89, 362 and 940 mg/kg/day	Male and female / Sprague-Dawley rats	**Positive trend** of elevated hepatocellular adenomas in male mice and thyroid c-cell tumor in male rats. Significantly elevated incidents of pancreatic adenomas,	
Atkinson et al., 1993	0, 11/12, 112/109, 320/347 and 1,147/1134 mg/kg/day	Male and female / Sprague-Dawley rats	Negative	Positive trend for thyroid follicular cell tumors found independently
Suresh, 1996	0, 7.4, 73.9, and 740.6 mg/kg/day	Male and female / Wister rats	Negative	

[210] (a) Wood, E., Dunster, J., Watson, P., and Brooks, P., "Glyphosate technical: Dietary combined chronic toxicity/carcinogenicity study in the rat," 2009a, Harlan Laboratories Limited, Page 156 of 227 Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-012. April, 23, 2009. MRID 49957404. From Glyphosate issue paper: Evaluation of carcinogenic potential, U.S. EPA's Office of Pesticide Programs, September 12, 2016.

Table 12
Summary of Bioassays for Detecting Carcinogenicity

Study	Doses / Concentration	Test gender / Strain	Tumor Incidences	Comments
Entomoto, 1997	0, 104/115, 354/393, 1127/1247 mg/kg/day	Male and female / Sprague-Dawley rats	Negative	Positive trend for kidney adenomas
Brammer, 2001	0, 121, 361 and 1,214 mg/kg/day	Male Wister rats	**Positive trend** in liver adenomas, positive significance at 1,214 dose	
Wood et al., 2009a	0, 95, 316.9 and 1,229.7 mg/kg/day	Female Wister Rats	**Positive trend** and significant incidences of mammary gland tumors at 1,229.7 mg/kg/day	

Furthermore, Dr. Portier, former director of the NIEHS (National Institute of Environmental Health Sciences) and a collaborator on IARC monographs, was able to review the complete animal laboratory data from chronic carcinogenicity studies of glyphosate and noted additional significant tumor trends that were not reported in the U.S. EPA's publication nor in the supplemental material from Greim, et al, 2015. This includes:

- Atkinson, et al., 1993. Thyroid follicular cell adenomas and carcinomas in male Sprague Dawley rats: 0/50, 0/50, 0/50, 2/50, 2/49 (p=0.04)
- Lankas, et al, 1981. Thyroid c-cell carcinomas in female Sprague Dawley rats 1/47, 0/49, 2/50, 6/47 (p=0.003)
- Entomoto, 1997. Kidney adenoma in male Sprague Dawley rats: 0/50, 0/50, 0/50, 4/50 (p=0.004)
- Wood, et al., 2009b. Skin keratocanthoma in male Wister rats: 2/51, 3/51, 0/51, 6/51 (p=0.03)

In the case of tumors in multiple tissue locations, the National Toxicology Program identified a chemical as "Reasonably Anticipated to be a Human Carcinogen" when:

> "*There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites or (2) by multiple routes of exposure or (3) to an unusual degree with regard to incidence, site, or type of tumor or age at onset.*" [211]

Carcinogenicity Studies in Mice

As with rat studies, two-year chronic carcinogenicity studies in laboratory mice provide valuable data with respect to identifying substances having the potential to be hazardous to humans. Typically two or more species of both sexes are employed to demonstrate the widest possible range of response and variability, though some studies limit sex and specie.

Knezevich and Hogan, 1983[212]

This chronic carcinogenicity study fed groups of 50 CD-1 mice (male and female) diets containing 99.78% pure glyphosate at doses of 0, 161, 835 and 4,945 mg/kg/day for male mice and 0, 195, 968, and 6,069 mg/kg/day for female mice for 24 months prior to termination. Complete necropsy examinations were performed on all animals which died or when they were sacrificed at termination.

Incidences of hepatocellular lesions were found to have statistically significant trends observed for central lobular hepatocyte hypertrophy, centrilobular hepatocyte necrosis and chronic interstitial nephritis in males and hypertrophy in females. Results appear in Tables 13 and 14.

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[211] National Toxicology Program, "Listing criteria," 2016, Report on Carcinogens, Public Health, U.S. Department of Health and Human Services, Retrieved from: https://ntp.niehs.nih.gov/pubhealth/roc/criteria/index.html

[212] Not published but reported in U.S. EPA, 2016, and in Greim et al., 2015, as Monsanto, (1983).

Table 13
Lesions in Male CD-1 Mice (Knezevich and Hogan, 1983)[213]

Condition	Sex	Concentrations of glyphosate in diet (PPM)			
		0	1,000	5,000	30,000
Urinary bladder hyperplasia	M	3/49	3/50	10/50	8/50
Hepatocellular centrilobular hypertrophy	M	9/49	5/50	3/50	17/50
	F	0/49	5/50	1/49	1/49
Hepatocellular centrilobular necrosis	M	0/49**[a]	2/50	2/50	10/50**[b]

** Denotes statistical significance at p= 0.01
[a] Cochran-Armitage Trend Test (p ≤0.01)
[b] Fisher's Exact test (p ≤0.01)[214]

Table 14
Kidney Tubular Cell Tumor Incidences in male CD-1 mice
(Knezevich and Hogan, 1983)[215]

Animal Dose in mg/kg/day	Incidence of Adenoma (%)	Incidence of Carcinoma (%)	Combined Incidences (%)
0	1/49 (2)	0/49 (0)	1/49 (2)
161	0/49 (0)	0/49 (0)	0/49 (0)
835	0/50 (0)	1/50 (2)	1/50 (2)
4,945	1/50 (2)	2/50 (4)	3/50 (6)

The US. EPA's OPP review noted an incidence of renal tubule tumors in the male mice, which are considered rare, but stated that there was limited historical data for this mice

[213] This table is adapted from Greim, et al., 2015. Fisher's Exact Test and Cochran-Armitage Trend Test results were performed by U.S. EPA.

[214] Fisher's Exact Test results are per the U.S. EPA.

[215] This table is adapted from U.S. EPA's, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs. Fisher's Exact Test and Cochran-Armitage Trend Test results were performed by U.S. EPA.

strain and no significant pairwise comparison. However, it should be noted that U.S. EPA's "Guidelines for Carcinogen Risk Assessment"[216] states that *"For the evaluation of rare tumors, even small tumor responses may be significant compared to historical data."*

Pavkov and Turnier, 1987

This two year study of chronic toxicity/carcinogenicity fed groups of CD-1 mice (male and female) diets containing glyphosate trimesium salt (56.2 % pure glyphosate) at doses of 0, 11.7, 118, and 991 mg/kg/day for male mice and 0, 16, 159 and 1,341 mg/kg/day for female mice. Sixty mice per sex were tested in the control group and 80 mice per sex were tested in the low and mid-dose group while 90 mice per sex were tested in the high dose group.

Results on neoplasms were considered to not be treatment-related by the authors and were not reported.

Atkinson, et al., 1993[217]

This chronic carcinogenicity study fed groups of 50 CD-1 mice (male and female) diets containing >97% pure glyphosate at doses of 0, 98, 297 and 988 mg/kg/day for male mice and 0, 102, 298, and 1,000 mg/kg/day for female mice for 24 months before termination.

Results of this study observed a statistically significant trend in hemangiosarcomas in male CD-1 mice. The only significant increase occurred at the high dose (see Table 15).

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[216] U.S. EPA, "Guidelines for carcinogen risk assessments," EPA/630/R-00-004, September 1986, page 6.

[217] Not published but reported in U.S. EPA, 2016, and in Greim, et al., 2015, as Cheminova, (1993b).

Table 15
Incidences of Hemangiosarcomas in Male CD-1 Mice[218] (Atkinson et al., 1993)

Animal Dose (mg/kg/day)	Tumor incidence	Percentage Incidence
0	0/47 **[a]	0
98	0/46	0
297	0/50	0
988	4/45 **	9

** Denotes significance at p = 0.01
[a] Cochran-Armitage Trend Test (p ≤ 0.01)

Sugimoto, K., 1997[219]

This chronic carcinogenicity study fed groups of 50 CD-1 mice (male and female) diets containing 94.6 and 97.6% pure glyphosate at doses of 0, 165, 838.1 and 4,348 mg/kg/day for male and 0, 153.2, 786.8 and 4,116 mg/kg/day for female mice equivalent to 0, 1,600, 8,000 and 40,000 PPM for male and female mice for 18 months before termination.

Results of this study observed a statistically significant trend in hemangioma in male CD-1 mice and a significantly increased rate of malignant lymphomas. The only significant increase in hemangioma occurred at the highest dose. Results are shown in Tables 16 and 17.

[218] This table is adapted from U.S. EPA's, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs. Fisher's Exact Test and Cochran-Armitage Trend Test results were performed by U.S. EPA.

[219] Not published but reported in U.S. EPA, 2016, and in Greim, et al., 2015, as Arysta Life Sciences, (1997a).

Table 16
Incidences of Hemangioma in Female CD-1 Mice[220] (Sugimoto, 1997)

Animal Dose (mg/kg/day)	Tumor incidence	Percentage Incidence
0	0/50 **[a]	0
153.2	0/50	0
786.8	2/50	4
4,116	5/50 **	10*[,b]

* Denotes significance at p = 0.05
** Denotes significance at p = 0.01
[a] Cochran-Armitage Trend Test (p ≤ 0.01), 2016
[b] Fisher's Exact Test (p ≤ 0.05)[221]

Table 17
Incidences of Malignant Lymphomas in Male CD-1 Mice
Which Survived Until Termination of the Experiment[222] (Sugimoto, 1997)

Animal Dose (mg/kg/day)	Tumor incidence	Percentage Incidence
0	0/26 [a]	0
165	0/34	0
838.1	1/27	4
4,348	5/29 **	17

** Denotes significance at p = 0.01
[a] Cochran-Armitage Trend Test (p ≤ 0.01)

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[220] This table is adapted from Wood et al., 2009b, in U.S. EPA's, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs. Fisher's Exact Test and Cochran-Armitage Trend Test results were performed by U.S. EPA.

[221] Fisher's Exact Test results are per the U.S. EPA.

[222] This table is adapted from Wood et al., 2009b, in U.S. EPA's, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs. Fisher's Exact Test and Cochran-Armitage Trend Test results were performed by U.S. EPA.

Kumar, 2001[223]

This chronic carcinogenicity study fed groups of 50 Swiss albino mice (male and female) diets containing > 95.14 % pure glyphosate at an average dose of 0, 14.7, 150.5 and 1,460.3 mg/kg/day for male equivalent to 0, 100, 1,000 and 10,000 PPM for male and female mice for 18 months before termination.

The mortality of mice after 18 months of the study was 44, 40, 44 and 54% for males and 32, 32, 40 and 40% in females in the control through high dose groups. Mortality was slightly elevated in the dosed mice above the control group. The authors determined that mortality was unusually high for the strain and was not dose related without adequate explanation. More recently, an unsubstantiated allegation of a former US EPA official (Jess Rowland) stated that the mice used in the study were suffering from a viral infection that might have caused cancer. Another alleged weaknesses with the study cited a high background of malignant lymphomas in control mice used for the study. However, as shown below in Table 18, only females revealed a high background rate of lymphoma. Results of this study observed a highly statistically significant Cochran-Armitage Trend Test ($p \leq 0.01$) and trend among male mice with only 1 positive lymphoma mouse in the control group and a significance ($p = 0.01$) incident rate of lymphoma amongst the high dose group as detailed in Table 18.

[223] Not published but reported in U.S. EPA, 2016, and in Greim et al., 2015, as Feinchemie Schwebda, (2001).

Table 18
Incidences of malignant lymphomas in Swiss Albino Mice[224] (Kumar, 2001)

		Glyphosate dose in PPM (percentage incidence)			
	Gender	0	100	1,000	10,000
Terminal sacrificed mice	Male	1/28 (4) [a]	3/30 (10)	3/28 (11)	6/23 (26) **
	Female	9/34 (26)	10/34 (29)	6/30 (20)	13/30 (43)
Dead and moribund mice	Male	9/22 (41)	12/20(60)	13/22 (59)	13/27 (48)
	Female	9/16 (56)	10/16 (63)	13/20 (65)	12/20 (60)
Combined	Male	10/50 (20) [a]	15/50 (30)	16/50 (32)	19/50 (38) **
	Female	18/50 (36)	20/50 (40)	19/50 (38)	25/50 (50)

** Denotes significance at p = 0.01
[a] Cochran-Armitage Trend Test (p ≤ 0.01)

The U.S. EPA's evaluation noted that the population of mice in the study had a viral infection and, therefore, did not include the results in their assessment.

Wood, et al., 2009b[225]

The study was conducted between October 2005 and November 2007 in which four groups of 51 male CD-1 mice received daily dietary doses of 0, 500, 1,500 and 5,000 PPM 95.7%-technical grade glyphosate (resulting in an average glyphosate consumption of 71.4, 234.2, and 810 mg/kg/day) for 80 weeks.[226]

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[224] Data in table is adapted "Tier II summaries for glyphosate carcinogenicity studies from Greim, et al., 2015 paper."

[225] Not published but reported in U.S. EPA, 2016, and in Greim, H., Saltmiras, D., Mostert, V., Strupp, C., "Evaluation of carcinogenic potential of the herbicide glyphosate drawing on tumor incidence data from fourteen chronic/carcinogenicity rodent studies, et al.," 2015, Critical Reviews in Toxicology, Vol. 45(3), pp. 185 - 208, as Nufram, (2009).

[226] Note that Greim, et al., referenced this as an 18 month study. Greim, H., Saltmiras, D., Mostert, V., Strupp, C., "Evaluation of carcinogenic potential of the herbicide glyphosate drawing on tumor

A statistically significant trend of increased incidence of lymphomas and lung adenocarcinomas was observed (Table 19). A statistically significant elevated lymphoma incidence was observed in the 810 mg/kg/day dose group. Additionally, significant lymphoid hyperplasia was observed at low and mid doses in males (71.4 and 234.2 mg/kg/day) while malignant lymphomas were significantly induced at 810 mg/kg/day.

Table 19
Incidence of Malignant Lymphomas in Male CD-1 Mice[227] (Wood et al., 2009b)

Doses (mg/kg/day)		**0**	**71.4**	**234.2**	**810**
Lung Adenocarcinoma	Incidences	5/51[a]	5/51	7/51	11/51
	% Incidences	10	10	14	22
Lymphomas	Incidences	0/51 [a]	1/51	2/51	5/51[b]
	% Incidences	0	2	4	10

[a] Cochran-Armitage Trend Test (p = 0.007)
[b] Fisher's Exact Test (p=0.028)

Summary of Mice Carcinogenicity Studies

Four out of six mice (***67%***) feeding studies with dietary doses within regulatory guidelines (i.e., at or near maximum tolerated dose or MTD)[228] had positive trends and/or significantly elevated tumors incidences. Two studies, Atkinson (1993) and Sugimoto (1997) observed significant trends of hemagiosarcomas including a significant incidence level at 4,116 mg/kg/day dose in Sugimoto (1997).

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incidence data from fourteen chronic/carcinogenicity rodent studies, et al.," 2015, Critical Reviews in Toxicology, Vol. 45(3), pg. 185 - 208.

[227] This table is adapted from Wood, et al., 2009b, in U.S. EPA's, "Glyphosate issue paper: Evaluation of carcinogenic potential," 2016, U.S. EPA's Office of Pesticide Programs. Fisher's Exact Test and Cochran-Armitage Trend Test results were performed by U.S. EPA.

[228] "Long-term animal studies at or near the maximum tolerated dose level (MTD) are used to ensure an adequate power for the detection of carcinogenic activity," in U.S. EPA "Guidelines for carcinogen risk assessment," EPA/630/R-00/004, September, 1986, page 5.

Significant trends of increasing incidences of malignant lymphomas were found with increasing glyphosate doses in Sugimoto (1997), Kumar (2001) and Wood, et al., (2009b). The Wood, et al., (2009b) study also found a significantly increased trend for incidences of lung adenocarcinomas and another study species showing significant results for malignancies in multiple tissues.

The National Toxicology Program identifies as their criteria for listing a chemical as "Reasonably Anticipated to be a Human Carcinogen" to be when:

> "*There is sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites or (2) by multiple routes of exposure or (3) to an unusual degree with regard to incidence, site, or type of tumor or age at onset.*" [229]

Based upon the U.S. EPA guidelines, **there is evidence** of uncommon tumor types, tumors at multiple sites, tumors in multiple species, strains and dose-related increases.

Table 20 presents a summary of the mice carcinogenicity studies cited herein.

[229] https://ntp.niehs.nih.gov/pubhealth/roc/criteria/index.html

Table 20
Summary of Bioassays for Detecting Mice Carcinogenicity

Study	Doses / Concentration	Test gender / Strain	Tumor Incidences	Comments
Knezevich and Hogan, 1983	0, 161, 835 and 4,945 mg/kg/day	Male / CD-1 Mice	None	Elevated incidences of hepatocellular necrosis and hypertrophy in mice. Also elevated urinary bladder hyperplasia. Elevated incidences of rare kidney tubular cell carcinoma; not to the level of statistical significance.
Pavkov and Turnier, 1987	0, 11.7/16, 118/159, and 991/1341 mg/kg/day	Male and female / CD-1 Mice	None	
Atkinson et al., 1993	0, 98, 297 and 988 mg/kg/day	Male / CD-1 Mice	**Positive trend** in hemangiosarcomas	
Sugimoto, 1997	0, 165/153.2, 838.1/786.8 and 4,348/4,116 mg/kg/day	Male and female / CD -1 Mice	**Positive trend** in hemangiosarcomas and significant incidence levels of hemangiosarcomas and **malignant lymphoma**	
Kumar, 2001	0, 14.7, 150.5, and 1,460.3 mg/kg/day	Male and female / Swiss Albino Mice	**Positive trend** and elevated incidence of **malignant lymphoma**	U.S. EPA OPP stated that a viral infection was present in the colony of mice. (unsubstantiated allegation)[230]
Wood, et al., 2009b	0, 71.4, 234.2 and 810 mg/kg/day	Male / CD-1 Mice	**Positive trend** and elevated incidence of **malignant lymphoma**	

[230] There are no documents available that provide any objective scientific evidence for viral infections. Rather, the health status of animals simply supported the plausibility of a viral infection.

Part D: Glyphosate Carcinogenicity Assessment

Introduction

A cancer slope factor (CSF) estimates the risk of cancer associated with exposure to a carcinogenic or potentially carcinogenic substance. Mathematically, a slope factor is an upper bound, approximating a 95% confidence limit. It is used to demonstrate cancer risk from a lifetime exposure to a substance by ingestion, dermal exposure or inhalation.

As previously noted, the generally-accepted, peer-reviewed toxicological literature is not based on unsubstantiated, subjective opinions. A responsible scientific investigation applies a generally accepted and well documented risk assessment methodology. Thus, calculating a reliable cancer slope factor is predicated upon applying the best available information "as per schedule" according to the prescribed methodology.

U.S. EPA guidelines[231] repeatedly stress the need for good information in its guidance, which is specific and demanding. U.S. EPA methodology recommends any study used for the purpose of calculating a cancer slope factor should meet the following criteria:

- Study should apply at least two dose groups plus a control group.
- Study should have sufficient sensitivity to provide data for multiple dose ranges
- Study should meet all statistical testing requirements.
- Study should characterize exposure at multiple exposure levels.
- Study should demonstrate statistically-significant results and show clear trends with respect to dose-response outcomes.

Following U.S. EPA methodology the Wood, et al., 2009b[232] study was chosen as the primary study to derive an exposure cancer slope factor for glyphosate since it is the most

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[231] U.S. EPA, "Guidelines for carcinogen risk assessment," EPA/630/P-03/001B, March, 2005

[232] (b) Wood, E., Dunster, J., Watson, P., and Brooks, P., "Glyphosate technical: Dietary carcinogenicity study in the mouse," 2009b, Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK. Study No. 2060-011. April, 22, 2009. MRID 49957402. From "Glyphosate issue paper: Evaluation of Carcinogenic Potentia," U.S. EPA's Office of Pesticide Programs, September 12, 2016.

sensitive study and meets and exceeds the statistical testing requirements. Wood, et al., 2009b, is the most recent chronic carcinogenicity study performed and used three large dose groups plus a control group. The study doses characterize exposure at low, mid and high exposure levels. Wood, et al., 2009b, also noted a significant trend in hepatocellular tumors and the observed trend was monotonic. As such, *the study exceeds the stated U.S. EPA assessment criteria*.

Dose-Response Data

Of the various studies noted herein, three chronic dietary bioassays provided incidence data for malignant lymphomas and occurred in mice only, these being: Sugimoto (1997), Kumar, (2001) and Wood, et al., (2009b). The dose-response data from each of these studies is summarized in Table 21. There were statistically significant increasing trends in tumor incidences in the males of the species.

Table 21

Incidence of Malignant Lymphomas in Male Mice Exposed to Glyphosate in Diet for two Years

Study	Strain/ Species	Animal dose (mg/kg/day)	Incidence of malignant lymphomas (percentage)	Numbers of animals examined
Sugimoto, 1997	CD-1 Mice	0	0 (0) [a]	26
		165	0 (0)	34
		838.1	1 (4)	27
		4,348	5 (17)	29
Kumar, 2001	Swiss Albino Mice	0	10 (20)	50
		14.7	15 (30)	50
		150.5	16 (32)	50
		1,460.3	19 (38)	50
Wood, et al., 2009b	CD-1 Mice	0	0 (0) [b] (monotonic)	51
		71.4	1 (2)	51
		234.2	2 (4)	51
		810	5 (10) [c]	51

[a] Cochran-Armitage Trend Test ($p \leq 0.01$)
[b] Cochran-Armitage Trend Test ($p = 0.007$)
[c] Fisher's Exact Test ($p=0.028$)

Dose Adjustments and Extrapolation Method(s)

Human equivalent doses (HEDs) were derived from the doses administered to the Wood, et al., 2009b study's male CD-1 mice using a body weight (BW) scaling factor of 0.75 as provided by the U.S. EPA.[233] HEDs were calculated using the following equation:

HED = animal $mg \cdot kg^{-1}$ dose x (animal weight (kg)/human weight (kg))$^{1-b}$

Where,

b = allometric exponent (0.75)

$$\text{HED} = 810\,\frac{\text{mg}}{\text{kg}}\,\text{bw x}\left(\frac{0.027\ kg}{70\ kg}\right)^{0.25} = 113.5\,\frac{\text{mg}}{\text{kg}}$$

For all HED calculations, a human body weight of 70 kg was used for the primary Wood, et al, study. The U.S. EPA "Exposure Factors Handbook" notes that 70 kg is commonly assumed in U.S. EPA risk assessments.[234] HEDs were also calculated for the other lymphoma studies as shown in Table 22.

The "Tier II summaries for glyphosate carcinogenicity studies from Greim, et al., 2015 paper" only provided the range of body weights of the mice used at the initiation of the experiment. Consequently, the lower animal doses provide a more conservative estimate of the human equivalent dose as the mice would have an increase in body weight over the 80 week feeding study period.

For Wood, et al., 2009b, the mice body weights ranged from 22 - 32 grams with the midpoint weight at 27 grams. The Sugimoto, 1997, study revealed mice body weights

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[233] U.S. EPA, "Recommended use of body weight 3/4 as the default method in derivation of the oral reference dose," 2011, (EPA/100/R11/0001), Office of the Science Advisor, Risk Assessment Forum, US Environmental Protection Agency, Washington, DC.

[234] U.S. EPA, "Exposures Factors Handbook: Chapter 8 – Body Weight Studies," 2011, U.S. Environmental Protection Agency.

that ranged from 15 - 25 grams with the midpoint at 20 grams. Kumar, 2001, cited mice weights ranging from 25 - 47 grams with the midpoint at 36 grams. The midpoint weights were used for HED determination.

Table 22

Calculated Human Equivalent Doses (HED) for the Lymphoma Incidence Data Used for Dose-Response Modeling

Study	Strain/ Species	Initial Midpoint Mice BW (kg)	Animal Dose (mg/kg/day)	HED (mg/kg/day)[a]
Sugimoto, 1997	CD-1 Mice	0.02	0	0
		0.02	165	21.5
		0.02	838.1	109
		0.02	4,348	565.3
Kumar, 2001	Swiss Albino Mice	0.036	0	0
		0.036	14.7	2.21
		0.036	150.5	22.7
		0.036	1,460.3	219.9
Wood, et al., 2009b	CD- 1 Mice	0.027	0	0
		0.027	71.4	10
		0.027	234.2	32.8
		0.027	810	113.5

[a] HEDs are calculated as HED = (animal dose) x (animal BW / Human BW)$^{0.25}$

Cancer Slope Factor

According to the U.S. EPA's "Guidelines for Carcinogen Risk Assessment,"[235] when quantifying the cancer risk of a chemical whose carcinogenic mode of action is not established, the linear approach is recommended as the default option. In the case of glyphosate, the genotoxic mode of carcinogenic action has been recently postulated[236] and there is limited human study evidence of genotoxicity. Thus, a linear low-dose extrapolation approach was used **as required by the methodology** to estimate human carcinogenic risk associated with glyphosate oral exposure.

Glyphosate Potential for Genotoxicity

There is evidence that that glyphosate is genotoxic and glyphosate-based formulations such as Roundup cause oxidative stress. The recent study of Suarez-Larios et al. (2017) reveals a genotoxic mode of action for glyphosate pesticides. An investigation was undertaken by Suarez-Larios, et al.,[237] to determine whether or not exposure to pesticides would induce double strand breaks (DSB) in cells (a lesion related to the formation of chromosomal rearrangements and increased leukemia risk). Of the eight pesticides tested (endosulfan, glyphosate, pentachlorophenol, permethrin, propoxur, AMPA, endosulfan lactone and paraoxon), four showed a significant effect on the number of cells with double strand breaks. However, glyphosate and paraoxon (both organo-phosphates) showed the greatest increase in the number of cells with DSB compared to the concentration. Further, it was determined that glyphosate and paraoxon reduced the number of viable cells in a dose-dependent manner; specifically, going from 100% cell viability to 70% with glyphosate.

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[235] U.S. EPA, "Guidelines for carcinogen risk assessment," 2005, EPA/630/P-03/001F, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC.

[236] Suarez-Larios, K., et al., "Screening of pesticides with the potential of inducing DSB and successive recombinational repair," 2017, Journal of Toxicology. Volume 2017.

[237] Suarez-Larios, K., et al., "Screening of pesticides with the potential of inducing DSB and successive recombinational repair," 2017, Journal of Toxicology. Volume 2017.

Not only did these two pesticides induce greater breakage, they also induced the phosphorylation[238] of KU80, a protein that participates in the c NHEJ recombinational repair pathway which is responsible for repair of the cells when DSB occur.

It was further noted in the study that these effects occurred at low concentrations in an acute treatment to cells in the laboratory setting. "*Effects over longer exposure in actual environmental settings are expected to produce cumulative damage if repeated events of recombination take place over time.*" In other words, the more often a cell is damaged by glyphosate-induced breakage, the less likely the c NHEJ recombinational repair pathway will be able to repair it. Thus, the linear approach required by the U.S. EPA methodology is appropriate as the mode of action proposed by Suarez-Larios et al. is not a threshold-based genotoxic mechanism. Other studies indicate that glyphosate can act as an endocrine disruptor[239] and has tumor-promoting activity.[240]

In vivo observations of human populations exposed to spraying of Roundup have revealed statistically significant outcomes demonstrating genotoxicity at low exposure levels[241] as well as *in vivo* studies of laboratory animals fed Roundup.[242] These studies challenge both animal and human systems providing *in vivo* doses of Roundup® with resulting genotoxicity.

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[238] Phosphorylation plays a critical role in the regulation of cellular processes.

[239] Gasnier, C., et al., "Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines," 2009, Toxicology, Vol. 262, pg. 184 -191.

Thongprakaisang, S., et al., "Glyphosate induces human breast cancer cells growth via estrogen receptors," 2013, Food and Chemical Toxicology, doi: http://dx.doi.org/10.1016/j.fct.2013.05.057

[240] George, J., et al., "Studies on glyphosate-induced carcinogenicity in mouse skin: A proteomic approach," 2010, Journal of Proteomics, Vol. 73, pg. 951 – 964.

[241] Paz-y-Miño, C., et al., "Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate*," 2007,* Genetics and Molecular Biology**, 30**(2).

Bolognesi, C., et al., "Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate," 2009, Journal of Toxicology and Environmental Health, Part A, Vol. 72, pg. 986 -997.

[242] Peluso, M., et al, "32P-postlabeling detection of DNA adducts in mice treated with herbicide roundup," 1998, Environmental and Molecular Mutagenesis. Vol. 31(1), pp. 55 -59. DOI: 10.1002/(SICI)1098-2280(1998)31:1<55::AID-EM8>3.0.CO;2-A

Furthermore, the human studies present conditions with "real world" dosing and concentrations.

The U.S. EPA's "Guidelines for Carcinogens" states that "*In the absence of sufficiently scientifically justifiable mode of action information, U.S. EPA generally takes public health-protective, default positions regarding the interpretation of toxicological and epidemiologic data: animal tumor findings are judged to be relevant to humans, and cancer risks are assumed to conform with low dose linearity*."[243]

Modeling: Cancer Slope Factor

According to the U.S. EPA's "Guidelines for Carcinogenic Risk Assessment," "*For linear extrapolation, the POD* (point of departure) *is used to calculate a slope factor."* Furthermore, the guidelines state that *"in a risk characterization, the POD is part of the determination of a margin of exposure.*"

The cancer slope factor (CSF) for glyphosate was derived via a linear extrapolation from the POD which was calculated by fitting the studies in the experimental dose response data to a curve in the U.S. EPA's "***Benchmark Dose Software***" (BMDS). The POD is the 95% lower confidence limit of the dose indicated by the model as the benchmark dose (BMD).

The BMD addresses the many limitations of the "No Observed Adverse Effect Level" (NOAEL) method as it is less dependent on dose selection and spacing and takes into account the shape of the dose-response curve. Furthermore, the BMD 95% lower confidence limit (BMDL) results in a point of departure that accounts for study quality issues (such as adequate sample size).[244] The CSF can be calculated from information provided from the BMD, as shown below:

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[243] U.S. EPA, "Guidelines for carcinogen risk assessment," 2005, EPA/630/P-03/001F, Risk Assessment Forum, U.S. Environmental Protection Agency, Washington, DC.

[244] "Dose-Response Assessment," n.d., Tox Tutor, U.S. National Library of Medicine, National Institute of Health, Retrieved from: https://toxtutor.nlm.nih.gov/06-003.html

CSF = BMR / BMDLHED

Where:

BMR: Benchmark Response Level

BMDLHED: Benchmark Dose Lower Bound Human Equivalent Dose

The dichotomous models in the Benchmark Dose Software (*BMDS version 2.6.0.1*) were fit to the lymphoma incidence data in mice. The mice doses were used for BMD modeling, and the BMDHED and BMDLHED values were calculated using the $BW^{3/4}$ scaling using the initial midpoint mice weights (final mice weights were not provided nor were individual mice weights) and a human body weight of 70 kg. For the models, a BMR of 10% extra risk was employed. BMDs and BMDLs from all models are shown in **Appendix A**.

The multi-stage model provided an adequate fit for the Sugimoto, 1997, CD-1 mice study as well as the Wood, et al., 2009b, CD-1 mice study. Other studies did not fit the multi-stage model adequately (see Table 23). The CD-1 mice were clearly the most sensitive species/strain, and the Wood, et al., 2009b, study is the most sensitive study as also shown in Table 23. Other models such as the probit model or log-logistic model could be used to provide adequate fit for the other cancer studies.

Table 23

BMD_{HED} and $BMDL_{HED}$ Values from Best-fit Models (using 10% BMR) to Lymphoma Incidence Data from Mice Exposed to Chronic Dietary Concentrations of Glyphosate Daily with Corresponding Cancer Slope Factors (CSFs)

Study	Gender/strain/ species	Carcinoma type	BMD_{HED} (mg/kg-day)	$BMDL_{HED}$ (mg/kg-day)	CSF $(mg/kg/day)^{-1}$
Sugimoto, 1997	Female CD-1 Mice	Hemangioma	1,239.7	822.4	1.21×10^{-4}
Sugimoto, 1997	Male CD-1 Mice	Malignant Lymphoma	1,832.16	1,000.15	1.0×10^{-4}
Wood, et al., 2009b	Male CD- 1 Mice	Malignant Lymphoma	100.76	59.28	1.7×10^{-3}

The multi-stage model using a 10% BMR is the standard method for establishing the cancer slope factor.[245] Consequently, the lymphoma cancer endpoint in CD-1 mice and the Wood, et al,, 2009b, study provided the best multi-stage model fit with p=0.91 (see Table 24).

Furthermore, a comparison of the BMD and BMDL estimates derived for mice from the Sugimoto, 1997, and Wood, et al., 2009b, studies indicate that male CD-1 mice are more sensitive to lymphoma induced by glyphosate compared to other species and tumor types.

[245] Crump, K., "The linearized multi-stage model and the future of quantitative risk assessment," 1996, Hum Exp. Tox, Vol. 15(10), pg. 787 – 798.

"Dose-Response Assessment," n.d., Tox Tutor, U.S. National Library of Medicine, National Institute of Health, Retrieved from: https://toxtutor.nlm.nih.gov/06-003.html

Therefore, the $BMDL_{10HED}$ was chosen as the POD. The Cancer Slope Factor (CSF) of 0.0017 mg/kg/day was calculated as follows:

$$CSF = \frac{0.10}{59.28 \text{ mg/kg-day } (BMDL_{10HED} \text{ for male CD1 mice})} = 0.00169$$

The calculation of a CSF for glyphosate is based upon the dose-response data for the most sensitive species and gender as well as the study providing the best fit of the multi-stage cancer model.

Table 24 shows a summary of BMD modeling results for glyphosate in diet/chronic carcinogenicity studies with significant dietary doses causing neoplasms. The BMD modeling results are shown in detail in **Appendix A**.

Table 24

Summary of BMD Modeling Results for Glyphosate in Diet/Chronic Carcinogenicity Studies with Significant Dietary Doses Causing Neoplasms

Study	Model[a]	Goodness of Fit			BMD_{10Pct}	$BMDL_{10Pct}$	Basis for Selection
		p-value	Scaled Residual	AIC			
Lankas, 1981	Multi-stage cancer 1st degree	0.112	0.096	77.615	29.8	14.8	Not an ideal model as p-value is less than 0.5.
Stout and Ruecker, 1990	Multi-stage cancer 1st degree	0.134	-0.104	133.96	1415	474	Not an ideal model as p-value is less than 0.5.
Brammer, 2001	Multi-stage cancer 1st degree	0.110	0.242	59.257	1490	743	Not an ideal model as p-value is less than 0.5.
Wood, et al, 2009a	Multi-stage cancer 1st degree	0.348	0.415	100.45	1151	591	Not an ideal model as p-value is less than 0.5.
Sugimoto, 1997; hemangioma	Multi-stage cancer 1st degree	0.606	1.11	82.019	1729	1147	1st degree and 2nd degree provided the exact same BMD and BMDL
Sugimoto, 1997;- lymphoma	Multi-stage cancer 1st degree	0.88	0.069	37.699	2506	1368	Select the model with the lower BMDL (1st Model)
Sugimoto, 1997; lymphoma	Multi-stage cancer 2nd degree	0.881	-0.021	39.649	2669	1375	
Wood et al., 2009b lymphoma	Multi-stage cancer 1st degree	0.905	-0.316	61.916	719	423	1st degree and 2nd degree provided the exact same BMD and BMDL

Criteria for model selection:

- Beta coefficient 2 of the multi-stage cancer 2 model hit a boundary
- *p*-value has to be greater than 0.5
- Scaled residual must be less than absolute 2
- AIC – the lower the AIC, the better

Assessment of Dose-Dependent Linear Extrapolation and Saturation Potential

Despite the U.S. EPA's recommendation of linear low dose extrapolation for genotoxic chemicals and chemicals with unknown mode of action, there exists some dissension among certain scientific points-of-view which challenges the appropriateness of a linear non-threshold, dose-response model as biologically valid for cancer risk assessment. In the current assessment, the recent study of Suarez-Larios et al. (2017) reveals a genotoxic mode of action for glyphosate that is linear with respect to double strand breaks and cumulative. In this study, it was determined that glyphosate reduced the number of viable cells in a dose-dependent manner; specifically, going from 100% cell viability to 70% with glyphosate. Additionally, glyphosate induced the phosphorylation[246] of KU80, a protein that participates in the c NHEJ recombinational repair pathway which is responsible for repair of the cells when DSB occur. The Suarez-Larios et al. study stated "*Effects over longer exposure in actual environmental settings are expected to produce cumulative damage if repeated events of recombination take place over time.*" In other words, the more often a cell is damaged by Glyphosate-induced breakage, the less likely the c NHEJ recombinational repair pathway will be able to repair it. Thus, the linear approach required by the U.S. EPA methodology is appropriate as the mode of action proposed by Suarez-Larios et al. is not a threshold-based genotoxic mechanism.

For example, the opinion article by *Exponent* published by James Bus (July 2017) summarizes this position. He argues that biological homeostatic mechanisms protect against adverse effects from low dose exposure to chemicals determined to be carcinogenic using high dose studies. Which is to say, the opinion is that certain high dose exposures in scientific studies should not be used to extrapolate human health risk at low doses.

The Bus article points out that there are protective biological cellular mechanisms for alleviating toxic effects at low doses creating a dose threshold effect. It also proposes that studies showing elevated dose-specific toxicity are associated with adverse health effects

[246] Phosphorylation plays a critical role in the regulation of cellular processes.

due to saturation of the biological mechanisms controlling the administration, distribution metabolism and excretion (ADME).[247] Based on these considerations, he opines:

- Against a linear, non-threshold hypothesis highlighting the development of Kinetically-derived Maximum Dose (KMD) that identifies the onset of non-linear ADME toxicity and proposed as an alternative or extension of the Maximum Tolerated Dose (MTD) currently accepted in toxicological health risk assessments.[248]
- Dosing in high throughput screening (HTS) *in vitro* testing (such as for determining genotoxicity), does not take into account chemical doses expected/attained *in vivo* (in real world situations in humans or model laboratory animals).

The determination of Roundup and other glyphosate-based formulations' genotoxicity as stated by IARC was not determined from *in vitro* testing in isolation. Rather *in vivo* observations of human populations exposed to spraying of Roundup revealed statistically significant outcomes demonstrating genotoxicity at low exposure levels[249] as well as *in vivo* studies of laboratory animals fed Roundup.[250] (This eliminates any confounding issues due to the controlled setting). These studies challenge both animal and human systems providing *in vivo* doses of Roundup® with resulting genotoxicity.

Furthermore, the human studies present conditions with "real world" dosing and concentrations. Perhaps the most compelling consideration comes from the objective

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[247] Bus, J., "The dose makes the poison: Key implications for mode of action (mechanistic) research in a 21st century toxicology paradigm," 2017, Current Opinion in Toxicology, DOI: 10.1016/j.cotox.2017.06.013

[248] OECD in Bus, J., "The dose makes the poison: Key implications for mode of action (mechanistic) research in a 21st century toxicology paradigm," 2017, Current Opinion in Toxicology, DOI: 10.1016/j.cotox.2017.06.013.

[249] Paz-y-Miño, C., et al., "Evaluation of DNA damage in an Ecuadorian population exposed to glyphosate," 2007, Genetics and Molecular Biology, 30(2).

Bolognesi, C., et al., "Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions: Association to occupational exposure to glyphosate," 2009, Journal of Toxicology and Environmental Health, Part A, Vol. 72, pg. 986 -997.

[250] Peluso, M., et al, "32P-postlabeling detection of DNA adducts in mice treated with herbicide roundup," 1998, Environmental and Molecular Mutagenesis. Vol. 31(1), pp. 55 -59. DOI: 10.1002/(SICI)1098-2280(1998)31:1<55::AID-EM8>3.0.CO;2-A

evidence in published epidemiological studies which documents Roundup® in the development of lymphoma, a further connection to Roundup's genotoxicity at a 95% level of certainty.[251]

It is important to understand that toxicity assays have traditionally relied on Maximum Tolerated Dose (MTD) as a strategy to compensate for the limited statistical power that comes with the use of a small number of test experimental animals and other such surrogates. The MTD is used to determine efficacy by testing increasing doses of a chemical until a dose that produces "acceptable" side effects is found[252] thereby assuming a linear response to chemical exposure.

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[251] DeRoos, A., et al., "Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men," 2003, Occup Environ Medical, Vol. 60.

[252] Chevret, S., "Maximum Tolerable Dose," 2008, Wiley Stats Ref: Statistics Reference Online, DOI: 10.1002/9781118445112.stat07089

NCI, "Maximum Tolerated Dose," n.d., NCI Dictionary of Cancer Terms, National Cancer Institute, National Institute of Health. Retrieved July, 6, 2017 from: https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=546597

Low Dose Linear Extrapolation versus. Kinetically-Derived Maximum Dose

There are important fundamental toxicological issues to consider here. At doses above the MTD, toxicity has been proposed to be associated with saturation of the biological mechanisms that control the administration, distribution, metabolism and excretion (ADME) [253] and is, therefore, non-linear in producing toxic adverse health effects. *However, direct, objective evidence to support this contention in humans is absent as glyphosate/Roundup® genotoxicity and lymphoma has been demonstrated in low exposure level human epidemiological studies that are statistically significant.*

Further evidence can be seen in animals in the current evaluation. The Cancer Slope Factor (CSF) was determined from a glyphosate feeding study in CD-1 mice[254] with a high-dose, statistically-significant increased incidence of lymphoma and low-dose linear extrapolation to determine the CSF over a statistically significant monotonic trend (p<0.007). Health effects observed in this study were not due to saturation as glyphosate was administered orally in diet (not via acute IV or intraperitoneal administration) allowing for absorption through the digestive system to dictate the concentration in blood. If saturation had occurred, a near perfectly linear dose-response curve would not have appeared in the Wood 2009b study.

A pharmacokinetic study[255] of glyphosate in rats demonstrates that 35 to 40% of the administered dose was absorbed from the digestive tract. An intravenous dosing study is more likely to saturate the ADME mechanism due to the acute bolus load into systematic circulation with a significant (~80%) portion of the administered dose eliminated primarily as un-metabolized glyphosate in urine within 24 hours of

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[253] Bus, J., "The dose makes the poison: Key implications for mode of action (mechanistic) research in a 21st century toxicology paradigm," 2017, Current Opinion in Toxicology, DOI: 10.1016/j.cotox.2017.06.013

[254] Wood, et al., "Glyphosate technical: dietary carcinogenicity study in the mouse," 2009b, Harlan Laboratories Limited, Shardlow Business Park, Shardlow, Derbyshire DE72 2GD, UK, Study No. 2060-011.

[255] Brewster, D., Warren, J., Hopkins, W., "Metabolism of glyphosate in Sprague Dawley rats: Tissue distribution, identification and quantitation of glyphosate-derived materials following a single oral dose," 1991, Fundamental and Applied Toxicology, Vol. 17, pg. 43-51.

administering the dose.[256] The pharmacokinetics of oral or dermally absorbed glyphosate is limited in its absorption rate into the blood without extreme high peak blood levels (which occurs with IV administration) and does not reach saturation of the ADME mechanisms.

As noted by Bus (2017), a large proportion of toxicological hazards are identified at doses only in the range of an MTD and, thus, *kinetically-derived maximum dose* (KMD) modeling will fail to identify these toxicological hazards particularly when hazard responses are limited to doses above the KMD.

Bus notes that "*The pragmatic end-result of KMD-based toxicity testing considerations is that the need for high-dose specific MoA [*mode of action*] investigations is substantially reduced*." Meaning, that a KMD approach (which doesn't include high dosages) will essentially eliminate the need for further investigation of many chemicals.

Human health risk assessments are designed to estimate cancer risks at levels of $1x10^{-4}$ to $1x10^{-6}$. Without the use of linear extrapolation from higher dose levels, approximately 400 lab animals in each dose-level group (1,600 animals total) would be required (assuming a doubling of the cancer rate) per dose group to determine a $1x10^{-4}$ cancer risk and 40,000 animals per dose group (160,000 animals total) to determine a $1x10^{-6}$ cancer risk level. In order to achieve bioassay sample sizes and statistical power that would be directly comparable to expected human exposure, thousands of test animals would be required. Such expectations are, quite simply, unrealistic. Possibly this is why a preferred approach of proponents of this "novel theory" is to ignore its practical consequences.

Furthermore, although Bus stated that "*the dose makes the poison,*" low dose linear extrapolation from high dose (MTD bioassays) factors in differences between animals and humans. It is by design protective of sensitive groups accounting for differences amongst humans such as their life stages – children are more susceptible to genotoxic chemicals than adults as are fetuses in pregnant individuals.

The information obtained from low dose linear extrapolation is used not only to develop a cancer slope factor for increased cancer risk but also to develop regulatory toxicity values.

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[256] Wester, R., et al., "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination,"1991, Fundamental and Applied Toxicology, Vol. 16, pg. 725-732.

To dispense with such an important set of critical goals for the sake of embracing an unproven theory without overwhelming objective evidence to support it is more than merely dangerous. The consequences of such a decision would be far-reaching and highly unlikely to demonstrate positive outcomes for those most directly affected.

Consequently, it is both unrealistic and dangerous to human health to eliminate low dose linear extrapolation. To do so would mean the exposed human population would find itself serving as an experimental laboratory for evaluating chemical carcinogenicity. It is doubtful that many of our citizens would volunteer for such an experiment.

Glyphosate Biomonitoring and Dose Measurements

Exposure models have been used for about 20 years to estimate the exposure of professional operators during application of pesticides. How well these models predict actual exposure is primarily determined by the pharmacokinetic studies and assumptions upon which they are based (such as the dermal absorption rate). Biomonitoring and dosimetry data are combined with PK models to reconstruct or estimate the exposure dose. PK models simulate the ADME within a living system. It is, therefore, essential to have a good understanding of the pharmacokinetics to ensure a good estimate of the exposure dose.

As most Monsanto glyphosate formulations are "trade secrets" and unpublished, it is not a surprise that the pharmacokinetics (or ADME) of glyphosate are not well understood by the scientific community. However, it appears they are also not well understood by the herbicide manufacturers themselves. As [redacted]

> *"ADME has always been the weak link in our argument…we have not got rid of that problem."*[257]

When assumptions in a key Monsanto-contracted pharmacokinetics study were questioned by the Spanish regulators, [redacted] wrote,

[257] MONGLY02221147

> *Even though we can absorb additional 'uncertainty factors' in our risk assessment based on our biomonitoring results, I feel uncomfortable with this discussion. This approach by Spain sets a precedent and contradicts the fact that we always claimed to fully understand the glyphosate pharmacokinetics.*[258]

Monsanto used its UK Predictive Operator Exposure Model (POEM) to calculate human exposure which regulatory agencies in Europe then compare to the acceptable operator exposure level (AOEL) during the pesticide registration process. As part of the exposure calculations, Monsanto assumes that only 3 % of the dermal exposure dose is absorbed. **This is based on Monsanto's own studies which have been shown to be flawed**.

Such discrepancies can be seen in another unpublished Monsanto study in which the percentage of dermal absorption was shown to be as high as 10% (TNO rat skin study). Since dermal exposure is the most significant route of exposure, a small change in the percentage of dermal exposure can have a great effect on the overall exposure. Monsanto acknowledges this fact directly in a July 2001 draft:

> *One of the product specific parameters that can make a big difference in the exposure assessment is the dermal uptake factor which is the fraction of the amount of active ingredient on the skin surface that is absorbed by the skin tissue.*[259]

There is evidence of a lack of objectivity which is possibly explained by Monsanto's desire for an herbicide formulation product to pass the regulatory process without obstacles. In an August 16, 2011, email, [redacted] wrote,

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[258] MONGLY02155829

[259] [redacted]. July 2001, Confidential draft. "Clustering glyphosate formulations with regard to the testing for dermal uptake."

In Europe, we are getting prepared to submit MON 79991 (720g/kg) for approval under the new Reg 1107/2009. We ran the UKPOEM model using a dermal penetration value of 3% and do not pass when applying 3.6kg/ha for the tractor-mounted sprayer. I am aware of the set of studies that you ran on dermal absorption using pure K-salt and IPA-salt and also MON 52276 and MON 79351 which showed dermal absorption values of 1%. Putting 1% in the model we get a good result, so will need to show that the 1% dermal absorption numbers are equally valid for the MON 79991 formulation.[260]

As a further example, a Monsanto document reveals their calculation of an estimation of the exposure during use of MON 76473 with a 5 liter home garden sprayer. The declared active ingredient (DAI) is glyphosate at a concentration of 360 mg/ml; neither the salt nor other ingredients are specified.

The dermal dose during mixing, loading and application is calculated to be 238.4 mg/day. The percent dermal absorption used in the calculations is 3% resulting in a dermal exposure of 7.152 mg/day. Combined with the inhalation exposure of 0.102857 mg/day (100% exposure absorbed), the total absorbed dose is **7.254 mg/day**. For a 60 kg operator, the result is a total exposure of 0.1209 mg/kg-day.[261]

If the dermal absorption is 10 % rather than 3 %, the resulting dermal exposure becomes 23.84 mg/day. The total exposure for a 60 kg operator would be

$$\frac{(23.84 + 0.102857)\ \text{mg/day}}{60\ \text{kg}} = 0.399\ \text{mg/kg per day}$$

This exposure is almost twice the AOEL of 0.2 mg/kg/day.

[260] MONGLY04107779

[261] UK POEM Tab 25 MONGLY06293737

Another operator exposure risk assessment prepared by Monsanto in June 2003 for MON 78273 under UK use conditions is summarized in Table 25.[262] This product is a potassium salt of glyphosate; the concentration of glyphosate in the formulation is 540 g/ml. This is a Tier 2 assessment based on a short-term rabbit teratogenicity study which resulted in an AOEL of 0.2 mg/kg/day.

Again, Monsanto assumed a dermal absorption of 3%. The table also shows the exposure estimates using 5% and 10% dermal absorption.

[262] (From Exposure assessment study.pdf) MONGLY06403283 - MONGLY06403322

Table 25

Estimation of Spray Operator Exposure

Handheld Outdoors Rotary Disc Atomizers	Dermal Exposure (Dose, mg/day)	Percentage dermal Absorption (%)	Dermal absorption (mg/day)	Total dose absorbed including 3.24 mg/day inhalation, (mg/day)	Exposure Level for a 60 Kg operator, (mg/kg/day)
No gloves	1782	3	53.460	56.700	0.945
No gloves	1782	5	89.100	92.340	1.539
No gloves	1782	10	178.200	181.440	3.024
Gloves during mixing/loading	1766.1	3	52.983	56.223	0.937
Gloves during mixing/loading	1766.1	5	88.305	91.545	1.526
Gloves during mixing/loading	1766.1	10	176.610	179.850	2.998
Gloves at all times	1183.41	3	35.502	38.742	0.646
Gloves at all times	1183.41	5	59.171	62.411	1.040
Gloves at all times	1183.41	10	118.341	121.581	2.026
Boots, gloves, coveralls	357.21	3	10.716	13.956	0.233
Boots, gloves, coveralls	357.21	5	17.861	21.101	0.352
Boots, gloves, coveralls	357.21	10	35.721	38.961	0.649

Hand held Outdoors Hydraulic Nozzles	Dermal Exposure (Dose, mg/day)	Percentage dermal Absorption (%)	Dermal absorption (mg/day)	Total dose absorbed including 3.24 mg/day inhalation, (mg/day)	Exposure Level for a 60 Kg operator, (mg/kg/day)
No gloves	2781	3	83.430	86.670	1.445
No gloves	2781	5	139.050	142.290	2.372
No gloves	2781	10	278.100	281.340	4.689
Gloves during mixing/loading	2755	3	82.650	85.890	1.432
Gloves during mixing/loading	2755	5	137.750	140.990	2.350
Gloves during mixing/loading	2755	10	275.500	278.740	4.646
Gloves at all times	1337.85	3	40.136	43.376	0.723
Gloves at all times	1337.85	5	66.893	70.133	1.169
Gloves at all times	1337.85	10	133.785	137.025	2.284
Boots, gloves, coveralls	507.6	3	15.228	18.468	0.308
Boots, gloves, coveralls	507.6	5	25.380	28.620	0.477
Boots, gloves, coveralls	507.6	10	50.760	54.000	0.900

Recent Glyphosate Risk Assessment Results

From March 3 to March 10, 2015, 17 experts from 11 countries convened at the International Agency for Research on Cancer (IARC) in France to review the currently available scientific research and evaluate the carcinogenicity of five organophosphate insecticides and herbicides. One of these herbicides was glyphosate which is found in Roundup herbicide.

This IARC meeting was preceded by a year of review by the IARC secretariat and this Working Group (WG). Their preparation included a comprehensive review of the latest available scientific evidence. As per their published procedures, the WG considered reports that were published or accepted for publication in openly available scientific literature and data from governmental reports that were publicly available. [263]

The IARC review conclusions[264] in March 2015 included the classification of glyphosate as "*probably carcinogenic to humans (Group 2A."* The IARC summarized that the basis of this decision was from:

- **Convincing evidence that glyphosate causes cancer in laboratory animals** as evidenced by tumors in mice in the U.S. EPA 1991 report as well as several more recent positive results providing the IARC with sufficient evidence of carcinogenicity in experimental animals.

- **Limited evidence of carcinogenicity in humans** for non-Hodgkin lymphoma based on studies of exposure in the U.S., Canada and Sweden published subsequent to 2001.

- A review of studies also demonstrated that **glyphosate caused DNA and chromosomal damage in human cells**; there were negative results in the tests using bacteria. A recent study of residents in a community where glyphosate was sprayed nearby showed increased blood markers of chromosomal damage (micronuclei).

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[263] IARC, "IARC Monographs Volume 112: Evaluation of five organophosphate insecticides and herbicides," 2015, International Agency for research on cancer, World Health organization Retrieved from: https://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf

[264] Id.

Consideration of Recent IARC Classification

The IARC's Group 2A classification means that the agent is "***probably*** *carcinogenic to humans."* This classification, according to IARC, specifically refers to agents for which the reviewed evidence demonstrates "*limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. Limited evidence means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations (called chance, bias or confounding) could not be ruled out. This category is also used when there is limited evidence of carcinogenicity in humans and strong data on how the agent causes cancer.*"[265]

It is difficult to reconcile this with an EFSA report (Nov 12, 2015) which concluded that Roundup® was "*unlikely to pose a carcinogenic hazard to humans*." However, the studies included in the EFSA report looked at the effects of glyphosate alone and none of the formulations. They acknowledge that:

> *Although POEtallowamine is not present in the representative formulation, for which data have been submitted under the European re-approval procedure and which were assessed by EFSA, the peer review concluded that the toxicity of formulations and, in particular, their genotoxic potential should be further considered and addressed. It is noted that* ***a number of human studies were not evaluated since the exposure was linked to glyphosate-based formulations of unknown composition****. Therefore, their assessment would not have changed the overall conclusion.*

It is highly significant that IARC reached its conclusions on the basis of data from assessments of **complete formulations** of Roundup® in conjunction with research on glyphosate alone from the animal studies. Additionally, IARC relied solely on **independent research** in rendering their conclusion. Monsanto-sponsored studies played little or no part in the IARC classification ruling.

[265] Id.

Cancer Risk Assessment Results: Cancer Slope Factor (CSF) Basis

Cancer risk level is determined as a consequence of applying a standard set of equations as established by U.S. EPA to specific variables as shown in the equations below. This section presents cancer risk level calculations using the cancer slope factor (CSF) for glyphosate exposures to herbicide applicators and the general population as well as dietary exposure cancer risk to the U.S. general population

Cancer Risk for Herbicide Applicators and the General Population

The cancer risks introduced from dietary glyphosate within the general U.S. population as well as to exposed farmers and applicators is calculated based on determined glyphosate exposure doses and the frequency and duration of exposure to the carcinogen (glyphosate). This is then spread across the lifetime of the individual. The calculation uses the cancer slope factor and is determined by the following equation:

$$Cancer\ Risk = \frac{Exposure\ dose\ X\ risk\ factor\ (cancer(oral)\ slope\ factor)X\ years\ of\ exposure}{70\ years\ (lifetime)}$$

Cancer Risk to the U.S. General Population via Dietary Exposure

Glyphosate exposures occur through dietary consumption of glyphosate residue on food and in drinking water. As reported in Solomon, (2016),[266] the U.S. EPA Dietary Exposure Evaluation Model (DEEM) estimates the average exposure of the general population to glyphosate as 0.088 mg/kg bw/day from an estimate that ranged from 0.058 – 0.23 mg/kg bw/day.

Consequently, the upper range of the dietary exposure cancer risk level is determined as:

$$Cancer\ Risk = \frac{\left[0.23\frac{mg}{kg}\ per\ day\ X\ 0.00169\ \left(\frac{mg}{kg}\ per\ day\right)^{-1}\ X\ 70\ years\right]}{70\ years\ (lifetime)} = 3.9\ X\ 10^{-3}$$

[266] Solomon, K., "Glyphosate in the general population and in applicators: a critical review of studies on exposures," 2016, Critical Reviews in Toxicology, Vol.46: sup 1, 21 -27, DOI: 10.1080/10408444.2016.1214678

Table 26 displays the range of cancer risk levels from typical dietary exposure.

Table 26

Cancer Risk Levels Based on the U.S. EPA DEEM Estimated Dietary and Drinking Water Exposure to Glyphosate
(US DEEM exposures from Solomon, 2016)

Exposure	Dietary Residue and Drinking Water Dose	Cancer Risk Level
Low	0.058 mg/kg bw/day	9.8×10^{-5}
Average	0.088 mg/kg bw/day	1.5×10^{-4}
High	0.23 mg/kg bw/day	3.9×10^{-4}

Acceptable risk levels have been generally recognized and applied in public health for decades. Levels exceeding the *de minimus* level are generally considered unsafe. In this context, the above levels of cancer risk to the general public are clearly unacceptable as the generally accepted *de minimus* benchmark level for cancer risk is 1×10^{-6} (one in one million). [267]

However, slightly higher levels of cancer risk are often used in public health and are based upon prudent regulatory judgement. Factors for consideration include the impacted population size, reasonable availability of technology to reduce risk, beneficial aspects of the ruling, etc. For example, chlorination of public water is extremely beneficial to reduce morbidity and mortality, but chlorination carries a low level risk of cancer due to the formation of trihalomethane contaminants in the water.

Thus, a *de minimus* benchmark increase to 1×10^{-5} (one in one hundred thousand) is occasionally applied in such a regulatory context, but the cancer risk levels shown in Table 26 far exceed this "enhanced" risk level as well.

[267] Payne-Sturges, DC, "Personal exposure meets risk assessment: A comparison of measured and modeled exposures and risks in an urban community," 2004, Environmental Health Perspectives, Vol. 112(5), pg. 589-598.

Additionally, a study by Caldwell, et al., discusses the history and use of the *de minimus* benchmark $1x10^{-6}$ risk level for hazardous air pollutants (HAPs).[268] The Caldwell study, with two of the three authors affiliated with the U.S. EPA, states that "*much of the needed information and science policy judgments were previously compiled for U.S.EPA's proposed rulemaking under section 112(g) of the CAA and were supplemented by information from several other data sources…known, probable, or possible human carcinogens representing the upper-bound of a one in a million excess probability of contracting cancer over a lifetime of exposure. This benchmark was based on provisions of CAA sections 112(f) and 112 (c)(9) that allow source categories to be exempted from regulation and residual risk to be negligible when posing less than a one in a million ($1x10^{-6}$ risk level) lifetime risk to the most exposed individual*."

Cancer Risk to Glyphosate Applicators

Also at risk are farmers and commercial applicators of glyphosate who are part of the agricultural industry and use glyphosate for weed management and in seeding and/or harvesting crops.

"The Agricultural Health Study" (AHS) is an ongoing cohort study which includes 89,000 farmers and their spouses from Iowa and North Carolina. The study is funded by the National Cancer Institute and the National Institute of Environmental Health Sciences and is partnered with the U.S. EPA and NIOSH.[269] In 1993, the AHS initial study[270] had a cohort of 20,235 private farmer and commercial applicators with 70.6 and 47.5 percent respectively reported to have applied herbicides. Their reported frequency of pesticide application is shown in Table 27.

[268] Caldwell, JC, "Application of health information to hazardous air pollutants modeled in EPA's cumulative exposure project," 1998, Toxicology and Industrial Health, Vol. 14(3), pg. 429-454.

[269] Alavanja, M., et al., "The Agricultural Health Study," 1996, Environmental Health Perspectives, Vol. 104 (4), pg. 362 – 369. Retrieved from: https://aghealth.nih.gov/

[270] Id.

Table 27

Demographic Characteristics of "The Agricultural Health Study"[271] Cohort
(Total applicators n = 20,235)

Days per year personally mixed or applied pesticide	Percentage of applicators in each category of days per year	Years personally mixed/applied pesticide	Percentage of applicators in each year of application category
<5	13.5	<1	3.3
5 – 9	17.2	2 – 5	12.8
10 – 19	22.7	6 – 10	14.9
20 – 39	17.7	11 – 20	27.9
40 – 59	5.8	21 – 30	17.0
60 – 150	5.5	>30	9.1
>150	1.3	Unknown	15.0
Unknown	16.4		
Median days	**23.3**	**Median Years**	**15.4**

The days of pesticide application as well as the years of use can be used to determine the lifetime years of exposure as:

$$\left(\frac{23.3 \text{ application days}}{365 \text{ days}}\right) x\ 15.4 \text{ years} = 0.983 \text{ years}$$

Consequently, the risk of cancer, given the exposure levels to glyphosate amongst applicators, is calculated using the equation:

$$\text{Cancer Risk for Applicators} = [\text{applicator risk}] + [\text{dietary risk}]$$

[271] Id.

Derivation of Dermal Toxicity Values

The oral cancer slope factor of 0.00169 mg/kg/day was determined from dietary doses of glyphosate and requires an adjustment for absorption through the gastrointestinal tract. The oral slope factor can be converted to an absorbed slope factor, which can be applied to the dermal absorbed dose to calculate a cancer risk. The absorbed slope factor can be derived using methods provided in the Risk Assessment for Superfund: Volume 1, Human Health Evaluation Manual, Part A (EPA/540/1-89/002). The absorbed slope factor can be calculated as:

$$\frac{\text{Oral Slope Factor}}{\text{GI Absorption Factor}} = \text{Slope Factor}_{\text{absorbed}}$$

The default Gastro Intestinal (GI) absorption factor, which is being applied in the absence of a determined GI absorption factor for glyphosate in humans is 50%[272] - the default for semi-volatile organic compounds per EPA Region 4's Supplemental Guidance to RAGS:

$$\frac{0.00169}{0.5} = 0.00338 \text{ i.e., } 3.38 \times 10^{-3} \text{ Slope Factor}_{\text{absorbed}}$$

Region 4 Bulletins Human Health Risk Assessment from November 1995.

For the highest exposure level reported among hand-held outdoor hydraulic nozzle applicators (see Tables 29 and 31), the cancer risk equation is:

[272] RAIS, "Toxicity Values" The Risk Assessment Information System. Retrieved from: https://rais.ornl.gov/tutorials/toxvals.html

Cancer Risk for Applicators = [applicator risk] + [dietary risk]

$$Cancer\ Risk = \frac{\left[4.635\frac{mg}{kg}per\ day\ X\ 0.00338\left(\frac{mg}{kg}per\ day\right)^{-1}\ X\ 0.983 years\right]+[0.23\frac{mg}{kg}per\ day X\ 0.00169\left(\frac{mg}{kg}per\ day\right)^{-1}\ X\ 70\ years]}{70\ years\ (lifetime)}$$

$$\frac{0.0154+0.0272}{70} = \frac{0.0426}{70} = 6.1\ X\ 10^{-4}$$

The resulting cancer risk level of **6.1 x 10^{-4}** is based on a mid-point dermal absorption rate of 10%[273] as shown in Tables 28 and 29.

The glyphosate exposure levels for applicators under various conditions were provided from Monsanto-derived exposure models and a realistic adjustment for glyphosate dermal absorption of 3%, 5% or 10% as shown in Tables 30 and 31.

It is important to note that exposure calculations should normally include the amount inhaled during herbicide spraying activity; however, the inhalation dose of 3.24 mg/day was excluded as the Inhalation Unit Risk (IUR) has not been established via inhalation chamber studies. *As a consequence, the risk values shown have been underestimated.*

[273] 10% Absorption was demonstrated in an unpublished Monsanto TNO study which is consistent with Wester et al. 1991, which revealed absorption range in primates of 4.4% - 22.6% with a midpoint value of 13.5%.

NO Study: Johan van Burgsteden, "In vitro percutaneous absorption study with [14C]-glyphosphate using viable rat skin membranes," June 14, 2002, Unaudited draft report V4478 (Tab 24).

Wester, R. et al. 1991. "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination". *Fundamental and Applied Toxicology* 16,725-732.

Tables 28 and 29 list the dose levels associated with each exposure scenario:

Table 28
Estimation of Spray Operator Exposure (Rotary Disc Atomizers)

Hand-held Outdoor Rotary Disc Atomizers	Dermal Exposure (Dose, mg/day)	Percentage Dermal Absorption (%)	Dermal Absorption (mg/day)	Exposure Level for a 60 Kg Operator, (mg/kg/day)
No gloves	1782	3	53.460	0.891
No gloves	1782	5	89.100	1.485
No gloves	1782	10	178.200	2.97
Gloves during mixing/loading	1766.1	3	52.983	0.883
Gloves during mixing/loading	1766.1	5	88.305	1.472
Gloves during mixing/loading	1766.1	10	176.610	2.944
Gloves at all times	1183.41	3	35.502	0.592
Gloves at all times	1183.41	5	59.171	0.986
Gloves at all times	1183.41	10	118.341	1.972
Boots, gloves, coveralls	357.21	3	10.716	0.179
Boots, gloves, coveralls	357.21	5	17.861	0.298
Boots, gloves, coveralls	357.21	10	35.721	0.595

Table 29
Estimation of Spray Operator Exposure (Hydraulic Nozzles)

Hand-held Outdoor Hydraulic Nozzles	Dermal Exposure (Dose, mg/day)	Percent Dermal Absorption (%)	Dermal Absorption (mg/day)	Exposure Level for a 60 Kg Operator, (mg/kg/day)
No gloves	2781	3	83.430	1.391
No gloves	2781	5	139.050	2.318
No gloves	2781	10	278.100	4.635
Gloves during mixing/loading	2755	3	82.650	1.378
Gloves during mixing/loading	2755	5	137.750	2.296
Gloves during mixing/loading	2755	10	275.500	4.592
Gloves at all times	1337.85	3	40.136	0.669
Gloves at all times	1337.85	5	66.893	1.115
Gloves at all times	1337.85	10	133.785	2.23
Boots, gloves, coveralls	507.6	3	15.228	0.254
Boots, gloves, coveralls	507.6	5	25.380	0.423
Boots, gloves, coveralls	507.6	10	50.760	0.846

Tables 30 and 31 list the calculated cancer risks associated with each exposure scenario:

Table 30
Cancer Risk Levels for Spray Operator Exposures (Rotary Disc Atomizers)

Hand-held Outdoor Rotary Disc Atomizers	Percentage Dermal Absorption (mg/day)	Exposure Level for a 60 kg Operator (mg/kg/day)	Cancer Risk Level	Including a Typical Average Dietary Risk Level of 1.5×10^{-4}
No gloves	3	0.891	4.2×10^{-5}	1.9×10^{-4}
No gloves	5	1.485	7.0×10^{-5}	2.2×10^{-4}
No gloves	10	2.97	1.4×10^{-4}	2.9×10^{-4}
Gloves during mixing/loading	3	0.883	4.2×10^{-5}	1.9×10^{-4}
Gloves during mixing/loading	5	1.472	7.0×10^{-5}	2.2×10^{-4}
Gloves during mixing/loading	10	2.944	1.4×10^{-4}	2.9×10^{-4}
Gloves at all times	3	0.592	2.8×10^{-5}	1.8×10^{-4}
Gloves at all times	5	0.986	4.7×10^{-5}	2.0×10^{-4}
Gloves at all times	10	1.972	9.3×10^{-5}	2.4×10^{-4}
Boots, gloves, coveralls	3	0.179	8.5×10^{-6}	1.6×10^{-4}
Boots, gloves, coveralls	5	0.298	1.4×10^{-5}	1.6×10^{-4}
Boots, gloves, coveralls	10	0.595	2.8×10^{-5}	1.8×10^{-4}

Table 31

Cancer Risk Levels for Spray Operator Exposures (Hydraulic Nozzles)

Hand-held Outdoor Hydraulic Nozzles	Percentage Dermal Absorption (mg/day)	Exposure Level for a 60 kg Operator, (mg/kg/day)	Cancer Risk Level	Including a Dietary Risk Level of 1.5×10^{-4}
No gloves	3	1.391	6.6×10^{-5}	2.1×10^{-4}
No gloves	5	2.318	1.1×10^{-4}	2.6×10^{-4}
No gloves	10	4.635	2.1×10^{-4}	3.7×10^{-4}
Gloves during mixing/loading	3	1.378	6.5×10^{-5}	2.1×10^{-4}
Gloves during mixing/loading	5	2.296	1.1×10^{-4}	2.6×10^{-4}
Gloves during mixing/loading	10	4.592	2.3×10^{-4}	3.7×10^{-4}
Gloves at all times	3	0.669	3.2×10^{-5}	1.8×10^{-4}
Gloves at all times	5	1.115	5.3×10^{-5}	2.0×10^{-4}
Gloves at all times	10	2.23	1.1×10^{-4}	2.5×10^{-4}
Boots, gloves, coveralls	3	0.254	1.2×10^{-5}	1.6×10^{-4}
Boots, gloves, coveralls	5	0.423	2.0×10^{-5}	1.7×10^{-4}
Boots, gloves, coveralls	10	0.846	4.0×10^{-5}	1.9×10^{-4}

Part E: Dose Calculations Relevant to Dewayne Johnson

Mr. Johnson used Ranger Pro® composed of 41% glyphosate and 8% surfactants which include tallowamine (POEA), polyethylene glycol (PEG), phosphate ester and dipropylene glycol. Additionally, he used Roundup® composed of 18% glyphosate.

As discussed in detail earlier in this report, Mr. Johnson mixed the Ranger Pro as per the pamphlet using 10 ounces of product to 5 gallons of water. However, he notes that the formulation could be stronger in certain applications. He has also testified spraying between 20-40 pesticide applications yearly (for 2-5 hours),[274] but deposition testimony reports a higher application frequency for more than 2 years prior to his T-cell lymphoma diagnosis.

Mr. Johnson also details high level, severe (upper body soaking) acute exposures. Mr. Johnson testified that he experienced drift exposure "*all the time*." There was no way to control the drift even by spraying on calm days or changing out nozzles to increase droplet size. During spraying, Mr. Johnson used personal protective equipment including gloves, boots, a "*sweatshirt-type hoodie,*" a permeable Tyvek suit, hat and goggles. (Although Mr. Johnson wore a Tyvek suit, it was apparently the fine cloth type as he explained that drift passed through it leaving him wet). Mr. Johnson testified that he was spraying sites at five different school locations at different times.

During Mr. Johnson's first high level, acute exposure, he testified that he was soaked with glyphosate when a hose broke off the 50 gallon pump unit and he attempted to access the unit to shut it off. "*The hose came [dis-attached] from the back of the truck and it was just juice everywhere, flying out the back of the truck. So that's when I had to hop in because the switches are in the back. There's no safety switch there ... I reach in the back there and turn it off and that's when I got it on the back of my neck and the back of my head and everywhere and on my face.*"[275]

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[274] Mr. Johnson testified, "..spraying sites at five different school locations at different times, usually would spray no more than 4-5 hours per day."

[275] At 12:37, he stated. "Cause it got down to my neck and got down to about the tip of my shoulder. I was able to rinse a lot of that off. I don't know if I'm wiping it in or I'm taking it off. ..But I'm using what I had at the time."

Mr. Johnson testified that there were noticeable and visible consequences of his initial exposure. He stated, "*When I got ahold of that liquid on my skin that day, it got red, it got irritated. I finished the day off. It was seven hours. Maybe six hours."* Mr. Johnson testified there were also other accidental high level exposures.

Mr. Johnson's exposure history falls within the parameters of "*The Agricultural Health Study*" Cohort in Table 27 (also see Tables 25, 27, 29 highlighted in yellow) which places him below the median exposures. Mr. Johnson worked as a mixer/applicator more than 40 days per year for approximately 2.25 year which results in over 90 exposures days. This represents a very conservative estimate as the acute soaking exposure doses left on the skin for prolonged periods of time were not included and would have resulted in much higher absorbed doses based on the referenced dermal absorption studies. Compared to "*The Agricultural Health Study*" Cohort in Table 27, Mr. Johnson's exposure frequencies were in the upper range of the table; however, his 2.25 years of application service was at the lower end. The extremes in both directions place him near the midpoint of the table.

Thus, it is my opinion that Mr. Johnson reasonably qualifies as an exposed glyphosate spray operator using a hydraulic nozzle (Table 29) with additional acute soaking exposures. His dosage can also be approximated from Tables 25 and 29; however, Mr. Johnson's high level acute exposures are not accounted for in these tables.

It should also be noted that, due to the persistent flash-back of aerosol due to building structure interference, Mr. Johnson's inhaled dose may have been higher than that shown in Tables 25 and 29.

IARC Classification of Glyphosate Carcinogenicity, Prevalence & Latency

I will be deferring any detailed epidemiological opinions in this matter with respect to IARC's classification of glyphosate as a carcinogen to Christopher J. Portier, Ph.D., Director of the National Center for Environmental Health and Director of the Agency for Toxic Substances and Disease Registry (ATSDR); Beate Ritz, M.D., Ph.D., Professor of Epidemiology at the University of California, Los Angeles (UCLA) Fielding School of Public Health and former chair of the UCLA Epidemiology Department; and Alfred I. Neugut, M.D., Ph.D., Professor of Cancer Research and Professor of Medicine and Epidemiology at Columbia University.

However, I have reviewed and relied on various epidemiological literature as cited and the general character of IARC's recent classification of glyphosate as a *"probable human carcinogen,"* as IARC's assessment of relevant studies of exposed glyphosate applicators provided evidence with respect to the latency period for non-Hodgkin's lymphoma (NHL). The toxicological community generally regards NHL as an uncommon malignancy in those in the 40 to 44 year old category. The National Cancer Institute Surveillance, Epidemiology and End Results (SEER) reveals an incidence rate of 13.0 per 100,000 person-years among 40 to 44 year old male African Americans.

Mr. Johnson was diagnosed with a rare type of lymphoma, CD4 folliculotropic and syringotropic mycosis fungoides with granulomatous features. Mycosis fungoides is a cutaneous T-cell lymphoma. (See Figure 2 below.) Based on studies by Wilson, et al.,[276] in the U.S. between the years 2004–2008, 1,713 patients were diagnosed with mycosis fungoides. Thus, using the official U.S. SEER registry statistics, the documented incidence rate for mycosis fungoides is only 5.6 per million persons.[277]

With respect to male/female or racial incident rate differences, mycosis fungoides reveals a trend for females to be less likely to present with a higher T-stage (T3–T4) than males with an odd ratio (OR) of 0.73 on multivariate analysis or about 27% less likely (not statistically significant at p=0.06). With respect to race, African Americans revealed significantly increased risk of presenting with a higher T-stage (T3–T4) of mycosis

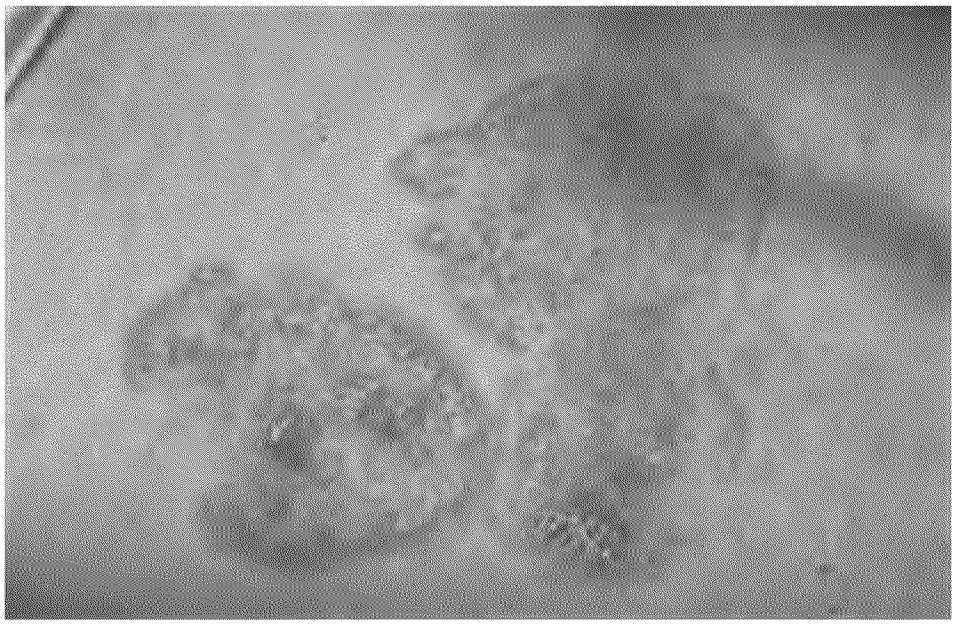
[276] Wilson, et al., "Age, race, gender, stage and the incidence of cutaneous lymphoma", Clinical Lymphoma Myeloma Leukemia. 2012, 12(5), pg. 291–296. doi:10.1016/j.clml.2012.06.010. NI

[277] Id.

fungoides with an OR of 1.72 (p=0.02), compared to Caucasians.[278] Further studies by Bradford, et al.,(2009)[279] reveal that Incident rates for mycoses fungoides were higher among African Americans than whites at 5.9 per million compared to 4.1 per million. However, for cutaneous peripheral T-cell lymphoma rates were higher among non-Hispanic whites compared to African Americans.

Figure 2: Mycosis fungoides image

(Source: https://www.skinsite.com/info_mycosis_fungoides.htm



With respect to potentially causative toxicological factors, it should be recognized that mycosis fungoides is not a common malignancy. Due to its rarity and the fact that the International Classification of Disease registry lists more than 60 different varieties of lymphoma in its ICD-10-CM Diagnosis Codes, it is not possible to determine a precise latency period specific only to mycosis fungoides.

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[278] Id.

[279] Bradford, et al., "Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases", 2009, Blood. 2009 May 21; 113(21): 5064–5073.

However, upon review of the key studies relied upon by IARC during its glyphosate carcinogenicity review, general latency year ranges with respect to glyphosate exposure are available. The IARC review methods appear to have followed objective, generally accepted assessment protocols. The IARC meetings were open, transparent and subject to comment. More than 1,000 studies were identified and screened before publishing any findings or conclusions. All participants had full access to relevant data. Fully-referenced "monographs" of findings were periodically published for download and review.[280]

With respect to real world glyphosate exposures, IARC noted similar NHL increases in different geographic regions at different times. The NHL prevalence increases corresponded to increased glyphosate usage in the same regions during the time periods noted. In the United States from 1975 to 2000, the annual age-adjusted NHL incidence rate increased more than 75% from 11.1 to 19.8 per 100,000 person-years. That is a highly significant increase as compared to other cancers. The NHL incidence rate has leveled recently (to 19.6 per 100,000 person-years) from 2003-2007, but incidence increases have also occurred in other developed countries. For example, NHL incidence rates increased across Europe from the 1960s. The cause is largely undetermined.[281]

In its glyphosate summary monograph, IARC further noted the study by Eriksson, et al., (2008) which reported the results of case-control exposures as a risk factor for NHL. The odds ratio for exposure to glyphosate was 2.02 (95% CI, 1.10-3.71) in a univariate analysis and 1.51 (95% CI, 0.77-2.94) in a multivariable analysis. When exposure for more than 10 days per year was considered, the odds ratio was 2.36 (95% CI, 1.04-5.37). With a latency period of >10 years, the odds ratio was 2.26 (95% CI, 1.16-4.40). As error rates were properly accounted for, these are statistically significant findings.

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[280] Glyphosate Monograph, IARC Monographs: Volume 112, Glyphosate Evaluation.

[281] Wheeler, et. al., "Spatial-temporal analysis of non-Hodgkin lymphoma in the NCI-SEER NHL case-control study," 2011, Environmental Health, 10:63, https://doi.org/10.1186/1476-069X-10-63

NHL Latency Estimates

There is no single peer-reviewed, generally-recognized latency range "threshold" for the more than 60 subtypes of lymphoma (Morton et al., 2014).[282] Various sources cite latency intervals ranging as high as 25 years or more. Most estimates are based upon absence of information as opposed to hard evidence. For this reason, only studies which adequately account for error rates via a 95% confidence interval (which accounts for most confounding variables) can be considered in any comparative compilation.

From the compilation of peer-reviewed latency estimates in Table 32, a surmised latency interval of *0.4 to 10 years* falls within the general estimates of the studies cited therein. Although no single study is conclusive and future studies will undoubtedly clarify this issue, the *weight of evidence* suggests that this range offers an acceptable degree of scientific credibility for purposes of an objective toxicological assessment.

[282] Morton, et. al., "Etiologic heterogeneity among non-Hodgkin lymphoma subtypes: the Inter-Lymph Non-Hodgkin Lymphoma Subtypes Project," August 2014, J Natl Cancer Inst Monogr. (48), pg. 130-44.

Table 32: Compilation of Peer-Reviewed NHL Latency Estimates

Study/Source	Summary of Findings	Latency
USEPA Glyphosate Issue Paper: September, 2016[283]	"Some have argued that the follow-up period (median=7 years) in De Roos, et al. (2005) is not sufficiently long to account for the latency of NHL (Portier, et al., 2016); however, the latency period for NHL following environmental exposures is relatively unknown and **estimates have ranged from 1-25 years** (Fontana et al., 1998; Kato et al., 2005; Weisenburger, 1992)."	1 to 25 yrs
USEPA Glyphosate Issue Paper: September, 2016[283]	"Eriksson, et al., (2008) evaluated the impact of time since first exposure. This study found an increased effect estimate for subjects with **more than 10 years of glyphosate exposure prior to diagnosis** of NHL. This finding suggests a potential for a longer latency for NHL than the follow-up period in De Roos, et al. (2005)."	10 yrs
USEPA Glyphosate Issue Paper: September, 2016[283]	"Two case-control studies evaluating the risk of NHL (Eriksson, et al., 2008 and McDuffie, et al., 2001) observed increased effect estimates in the highest exposure categories analyzed. Eriksson, et al. (2008) found a greater effect estimate for subjects with >10 days (based on the median days of exposure among controls) and >10 years of exposure (for latency analysis) when compared to subjects with =10 days and 1-10 years of exposure, respectively; … however, given the latency analysis of NHL was limited to Eriksson, et al. (2008) and lack of NHL latency understanding in general, **further studies are needed to determine the true latency of NHL**. McDuffie, et al. (2001), stratifying based on the average number of days per year of exposure, observed similar effect estimates in the lower exposure category (>0 and =2 days/year) while a greater effect estimate was observed in the highest exposure category (>2 days/year)."	10 yrs
9-11 Monitoring and Treatment, World Trade Center Health Program[284]	"**A minimum latency period of 2 years** has been reported for non-Hodgkin lymphoma (Bennett, et al. 1991) following treatment of Hodgkin disease with chemotherapy and radiotherapy which is similar to the latency for secondary acute leukemia (Nadler and Zurbenko 2013; Tucker et al. 1988)."	0.4 to 2 yrs *(minimum)*

[283] USEPA, "Glyphosate Issue Paper: Evaluation of Carcinogenic Potential," USEPA's Office of Pesticide Programs, September 12, 2016, https://www.epa.gov/sites/production/files/2016-09/documents/glyphosate_issue_paper_evaluation_of_carcincogenic_potential.pdf

[284] "Minimum Latency & Types or Categories of Cancer," World Trade Center Health Program, Revised: January 6, 2015, https://www.cdc.gov/wtc/pdfs/WTCHP-Minimum-Cancer-Latency-PP-01062015.pdf

Summary of Objective Toxicological Factors

The following represent primary considerations in formulating an objective toxicological assessment of Mr. Johnson with respect to his glyphosate exposure as reported.

- **Chronic Glyphosate Exposure:** It is clear from deposition testimony that Mr. Johnson's exposure was ongoing and consistent. "*I have sprayed gallons, thousands of gallons of this.*"[285] His reported regular penetration of glyphosate formulation through his Tyvek suit as a consequence of constant drift exposures of the liquid as well as his acute heavy soaking liquid exposures is consistent with certain Tyvek suits with known characteristic of microparticulate protection (> 1 micron).[286] However, the most common, least expensive and disposable suits such as the Tyvek 400 has limited water and vapor protection as the manufacturer refers to this as "breathability."[287] It is, therefore, accurate that glyphosate passing through the Tyvek suit mixes with natural sweat on the skin and is available for dermal absorption. Hence, Mr. Johnson's testimony of the pesticide penetrating his suit is valid.

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[285] Workman's Compensation Deposition of Mr. Johnson dated October 28, 2015, pg. 98.

[286] "DuPont Tyvek TY122S WH suit offers hooded and feet protection. This suit keeps you safe in a variety of applications. Tyvek® 400 garments are composed of flash spun high density polyethylene which creates a unique, nonwoven material available only from DuPont. Tyvek® 400 provides an ideal balance of protection, durability and comfort of any limited use fabric technology. Tyvek® 400 fabric offers an inherent barrier against particles (down to 1.0 micron in size). Protection is built into the fabric itself; there are no films or laminates to abrade or wear away. Tyvek® 400 fabric's durability advantage over microporous film fabrics delivers consistently better barrier, even after wear and abrasion. Applications include: lead and asbestos abatement/remediation, general maintenance/operations, spray painting, general clean-up. Comfort fit design based on extensive wearer input to provide our most comfortable garment design that: enables a greater range of movement while stretching and bending, provides a more tailored fit, offers reinforcement in high stress areas for fewer blowouts, utilizes a longer zipper for easier donning and doffing and an elastic waist to better position the garment. Attached respirator-fit hood with elastic around face opening, designed to cover neck and chin and fit around respirator face mask Longer zipper extends to chin for complete coverage of neck area Elastic opening for tighter fit at wrist Attached Tyvek® FC boots have special coating to provide added skid-resistance." https://www.envirosafetyproducts.com/dupont-tyvek-coveralls-with-attached-hood-boots-and-elastic-wrists-serged-seams-white-1-ea.html

[287] Tyvek, "Understanding Vapor Permeability," DuPont Corporation, http://www.dupont.com/products-and-services/construction-materials/building-envelope-systems/articles/understanding-vapor-permeability.html

- **Excessive Dose:** Mr. Johnson explained to Dr. Fishman that he sprayed 3-4 times per week at a rate of 20-50 gallons and sometimes as much as 100 gallons. Dr. Fishman states that he *"does not understand"* how Mr. Johnson was exposed to Ranger Pro in 2012 given the PPE he was wearing and deferred his opinion to an environmental hygienist. It seems the physician was either unaware of Tyvek's micro-particulate/vapor permeability or chose not to mention it in his *"no-opinion"* finding.

- **Erroneous Assessment by Attending Physician:** With respect to Mr. Johnson's mycosis fungoides diagnosis, Dr. Fishman noted in his report that males are twice as likely as females to develop mycosis fungoides and that African Americans are twice as likely to develop it. Dr. Fishman's finding of a factor-of-four increase in risk is not supported by peer-reviewed studies based on official U.S. SEER registry statistics. Dr. Fishman stated that these were *"…the only factors impacting an onset of mycosis fungoides."* Excluding glyphosate exposure as a potential causative factor is not scientifically credible in view of the totality of objective evidence.

- **Disinformation:** Mr. Johnson stated several times in testimony that he had not been exposed to Ranger Pro or Roundup or other glyphosate products until he began working at Benicia in June 2012. It is also clear from Mr. Johnson's testimony that he took only limited precautions at work as he had been specifically trained to believe that glyphosate was harmless. *"We had been trained that the glyphosate was okay enough for us to drink."*[288] His actions at the times of his various exposures are thus explicable in view of the information given to him.

- **Non-Credible Manufacturer Contentions:** It has been demonstrated in this report that Monsanto employees have attempted (knowingly or unknowingly) to minimize glyphosate's true absorption characteristics.

[288] Deposition of Dewayne Johnson dated December 8, 2017, 09:47:22

- **Dermal Absorption Rates Higher than Calculated by Monsanto:** As previously discussed in great detail, the correct dermal absorption rate for glyphosate ranges between 4.4% and 22.6% (as opposed to the 1% and 3% values published by Monsanto). Thus, exposures of applicators performing mixing and application work using hydraulic spray systems similar to that of Mr. Johnson often exceeded the accepted operator exposure level (AOEL) of 0.2 mg/kg/day (Tables 25, 29).

- **Excessive Dermal Exposure Doses:** The dermal absorption rate for glyphosate of 4.4% to 22.6% is for glyphosate only, without co-formulants. It is known that co-formulants in glyphosate-based formulations (GBF's) individually (or in combination with one other) increase dermal absorption. Based on this and upon Monsanto's own in-house expert's opinions, it is apparent that co-formulants further increase dermal absorption. However, beyond the underestimation of dermal absorption by Monsanto, there are additives within Roundup® formulations that further increase dermal absorption of glyphosate. There are numerous factors governing the rate and degree of glyphosate dermal absorption, both intrinsically and potentially. These include (a) "co-formulants" (ingredients other than the active ingredient such as detergents or anti-foam agents), (b) surfactants (compounds which lower surface tension), (c) humectants (to inhibit moisture loss) and (d) adjuvants (chemicals which modify the effect of other agents).

  The fact that Mr. Johnson was exposed to these co-formulants under these conditions (in part due to the semi-permeable Tyvek suit he wore) enhanced his absorption rate. Reports of the primary exposure events are consistent with this observation inasmuch as (a) Mr. Johnson reported that the interior of his suit was wet and (b) the Tyvek failed to completely shield Mr. Johnson's body from the herbicide. Indeed, the Tyvek served to keep the liquid (including condensed vapor) "sandwiched" against Mr. Johnson's skin and, to some degree, prevented the liquid from evaporating normally.

- **"Agricultural Health Study" (AHS) Doses Underestimated by a Factor of 4.5**: The calculated doses used in Tables 27 and 29 were referenced from the "The Agricultural Health Study" (AHS)[289] which is an ongoing cohort study which includes 89,000 farmers and their spouses from Iowa and North Carolina. Urine was collected and analyzed to determine glyphosate dose based on Monsanto's incorrect methodology stating that glyphosate is almost completely eliminated in the urine without consideration of fecal elimination. However, prior referenced studies reveal that when a dose is absorbed slowly via dermal absorption verses intravenous injection (IV), it is excreted *predominantly in the feces, not urine*. The methodology used to evaluate the applicators in the AHS cohort only measured urinary excretion and not feces.

  Thus, the AHS data is misleading and is erroneously low. Based on Monsanto's primate study,[290] the observed applicator exposure doses reported (as shown in Table 27 and 29) are off by a factor of 4.5x (not including correction for dermal absorption rates) as previously documented on pages 59-60 and Table 4 detailed within the current report. Thus, the doses in Tables 27 and 29 are actually 4.5 times higher than shown and the cancer risk levels in Table 31 are actually 4.5 times higher than shown.

- **Latency of Non-Hodgkin's Lymphoma:** The compilation of peer-reviewed latency estimates presented herein offers a surmised latency interval of *0.4 to 10 years*. This range falls within the estimates in the cited studies (see Table 32). Based upon the study findings, the *weight of available evidence* indicates that a latency interval of 0.4 to 10 years is scientifically reliable. Thus, Mr. Johnson's emergence of NHL falls within reasonable latency parameters.

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[289] Alavanja, M., et al., "The Agricultural Health Study," 1996, Environmental Health Perspectives, Vol. 104 (4), pg. 362 – 369. Retrieved from: https://aghealth.nih.gov/

[290] Wester, R. et al., "Glyphosate skin binding, absorption, residual tissue distribution and skin decontamination," 1991, Fundamental and Applied Toxicology 16, pp. 725-732.

Toxicological Conclusions

Toxicologists cannot assume a position of advocacy. A scientifically credible expert opinion is based solely on objective, reliable evidence. Additionally, analysis must be performed without deviation from the prescribed methodology. Weight of evidence must take all possible factors into account before reaching any conclusions. A strong attempt has been made to apply those principles throughout this assessment.

Based on the totality of evidence available at this time, it is my opinion to reasonable toxicological certainty that the recent IARC classification of glyphosate as a Level 2A carcinogen is appropriate. Additionally, it is my opinion to reasonable toxicological certainty that some formulations of glyphosate have greater potential for carcinogenic health risks then calculated above based on enhanced absorption by adjuvants used in the products. Glyphosate has been demonstrated to induce (but may not be limited to) lymphopoietic malignancies as supported by multiple, independent chronic dietary animal studies as well as the body of human epidemiological literature as assessed by IARC.

Mr. Dewayne Johnson was diagnosed with mycosis fungoides, an infrequently encountered, rare T-cell lymphoma, approximately 2.25 years following his frequent mixing and application of glyphosate/co-formulants for the Benicia Unified School District. His absorbed dose of glyphosate was within the range of that encountered within the generally accepted toxicological and epidemiological literature among hydraulic applicators. Mr. Johnson's medical history, family history, genetic predisposition, prior occupational chemical exposures or lifestyle risk factors do not reveal any known risk factors for lymphoma. Based on the documented and inherent properties of glyphosate to produce lymphoma in animal studies as well as the results of statistically significant human epidemiological studies, I am certain to reasonable toxicological certainty that Mr. Johnson's glyphosate exposures induced or significantly contributed to the onset of his T-cell lymphoma (mycosis fungoides).



William R. Sawyer, Ph.D., D-ABFM

Chief Toxicologist

Appendix A: Using EPA Software to Calculate Cancer Slopes

The following pages show computer-generated output from the U.S. EPA's "*Benchmark Dose Software*" (BMDS version 2.6.0.1). This is the standard computer software package provided by U.S. EPA for automated cancer slope factor calculation and statistical plotting under a variety of experimental modelling conditions.

The software-calculated cancer slope factors (CSF) for glyphosate use a very standard set of modelling parameters. CSF was derived via a linear extrapolation from the POD (point of departure), which is the 95% lower confidence limit of the dose indicated by the model as the benchmark dose (BMD). Study-reported values were applied as inputs to fulfill the required dose response data parameters. The dichotomous models in the Benchmark Dose Software were fit to the lymphoma incidence data in mice. The mice doses were used for BMD modeling. The "BMDHED" and "BMDLHED" values were calculated using "BW3/4 scaling" by applying the initial mid-point mice weights. This was done because neither final mice weights nor individual mice weights were provided in the available study data. A human body weight of 70 kg was used throughout.

The following cancer slopes were calculated based on the indicated studies:

No.	Contents	Page
1	Malignant Lymphoma in Male CD-1 Mice Exposed to Glyphosate in Diet for 80 Weeks (Wood et al., 2009b)	A-2
2	Lymphomas in Male CD-1 Mice Exposed to Glyphosate in Diet for Two Years (Sugimoto, 1997)	A-5
3	Hemangioma in male CD-1 Mice Exposed to Glyphosate in Diet for Two Years (Sugimoto, 1997)	A-8
4	Mammary Gland Tumors in Female Wister Rats Exposed to Glyphosate in Diet for 2 Years (Wood et al, 2009a)	A-11
5	Liver Adenomas in Male Wister Rats Exposed to Glyphosate in Diet for 2 Years (Brammer, 2001)	A-14
6	Pancreatic Islet Cells Adenoma in Male Sprague Dawley Rats Exposed to Glyphosate in Diet for 2 Years (Stout and Ruecker, 1990)	A-17
7	Testicular Interstitial Tumors in Male Sprague-Dawley Rats Exposed to Glyphosate in Diet for 784-785 Days (Lankas 1981)	A-20

Figure A-1
Malignant Lymphoma in Male CD-1 Mice Exposed to Glyphosate in Diet for 80 Weeks (Wood et al., 2009b)

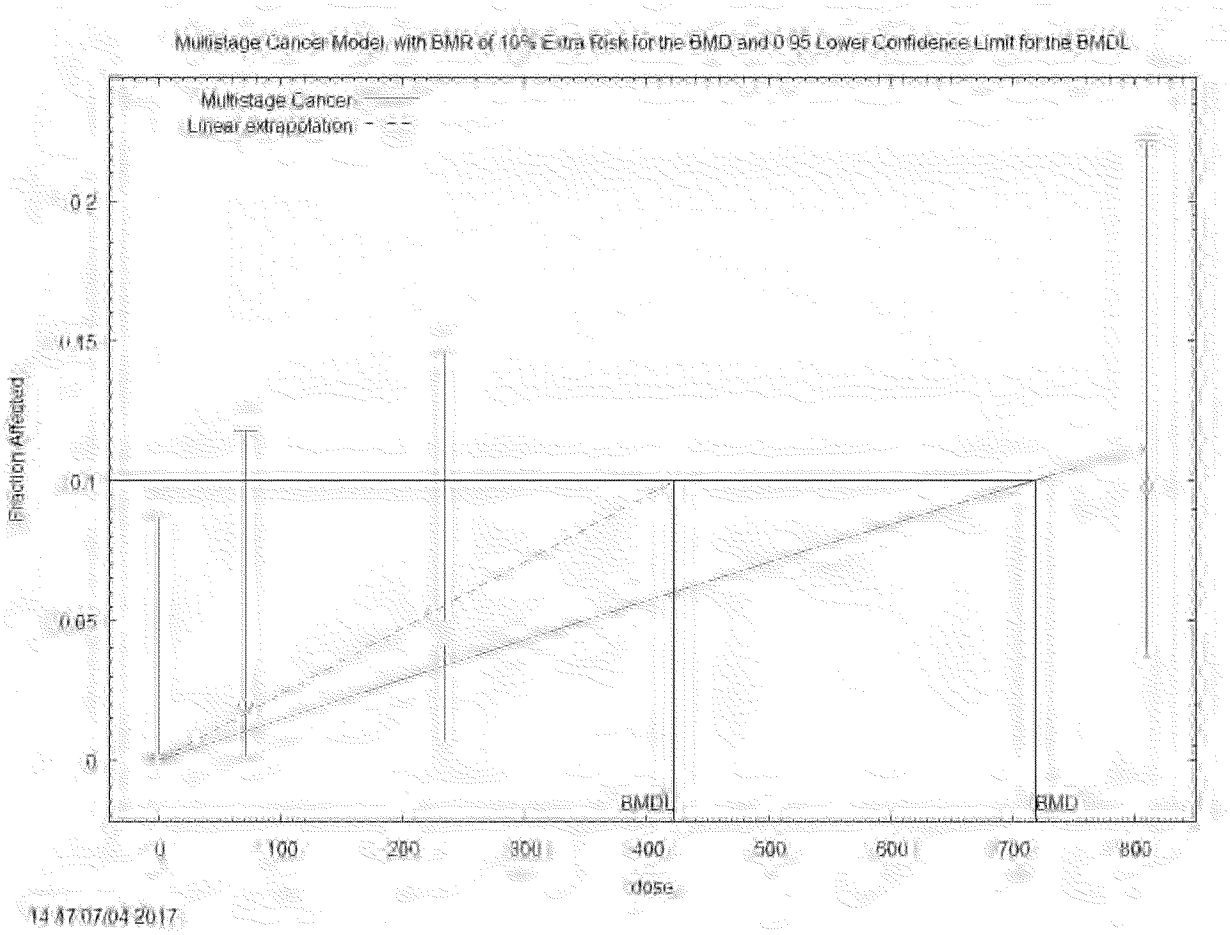


Figure A-1: Malignant lymphoma in male CD-1 mice exposed to glyphosate in diet for 80 weeks, Wood et al., 2009b

```
================================================================
        Multistage Model. (Version: 3.4  Date: 05/02/2014)
  Input Data File: C:/TCAS/BMDS2601/Data/glyphosate wood 2009/7-Wood
 et al__ 2009b glyphosate-Malignant Lymphoma-MultiCanc2-10Pct-4d.(d)
  Gnuplot Plotting File:  C:/TCAS/BMDS2601/Data/glyphosate wood 2009/7-
Wood et al__ 2009b glyphosate-Malignant Lymphoma-MultiCanc2-10Pct-4d.plt
                        Tue Jul 04 14:47:13 2017
================================================================
```

```
BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(-beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
 Degree of polynomial = 2

 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =   0.00703816
                        Beta(1) =  0.000120778
                        Beta(2) =            0

           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background    -Beta(2)
                 have been estimated at a boundary point, or have been specified by
   the user, and do not appear in the correlation matrix )

               Beta(1)

   Beta(1)            1

                                Parameter Estimates

                                                          95.0% Wald Confidence
   Interval
       Variable      Estimate     Std. Err.  Lower Conf. Limit  Upper Conf. Limit
     Background             0            NA
        Beta(1)    0.00014663  5.18611e-005       4.49837e-005        0.000248276
        Beta(2)             0            NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-29.718	4			
Fitted model	-29.958	1	0.480071	3	0.9232
Reduced model	-33.7505	1	8.06497	3	0.04469

AIC: 61.916

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	51.000	0.000
71.4000	0.0104	0.531	1.000	51.000	0.647
234.2000	0.0338	1.722	2.000	51.000	0.216
810.0000	0.1120	5.711	5.000	51.000	-0.316

Chi^2 = 0.56 d.f. = 3 P-value = 0.9045

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 718.548

BMDL = 422.73

BMDU = 2009.66

Taken together, (422.73 , 2009.66) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.000236558

Figure A-2
Lymphomas in Male CD-1 Mice Exposed to Glyphosate in Diet for Two Years (Sugimoto, 1997)

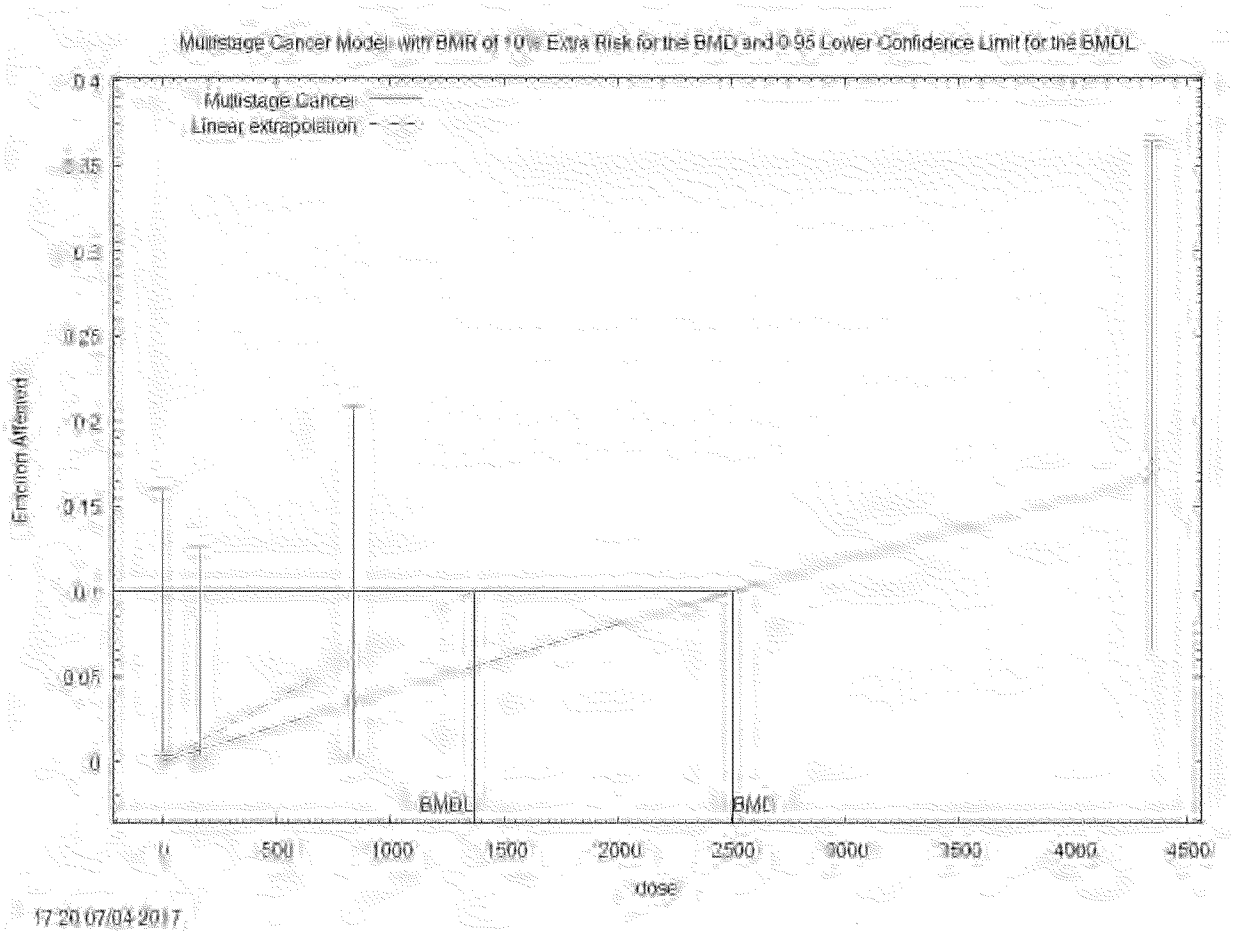


Figure A-2: Lymphomas in male CD-1 mice exposed to glyphosate in diet for two years, Sugimoto, 1997

```
================================================================================
        Multistage Model. (Version: 3.4  Date: 05/02/2014)
   Input Data File: C:/TCAS/BMDS2601/Wizard/Glyphosate/7-Sugimoto_
                    1997-Lymphoma-MultiCanc1-10Pct-4d.(d)
Gnuplot Plotting File:  C:/TCAS/BMDS2601/Wizard/Glyphosate/7-Sugimoto_
                    1997-Lymphoma-MultiCanc1-10Pct-4d.plt
                          Tue Jul 04 17:20:56 2017
================================================================================
```

```
BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =            0
                        Beta(1) = 4.41484e-005

           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been specified by
   the user, and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1

                                Parameter Estimates

                                                          95.0% Wald Confidence
   Interval
       Variable      Estimate     Std. Err.  Lower Conf. Limit  Upper Conf. Limit
     Background             0            NA
        Beta(1)  4.20439e-005  1.71844e-005       8.36305e-006       7.57247e-005

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-17.6082	4			
Fitted model	-17.8493	1	0.482235	3	0.9228
Reduced model	-23.6131	1	12.0098	3	0.00735

AIC: 37.6986

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	26.000	0.000
165.0000	0.0069	0.235	0.000	34.000	-0.487
838.1000	0.0346	0.935	1.000	27.000	0.069
4348.0000	0.1671	4.845	5.000	29.000	0.077

Chi^2 = 0.25 d.f. = 3 P-value = 0.9696

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 2505.97

BMDL = 1368.42

BMDU = 5346.74

Taken together, (1368.42, 5346.74) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 7.30769e-005

Figure A-3
Hemangioma in Male CD-1 Mice Exposed to Glyphosate in Diet for Two Years (Sugimoto, 1997)

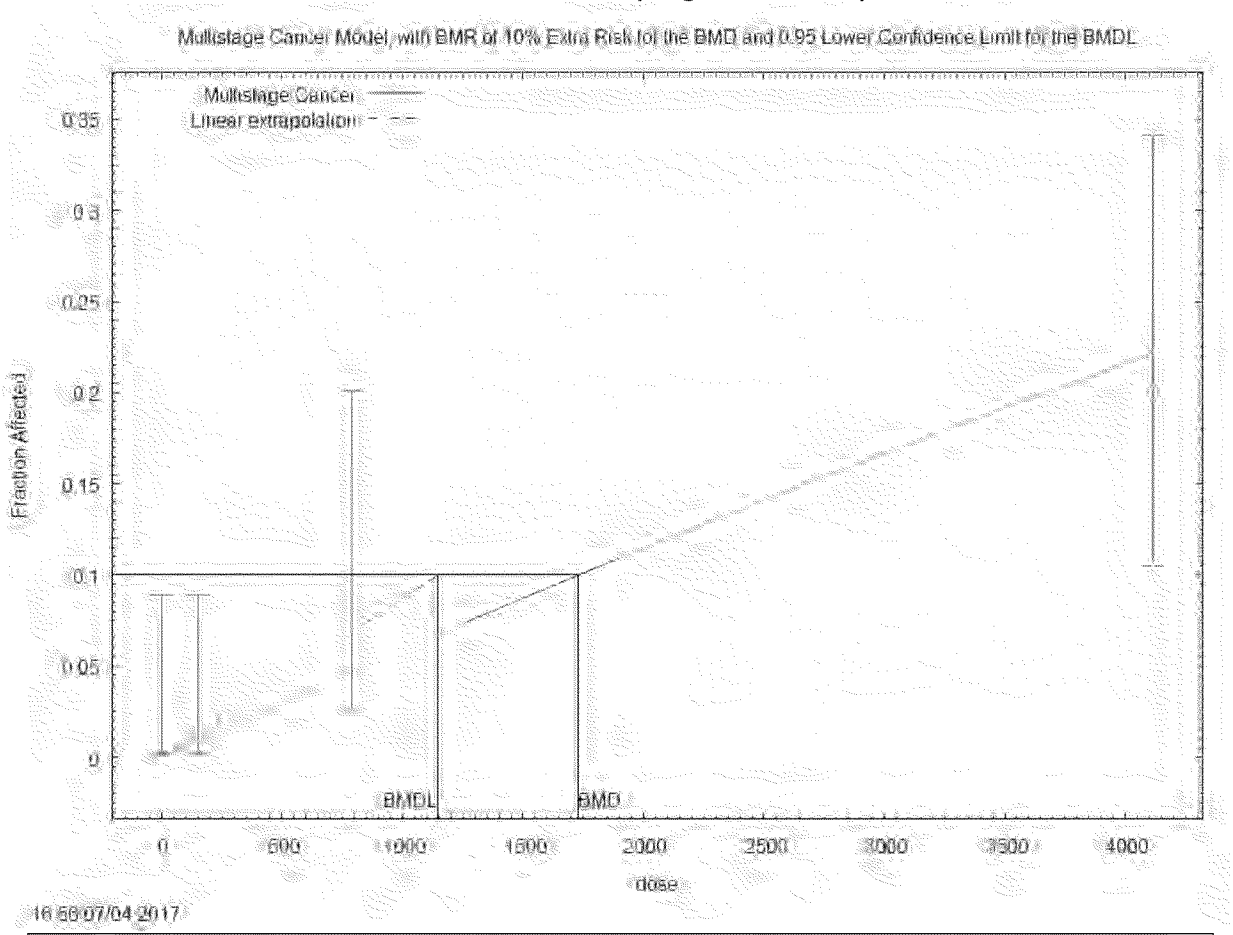


Figure A-3: Hemangioma in male CD-1 mice exposed to glyphosate in diet for two years, Sugimoto, 1997

```
=================================================================
        Multistage Model. (Version: 3.4  Date: 05/02/2014)
       Input Data File: C:/TCAS/BMDS2601/Wizard/Glyphosate/
       7-Sugimoto_ 1997-Hemangioma-MultiCanc1-10Pct-4d.(d)
    Gnuplot Plotting File:  C:/TCAS/BMDS2601/Wizard/Glyphosate/
       7-Sugimoto_ 1997-Hemangioma-MultiCanc1-10Pct-4d.plt
                    Tue Jul 04 16:56:21 2017
=================================================================
```

```
BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =    0.0092153
                        Beta(1) = 5.33016e-005

           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -Background
                 have been estimated at a boundary point, or have been specified by
   the user, and do not appear in the correlation matrix )

                Beta(1)

   Beta(1)            1

                                Parameter Estimates

                                                        95.0% Wald Confidence
   Interval
       Variable      Estimate     Std. Err.  Lower Conf. Limit  Upper Conf. Limit
     Background             0            NA
        Beta(1)  6.09293e-005   1.6315e-005       2.89526e-005        9.2906e-005

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-38.9586	4			
Fitted model	-40.0094	1	2.10168	3	0.5516
Reduced model	-50.7278	1	23.5384	3	<.0001

AIC: 82.0189

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	50.000	0.000
153.2000	0.0093	0.465	0.000	50.000	-0.685
786.8000	0.0468	2.340	4.000	50.000	1.111
4116.0000	0.2218	11.091	10.000	50.000	-0.371

Chi^2 = 1.84 d.f. = 3 P-value = 0.6060

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1729.23

BMDL = 1146.93

BMDU = 2782.4

Taken together, (1146.93, 2782.4) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 8.71892e-005

Figure A-4
Mammary Gland Tumors in Female Wister Rats Exposed to Glyphosate in Diet for 2 Years (Wood et al, 2009a)

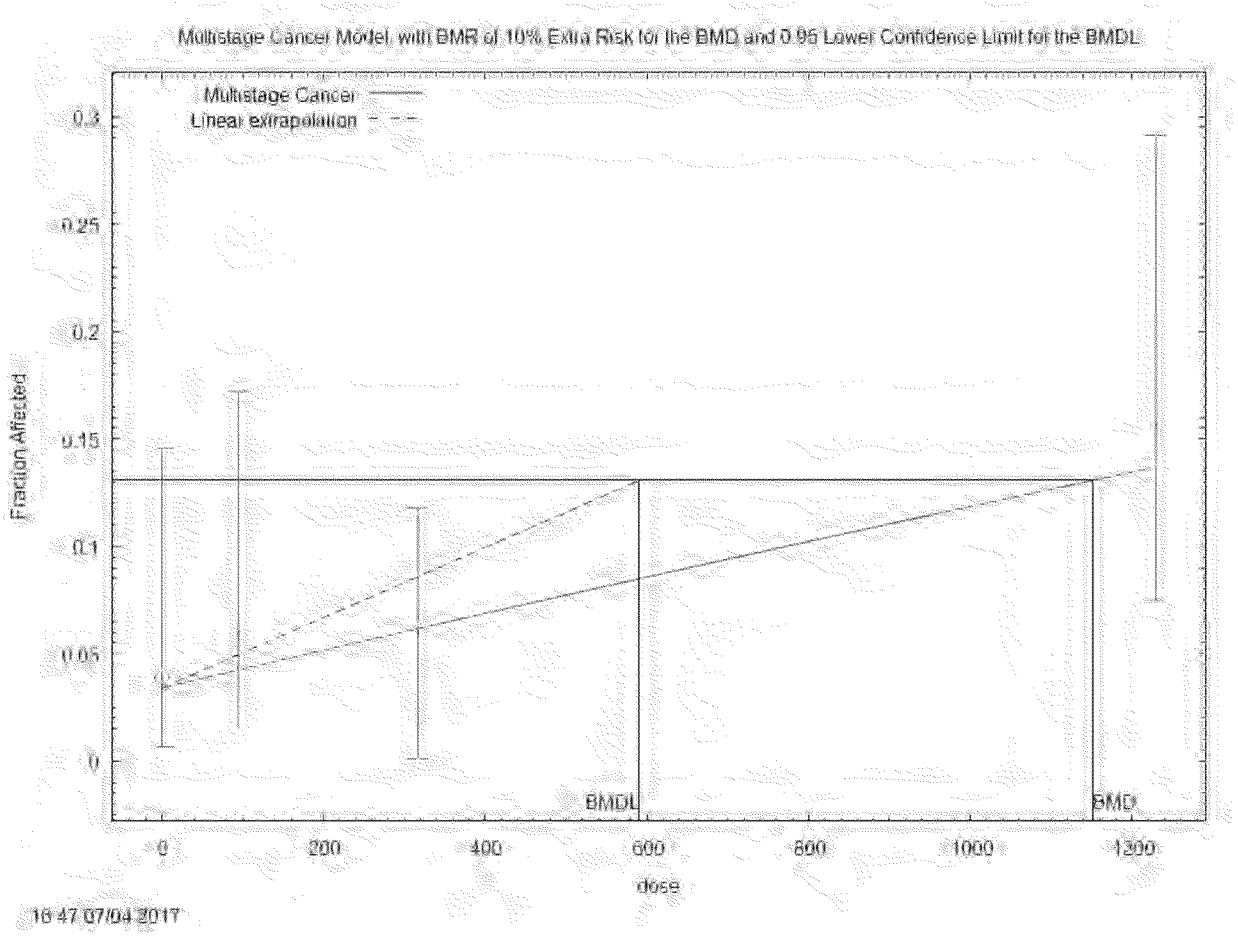


Figure A-4: Mammary gland tumors in female Wister rats exposed to glyphosate in diet for 2 years, Wood et al. 2009a

```
================================================================
        Multistage Model. (Version: 3.4  Date: 05/02/2014)
       Input Data File: C:/TCAS/BMDS2601/Wizard/Glyphosate/
 7-Wood et al__ 2009a-Mammary Gland Tumors-MultiCanc1-10Pct-4d.(d)
   Gnuplot Plotting File:  C:/TCAS/BMDS2601/Wizard/Glyphosate/
 7-Wood et al__ 2009a-Mammary Gland Tumors-MultiCanc1-10Pct-4d.plt
                    Tue Jul 04 16:47:02 2017
================================================================
```

```
BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                -beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =    0.0280282
                        Beta(1) =  0.000108031

           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.45

   Beta(1)        -0.45            1

                                Parameter Estimates

                                                        95.0% Wald Confidence
   Interval
      Variable      Estimate     Std. Err.  Lower Conf. Limit  Upper Conf. Limit
    Background     0.0340885     0.0173758       3.25953e-005          0.0681444
       Beta(1)  9.14996e-005   4.5833e-005       1.66846e-006        0.000181331
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-46.9252	4			
Fitted model	-48.2259	2	2.60148	2	0.2723
Reduced model	-51.0151	1	8.17987	3	0.04244

AIC: 100.452

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0341	1.739	2.000	51.000	0.202
95.0000	0.0424	2.165	3.000	51.000	0.580
316.9000	0.0617	3.146	1.000	51.000	-1.249
1229.7000	0.1369	6.981	8.000	51.000	0.415

Chi^2 = 2.11 d.f. = 2 P-value = 0.3482

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1151.49

BMDL = 590.749

BMDU = 4185.77

Taken together, (590.749, 4185.77) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.000169277

Figure A-5
Liver Adenomas in Male Wister Rats Exposed to Glyphosate in Diet for 2 Years (Brammer, 2001)

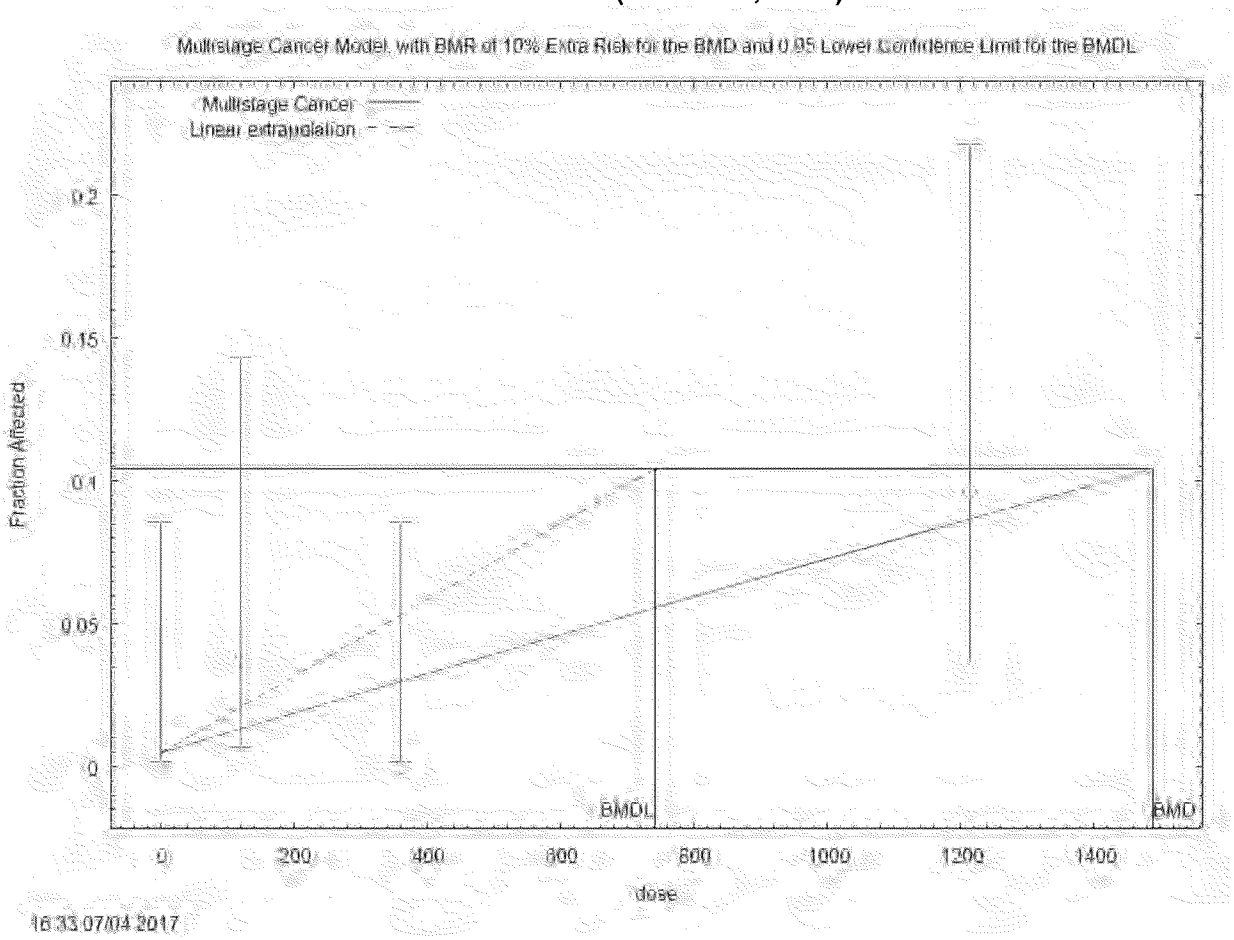


Figure A-5: Liver adenomas in male Wister rats exposed to glyphosate in diet for 2 years. Brammer, 2001

```
================================================================================
        Multistage Model. (Version: 3.4  Date: 05/02/2014)
    Input Data File: C:/TCAS/BMDS2601/Data/glyphosate wood 2009/
       7-Brammer_ 2001-Liver Adenomas-MultiCanc1-10Pct-4d.(d)
Gnuplot Plotting File:  C:/TCAS/BMDS2601/Data/glyphosate wood 2009/
       7-Brammer_ 2001-Liver Adenomas-MultiCanc1-10Pct-4d.plt
                    Tue Jul 04 16:33:17 2017
================================================================================
```

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BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =   0.00303517
                        Beta(1) = 7.55647e-005

           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.59

   Beta(1)        -0.59            1

                                Parameter Estimates

                                                        95.0% Wald Confidence
   Interval
      Variable      Estimate     Std. Err.  Lower Conf. Limit  Upper Conf. Limit
    Background    0.00482209     0.0113824          -0.017487          0.0271312
       Beta(1)  7.07342e-005  3.81234e-005      -3.98623e-006        0.000145455
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-24.9378	4			
Fitted model	-27.6285	2	5.38154	2	0.06783
Reduced model	-30.6223	1	11.369	3	0.009889

AIC: 59.2571

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0048	0.251	0.000	52.000	-0.502
121.0000	0.0133	0.692	2.000	52.000	1.583
361.0000	0.0299	1.555	0.000	52.000	-1.266
1214.0000	0.0867	4.509	5.000	52.000	0.242

Chi^2 = 4.42 d.f. = 2 P-value = 0.1096

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 1489.53

BMDL = 742.769

BMDU = 5308.29

Taken together, (742.769, 5308.29) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.000134631

Figure A-6
Pancreatic Islet Cells Adenoma in Male Sprague Dawley Rats Exposed to Glyphosate in Diet for 2 Years (Stout and Ruecker, 1990)

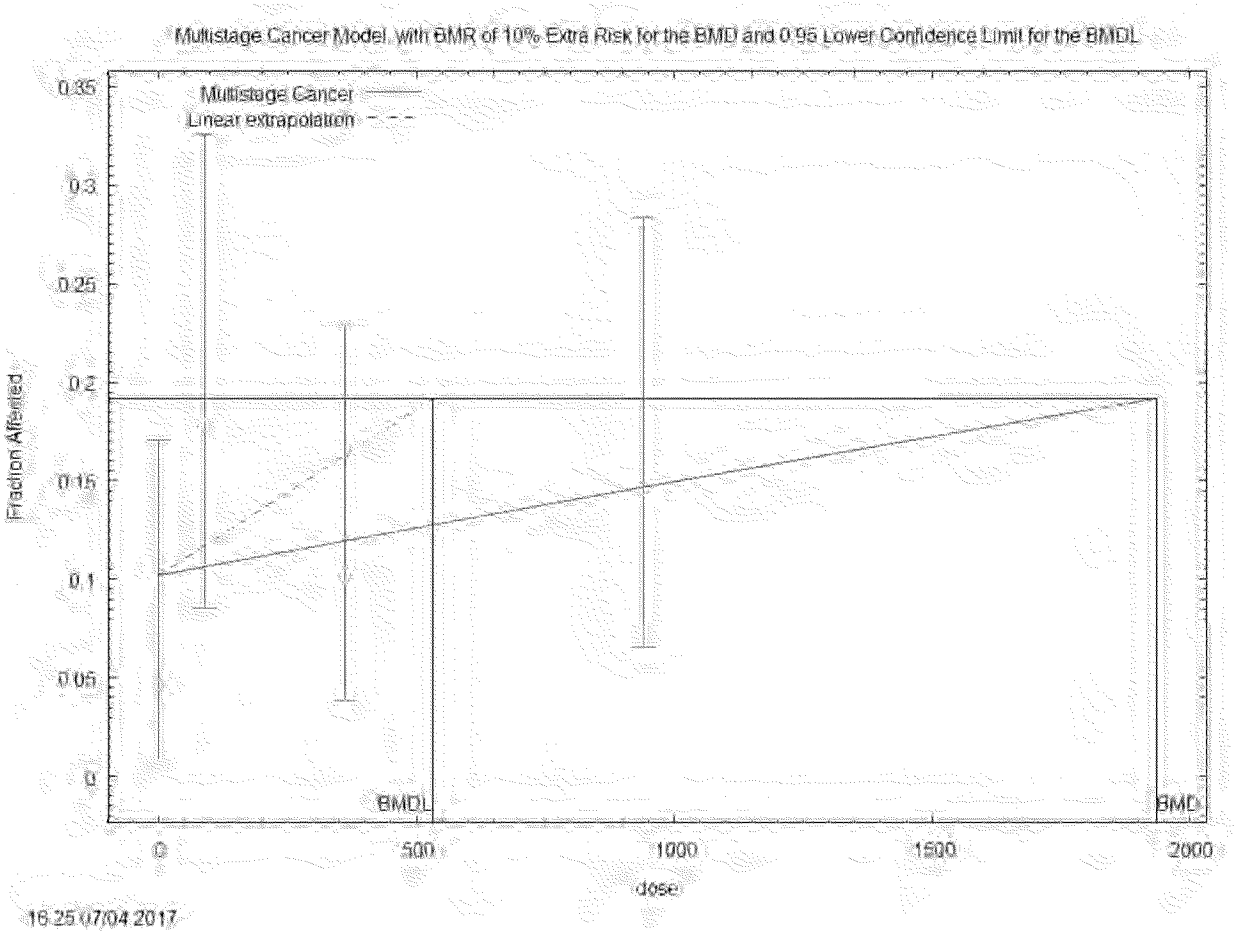


Figure A-6: Pancreatic islet cells adenoma in male Sprague Dawley rats exposed to glyphosate in diet for 2 years, Stout and Ruecker, 1990

```
=================================================================
        Multistage Model. (Version: 3.4  Date: 05/02/2014)
   Input Data File: C:/TCAS/BMDS2601/Data/glyphosate wood 2009/7-Stout
  and Ruecker_ 1990-Pancreatic Islet Cells Adenoma-MultiCanc1-10Pct-4d.(d)
Gnuplot Plotting File:  C:/TCAS/BMDS2601/Data/glyphosate wood 2009/7-Stout
  and Ruecker_ 1990-Pancreatic Islet Cells Adenoma-MultiCanc1-10Pct-4d.plt
                      Tue Jul 04 16:25:26 2017
=================================================================
```

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BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =     0.103535
                        Beta(1) = 5.13653e-005

           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1        -0.67

   Beta(1)        -0.67            1


                                Parameter Estimates

                                                        95.0% Wald Confidence
   Interval
      Variable      Estimate     Std. Err.  Lower Conf. Limit  Upper Conf. Limit
    Background      0.101588     0.0324986          0.0378924           0.165284
       Beta(1)  5.44275e-005  7.92176e-005       -0.000100836        0.000209691
```

```
                    Analysis of Deviance Table

      Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model        -65.2367         4
   Fitted model        -67.2273         2       3.98124      2          0.1366
  Reduced model        -67.4816         1       4.48991      3          0.2132

          AIC:         138.455


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size        Residual
  ---------------------------------------------------------------------------
    0.0000     0.1016         4.368     2.000      43.000       -1.195
   89.0000     0.1059         4.767     8.000      45.000        1.566
  362.0000     0.1191         5.837     5.000      49.000       -0.369
  940.0000     0.1464         7.027     7.000      48.000       -0.011

 Chi^2 = 4.02      d.f. = 2        P-value = 0.1341


   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =         1935.8

            BMDL =        530.775


BMDU did not converge for BMR = 0.100000
BMDU calculation failed
            BMDU = Inf
```

Figure A-7
Testicular Interstitial Tumors in Male Sprague-Dawley Rats Exposed to Glyphosate in Diet for 784-785 Days (Lankas 1981)

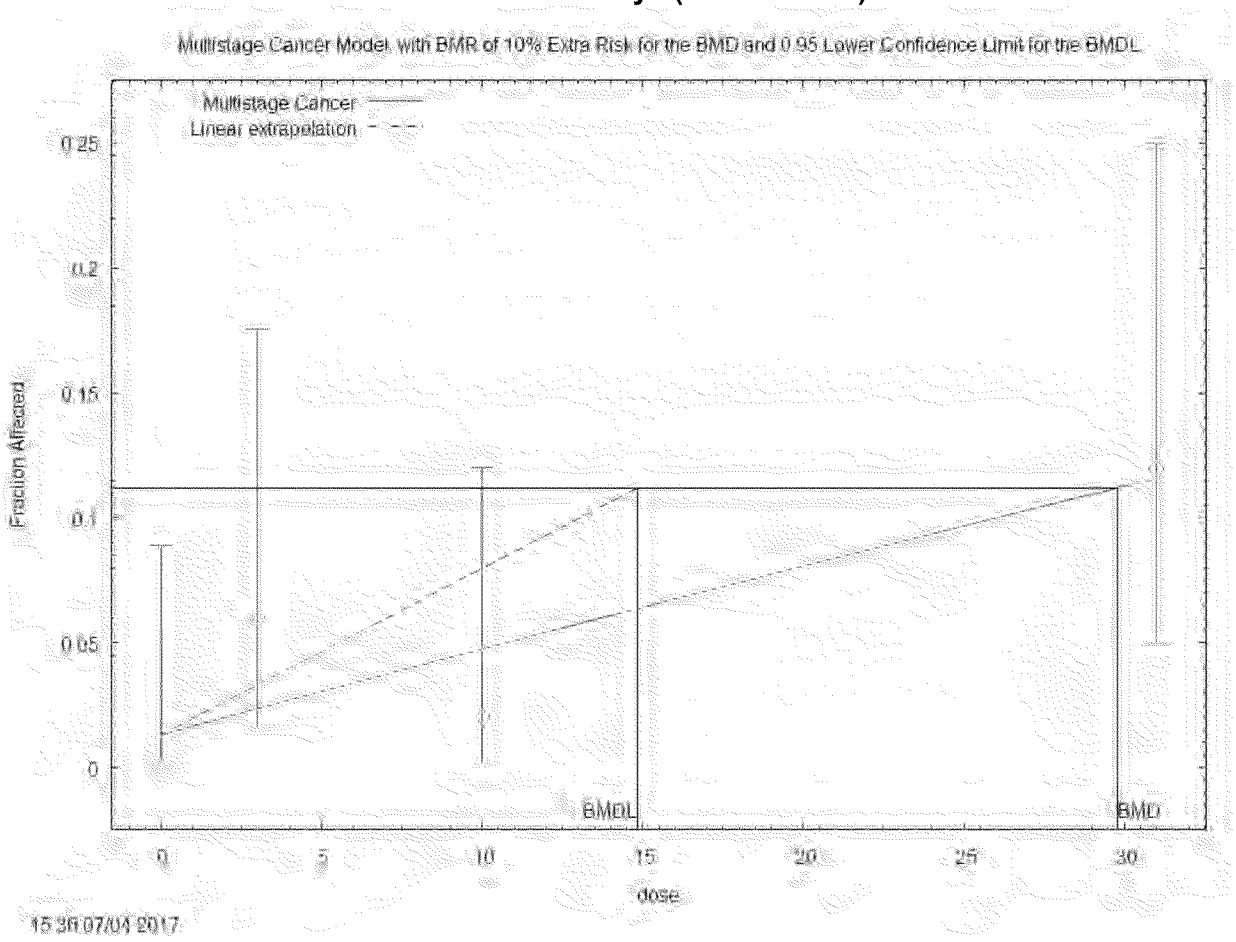


Figure A-7: Testicular interstitial tumors in male Sprague-Dawley rats exposed to glyphosate in diet for 784-785 days, Lankas 1981

```
================================================================================
        Multistage Model. (Version: 3.4  Date: 05/02/2014)
    Input Data File: C:/TCAS/BMDS2601/Data/glyphosate wood 2009/
7-Lankas 1981-Testicular Interstitial Tumors-MultiCanc1-10Pct-4d.(d)
 Gnuplot Plotting File:  C:/TCAS/BMDS2601/Data/glyphosate wood 2009/
7-Lankas 1981-Testicular Interstitial Tumors-MultiCanc1-10Pct-4d.plt
                    Tue Jul 04 15:36:01 2017
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```

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BMDS_Model_Run
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   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1)]

   The parameter betas are restricted to be positive

   Dependent variable = Incidence
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 2
 Total number of specified parameters = 0
 Degree of polynomial = 1

 Maximum number of iterations = 500
 Relative Function Convergence has been set to: 1e-008
 Parameter Convergence has been set to: 1e-008

                  Default Initial Parameter Values
                     Background =    0.0140572
                        Beta(1) =   0.00348372

           Asymptotic Correlation Matrix of Parameter Estimates

             Background      Beta(1)

Background            1         -0.6

   Beta(1)         -0.6            1

                                Parameter Estimates

                                                        95.0% Wald Confidence
   Interval
      Variable      Estimate     Std. Err.  Lower Conf. Limit  Upper Conf. Limit
    Background      0.013197     0.0158843         -0.0179357          0.0443297
       Beta(1)    0.00353628    0.00182841      -4.73309e-005         0.00711989
```

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-34.5966	4			
Fitted model	-36.8074	2	4.42156	2	0.1096
Reduced model	-39.703	1	10.2129	3	0.01684

AIC: 77.6147

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0132	0.660	0.000	50.000	-0.818
3.0000	0.0236	1.181	3.000	50.000	1.695
10.0000	0.0475	2.374	1.000	50.000	-0.914
31.0000	0.1157	5.783	6.000	50.000	0.096

Chi^2 = 4.38 d.f. = 2 P-value = 0.1116

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 29.7942

BMDL = 14.8213

BMDU = 107.093

Taken together, (14.8213, 107.093) is a 90 % two-sided confidence interval for the BMD

Cancer Slope Factor = 0.00674706

Appendix B: Curriculum Vitae of Dr. William R. Sawyer

Introduction

Dr. William Sawyer is a professional toxicologist with a doctorate in toxicology from Indiana University School of Medicine. He is a diplomate of the American Board of Forensic Medicine with more than 28 years of experience in public health and forensic toxicology including five years of governmental service. His specialized areas of expertise include causation analyses (defendant, plaintiff or criminal), dioxins, solvents, heavy metals, petroleum, crude oil, radionuclides/NORM, alcohol toxicology, drugs-of-abuse, pharmaceuticals, herbal products and other substances.

Contact Information

Toxicology Consultants & Assessment Specialists, LLC (*TCAS, LLC*)
6450 Pine Avenue
Sanibel, Florida 33957

Toxicology Consultants & Assessment Specialists, LLC (*TCAS, LLC*)
29 Fennell Street
Skaneateles, New York 13152

Telephone: 800-308-0080
239-472-2436 (FL)
315-685-2345 (NY)

E-mail: drsawyer@experttoxicologist.com

Education

Indiana University School of Medicine 1983 - 1988
Indianapolis, Indiana
Robert B. Forney, Ph.D., Committee Chairman
Ph.D., Toxicology, 1988

State University of New York at Geneseo 1979 -1982
Edward Ritter, Ph.D., Committee Chairman
Master of Science degree, Cellular & Molecular Biology, 1982

State University of New York at Geneseo Bachelor of Science degree, Biology, 1978	1976 -1978
State University of New York Agricultural and Technical College at Morrisville Associate degree, 1976	1974 -1976

Experience

As a scientist and communicator in forensic toxicology, Dr. Sawyer provides services to governmental agencies, corporations, investigators and select defendants or plaintiffs. Dr. Sawyer currently serves as chief toxicologist for Toxicology Consulting and Assessment Specialists, LLC. He has served for 23 years as an assistant professor (adjunct) with the Department of Medicine, Upstate Medical University, Syracuse, New York. Dr. Sawyer also has approximately 14 years of experience as a licensed clinical and environmental laboratory director in several states.

Dr. Sawyer routinely provides impartial toxicological evaluations involving chemical exposures, alcohol ingestion, intentional poisonings, carcinogens, pharmaceuticals, pyrolysis products, heavy metals, organic chemicals and drugs-of-abuse in civil and criminal litigation. Toxic exposure investigations include analytical protocol, referral of autopsy material for analyses, environmental and occupational health risk assessments and site assessment and causation determination. Final work products that include scientific methods and validation, forensic documentation and written reports used on both forensic and routine (non-judicial) assessments are provided to multiple, nationwide clients.

Forensic Environmental and Laboratory Analyses

Through education, training and experience, Dr. Sawyer has gained extensive expertise in forensic petroleum analyses as well as environmental and clinical forensic analyses. With more than 23 years of laboratory experience, Dr. Sawyer has directed laboratory analyses, sampling protocol and chain-of-custody documentation in criminal and civil matters. He has also provided petroleum spill assessments to multiple clients including governmental environmental agencies (NYSDEC), various state attorney general offices (New York), defense and plaintiff law firms and industry. Petroleum spill and exposure

assessment reports have provided objective evidence of characterization, age and source within reasonable scientific certainty.

Professional Experience

Chief Toxicologist 1990-Present
Toxicology Consultants & Assessment Specialists, LLC
Sanibel, Florida
Registered, DBA, 1990
Incorporated, January, 1994 (New York)
Limited liability corporation, January 2009 (Florida)

Peer Reviewer 1998-Present
Editorial Advisory Board for the "The Forensic Examiner"

Assistant Professor (adjunct) 1988-2012
SUNY Upstate Medical University
Department of Medicine
Syracuse, New York

Laboratory Director 1993-2002
EXPRESSLAB, Inc. (Lozier Laboratories)
Middlesex, New York

- NYSDOH Clinical License #SAWYW1 (1988-2000)
- NYS Environmental License (ELAP) #11369
- National Environmental Laboratory Accreditation Program (NELAP) #11369
- New Jersey DEPE License #73744
- South Carolina License #9101100
- California Environmental License

Associate Editor 1997-2000
Practical Reviews in Forensic Medicine & Sciences
Published by Oakstone Medical Publishing, Inc.
Jointly sponsored by Albert Einstein College of Medicine
and Montefiore Medical Center; CME
(continuing medical education) accredited

Toxicologist 1988-1993
Onondaga County Department of Health
Syracuse, New York

Responsible for municipal and civil risk assessment, evaluation of environmental exposures and design and execution of environmental monitoring studies. Advise and communicate with the Office of the Environment/County Executive and legislative subcommittees with respect to public health and environmental health issues. Established a clinical and environmental toxicology laboratory licensed under the NYS DOH and NYS ELAP agencies (NYSDOH #SAWYW1 and NY ELAP license #10183)

Licensed Laboratory Director 1988-1993
Onondaga County Department of Health
Syracuse, New York
Licensed clinical laboratory, chlorinated hydrocarbons (NYS CLEU)
NYS License #SAWYW1
Assistant Director
NYS ELAP License #10183

Analytical Toxicologist (part-time) 1983-1988
State Department of Toxicology
Indianapolis, Indiana

Laboratory Technician (part-time) 1979-1983
Clinical Research Center
(National Institute of Health)
Strong Memorial Hospital
Rochester, New York

Laboratory Technician (part-time) 1979-1983
Highland Hospital
Special Determinations Laboratory
Rochester, New York

Certifications

Board Certification Diplomate, American Board of Forensic Medicine (D-ABFM)	1996-Present
Board Certification Diplomate, American Board of Forensic Examiners (D-ABFE)	1994-Present
OSHA 29 CFR1910.120 Hazardous Waste Operations & Emergency Response 40 hour certified	Re-certified December 2004
Clinical Laboratory Director New York State Department of Health Certificate of Qualification License Code #SAWYW1	Inactive
Environmental Laboratory Director New York State Department of Health ELAP License #11369 ELAP License #10183	Inactive
South Carolina Department of Health Environmental Laboratory Director ELAP License #9101100	Inactive
New Jersey DEPE Laboratory Director License #73744	Inactive
Asbestos Inspector EPA Certificate #10-111-50-1303	Inactive

Societies and Honors

Sigma Xi, The Scientific Research Society Associate Member	1986- Present

American College of Forensic Examiners Member	1995-Present
National Myositis Association Medical Advisory Board Member	1995-1997
American Academy of Forensic Sciences Member, promoted to Fellow, 1998	1985-Present
Society of Automotive Engineering Member	1986-Present
International Association of Forensic Toxicologists Member	1985-Present
Sigma Xi Research Competition Fifth place	1987
Sigma Pi Alpha Scholastic Honor Society Academic Award	1984

Professional Presentations

Sawyer, W.R. and Rigle, D.A., Featured continuing medical education credit workshop (2.00 credit hours) entitled, "Fundamentals of Medical Toxicology," Annual Scientific Meeting of The American College of Forensic Examiners, American Board of Forensic Medicine, Las Vegas, Nevada, October 24 – October 27, 2000.

Sawyer, W.R. and Rigle, D.A., Featured continuing medical education credit workshop (3.75 credit hours) entitled, "Forensic Medicine Toxicology," and "Reactive Airways Dysfunction Syndrome (RADS)," Annual Scientific Meeting of The American College of Forensic Examiners for the American Board of Forensic Medicine, New York, New York, October 29 - November 1, 1999.

Sawyer, W.R. and Rigle, D.A., "The Medical Aspects of Toxic Exposure Assessments," Annual Scientific Meeting of The American Board of Forensic Medicine and The American College of Forensic Examiners, Naples, Florida, October 12-14, 1998.

Sawyer, W.R. and Rigle, D.A., “Evaluating Toxic Exposures after Daubert," Featured presentation at the 4th Annual National Expert Witness & Litigation Seminar, Hyannis, Massachusetts, June 23, 1995.

Articles, Abstracts, Treatises and Editorial Publications

Sawyer, W.R. *"Alcohol Content of Beer and Malt Beverages: Forensic Considerations,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 6, February 2000, Oakstone Medical Publishing, Inc. from Logan, B.K., et al., Journal of Forensic Sciences, November 1999, Vol. 44, No. 6, pg. 1292-1295.

Sawyer, W.R. *"Fulminant Liver Failure in a Young Child Following Repeated Acetaminophen Overdosing,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 6, February 2000, Oakstone Medical Publishing, Inc. from Bauer, M, et al., Journal of Forensic Sciences, November 1999, Vol. 44, No. 6, pg. 1299-1303.

Sawyer, W.R. *"Exposure to Contaminated Milk Presents 'Difficult Case' for Application of Daubert Reliability Standard,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 4, December 1999, Oakstone Medical Publishing, Inc. published in Expert Testimony, Evidence, & Trial Consultants, October 1999, Vol. 7, Issue 10, pg. 3.

Sawyer, W.R. *"The Extent of Postmortem Drug Redistribution in a Rat Model,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 4, December 1999, Oakstone Medical Publishing, Inc. from Hilberg, M.D., et al., Journal of Forensic Sciences, September 1999, Vol. 44 No. 5, pg. 956-62.

Sawyer, W.R. *"Potassium Nitrite Reaction with 11-Nor-Delta9-Tetrahydrocannabinol-9-Carboxylic Acid in Urine in Relation to the Drug Screening Analysis,"* (Special Article Review Presentation, Critical Assessment and Original Abstract), Practical Reviews in Forensic Medicine and Sciences, Vol. 2., No. 3, November 1999, Oakstone Medical Publishing, Inc. from Lewis, S.A., Journal of Forensic Sciences, September 1999, Vol. 44 No. 5, pg. 951-55.

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Personal Information

Dr. Sawyer is a member of the Gulf Coast Swim Team as a distance swimmer and completed several "*Swim Around Key West"* 12.5 mile ocean swim races in under six hours. He is also a triathlete with the distinction of being a four-time Ironman. He loves to fish and SCUBA dive in northern New York State and the Gulf of Mexico.

Place of Birth:	Webster, New York
Citizenship:	United States
Marital Status:	Married, 1989

Exhibit 9

Effects of Surfactants on the Toxicitiy of Glyphosate, with Specific Reference to RODEO

Submitted to:

Leslie Rubin, COTR
Animal and Plant Health Inspection Service (APHIS)
Biotechnology, Biologics and Environmental Protection
Environmental Analysis and Documentation
United States Department of Agriculture
Suite 5A44, Unit 149
4700 River Road
Riverdale, MD 20737

Task No. **5**
USDA Contract No. **53-3187-5-12**
USDA Order No. **43-3187-7-0028**

Prepared by:

Gary L. Diamond
Syracuse Research Corporation
Merrill Lane
Syracuse, NY 13210

and

Patrick R. Durkin
Syracuse Environmental Research Associates, Inc.
5100 Highbridge St., 42C
Fayetteville, New York 13066-0950

Telephone: (315) 637-9560
Fax: (315) 637-0445
CompuServe: 71151,64
Internet: SERA@interserv.com

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EXECUTIVE SUMMARY

Rodeo is an aqueous solution of the isopropyl amine salt of glyphosate. The manufacturer recommends use of a nonionic surfactant with all applications of Rodeo to improve efficacy. Surfactant formulations that are used with Rodeo include:

Agri-Dex (Setre Chemical Co.)
LI 700 (Loveland Industries, Inc.)
R-11 (Wilbur-Ellis Co.)
Latron AG-98 (Rohm and Haas Co.)
Latron AG-98 AG (Rohm and Haas Co.)

This report describes the components of the above surfactant formulations and notes those components that are listed in the U.S. EPA List of Inert Ingredients in Pesticides. All of the formulations are chemical mixtures and must be considered as mixtures in toxicity assessments. In this context, an assessment of the specific surfactants in any of the formulations or generalizations about the toxicology of surfactants as a group may not apply to the formulations. This consideration places extreme importance on data regarding the toxicity of the formulations themselves. The lack of such data will render any predictions about the effects of the formulations on glyphosate highly uncertain.

Based on the results of searches of the published literature and the Toxic Substances Control Act Test Submission (TSCATS) database, little data are available regarding the toxicity of the surfactant formulations. The available data on the formulations consist of acute lethality studies of LI 700 in rats and rabbits; dermal and eye irritation studies of LI 700 in rabbits; aquatic toxicity studies of LI 700, R-11 and Agri-Dex in fish and invertebrates; and a study of the effects of Triton AG-98 (Latron AG-98) on the fungus *Mucor mucedo* (*Mucor* rot). These studies indicate that the aquatic toxicity potency of R-11 may be considerably greater (10 to 50 times greater) than that of LI 700 and Agri-Dex.

The lack of toxicology studies of the surfactant formulations makes it difficult to predict what effects, if any, the formulations may have on the toxicity of Rodeo. The toxicologies of some of the surfactants in the various formulations were studied (summaries are provided in this report); however, the studies alone do not provide a basis for predicting either the toxicity of the formulations or their effects on the toxicity of Rodeo.

Information regarding the surfactants in the glyphosate formulations Roundup and Roundup Pro is summarized in this report; the summary was extracted from the draft report, *Selected Commercial Formulations of Glyphosate - Accord, Rodeo, Roundup and Roundup Pro. Risk Assessment Final Report,* prepared for USDA by Syracuse Environmental Research Associates (SERA, 1996). There is some uncertainty in the interpretation of the toxicity data on Roundup with respect to the potential significance of the surfactant; however, since the available toxicity data on Roundup are adequate for identifying toxic thresholds, the

uncertainty regarding the surfactant is a relatively minor one. There is much less toxicological information available on Roundup Pro and the surfactant used in Roundup Pro. Based on a comparison of the available toxicity data on Roundup Pro with corresponding data on Roundup, it appears that these two formulations will have similar toxicological properties, although Roundup Pro may be somewhat less irritating to the skin and eyes.

A major qualitative difference between the effect of glyphosate and glyphosate formulations on aquatic and terrestrial organisms concerns the surfactant used in Roundup. The surfactant is much more toxic than glyphosate to aquatic organisms. Unlike glyphosate, the surfactant is more toxic in alkaline water than in acidic water. Thus, the relative potency of the surfactant with respect to glyphosate is pH dependent. There is relatively little information regarding the toxicity of Roundup Pro to aquatic species. Nonetheless, the acute lethal potencies of Roundup and Roundup Pro are similar.

1. INTRODUCTION

Rodeo is an aqueous solution of the isopropyl amine salt of glyphosate. The manufacturer recommends use of a nonionic surfactant with all applications of Rodeo to improve efficacy. Surfactant formulations that are used with Rodeo include:

Agri-Dex (Setre Chemical Co.)
LI-700 (Loveland Industries, Inc.)
R-11 (Wilbur-Ellis Co.)
Latron AG-98 (Rohm and Haas Co.)
Latron AG-98 AG (Rohm and Haas Co.)

All of the above formulations are mixtures containing various surfactants and other ingredients (e.g., solvents, antifoam compounds).

The term *surfactant* refers to chemicals that have pronounced surface activity in aqueous solutions. Surface activity derives from the orientation of hydrophillic and hydrophobic groups within the surfactant molecule which yield oriented films at the aqueous boundaries that can decrease surface tension. In the formulations listed above, the hydrophillic portion of the surfactants consists of an oxyethyl polymer or, in one of the surfactants in LI-700, a choline phosphate ester of glycerol. Surfactant hydrophobicity is derived from saturated hydrocarbon chains of various length and linkages to the hydrophillic group. With the exception of phosphatidylcholine choline, all of the surfactants are nonionic.

The following general issues must be considered in an assessment of the effects of surfactant formulations on the toxicity of glyphosate:

1. The formulations are chemical mixtures and must be considered as mixtures in toxicity assessments. In this context, an assessment of the specific surfactants in any of the formulations or generalizations about the toxicology of surfactants as a group may not apply to the formulations. This consideration places extreme importance on data regarding the toxicity of the formulations themselves. The lack of such data will render any predictions about the effects of the formulations on glyphosate highly uncertain.

2. The same structural characteristics that produce surface activity in aqueous solutions allow surfactants to interact with biological membranes which are, in themselves, oriented films of surfactants, mainly, lipid phosphatides (Edidin and Sessions 1983). Thus, surfactants can be expected to interact with and perturb the structure, physical properties, and function of membranes. The degree to which these interactions occur depends on the physical and chemical properties of the surfactant (Caux et al. 1993, Wax et al. 1994). The wide range of possible effects of such interactions makes it extremely difficult to predict, with any certainty, the toxicity of surfactants or their

effects on the disposition or toxicity of other chemicals based on structural, mechanistic, or theoretical considerations alone. This point underscores the importance of toxicity assays (e.g., acute, chronic, different routes) in predicting the toxicity of the surfactants on humans or other species or the effects of the surfactants on the toxicity of glyphosate.

3. Possible mechanisms by which the surfactants might exert biological effects or affect the toxicity of glyphosate include: decreasing surface tension (Ernst and Arditti 1980, Imai et al. 1994); perturbing membrane permeability or transport function of membranes or other diffusion barriers (e.g., leaf cuticle), including permeability to glyphosate (Coret and Chamel 1993, 1994, Wax et al. 1994); and interacting directly with glyphosate to alter the disposition of glyphosate. Evidence for specific mechanisms of interactions between glyphosate and surfactants is lacking.

4. The structural characteristics of extreme hydrophillicity and hydrophobicity of surfactants may result in very different interactions with hydrophobic and hydrophillic herbicides. Thus, the relatively water-soluble isopropyl amine salt of glyphosate may interact differently with surfactants than the less water-soluble parent compound or other more insoluble herbicides (Coret and Chamel, 1993, 1994). The dependence of surfactant-herbicide interactions on herbicide structure will introduce uncertainty into extrapolations based on data for other herbicides.

5. At concentrations exceeding a critical value, surfactants in aqueous solutions form micelles in which the hydrophobic groups orient toward the inside of the micelle and the hydrophillic groups are oriented toward the outside aqueous environment. The concentration at which a surfactant forms micelles varies with the structure of the surfactant and properties of the aqueous solution and is known as the critical micelle concentration (CMC). It is very likely that the toxicology and any interactions that occur between surfactants and glyphosate will be different at surfactant concentrations above and below the CMC because of the extreme differences in the physical properties of the micelle and the "free" surfactant molecule. This means that predictions that are based on toxicity assays conducted at concentrations below the CMC may not apply to conditions in which the surfactant concentration exceeds the CMC, and *vice versa*. The CMC for the surfactants cannot be estimated from the information available on the various formulations. Furthermore, the consequences of exceeding the CMC on the toxicity of the surfactants and on the toxicity of glyphosate is not predictable given our lack of understanding about mechanisms of toxicity and interactions with glyphosate.

6. The biological effects of surfactants and their interactions with glyphosate are expected to be highly sensitive to the structural characteristics that determine the absolute and relative hydrophobicity and hydrophillicity of the surfactant (Coret and Chamel 1994, Ernst and Arditti 1980, Imai et al. 1994, Knoche et al. 1992). This expectation introduces uncertainties in the predictions of the biological effects of surfactant

mixtures of varying and/or unknown structure, based on data for any given surfactant. A related issue is that product labels, manufacturer data sheets, and material safety data sheets (MSDS) do not identify the exact chemical structures of the surfactants in the various formulations.

The above considerations reinforce the importance of bioassay data on the surfactant formulations to support assessments of toxicity or interactions with glyphosate. For this reason, the emphasis of this report is on characterizing the types of toxicological data that are available for making such assessments.

Chapter 2 of this report, which follows the Introduction, describes the components of the various surfactant formulations and notes those components that are listed in the U.S. EPA List of Inert Ingredients in Pesticides. Chapter 3 summarizes data that are available on the toxicity of the formulations and on the surfactants in the formulations. The objective of the summary is to present an overview of the types of data available on the formulations and surfactants and is not intended to be an in depth evaluation or analysis of the data. Chapter 4 summarizes information on the surfactants that are in the glyphosate formulations Roundup and Roundup Pro. This summary was extracted from the draft report, *Selected Commercial Formulations of Glyphosate - Accord, Rodeo, Roundup and Roundup Pro. Risk Assessment Final Report*, prepared for USDA by Syracuse Environmental Research Associates (SERA, 1996). References are provided in Chapter 5.

2. CONSTITUENTS OF SURFACTANT FORMULATIONS USED WITH RODE0

Constituents of the surfactant formulations Agri-Dex, LI-700, R-11, Latron AG-98 and Latron AG-98 AG are presented in Table 2-1. Those constituents that appear on the U.S. EPA Lists of Inert Ingredients in Pesticide Products (U.S. EPA, 1987, 1994) are noted. U.S. EPA (1987) established four categories of inert ingredients of pesticide products. List 1 includes inerts of toxicological concern; List 2 includes potentially toxic inerts with high priority for testing; List 3 includes inerts of known toxicity; and List 4 includes inerts of minimal concern. In 1994, U.S. EPA (1994) further subdivided List 4 into List 4A, which contains all chemicals on the 1987 List 4, and List 4B, which includes inerts for which EPA has concluded that there is *"sufficient information to conclude that current use patterns in pesticide products will not adversely affect public health and the environment."* The empirical bases for the above conclusions were not available for this assessment and presumably include toxicology and ecotoxicology assays (Levine, 1996).

2.1. AGRI-DEX

According to the Material Safety Data Sheet (MSDS), Agri-Dex is a blend of polyoxyethylated polyol fatty acid ester, polyol fatty acid ester, and paraffin base petroleum oil (Setre Chemical Co.). The surfactant activity of the formulation is provided by the polyoxyethylated polyol fatty acid ester and polyol fatty acid ester. The name polyoxyethylated polyol fatty acid ester refers to a group of chemicals that consist of unspecified fatty acid esters of unspecified polyoxyethylated alcohols. Similarly, the name polyol fatty acid ester refers to unspecified fatty acid esters of unspecified alcohols. A more specific identification of these surfactants was not available.

The paraffin base petroleum oil assigned the CAS numbers in Table 1 is described in the Registry File of Chemical Abstracts (STN, International 1997) as a solvent refined paraffinic distillate containing a mixture of hydrocarbons having carbon numbers predominantly in the range C20-C50 (heavy paraffinic, 64741-88-4) or C15-C30 (light paraffinic, 64741-89-5). The paraffinic oil mixtures are not on the U.S. EPA lists of Inert Ingredients of Pesticides, although other paraffinic oils are on the list. For example, light (C15-C30) and heavy (C20-C50) paraffinic oils produced by vacuum distillation of the residue from atmospheric distillation of crude oil (CAS Nos. 64741-50-0 and 64741-51-1) are on List 2. The reason why certain paraffinic oils are on the U.S. EPA inerts list and others are not is not apparent.

2.2. LI-700

According to the manufacturer data sheet, LI 700 is a mixture of phosphatidylcholine, propionic acid, and alkylpolyoxyethylene ether (Loveland Industries, Inc.). These ingredients comprise 80% of the formulation; the remaining 20% is identified as *"constituents ineffective as adjuvant."* The MSDS for LI 700 lists only phosphatidylcholine and propionic acid as constituents and lists only propionic acid as a hazardous component of the mixture. The surfactant activity of the formulation is provided by phosphatidylcholine and alkylpolyoxyethylene ether.

Table 2-1. EPA inerts list classification for constituents of selected surfactants[a]

Surfactant Product	Chemical Constituents[b]	CAS No.	EPA Inerts Classification
Agri-Dex	Polyol fatty acid esters[c]	NA	--
	Polyoxyethyl polyol fatty acid esters[c]	NA	--
	Paraffin base petroleum oil	64741-88-4 64741-89-5	NL NL
LI 700	Phosphatidylcholine	8002-43-5[d]	4A
	Propionic acid	74-09-4	4B
	Alkylpolyoxyethylene ether[c]	NA	--
R-11	Octylphenoxypolyethoxyethanol	9036-19-5[e]	4B
	n-Butanol	71-36-3	4B
	Compounded silicone[c]	NA	--
Latron AG-98	Nonylphenoxypolyethoxyethanol	68412-54-4	3
	n-Butanol	71-63-3	4B
	Silicone antifoam compound[c]	NA	--
Latron AG-98 AG	Octylphenoxypolyethoxyethanol	9036-19-5	4B
	Isopropanol	67-63-0	4B
	Polydimethylsiloxane	63148-62-9	4B

[a]U.S.EPA lists of Inert Ingredients in Pesticides (U.S. EPA, 1994): List 1 = Toxicological concern; List 2 = Potentially toxic with high priority for testing; List 3 = Unknown toxicity; List 4 = minimal concern (further subdivided into List 4A = classified in U.S. EPA, 1987 as List 4 and List 4B = *sufficient information to conclude that current use patterns in pesticide products will not adversely affect public health and the environment.*

[b]Sources: Technical data sheets, material safety data sheets for surfactant products.

[c]Not sufficiently described to identify the specific consituent(s).

[d]lecithins

[e] polyoxyethylene (1,1,3,3-tetramethylbutyl)phenyl ether

NA = Not available; NL= not listed.

The name phosphatidylcholine refers to a group of chemicals that consist of unspecified fatty acid diglycerides linked to the choline ester of phosphoric acid. This group includes the

naturally occurring lecithins which are prominent phospholipids in biological cell membranes (Edidin and Sessions, 1983). The U.S. EPA lists lecithins (CAS No. 8002-43-5) and soya lecithins (CAS No. 8030-76-0) on List 4A of Inert Ingredients of Pesticides. Soya lecithins are used as emulsifiers in a variety of food products. The exact identity of the phosphatidylcholine in LI 700 could not be determined from the manufacturer data sheet or the MSDS.

The name alkylpolyoxyethylene ether refers to a chemical group of unspecified alkyl ethers of polyoxyethylene. A more specific identification of these surfactants was not available.

Propionic acid, a third constituent of LI 700, is on List 4B of the U.S. EPA List of Inert Ingredients of Pesticides.

2.3. R-11

According to the manufacturer data sheets, R-11 is a mixture of octylphenoxypolyethoxyethanol, n-butanol and compounded silicone (Wilbur-Ellis Co.). These ingredients comprise 90% of the formulation; the remaining 10% is identified as *"constituents ineffective as spray adjuvant."* The MSDS for R-11 lists the hazardous ingredients as 20% butyl alcohol and 80% nonionic surfactants. The surfactant activity of the formulation is provided by octylphenoxypolyethoxyethanol.

The name octylphenoxypolyethoxyethanol refers to a group of chemicals that consist of an 8-carbon alkylphenol linked to an ethoxyethanol polymer of unspecified length. A search of the Registry File of Chemical Abstracts (STN, International 1997) for the name octylphenoxypolyethoxyethanol found polyoxyethylene (1,1,3,3-tetramethylbutyl)phenyl ether, CAS No. 9036-19-5. This chemical is on List 4B of the U.S. EPA List of Inert Ingredients of Pesticides. It is possible that R-11 contains octylphenoxypolyethoxyethanols other than polyoxyethylene (1,1,3,3-tetramethylbutyl)phenyl ether.

n-Butanol is on List 4B of the U.S. EPA List of Inert Ingredients of Pesticides.

A more specific identification of the compounded silicone constituent of R-11 is not available. It may be the same (or similar) antifoam compound as that in Latron AG-98 AG, polydimethylsiloxane, which is on List 4B of the U.S. EPA List of Inert Ingredients of Pesticides.

2.4. LATRON AG-98

According to the manufacturer data sheets, Latron AG-98 is a mixture of nonylphenoxypolyethoxyethanol, n-butanol and a silicon antifoam compound (Rohm and Haas Co.). Nonylphenoxypolyethoxyethanol and n-butanol make up 90% of the formulation with 10% being *"constituents ineffective as spray adjuvants,"* which presumably includes the silicon antifoam compound. The surfactant activity is provided by nonylphenoxypolyethoxyethanol.

The name nonylphenoxypolyethoxyethanol refers to a group of chemicals that consist of a 9-carbon alkylphenol linked to an ethoxyethanol polymer of unspecified length. Nonylphenoxypolyethoxyethanol is on List 3 of the U.S. EPA List of Inert Ingredients of Pesticides. n-Butanol is on List 4B of the U.S. EPA List of Inert Ingredients of Pesticides. The antifoam compound could not be identified from the manufacturers' literature or MSDS. It may be polydimethylsiloxane which is a component of a similar formulation, Latron AG-98 AG (Rohm and Haas, Co.) and which is on List 4B.

2.5. LATRON AG-98 AG

According to the manufacturer data sheets, Latron AG-98 AG is a mixture of octylphenoxypolyethoxyethanol, isopropanol and polydimethylsiloxane (Rohm and Haas Co.). Surfactant activity of the mixture is provided by octylphenoxypolyethoxyethanol. As previously noted for R-11, the octylphenoxypolyethoxyethanol, polyoxyethylene (1,1,3,3-tetramethylbutyl)phenyl ether (CAS No. 9036-19-5), is on List 4B of the U.S. EPA List of Inert Ingredients of Pesticides. However, it is not clear from available information if the surfactant in Latron AG-98 is the same octylphenoxypolyethoxyethanol mixture as in R-11. Surfactants in the two formulations could have different structural features that might affect their toxicity and/or their effect on glyphosate toxicity. For example, there could be differences in the degree of branching of the hydrophobic alklyphenylether portion of the surfactant(s) or length of the hydrophyllic polyoxyethylene chain.

Isopropanol and polydimethylsiloxane(s) are on List 4B.

3. INFORMATION ON EFFECTS OF SURFACTANT FORMULATIONS ON THE TOXICITY OF RODEO

3.1. HUMAN HEALTH

A search of the scientific literature (AGRICOLA, TSCATS, EMIC, EMICBACK and TOXLINE) was conducted to find studies on the toxicology of the surfactant formulations described in Chapter 2. No studies were found.

The only available toxicity studies of any of the formulations are acute lethality studies and a dermal irritation study of LI 700; these are described in attachments to a letter from Rudy Lapurga of the California EPA to John Borrecco of USDA (Lapurga 1996) (described below). As noted in Chapter 1 (Introduction), the lack of toxicology studies regarding the formulations themselves makes it difficult to predict what effects, if any, the formulations may have on the toxicity of Rodeo. The toxicologies of some of the surfactants in the various formulations have been studied; however, these studies alone do not provide a basis for predicting either the toxicity of the formulations or their effects on the toxicity of Rodeo.

Searches were conducted to find toxicological studies of the surfactants in the various surfactant formulations to determine if a basis might exist for attempting a component-based risk assessment of the formulations. No attempt was made to review the individual studies for quality or applicability to quantitative risk assessment. Nevertheless, the results of the search give some idea of the type of data that are available on the toxicology of the surfactants. Based on this cursory survey, combined with uncertainty about the exact chemical structures of the surfactants in the formulations, there does not appear to be adequate data to develop quantitative risk assessments of the surfactants. It should be kept in mind that this survey of the literature did not include direct queries to the manufacturers; it is possible that more adequate data exist that are not publicly available. The results of the search are summarized below (searches of the surfactants in Agri-Dex were not attempted because the identity of the surfactant compounds in the formulation could not be determined).

3.1.1. LI 700. Acute lethality studies and a dermal irritation study of LI 700 are described in attachments to a letter from Rudy Lapurga of the California EPA to John Borrecco of USDA (Lapurga 1996). The single-dose oral LD_{50} (observation period not specified) was reported as >5.0 and 5.9 g/kg in male and female rats, respectively. Animals that died had congested kidneys and gastrointestinal irritation. The dermal LD_{50} for a 24-hour exposure was reported as >5.0 g/kg in rabbits. Animals that died had discoloration of the lungs and pleural cavity, discoloration of the liver, congestion of the kidneys, and bloody urine. Eye and dermal irritation assays in the rabbit showed that LI 700 produced eye irritation when introduced into the eyes and dermal irritation when applied to the skin.

3.1.2. Phosphatidylcholine. Phosphatidylcholine is a surfactant component of LI 700. The human nutritional and clinical experience with the phosphatidylcholine, lecithin, is quite extensive. In 1974, the World Health Organization (WHO, 1974) reported that the average

diet provides 1-5 g lecithin/day and concluded that the acceptable daily intake was *"not limited"* based on nutritional experience with humans. (Note, there appears to be some confusion in the literature regarding the terminology applied to phosphatidylcholine and lecithin and this needs to be considered in any cursory review of literature. In some cases, the terms phosphatidylcholine and lecithin are used interchangeably to refer to a specific class of phospholipids associated with cell membranes. The term lecithin also is applied to commercial formulations of lecithins that contain phosphatidylcholine and other lipid phosphatides.) The Life Sciences Research Office of the Federation of the American Societies for Experimental Biology, at the request of the Food and Drug Administration, conducted a review of the status of lecithin, phosphatidylcholine and choline therapy as dietary supplements (Wood et al., 1981). In a summary report of this review, Wood and Allision (1982) reported that the clinical case literature includes cases in which oral dosages of 20-40 g/day phosphatidylcholine (in commercial lecithin formulations) was *"tolerated"* without adverse *"side effects."*

Liposomes (micelles) composed of phosphatidylcholine were explored as inhalant vehicles for delivering drugs into the respiratory tract; acute inhalation toxicology studies relevant to this use are available in the literature (e.g., Thomas et al., 1991).

3.1.3. Alkylpolyoxyethylene ether. Berberian et al. (1965) studied the acute toxicity of a polyoxyethyene dodecyl ether, Laureth 9, a spermicidal agent intended for use in contraceptive foams. The acute 24-hour LD_{50} in mice was 3300 mg/kg and the 7-day LD_{50} was 3050 mg/kg. The LD_{50} for a 5-day oral exposure was 1190 mg/kg/day. Daily dosages of 390 mg/kg/day for 22 days resulted in depressed growth rates in mice and a dosage of 780 mg/kg/day resulted in 20% mortality. Grubb et al. (1960) reported 7-day LD_{50} values for a polyoxyethyene dodecyl ether of 1170 mg/kg in mice and 4150 mg/kg in rats.

Ernst and Arditti (1980) examined the structure-activity relationships for the cytotoxicity of nonionic alkylpolyethoxyethanol surfactants in isolated human skin fibroblast cell cultures (HeLa cells). Cytotoxic potency decreased with increasing polyoxyethyl chain length (increasing hydrophobicity) when the alkyl chain length remained constant. When the polyoxyethyl chain length was held constant, cytotoxicity increased with increasing alkyl chain length (increased hydrophobicity). This study and other structure-activity studies (Coret and Chamel 1993, 1994, Knoche et al. 1992) suggest that biological activity of nonionic surfactants will vary with size of the hydrophobic and hydrophillic domains of the surfactants.

3.1.4. Octylphenoxypolyethoxyethanol. Octylphenoxypolyethoxyethanol is a surfactant in AN R-11 and Latron AG-98 AG. Octylphenoxypolyethoxyethanol also is the sole component of the surfactant formulations, Triton X-100, Triton X-102, and Triton X-15 (Union Carbide Chemical and Plastics Company, Inc.). Toxicology studies of various Triton X formulations have been reported in submissions to the U.S. EPA under Section 8E of the Toxic Substances Control Act and were located by searching the TSCATS database (Union Carbide, 1992a,b,c,d). These studies suggest that octylphenoxypolyethoxyethanol is a skin irritant and eye irritant in rabbits. The LD_{50} for a single oral dose in the rats was approximately 1-5 g/kg.

The LD_{50} for a single percutaneous dose in rabbits was approximately 12 g/kg. Administration of percutaneous octylphenoxypolyethoxyethanol (Triton X-100) to pregnant rats on days 6-15 of gestation (0.4 - 4 g/day) resulted in skeletal abnormalities in pups (extra ribs and enhanced ossification). The same types of skeletal effects were observed in pups when rats were exposed to Triton X-100 in the diet (0.06% or 0.3%) on days 6-17 of gestation.

Thompson and Gibson (1984) reported a single-dose oral 14-day LD_{50} for Triton X-15 (octylphenoxypolyethoxyethanol) of 11.6 and 4.2 g/kg in male and female Sprague-Dawley rats, respectively (the authors observed higher LD_{50} values in male rats for six other chemicals tested but provided no explanation). Rats were administered a single oral dose of Triton X-15 at the estimated LD_{01}, LD_{10}, and LD_{30} level and killed 20 hours after dosing. Bone marrow cells were collected for assessment of chromosomal abnormalities and suppression of mitosis (mitotic index). No chromosomal abnormalities were observed in rats that received Triton X-15. Male rats that received an LD_{10} or LD_{30} (10.2 or 11.0 g/kg) had significantly depressed mitotic indices ($p <= 0.05$, approximately 50% reduction from controls). Female rats that received a single LD_{10} or LD_{30} dose (3.0 or 3.7 g/kg) had no significant depression of mitotic index.

Long et al. (1982) reported an *in vitro* study of transforming activity of Triton X-100 (octylphenoxypolyethoxyethanol) in mouse BALB/3T3 and 10T1/2 fibroblasts. Triton X-100 was inactive in both systems.

3.1.5. Nonylphenoxypolyethoxyethanol. Nonylphenoxypolyethoxyethanol is a surfactant component of Latron AG-98. It also is the sole component of the surfactants Triton N-60, IGEPAL C0-630 (also known as NP-9). Toxicology studies of these formulations have been reported in submissions to the U.S. EPA under Section 8E of the Toxic Substances Control Act and were located by searching the TSCATS database (Rhone-Poulenc, Inc. 1991, Rohm and Haas Co. 1992). These studies suggest that nonylphenoxypolyethoxyethanol is a skin and eye irritant in the rabbit.

A search of the published toxicological literature found an *in vitro* study of transforming activity in mouse BALB/3T3 and 10T1/2 fibroblasts (Long et al. 1982). The nonylphenoxypolyethoxyethanol mixture (NP-9, also known as IGEPAL-630) induced transformations in both cell cultures.

Nonylphenoxypolyethoxyethanol has been used as a spermicide in vaginal contraceptive foams. Toxicological studies of the effects of vaginal applications of nonylphenoxypolyethoxyethanol on vaginal physiology have been reported (e.g., Levin 1987). Anticipated human exposure to surfactants from pesticide applications is not analogous to the type of exposure that would occur from use of the surfactant as a contraceptive foam (i.e., intravaginal).

Long et al. (1982) reported an *in vitro* study of transforming activity of NP-9 (also known as IGEPAL-630) in mouse BALB/3T3 and 10T1/2 fibroblasts. NP-9 induced transformations in both mouse cell transformation systems.

3.2. ECOLOGICAL EFFECTS

Aquatic toxicity studies of LI 700 were described in attachments to a letter from Rudy Lapurga of the California EPA to John Borrecco of USDA (Lapurga 1996) (Table 3-1). The acute 96-hour LC_{50} (nominal concentration, static exposure conditions) in juvenile Bluegill sunfish (*Lepomis macrochirus*) was 210 mg/L, and 130 mg/L in juvenile Rainbow trout (*Oncorhynchus mykiss*). The acute 48-hour LC_{50} in *Daphnia magna* was190 mg/L.

The same letter (Lapurga 1996) describes studies of the aquatic toxicity of R-11. The acute 96-hour LC_{50} (nominal concentration, static exposure conditions) in juvenile Bluegill sunfish (*Lepomis macrochirus*) was 4.2 mg/L, and in juvenile Rainbow trout (*Oncorhynchus mykiss*), 3.8 mg/L. The acute 48-hour LC_{50} in *Daphnia magna* was 19 mg/L.

Acute toxicity data on LI 700, R-11 and Agri-Dex are summarized in a report entitled *Use of the Registered Aquatic Herbicide Fluridone (SONAR) and the Use of the Registered Aquatic Herbicide Glyphosate (Rodeo and Accord) in the State of New York*, prepared by McLaren/Hart for DowElanco and Monsanto (McLaren/Hart 1995) (Table 3.2). Note that the values for LI 700 and R-11 are nearly identical to those reported in Lapurga (1996), except that the 48-hour LC_{50} for LI 700 in *Daphnia magna* is reported as 170 mg/L in McLaren/Hart (1995) and 190 mg/L in Lapurga (1996). The similarities between the data in the two reports are so striking that the possibility that they represent the exact same studies should be considered.

The above studies indicate that the toxicity potency of R-11, as assessed by lethality in these species, is considerably greater than LI 700 or Agri-Dex (10 to 50 times greater). Considerable uncertainty would be attached to any extrapolations of these results to other species or exposure durations.

A search of the scientific literature (AGRICOLA, TSCATS, EMIC, EMICBACK and TOXLINE) was conducted to find studies on the ecotoxicology of the surfactant formulations described in Chapter 2. The search found one study on the effect of Triton AG-98 (Latron AG-98) on *in vitro* spore germination and germ tube growth of the fungus, *Mucor mucedo*, the causative agent of a fungal rot in stored fruit (Reyes 1992). As noted for the survey of data relevant to the assessment of human health effects, the lack of toxicology studies on the formulations themselves makes it difficult to predict what effects, if any, the formulations may have on the ecotoxicity of Rodeo. A search was conducted for studies concerning the toxicity of individual surfactants in the formulations to determine whether there might be a basis for a component-based assessment of the formulations. A study of toxicity in marine shrimp and a study of toxicity in aphids were found as well as several studies on the phytotoxicity of various surfactants. No studies were found regarding toxicity to aquatic or terrestrial vertebrates

(other than those on rats and rabbits described in Section 3.1 on human health). Therefore, data appear to be inadequate for a quantitative assessment of ecological effects of the surfactants. Here again, this survey did not query the manufacturers for data that might not be publicly available. The available studies are summarized below.

A study of the acute toxicity of IGEPAL CO-210 (GAF Corporation) to the opossum shrimp (*Mysidosis Bahia*) was submitted to the U.S. EPA under Section 8D of the Toxic Substances Control Act (Quantum Chemical Corp. 1992). Nonylphenoxypolyethoxyethanol is the sole ingredient of IGEPAL CO-210. An acute (48-hour) LC_{50} of 0.26 mg/L was reported.

Table 3-1. Lethality of surfactant formulations LI 700 and R-11 to aquatic species[a]

Genus species	LC_{50} (mg/L)[b]	
	LI 700	**R-11**
Lepomis macrochirus (Bluegill sunfish)	210	4.2
Oncorhynchus mykiss (Rainbow trout)	130	3.8
Daphnia magna	190	19

[a]Source: Lapurga 1996

[b]Nominal concentration under static conditions. 96-hour exposure of *Lepomis macrochirus* and *Oncorhynchus mykiss*; 48-hour exposure of *Daphnia magna*.

Table 3-2. Lethality of surfactant formulations LI 700, R-11 and Agri-Dex to aquatic species[a]

Genus species	LC_{50} (mg/L)[b]		
	LI 700	**R-11**	**Agri-Dex**
Lepomis macrochirus (Bluegill sunfish)	210	4.2	> 1000
Oncorhynchus mykiss (Rainbow trout)	130	3.8	> 1000
Daphnia magna	170	19	> 1000

[a]Source: McLaren/Hart 1995

[b]96-hour exposure of *Lepomis macrochirus* and *Oncorhynchus mykiss*; 48-hour exposure of *Daphnia magna*.

Imai et al. (1994) compared the lethality of various surfactants in laboratory cultures of green peach aphid, *Myzus persicae*. Lethality varied considerably among various preparations of nonly- and octylphenoxypolyethoxyethanols, and alkylpolyoxyethyl ethers. Lethality was

highly correlated with surface activity of the preparations; that is, lethality increased with decreasing surface tension of the surfactant preparations.

Caux et al. (1993) examined membrane structure and composition of *Lemna minro L.* plants (a macrophyte commonly used in aquatic toxicity studies) that were exposed to one of several Triton X formulations, including Triton X-15 and X-100 in which the sole component is octylphenoxypolyethoxyethanol. Exposures to Triton X-15 and Triton X-100 produced changes in the phospholipid composition of membranes and increased fluidity of chloroplast membranes. Exposures to radiolabeled Triton X-100 resulted in incorporation of surfactant lipid into chloroplast membranes. This study indicates that surfactant lipids are incorporated into biological membranes and can affect membrane composition and function.

Knoche et al. (1992) reported that the phytotoxicity of octylphenoxypolyethoxyethanols and nonylphenoxypolyethoxyethanols varied with the oxyethyl chain length. Phytotoxicity was highest in surfactants that had 9 to 10 oxyethyl groups, with phytotoxicity decreasing with shorter or longer oxyethyl chain lengths. There are numerous studies regarding structure-activity relationships for the effects of polyethoxyethyl surfactants on the penetration of herbicides into leaf cuticles (e.g., Corbet and Chamel 1992, 1994). The studies show that the effect of the surfactant on herbicide penetration will vary with the oxyethyl chain length and that the physical and chemical properties of the pesticide may affect the structure-activity relationship (e.g., differences in water solubility). These studies have important implications for the assessment of the effects of surfactant formulations on the toxicity of Rodeo because they suggest that certain effects of the octylphenoxypolyethoxyethanols and nonylphenoxypolyethoxyethanols may vary with the length of the oxyethylene moiety, which may be different in the various formulations. This point underscores the importance of data on the toxicity of the formulations and of information on the exact chemical structure of the surfactant components of the formulations.

Knoche and Bukovac (1992) examined the effects of a variety of surfactant formulations, including Triton AG-98 (Latron AG-98) on penetration of gibberellic acid into sour cherry leaves (*Prunus cerasus L. cv Montmorency*). Triton AG-98 enhanced gibberellic acid penetration.

Lewis and Hamm (1987) compared the potencies of various surfactants to depress photosynthesis and growth of freshwater algae. For *in situ* depression of photosynthesis, the 3-hour EC_{50} values were 28.7 mg/L for octylphenoxypolyethoxyethanol and 2.1 mg/L for alkylethoxyethanol. The mean 96-hour EC_{50} values for growth depression in laboratory cultures of green algae (*Selenastrum capricornutum*), blue-green algae (*Microcystis aeruginosa*) and diatoms (*Naviculla pelliculosa*) were 0.21 mg/L for octylphenoxypolyethoxyethanol and 0.09 mg/L for alkylethoxyethanol.

4. SURFACTANTS IN THE GLYPHOSATE FORMULATIONS ROUNDUP AND ROUNDUP PRO

Roundup is an aqueous solution of the isopropylamine salt of glyphosate with a polyethoxylated tallow amine surfactant. This material is referred to in the literature as MON 0139, with the MON presumably referring to Monsanto, or polyoxyethyleneamine (POEA) (Smith and Oehme 1992). The surfactant in Roundup is present at 15% (Hoogheem 1987, Sawada et al. 1988) or 150 g/L assuming that the 15% value refers to the level in terms of weight per unit volume. Presumably, the Roundup surfactant is a derivative of tallow, a complex mixture of fat from the fatty tissue of cattle or sheep. Tallow contains a variety of fatty acids including oleic (37–43%), palmitic (24–32%), stearic (20–25%), myristic (3–6%), and linoleic (2–3%) acids as well as small amounts of cholesterol, arachidonic, elaidic, and vaccenic acids (Budavari 1989). An ethoxylated tallow amine (CAS No. 61791-26-2), is on the U.S. EPA List 3 of Inert Ingredients of Pesticides (U.S. EPA 1987, 1994). The surfactant used in Roundup contains 1,4-dioxane as an impurity. The upper limit of this compound in Roundup is about 0.03% (Monsanto 1990). In a previous review, the U.S. Forest Service determined that the amount of exposure to 1,4-dioxane is toxicologically insignificant (Borrecco and Neisess 1991).

Roundup Pro is a recently introduced formulation of glyphosate that contains a phosphate ester neutralized polyethoxylated tallow amine surfactant at a level of 14.5% (Monsanto 1995a,b, 1996) or 145 g/L. Other than the specification that the tallow amine surfactant in Roundup Pro is a phosphate ester of POEA, there is no published information regarding the chemical differences between the surfactant in Roundup and Roundup Pro.

4.1. HUMAN HEALTH

The potential role of the surfactant in the toxicity of Roundup was first emphasized by Sawada et al. (1988) in their analysis of poisoning cases in humans. They indicate that the acute LD_{50} of POEA is *"less than one-third that of roundup and its active ingredient"* and reference this statement to a chapter by Atkinson (1985) in *The Herbicide Glyphosate* (Grossbard and Atkinson 1985). The Sawada reference has been quoted in turn by Martinez and Brown (1991) as indicating that " . . . *POEA by itself has a LD_{50} of 1-2 g/kg.*" The original experimental reference documenting these statements was not identified in the process of preparing this risk assessment.

Atkinson (1985) does cite an LD_{50} of 4.3 g/kg for glyphosate [a rounding of the rat oral LD_{50} of 4320 mg/kg reported in U.S. EPA (1986) and earlier U.S. EPA reports] and indicates that this is about the same as the acute oral LD_{50} in for isopropylamine salt in rats, 4.9 g/kg. Atkinson (1985), however, does not give an acute oral LD_{50} for POEA or any other surfactant.

An acute oral LD_{50} for POEA of 1200 mg/kg was reported in the previous EIS (USDA 1989b, p. 3-49, Coastal Plain/Piedmont Appendices). This value has been verified by Monsanto Co.

and is consistent with the acute toxic potency of other surfactants: in general, acute LD_{50} values for surfactants range from several hundred to several thousand mg/kg (Kosswig 1994, Grayson and Eckroth 1983).

The acute oral toxicity of Roundup (glyphosate and surfactant, LD_{50} in rats of 5400 mg/kg) is almost the same as that of glyphosate (LD_{50} in rats of 5600 mg/kg) (Monsanto Co. 1982a,b, 1983a). Based on these LD_{50} values, the LD_{50} of the surfactant can be estimated under the assumption of dose addition (Finney 1971). This assumption requires that the components in the mixture have the same mode of action. This assumption is not certain, but it is consistent with the observation by Talbot et al. (1991) that both glyphosate and POEA may exert some of their acute toxicity via irritation of biological membranes. The assumption of dose addition is also not interactive—that is, it assumes that the components in the mixture do not influence the toxicity of one another. This assumption is conservative, compared with other non-interactive models of joint action (Mumtaz et al. 1994).

For some uniform measure of toxicity (ζ) (e.g., LD_{50}), the toxicity of any mixture (ζ_M) is predicted, under the assumption of dose addition, by:

$$\zeta_M = \frac{\zeta_1}{(\pi_1 + \rho\pi_2)} \qquad (4\text{-}1)$$

where ζ_1 is the effective exposure (e.g., LD_{50} or LD_{95} values) for one compound, π_1 and π_2 are the proportions of each compound in the mixture, and ρ is the potency defined as $\zeta_1 \div \zeta_2$. Furthermore, given the toxicity of a defined mixture (ζ_M) and one of the components (ζ_1), the potency of the second component can be calculated as:

$$\rho = \frac{(\zeta_1 / \zeta_M) - \pi_1}{\pi_2} \qquad (4\text{-}2)$$

Here, the term *defined mixture* indicates that π_1 and π_2 are known. From this relationship, the effective exposure (i.e., toxic potency) of the second component (ζ_2) can be estimated as:

$$\zeta_2 = \frac{\zeta_1}{\rho} \qquad (4\text{-}3)$$

Using the nominal LD_{50} for Roundup of 5400 mg/kg, a π_1 of 0.356 for glyphosate (356 g/L), and π_2 of 0.15 for POEA (150 g/L), the estimated LD_{50} for POEA would be almost exactly 1200 mg/kg, consistent with dose additivity. This approach, however, would be a misapplication of the above equations.

To estimate the toxicity of POEA from the Roundup (glyphosate+POEA) LD_{50}, this LD_{50} must be converted from units of glyphosate to total mixture mass (glyphosate+POEA). In other words, an LD_{50} of 5400 mg glyphosate/kg bw is equivalent to a combined mass

(glyphosate and POEA) of about 7560 mg [1.4·5,400 mg], since the ratio of POEA to glyphosate is approximately 0.4 [150 g/L ÷ 356 g/L]. Similarly, the correct π_1 for glyphosate is about 0.7 [356 ÷ (150+356)] and the correct π_2 for POEA is about 0.3 [150 ÷ (150+356)]. Using this approach, the potency of POEA relative to glyphosate is about 0.14 and the estimated oral LD_{50} in rats is for POEA is about 40,000 mg/kg [5,600 mg/kg ÷ 0.14]. This estimate is consistent with the published results of Martinez, summarized in the following paragraph, in which no mortality was noted in rats after oral doses of up to 14,286 mg/kg POEA.

Martinez and coworkers (Martinez and Brown 1991; Martinez et al. 1990) conducted a series of experiments specifically designed to assess the role of the surfactant in the acute toxicity of Roundup. In these studies, compounds were administered to groups of five rats either by gavage (direct instillation into the stomach) or direct installation into the trachea. Oral exposure to Roundup at doses of 1, 3, and 5 mL/animal caused 0%, 40%, and 100% mortality, respectively, over a 24-hour observation period. Taking an average body weight of 350 g/rat reported by Martinez and Brown (1991), the mid-dose level corresponds to approximately 3050 mg/kg [3 mL · 356 mg a.e./mL ÷ 0.350 kg], only somewhat less than and consistent with the reported LD_{50} for Roundup of 5400 mg/kg (Monsanto Co. 1982a,b). POEA, administered by gavage, caused no deaths at doses of 1, 3, and 5 mL/animal. Since ethoxylated surfactants generally have a density of about 1 g/mL (Kosswig 1994, p. 789), the doses of POEA correspond to approximately 2857, 8571, and 14,286 mg/kg. The low acute oral toxicity of POEA is consistent with the similarity between the acute oral toxicity of glyphosate and Roundup, discussed above.

In the earlier study by Martinez et al. (1990), an oral dose with Roundup RTU or Roundup concentrate caused delayed (6 hours) pulmonary edema, consistent with clinical observations in humans, as summarized above. The authors concluded that "*. . . delayed pulmonary edema combined with blood stained weeping from the nose, diarrhea, distended GI tract, and ascites is in excellent agreement with . . . The clinical picture of . . . hypovolemic shock,*" as described by Sawada et al. (1988). In the individuals involved in the Taiwan studies of glyphosate poisoning, however, hematocrit, blood urea nitrogen, and central venous pressure determinations were not consistent with hypovolemia.

Intratracheal instillations in rats resulted in much more toxic effects at much lower dose levels. Roundup at doses of 0.1, 0.2, and 0.4 mg/animal caused 80% mortality at the low dose and 100% mortality at the two higher doses as well as an increase in lung weights. POEA, at the same dose levels, caused 20%, 70%, and 100% mortality as well as increases in lung weights, although the increases were less than those observed with Roundup (Martinez and Brown 1991, Table 1, p. 44). Pathological examinations indicated that both Roundup, and to a lesser extent POEA, cause hemorrhaging and congestion of the lungs after intratracheal instillations. Martinez and Brown (1991) conclude that POEA potentiates the pulmonary toxicity of glyphosate. Since, however, these investigators did not test glyphosate alone, the basis for their conclusion is not clear.

Based on drinking water studies of both glyphosate and Roundup (i.e., glyphosate with POEA), the surfactant does not affect the rapid elimination rate of glyphosate (NTP 1992).

Pertinent data regarding the subchronic or chronic toxicity of POEA were not located in the published literature. In a letter to the Forest Service concerning a review of the previous EIS, Monsanto provides single page summaries of two studies conducted by Bionetics on what is characterized as the *Roundup surfactant* (Long 1987, letter to Larry Gross dated March 12, 1987). In the first study, dietary concentrations of 0, 1250, 2500, or 5000 ppm (0, 1.6, 3.8, or 6.5 mg/kg/day) were fed to Sprague-Dawley rats for 13 weeks. The study is identified as LBI Project No. 2290. The results of the study are summarized as follows:

> *No toxic signs were observed except for slow acclimation to the highest dosage in the first three weeks. Clinical laboratory tests failed to reveal important differences between controls and test animals. Microscopic examination of organs collected at necropsy revealed only histiocytic infiltrations of the lamina propria of the small intestines and sinusoids of mesenteric lymph nodes at all dosage levels.*

In the second study, the surfactant was fed to dogs via gelatin capsules at doses of 0, 10, 20, and 30 mg/kg, 3 times/day, over the final 10 weeks of a 14-week study. Dosing during the first 4 weeks, if any, is not specified, and the LBI project number is not specified. The summary states:

> *The material showed no effect with regard to survival, general appearance, behavior, neurologic, electrocardiographic or histopathological parameters. Changes observed during the study included decreased food consumption, depressed growth rate, reduced serum calcium and total protein, increased relative and absolute renal and cardiac weights, and increased relative adrenal weights. None of the observed changes would preclude the use of Roundup surfactant as an adjuvant in a herbicide formulation.*

No further information is provided. Superficially, these studies increase rather than lessen concern about the presence of the surfactant.

Very little information is available regarding the surfactant in Roundup Pro. The surfactant in Roundup Pro is described as a *phosphate ester neutralized polyethoxylated tallow amine* (Monsanto 1996). Like the polyethoxylated tallow amine in Roundup, this surfactant is produced, presumably, by the ethoxylation of tallow amine with ethylene glycol. Since tallow is a complex and variable mixture of fatty acids and other minor components and since the nature and extent of ethoxylation can vary according to the conditions during synthesis, the significance of the difference between the surfactants used in Roundup and Roundup Pro is not apparent from the available chemical descriptions of these two surfactants. There is relatively little data regarding the toxicity of Roundup Pro.

4.2. ECOLOGICAL EFFECTS

A major qualitative difference between the effect of glyphosate and glyphosate formulations on aquatic and terrestrial organisms concerns a polyethoxylated tallow amine surfactant (POEA) used in Roundup. For aquatic organisms, the surfactant is much more toxic than glyphosate. Unlike glyphosate, POEA is more toxic in alkaline water than in acid water. Thus, the relative potency of POEA with respect to glyphosate is pH dependent. There is relatively little information regarding Roundup Pro, a formulation of glyphosate that contains a phosphate ester neutralized polyethoxylated tallow amine surfactant. Nonetheless, the available data suggest that this formulation is quite similar to Roundup.

There is an extensive amount of literature on glyphosate specifically (Boerboom and Wyse 1988, Clay and Lawrie 1988, Cranmer and Linscott 1991, Sherrick et al. 1986, Turner 1985) and many other compounds (Green et al. 1992, Prasad 1989) indicating that the addition of surfactants can greatly enhance the phytotoxicity of herbicides.

Two aquatic toxicity studies (Folmar et al. 1979, Wan et al. 1989) have been conducted on glyphosate, POEA, and Roundup which permit a quantitative assessment of the relative toxicities of glyphosate and POEA as well as the effects of combined exposures to these agents. Both of these studies indicate that POEA is substantially more toxic than glyphosate.

Folmar et al. (1979) conducted bioassays on four species of fish and one invertebrate (midge larvae). The LC_{50} values for glyphosate, POEA, and Roundup are presented in Table 4-1. Also shown in Table 4-1 is the relative potency (ρ) of POEA with respect to glyphosate, estimated as the LC_{50} of glyphosate divided by the corresponding LC_{50} for POEA. For example, for rainbow trout at pH 6.5, the LC_{50} for POEA is 7.4 mg/L and the corresponding LC_{50} for glyphosate is 140 mg/L. Thus, the relative potency of POEA with respect to glyphosate is about 19 [$140 \div 7.4 = 18.92$].

Table 4-1. Estimates of relative potency and toxicological interaction of glyphosate and POEA[a]

Species/Assay/Study	Observed LC_{50} values					
	Glyphosate	POEA	Roundup[b]	•	Predicted LC_{50}	Pred.÷ Obs.
			pH 6.5			
Rainbow trout	140	7.4	10.8	19	22	2.0
Bluegills	140	1.3	6.0	108	3.1	0.5
	pH 7.2, 96 hr unless specified					
Midge larvae, 48 hr.	55	13	25	4.2	28	1.1
Rainbow trout	140	2	11.8	70	6.5	0.6
Fathead minnow	97	1.0	3.2	97	3.2	1.0
Channel catfish	130	13	18	10	35	1.9
Bluegills	140	3.0	7.1	47	9.5	1.3
			pH 9.5			
Rainbow trout	240	0.65	2.0	369	2.1	1.1
Bluegills	220	1.0	2.6	220	3.3	1.3

[a]Data from Folmar et al. (1979).

[b]Value reported by Folmar as mg a.i multiplied 1.42 to account for added mass of surfactant.

• = LC_{50} of glyphosate ÷ LC_{50} of POEA.

In mixtures, the concept of relative potency provides an explicit tool for identifying the most significant toxic agent(s) in a mixture as well as for assessing potential interactions among agents in a mixture (Durkin 1981, Mumtaz et al. 1994). For example, for a mixture of two agents with the same potency present in a mixture in proportions of π_1 and π_2, the fractional contribution of each agent to the toxicity of the mixture is simply the proportion (π_1 or π_2) of the agent in the mixture. When the potencies differ, both agents contribute equally to the toxicity of the mixture when π_1 is equal to $\rho\pi_2$. As above, ρ is defined here as the LC_{50} of component 1 divided by the LC_{50} of component 2.

In Roundup, glyphosate is present at 356 g/L and POEA is present at 150 g/L. The proportion of glyphosate in Roundup (π_G), ignoring the only other constituent, which is water, is about 0.7 [356÷(356+150)]. Similarly, the proportion of POEA (π_S for proportion of surfactant) in the mixture is about 0.3 [150÷ (356+150)]. Both constituents would contribute equally to the mixture if the relative potency of POEA was about 2.3 [0.7÷0.3]. The relative potency of POEA with respect to glyphosate is much greater than 2.3, at least for fish species (Table 4-1). Thus, POEA is the more significant toxic agent in the mixture.

The magnitude of the difference can be expressed in various ways, the simplest of which is the ratio of the concentrations or equivalently the ratios of the proportions adjusted for the difference in potency:

$$\frac{\rho \cdot \Pi_2}{\Pi_1} \qquad (4-4)$$

For example, if the relative potency is 70, as it is in Table 4-1 for rainbow trout at pH 7.2, POEA may be said to contribute 30 times [70 · 0.3 ÷ 0.7] more than glyphosate to the toxicity of the mixture.

This method of describing relative toxic contribution is based on the assumption that the components in the mixture do not affect one another (i.e., there are no toxicological interactions). For terrestrial plants, such interactions have been clearly documented. One method for assessing whether or not similar interactions are plausible in aquatic species is to compare the observed LC_{50} values for Roundup with the LC_{50} values that would be predicted by one model of non-interactive joint action, simple similar action (Finney 1971, Durkin 1981). Using this assumption, the expected LC_{50} can be calculated as:

$$LC_{50_{Roundup}} = \frac{LC_{50_{Glyphosate}}}{(\Pi_G + \rho\Pi_S)} \qquad (4-4)$$

where π and ρ are as defined above.

The predicted LC_{50} values for Roundup based on this assumption are presented in the second to the last column of Table 4-1, and the ratio of the predicted to observed LC_{50} values are given in the last column. Ratios > 1 suggest some form of greater than additive toxicity, and, conversely, ratios < 1 indicate less than additive toxicity. Note also that the observed LC_{50} values for Roundup are presented as the total concentration of glyphosate and POEA. In other words, the LC_{50} values for Roundup reported in Folmar et al. (1979) are multiplied by 1.42 ((352 + 150) ÷ 352) and give the LC_{50} values in units of weight of both glyphosate and POEA. These units are required for the above equation 4-2.

As indicated in Table 4-1, there is a tendency for the toxicity of glyphosate to decrease (i.e., the LC_{50} values increase—as the pH increases), although the changes are not substantial. The effect of pH on POEA is also not substantial but the effect seems to be the opposite of the effect that pH has on glyphosate. In all of the bioassays, the surfactant is more toxic than glyphosate. Because of the effect of pH on toxicity, the relative potency of POEA increases as pH increases. At all pH levels, the ratio of predicted to observed LC_{50} values for Roundup does not deviate remarkably or systematically from unity, suggesting that no substantial interactions take place between these two compounds.

Table 4-2. Estimates of relative potency and toxicological interaction of glyphosate and POEA in five species of salmonids[a]

Species/Assay/ Study	Observed 96-hour LC_{50} Values					
	Glyphosate	POEA	Roundup[a]	•	Predicted LC_{50}	Pred.÷ Obs.
	Soft Water pH 6.3					
Coho	27	4.6	32	5.9	10.9	0.34
Chum	10	2.7	20	3.7	5.5	0.28
Chinook	19	2.8	33	6.8	6.9	0.21
Pink	14	4.5	33	3.1	8.5	0.26
Rainbow	10	2	33	5	4.5	0.13
	Soft Water pH 7.2					
Coho	36	3.2	27	11.3	8.8	0.33
Chum	22	4.2	19	5.2	9.7	0.51
Chinook	30	2.8	27	10.7	7.5	0.28
Pink	23	2.8	31	8.2	7.2	0.23
Rainbow	22	2.5	15	8.8	6.6	0.44
	Hard Water pH 8.2					
Coho	210	1.8	13	117	5.9	0.45
Chum	202	1.4	11	144	4.6	0.41
Chinook	220	1.7	17	129	5.6	0.32
Pink	380	1.4	14	261	4.6	0.33
Rainbow	220	1.7	14	129	5.6	0.40

[a]Data from Wan et al. (1989)

[b]As reported by Wan et al. (1989) in units of mg product/L.

A similar analysis of the results presented by Wan et al. (1989) is summarized in Table 4-2. In general, this study agrees well with the earlier study by Folmar et al. (1979). In all cases, the surfactant is substantially more toxic than glyphosate. The effect of pH is more consistent and more substantial: the toxicity of glyphosate decreases and the toxicity of the surfactant increases with increasing pH. Consequently, the relative potency of the surfactant to glyphosate also increases with increasing pH. The LC_{50} values reported in Wan et al. (1989)

for Roundup are expressed as "*mg product/L.*" In calculating the expected LC_{50} values for Roundup in Table 4-2, it is assumed that these LC_{50} values include the concentrations of both glyphosate and the surfactant. As indicated in the last column of this table, the ratio of the predicted to observed LC_{50} values for Roundup are consistently < 1, indicating a less than additive interaction.

Comparable data allowing for an assessment of the joint action of glyphosate with the surfactant used in Roundup Pro are not available. The surfactant used in Roundup Pro is a *phosphate ester neutralized polyethoxylated tallow amine* (Monsanto 1996) that is probably similar to the *polyethoxylated tallow amine* used in Roundup. Consequently, it is reasonable to assume that the surfactant in Roundup Pro will enhance the toxicity of glyphosate to aquatic species. It is not clear, however, that this enhancement will be pH dependent.

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Exhibit 10

August 9, 2017, 1:00 AM PDT

Monsanto Was Its Own Ghostwriter for Some Safety Reviews

Academic papers vindicating its Roundup herbicide were written with the help of its employees.

By Peter Waldman, Tiffany Stecker, and Joel Rosenblatt



ILLUSTRATION: ELIZABETH PICH

Monsanto Co. started an agricultural revolution with its "Roundup Ready" seeds, genetically modified to resist the effects of its blockbuster herbicide called Roundup. That ability to kill

weeds while leaving desirable crops intact helped the company turn Roundup's active ingredient, the chemical glyphosate, into one of the world's most-used crop chemicals. When that heavy use raised health concerns <https://www.bloomberg.com/news/features/2017-07-13/does-the-world-s-top-weed-killer-cause-cancer-trump-s-epa-will-decide> , Monsanto noted that the herbicide's safety had repeatedly been vetted by outsiders. But now there's new evidence that Monsanto's claims of rigorous scientific review are suspect.

Dozens of internal Monsanto emails <http://baumhedlundlaw.com/pdf/monsanto-documents/> , released on Aug. 1 by plaintiffs' lawyers who are suing the company, reveal how Monsanto worked with an outside consulting firm to induce the scientific journal *Critical Reviews in Toxicology* to publish a purported "independent" review <http://www.tandfonline.com/doi/full/10.1080/10408444.2016.1214677> of Roundup's health effects that appears to be anything but. The review, published along with four subpapers in a September 2016 special supplement, was aimed at rebutting the 2015 assessment by the International Agency for Research on Cancer (IARC) that glyphosate is a probable human carcinogen <https://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf> . That finding by the cancer-research arm of the World Health Organization led California last month to list glyphosate as a known human carcinogen. It has also spurred more than 1,000 lawsuits in state and federal courts by plaintiffs who claim they contracted non-Hodgkin lymphoma from Roundup exposure.

Monsanto disclosed that it paid Intertek Group Plc's consulting unit to develop the review supplement, entitled "An Independent Review of the Carcinogenic Potential of Glyphosate." But that was the extent of Monsanto's involvement, the main article said. "The Expert Panelists were engaged by, and acted as consultants to, Intertek, and were not directly contacted by the Monsanto Company," according to the review's Declaration of Interest statement. "Neither any Monsanto company employees nor any attorneys reviewed any of the Expert Panel's manuscripts prior to submission to the journal."

Monsanto's internal emails tell a different story. The correspondence shows the company's chief of regulatory science, William Heydens, and other Monsanto scientists were heavily involved in organizing, reviewing, and editing drafts submitted by the outside experts. At one point, Heydens even vetoed explicit requests by some of the panelists to tone down what one of them wrote was the review's "inflammatory" criticisms of IARC.

"An extensive revision of the summary article is necessary," wrote that panelist, John Acquavella, an epidemiologist at Aarhus University in Denmark, in a February 2016 email attached to his suggested edits of the draft. Alarmed, Ashley Roberts, the coordinator of the glyphosate papers for Intertek, forwarded Acquavella's note and edits to Heydens at Monsanto, with the warning: "Please take a look at the latest from the epi(demiology) group!!!!"

Heydens reedited Acquavella's edits, arguing in six different notes in the draft's margin that statements Acquavella had found inflammatory were not and should not be changed, despite the author's requests. In the published article, Heydens's edits prevailed. In an interview, Acquavella says that he was satisfied with the review's final tone. According to an invoice he sent Monsanto, he billed the company $20,700 for a single month's work on the review, which took nearly a year to complete.

Monsanto defends the review's independence. Monsanto did only "cosmetic editing" of the Intertek papers and nothing "substantive" to alter panelists' conclusions, says Scott Partridge, Monsanto's vice president for global strategy. While the "choice of words" in the Declaration of Interest "was not ideal," he says, "it didn't change the science."

In July 2016, the journal's editor, Roger McClellan, emailed his final instructions to Roberts at Intertek on what the paper's Acknowledgment and Declaration of Interest statements should include. "I want them to be as clear and transparent as possible," he wrote. "At the end

of the day I want the most aggressive critics of Monsanto, your organization and each of the authors to read them and say–Damn, they covered all the points we intended to raise."

Specifically, McClellan told Roberts to make clear how the panelists were hired–"ie by Intertek," McClellan wrote. "If you can say without consultation with Monsanto, that would be great. If there was any review of the reports by Monsanto or their legal representatives, that needs to be disclosed."

Roberts forwarded McClellan's emails, along with a more technical question, to Heydens, who responded, "Good grief." The Declaration of Interest statement was rewritten per McClellan's instructions, despite being untrue. There was no mention of the company's participation in the editing.

Monsanto's editorial involvement appears "in direct opposition to their disclosure," says Genna Reed <http://www.ucsusa.org/about/staff/staff/genna-reed.html> , a science and policy analyst at the Union of Concerned Scientists' Center for Science and Democracy. "It does seem pretty suspicious."

In response to questions, McClellan wrote in an email on Aug. 7 that he'd been unaware of the Monsanto documents and has forwarded the matter to the journal's publisher, Taylor & Francis, in Abingdon, England. "These are serious accusations relative to scientific publishing canons and deserve very careful investigation," he wrote. "I can assure you that Taylor and Francis, as the publisher, and I, as the Scientific Editor of *Critical Reviews in Toxicology*, will carefully investigate the matter and take appropriate action." A Taylor & Francis spokeswoman says it has begun an investigation.

The Monsanto documents, more than 70 in all, were obtained through pretrial discovery and posted online by some of the plaintiffs' lawyers, who claim Monsanto missed a 30-day window to object to their release. Monsanto says it was blindsided by the disclosures and has asked U.S. District Judge Vince Chhabria in San Francisco to order the documents pulled from

the web and to punish the attorneys for violating confidentiality orders. Says Monsanto's Partridge: "It's unfortunate these lawyers are grandstanding at the expense of their clients' interests."

Other emails show that Monsanto's lead toxicologist, Donna Farmer, was removed as a co-author of a 2011 study on glyphosate's reproductive effects, but not before she made substantial changes and additions to the paper behind the scenes. The study, published in Taylor & Francis's *Journal of Toxicology and Environmental Health*, served to counter findings that glyphosate hampers human reproduction and development. Partridge says Farmer's contributions didn't warrant authorship credit. While almost all of her revisions made it into the published paper <http://www.tandfonline.com/doi/abs/10.1080/10937404.2012.632361> , her name doesn't even show up in the acknowledgments.

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