EXHIBIT 95

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

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IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION

MDL No. 2741

Case No. 16-md-02741-VC

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This document relates to:

ALL ACTIONS

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DEPOSITION OF CHRISTOPHER JUDE PORTIER, Ph.D.

New York, New York

September 5, 2017

Reported by: MARY F. BOWMAN, RPR, CRR

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September 5, 2017
9:04 a.m.

Deposition of CHRISTOPHER JUDE PORTIER, Ph.D., held at the offices of Weitz & Luxenberg, 700 Broadway, New York, New York, before Mary F. Bowman, a Registered Professional Reporter, Certified Realtime Reporter, and Notary Public of the State of New Jersey.

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Also Present:
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Pedram Esfandiary, Esq. (By telephone)
Matthew Smith, Videographer

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THE VIDEOGRAPHER: This begins media labeled No. 1 of the video-recorded deposition of Dr. Christopher Portier in the matter of In re: RoundUp Products Liability Litigation, for the United States District Court, Northern District of California.

This deposition is being held at 700 Broadway in New York, New York on September 5, 2017, at approximately 9:04 a.m.

My name is Matthew Smith for TSG Reporting, Incorporated. I'm the legal video specialist.

The court reporter is Mary Bowman in association with TSG Reporting.

Will counsel please introduce yourself for the record.

(Whereupon counsel placed their appearances on the audio record. All attorney appearances will be on the final transcript).

THE VIDEOGRAPHER: Thank you. Will the court reporter please

swear in the witness.

CHRISTOPHER PORTIER,

called as a witness by the parties, having been duly sworn, testified as follows:

EXAMINATION BY

MR. LASKER:

Q. Good morning, Dr. Portier.

Dr. Portier, you served in May of 2005 as the chair of the IARC Science Advisory Board that recommended amendments to the preamble of the IARC monograph series, correct?

A. I'm not sure of the date. But the last time they did the preamble, I served as the chair. Actually, I was cochair.

Q. And the preamble is the document that sets forth the methodology that IARC working groups are required to follow in reaching their carcinogenicity classifications, correct?

A. That is correct.

Q. The group that you chaired recommended a number of revisions to the

monograph, correct?

MS. GREENWALD: Objection, form.

A. The group that IARC brought in, advisors, recommended a few changes to the preamble.

Q. For example, the science advisory board that you chaired recommended that IARC place greater weight on mechanistic data in reaching its cancer evaluations, correct?

A. The advisory group suggested that the mechanism data that was now becoming available was substantially different than what it was when the first preamble was written and they -- that the preamble needed to be revised to take into account modern mechanistic understanding of cancer.

Q. One of the things, for example, that your group recommended was that an agent might be classified as possibly carcinogenic to humans based solely on strong mechanistic data, correct?

MS. GREENWALD: Objection, form.

A. I don't know. I'd have to see the document to be certain that's the case,

and I'd have to see the previous document to see that it wasn't in the previous preamble.

MR. LASKER: Let me -- actually, let me mark both of these.

So we will mark as Exhibit 15-1 the report of the Science Advisory Group from May of 2005.

(Exhibit 15-1, document entitled, "IARC Monographs on Evaluation of Carcinogenic Risks to Humans," marked for identification, as of this date.)

MR. LASKER: And then we will mark as 15-2 a document that is labeled "Discussion of Changes in the Draft Preamble," which was prepared the same time -- or following the Science Advisory Board meeting.

(Exhibit 15-2, document entitled, "Discussion of Changes to Draft Preamble," marked for identification, as of this date.)

Q. Dr. Portier, just to clarify the record, Exhibit 15-1 is the report that your advisory group prepared for IARC,

correct?
MS. GREENWALD: Objection, form.
A. It does look like the report that we prepared for IARC.
Q. And on the second page of the report, in the listing of the participants, you are identified as the chair of this advisory group, correct?
A. That is correct. The cochair got ill, had to leave on the first date. That's why I am listed as the only chair and he is not listed.
Q. If we look at -- and the question was about the mechanistic data and some of the recommendations of your committee.
If you could look at Exhibit 15-2, and particularly at page 7 -- I'm sorry.
15-2 would be the changes, Dr. Portier?
You're looking at 15-1?
A. Yes. Sorry.
Q. 15-2 is discussing some of the changes following your advisory group recommendations.

And on page 7, towards the bottom of the page --
A. Yes.
Q. -- there is a paragraph that starts, "The expert workshop recommended in the consensus report."
Do you see that paragraph?
A. Yes.
Q. And then there is the sentence:
"Accordingly, the Advisory Group recommended that an agent can be characterized as possibly carcinogenic to humans based solely on strong mechanistic data."
Correct?
A. That's what it says.
Q. And that was one of the recommendations of your advisory group?
A. That's recommendation 12(d).
MS. GREENWALD: Objection, form.
A. So the advisory group cites the paper by McGregor, et al., which had looked at the presence or the ability to have data on animal carcinogenicity studies for an IARC monograph review, and McGregor

concluded that animal cancer bioassays were being used less and less in looking at the carcinogenicity of compounds and more and more other types of mechanistic studies were being used to supplant the need for a two-year chronic animal carcinogenicity study.
So that was the basis from which the discussion went on to look at the rest of it.
Q. Dr. Portier, my question is a simple one.
A. I know. I'm trying to find it in here.
"Changing the preamble to reflect this possibility, also taking into account" ...
Yes, that's exactly what the group said.
Q. So the Science Advisory Board, the chair recommended that the preamble be amended to mechanistic data alone could support a finding of possible carcinogenicity, correct?
MS. GREENWALD: Objection, form.

A. There is more verbiage to it than that.
Q. But in effect, that was the recommendation, correct?
MS. GREENWALD: Objection, form.
A. No, there is more verbiage to it than that. The verbiage deals with extremely strong and strongest from other relevant data could potentially be classified by IARC in Group 2B.
Q. OK. I stand corrected.
A. And to be clear, it says, "Similarly, an agent for which there is less than sufficient evidence from animal studies."
That means you could have limited evidence in animal studies, including inadequate evidence, and strong evidence from other relevant data could potentially be classified in Group 2B.
So it's important that that is linked with the strong data. You can't do it just because you have mechanistic data.
Q. Understood.
Your advisory group also

recommended that the preamble be amended, and if you want to look at pages 6 and 7 of the document, Exhibit 15-2, Discussion of Changes in Draft Preamble, your Science Advisory Board also recommended that the preamble be amended to allow for the finding of sufficient evidence of carcinogenicity in animals based on the results in a single animal study, correct?

MS. GREENWALD: Objection, form.

Q. And that is on the bottom of page 6, top of page 7.

MS. GREENWALD: Objection, form.

A. That is correct.

The previous preamble required that you have positive results from studies in two separate labs. The new preamble states that results in both sexes of a single species in a GLP study can provide sufficient evidence of carcinogenistic.

So you still have to have two positive findings of the carcinogenicity but they don't have to come from two separate laboratories.

Q. Your Science Advisory Board also

endorsed -- page 3 on the changes, Exhibit 15 -- 15-2 -- also endorsed the use of metanalyses to evaluate the human epidemiological data, correct?

A. Can you tell me where it is on here?

Q. Page 3, numeral 8 at the bottom.

A. Oh, it's right there.

Yes.

Q. And if you look at -- let me go back to 15-1, which is a report.

Page 4 of 5 discusses the fact that your group also reaffirmed the preamble's guidance that IARC working groups could only consider scientific studies in the published literature or publicly available reports from national and international agencies, correct?

MS. GREENWALD: Objection, form.

A. Do you know which issue this is?

Q. Page 4 and 5 in Exhibit 15-1 at the bottom, it says, "Data from monographs"?

A. Yes.

Q. And again, the question is that

your Science Advisory Board also reaffirmed the preamble's guidelines that IARC working groups could only consider scientific studies in the published literature or publicly available reports from national or international agencies, correct?

MS. GREENWALD: Objection, form.

A. That is correct.

Q. In December of --

A. But I believe that was in the previous preamble as well. We are simply agreeing with the previous preamble.

Q. Correct. That was the question.

A. Actually, the only change we changed from the previous preamble, what we were changing there was we could use government and international agency documents provided they were publicly available.

That was not in the previous preamble.

Q. Got it.

In December of 2005, you then served on the advisory group that reviewed and largely approved the recommendations

that had been made by your Science Advisory Board, correct?

MS. GREENWALD: Objection, form.

Q. And I can show you the documents if that would make it easier for your call.

A. I certainly don't remember that. Please.

MR. LASKER: So this will be Exhibit 15-3.

(Exhibit 15-3, document entitled, "IARC Monographs on Evaluation of Carcinogenic Risks to Human, Internal Report 6/001," marked for identification, as of this date.)

Q. You can turn to the second page -- third page, you will see your name listed as part of the advisory group.

A. Yes, but so were many of the others who helped were on the first advisory group.

Q. Just so we have a clear record, in December of 2005, you also served on the advisory group that reviewed and largely approved the recommendations made by your earlier Science Advisory Board, correct?

MS. GREENWALD: Objection, form.
A. There were several pieces to that question. Could you repeat it for me, please.
Q. In December of 2005, you served on the advisory group that reviewed and then approved the amendments to the preamble, correct?
A. In 2005, I served on two advisory groups. One made recommendations. The second one reviewed the new preamble to make sure that it actually matched the recommendations.
Q. From 2013 to 2014, you served as a visiting scientist at IARC, correct?
A. From, I believe, October 2013 'til April, March 2014, yes.
Q. What work were you doing for IARC during this period?
A. What work was I doing for IARC during this period?
I did several things. There was some joint collaborations on looking at genotoxicity due to a variety of chemicals using proteomics, metabolomics and

genomics.
I gave a seminar on genomics and genomic issues and some network modeling that allows you to pull up our genomic data and gave talks on that.
We worked on a manuscript that was recently published that looked at the ten characteristics of carcinogenesis, so I worked on that.
We were working on a review of the model -- of the Monographs 100. The Monographs 100 reviewed all of the known human carcinogens, and we had a couple of questions we wanted to ask from the known human carcinogens, such as how often do cancer seen in the animal match the cancer seen in humans? And other issues along those lines. How many times do rats match mice and how often is a mechanism tied to a specific tumor in humans rather than any tumor in humans?
So we were analyzing that data. And then we were using that at the same time to put together some guidance -- some points for guidance for mechanistic work

groups.
On the IARC monographs, when they came in to look at mechanistic data, I didn't end up putting those points together. That was done by IARC staff long after I left.
Q. Were you paid for your work as a visiting scientist at IARC?
A. IARC's visiting scientists are reimbursed for their expenses while they're in Lyon during that period of time. And I was reimbursed for those expenses; however, they were reimbursement of expenses. It was not salary.
Q. In April of 2014, you then served as the chair of the IARC advisory committee that designated glyphosate as a medium priority for review for carcinogenicity, correct?
MS. GREENWALD: Objection to form.
A. In -- was it April of 2014 -- if that's the correct date, I can't be absolutely certain -- in April of 2014, I chaired the IARC working group that looked

at approximately 200 chemicals that were nominated to the program by outside individuals to see what priority should be placed on evaluating those 200 compounds in the next five years for the IARC.
Q. And that group, among other decisions it made, designated glyphosate as a medium priority for review, correct?
A. Yes, that group recommended glyphosate for medium priority review.
Q. Do you recall who asked you to serve as the chair of that committee?
A. I don't remember which member of the staff was running that committee but probably Kurt Straif, the head of the program.
Q. At the time you served as the chair of this 2014 advisory committee, you had been serving as well for over a year as a senior scientist for the Environmental Defense Fund, correct?
A. I was working one day per week as a senior contributing scientist with the Environmental Defense Fund, yes.
Q. The Environmental Defense Fund

was founded in the late 1960s in connection with concerns about a pesticide called DDT, correct?

MS. GREENWALD: Objection, form.

A. I've never spent time looking at the history of the Environmental Defense Fund. So I really have no idea.

I've heard the same story as you.

Q. So your understanding is the Environmental Defense Fund got started around the issue of the pesticide DDT?

MS. GREENWALD: Objection, form.

A. Someone has told me that the Environmental Defense Fund began from a group of scientists on Long Island in New York who were trying to get DDT, a terrible environmental toxin, out of the -- out of their water, out of their air.

Q. And the Environmental Defense Fund over the ensuing 50 years continued to be active in opposing various pesticides, correct?

MS. GREENWALD: Objection, form.

A. I have no knowledge of that.

Q. During the same time that you

were working with IARC in reviewing glyphosate and other pesticides, you were also working with the Environmental Defense Fund in promoting a wristband project which was seeking to measure human exposures to pesticides and other chemicals, correct?

MS. GREENWALD: Objection, form.

A. I can't -- I do not know the answer to that question. The time frame is the issue here.

Q. So you do recall that you worked with the Environmental Defense Fund on the wristband project, correct?

A. But I can't be certain such work was done while I was also at IARC.

Q. I understand. I want to see if I get a clear answer to this: You do recall working with the Environmental Defense Fund on their wristband project, correct?

A. I do recall advising them on their wristband project, yes.

Q. And the wristband project was measuring human exposures to pesticides and other chemicals, correct?

A. It was measuring anything in the

person's environment that adhered to the latex -- the special latex that's on the wristband, and then that was in turn evaluated by GC mass spec to find out how much of each of these the people had encountered.

Q. Again, the wristband project that the Environmental Defense Fund conducted and you advised on was measuring human exposures to pesticides and other chemicals, correct?

MS. GREENWALD: Objection, asked and answered.

A. I don't really know if they had pesticides on the list of chemicals they measured. I can remember some of them but I can't remember exactly whether there were pesticides on there. But certainly, there were chemicals on that list.

(Exhibit 15-4, e-mail chain, dated October 21, 2015, marked for identification, as of this date.)

Q. Dr. Portier, I have provided you with a copy of an e-mail exchange. It starts off as an e-mail exchange between

you and Linda Birnbaum on October 21, 2015. Correct?

A. October 21, 2015, to Linda Birnbaum at -- at NIEHS, yes.

Q. For the record, who is Linda Birnbaum?

A. Linda Birnbaum is the director of the National Institute of Environmental Health Sciences and the director of the National Toxicology Program, former president of the Society of Toxicology, and a lot of other big, important titles.

Q. In this e-mail, you discuss two issues with Dr. Birnbaum: One dealing with work you're doing for the Environmental Defense Fund, and the second being work that you're doing in connection with glyphosate, correct?

MS. GREENWALD: Objection, form.

A. Could you ask the question again, please.

Q. Sure.

In your e-mail of October 21, 2015, you are discussing two issues: One is the work that you are doing for the

Environmental Defense Fund, and the second is the work that you have been doing with respect to glyphosate and a European regulatory decision about cancer, correct?

MS. GREENWALD: Objection, form.

A. Why is there a blacked-out section in this letter? I don't understand that.

Q. This was a document that was produced by the government and they blacked it out.

A. OK.

Anyway, the first paragraph deals with the work I'm doing in Europe on reregistration of glyphosate, which I find fascinating, and the second part deals with the work on wristbands with EDF.

MR. LASKER: And then if we can mark as Exhibit 15-5.

(Exhibit 15-5, report entitled, "Chem Daily Text Project: New Technology Sheds Light on Chemicals in Our Environment," marked for identification, as of this date.)

Q. And this Exhibit 15-5 is the

Environmental Defense Fund's report on its wristband project, correct?

MS. GREENWALD: Objection, form.

A. Yes, I believe this is EDF's report on their wristband testing project.

Q. As reflected in this report, the wristband project that you consulted on for Environmental Defense Fund reported results for detections of pesticides as -- if you look at the second page, 12 different pesticides as part of its analysis and the findings of pesticides in 93 percent of the participants, correct?

MS. GREENWALD: Objection, form.

A. This does then clarify that I couldn't remember if there were pesticides, but yes, obviously, there were pesticides in here. And that the pesticides were seen in -- I have to look and find that percentage. I'm sorry.

Q. The first page will show you the percentage in the blocked-out, gray area in the gray box.

A. 93 percent detected one or more pesticides, that is correct.

Q. Your affiliation with the Environmental Defense Fund was not disclosed in that April 2014 IARC advisory committee report, correct?

MS. GREENWALD: Objection, form.

A. Again, could you repeat the question.

Q. Sure.

April 2014, you served as the chair of the IARC advisory committee that designated glyphosate as a medium priority?

A. Correct.

Q. Your affiliation with the Environmental Defense Fund was not disclosed in that IARC advisory committee report, correct?

MS. GREENWALD: Objection, form.

A. The IARC advisory committee report did not list -- well, I'd have to look now. I'd have to see a copy of the report. I'm sorry.

Q. Do you recall whether IARC knew -- at the time that you served as chair of their advisory committee, do you know if they knew of your work with the

Environmental Defense Fund?

A. Yes.

Q. Shortly after your advisory group designated glyphosate as a medium priority, IARC announced it would be convening a working group to evaluate a number of pesticides for -- to determine whether they could be classified as carcinogens, correct?

A. I don't know.

MR. LASKER: I'm going to mark as -- we will make this the next two in line, Exhibit 15-6 and 15-7, two notices from IARC announcing upcoming meetings, particularly meeting 112.

And for the record, I will represent that these documents were pulled off of IARC's website using something called a Wayback Machine, which allows you to actually date when it appeared on the IARC website.

So the first document is dated July 16, 2014, and the second is October 7, 2014.

(Exhibit 15-6, IARC announcement,

dated July 16, 2014, marked for identification, as of this date.)

(Exhibit 15-7, IARC announcement, dated October 7, 2014, marked for identification, as of this date.)

MS. GREENWALD: Which is which?

MR. LASKER: July 16 is the 6, and October 7 is the 7. So chronological order.

Q. So just so we have the timing correct, in April of 2014, your advisory committee designated glyphosate as medium priority, correct?

MS. GREENWALD: Objection, form.

A. In --

Q. April of 2014.

A. -- '14, the advisory group recommended several compounds for high priority and some for medium priority, of which glyphosate is one of the products.

Q. And in July of 2014, IARC announced meeting 112, which was going to be focused on organophosphate insecticides, correct?

MS. GREENWALD: Objection, form.

A. It appears from your Wayback Machine review that that is the date which IARC put up this notice that says, "Some organophosphate insecticides, not specifically glyphosate."

Q. And then October 7, 2014, that notice was amended and for meeting 112, they now also include glyphosate to be reviewed, correct?

MS. GREENWALD: Objection, form.

A. It appears that, from your Wayback Machine, October 7, that that is correct, that in October, IARC appended herbicides to their organophosphate insecticides review.

It is not uncommon for IARC to group chemicals when they do reviews if the chemicals have similar behavior or the datasets for the chemicals come from similar sources.

So because many people -- many of the epidemiology studies were pesticides and herbicides combined, it makes good sense to do it here because you're reviewing the same epidemiological studies.

Q. But just to be clear, glyphosate is not an organophosphate insecticide, correct?

A. That is correct.

Q. The working group 112, you ultimately were asked to serve as an invited specialist to this committee, correct?

A. I was asked to serve as an invited specialist to this committee. I was asked -- yes.

Q. Let me ask: Did you ask to serve on the committee or did somebody ask you to serve on the committee?

A. I was asked in the normal way that IARC asks people to serve on these committees, by an e-mail sent to me -- first, they call you and say, "Are you interested?" And then they send you an e-mail.

Q. Do you recall who asked you to serve as an invited specialist for working group 112?

A. No. I really don't recall. It could have been any member of the staff.

Q. An invited specialist is someone whom IARC believes has critical knowledge and experience on a matter but has real or apparent conflicts of interest, correct?

MS. GREENWALD: Objection, form.

A. The definition of an "invited specialist" is part of the preamble. And if what you have just said is a quote from the preamble, then that would be correct.

Q. Well, why don't we take a look at the preamble then.

A. I don't have it yet.

Q. You are about to get it.

A. I thought you had given it to me.

(Exhibit 15-8, document entitled, "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Preamble, marked for identification, as of this date.)

Q. If you could look at page 4 of the preamble, line 32 to 33 -- they are nice enough to have line numbers for us.

A. That is the definition.

Q. So invited specialist is someone who IARC believes has critical knowledge

and expertise on the matter but who has a real or apparent conflict of interest, correct?

A. That is what it says, that is correct.

Q. Your conflict of interest arose because of your role with the Environmental Defense Fund, correct?

MS. GREENWALD: Objection, form.

A. To be clear, it's a perceived conflict of interest, not necessarily a conflict of interest. And they're very clear here on the language that it have -- they talk about apparent or real.

In this case, it is a perception that this is a conflict of interest. But yes, that was the perceived conflict of interest that they were concerned about.

Q. And you had that same conflict of interest when you served as the chair of the advisory committee that prioritized glyphosate for evaluation, correct?

MS. GREENWALD: Objection, form.

A. The correct answer to the question is no.

And here is why that's the correct answer to the question as you asked it: The 2014 meeting was an advisory group, not a monograph meeting. So it doesn't work under the same rules as the preamble. So that's case No. 1.

But IARC does give you a form that you have to fill out for potential conflicts of interest for every meeting.

For that meeting, because it was an advisory group, and because I was only doing work with the Environmental Defense Fund on issues related to air pollution and climate change and hydraulic fracking, in my opinion, I did not think it was a conflict of interest, and therefore, I did not list it.

Q. And do you recall, sitting here today, whether during that period in April of 2014, you had begun consulting with the Environmental Defense Fund on the wristband project?

A. I do not recall.

Q. Aside from your role on the advisory committee that prioritized

glyphosate for review, had you reviewed the science on glyphosate prior to being appointed to working group 112?

MS. GREENWALD: Objection to form.

A. Prior to being appointed to working group 112, I had not looked at any of the scientific evidence on the carcinogenicity of glyphosate.

Q. Let me show you an e-mail that we received from one of the other working group members.

MR. LASKER: And we will mark this as 15-9.

(Exhibit 15-9, e-mail dated March 3, 2015, marked for identification, as of this date.)

A. What is this?

Q. This is an e-mail that is dated March 3, 2015, which was the beginning of the IARC 112 working group time period.

A. OK.

Q. The subject line is "E-mail Subgroup 4," which is the subgroup on mechanisms, correct?

A. That would usually -- yes, that would be it.

Q. And this is creating an e-mail tree of the members on this subcommittee, correct?

A. That appears to be the case, yes.

Q. And you were included as one of the individuals working on subgroup 4 at working group 112, correct?

A. That is correct.

Q. Were you assigned by IARC to work with the mechanism subgroup?

A. Yes, I was.

Q. Were you tasked with preparing any analyses before the actual physical meeting in Lyon?

A. No, I was not.

Q. We have a couple of other e-mails between the mechanistic subgroup members I would like to ask you about.

(Exhibit 15-10, e-mail dated March 4, 2015, marked for identification, as of this date.)

Q. This March 4, 2015 e-mail, again, to members of subgroup 4, and you're

included, correct, as a recipient of this e-mail?
A. Yes, I'm included, and yes, it's an e-mail to it appears to be subgroup 4 with a copy to Kate Guyton.
Q. This March 4, 2015 e-mail to you and the other mechanism folks attached an early draft of Sections 4.6 and a summary of 4.5 for each of the four chemicals being reviewed, including glyphosate, correct?
MS. GREENWALD: Objection, form.
A. It seems to say that Section 4.6 in summary of 4.5, two- or-three sentence summary, was attached.
Q. And Dr. Martin is providing you all with this summary to provide folks with something to include in their respective 4.6 sections, correct?
MS. GREENWALD: Objection, form.
A. I don't know.
Q. The last clause --
A. Oh, I see, yes, Section 4.6 is the summary of the Section 4 evaluation.
Q. And were you working on one of the 4.6 sections?

A. No, I don't write any of the sections in the IARC monograph.
MR. LASKER: We also have a March 6, 2015 e-mail. This will be Exhibit 15-11.
(Exhibit 15-11, e-mail dated March 6, 2015, marked for identification, as of this date.)
Q. And this is a -- this e-mail is from Kathryn Guyton, and she is with the IARC staff, correct?
A. Uh-huh. Yes.
Q. And there is an e-mail to you and other subgroup 4 working group folks again talking about the work that the mechanistic subgroup was doing during this period, correct?
MS. GREENWALD: Objection, form.
A. It's a complicated question.
Q. OK, I'm not sure it's complicated but I'll ask it again.
This e-mail between you and the other individuals working on the mechanism subgroup was part of the work that was done during that week on mechanisms at working

group 112, correct?
MS. GREENWALD: Objection, form.
A. This is an e-mail. It deals with the work of Section 4 during the IARC monograph.
Q. During the working group 112, did you spend all of your time when the meeting was not in plenary session with the mechanism subgroup?
A. No.
Q. What other subgroups did you -- well, let me ask this: Did you go from different subgroup to different subgroup during the meeting?
A. No. I spent a short period of time with the animal carcinogenicity subgroup.
Q. Do you recall when that was?
A. No, I do not recall.
Q. Did they ask for you to help them out or did you decide on your own to spend some time with them?
A. They asked for me to help them out.
Q. Do you recall what specifically

they asked you to help them with?
A. Yes, I do.
Q. What was that?
A. The topic dealt with the, I believe, kidney tumors in the Knezevich and -- I forget the name of the authors -- rat study, and the question had to deal with historical controls.
Q. So just to be clear, is this a Knezevich rat study or a Knezevich mouse study?
A. I guess Knezevich I'm hoping was a mouse study and it's -- the mouse study. Sorry.
There are so many studies, I get confused.
Q. Do you recall specifically what their question was with respect to historical controls?
A. The question was did this tumor appear to be significant because of the historical control population that had been identified, and then, also, where could they get code to do a trend test on that particular data.

Q. Did you provide them with the -- did you advise them as to where they could find code to conduct a trend test on the data?
A. I gave them some suggestions of where to look. I was unaware of any place where it could be found, if I recall -- if I recall correctly.
Q. Did you assist in calculating the -- the trend test that appears for that study in the IARC monograph?
MS. GREENWALD: Objection, form.
A. I'm not sure what you're asking me.
Q. The IARC --
A. The p-value was obtained from a program identified by one of the members in either that subgroup or the mechanism subgroup, and that person ran the code.
Q. Do you recall who that was?
A. I think it -- I'd have to see a list of the authors of the monograph and I could probably pull -- I'm terrible with names -- I could probably pull it from the list.

Q. Did you review the statistical analysis after it was conducted?
A. Yes, I did.
Q. While you were at the monograph meeting?
A. Yes, I did.
Q. And did you verify that that analysis was conducted correctly?
MS. GREENWALD: Objection, form.
A. I verified that the approximate p-value from the Armitage linear trend test that was run in that analysis appeared to be correct.
Q. Did you understand at the time that that was an approximate trend test?
MS. GREENWALD: Objection, form.
A. I did not know it either way.
Q. Did you attend any of the plenary suggestions that was conducted during that week for working group 112?
A. All of them.
Q. And about midway through the week, there was a -- there was a presentation before the plenary in which the subgroups provided their initial

assessment of the data.
Do you recall that?
MS. GREENWALD: Objection, form.
A. At every IARC monograph meeting about midweek there were presentations from each of the working groups as to where they are and where they think the decisions are going.
Q. Let me show you copies of some handwritten notes that we received from Dr. Matthew Ross from Mississippi State.
MR. LASKER: And we will mark this as next in line. It's 15-12.
(Exhibit 15-12, handwritten notes dated 3/6/15, marked for identification, as of this date.)
Q. Dr. Ross was a member of the mechanism subgroup with you, correct?
MS. GREENWALD: Objection, form.
A. Dr. Ross was a member of the mechanism subgroup.
Q. Now, on the last page of these notes, Dr. Ross has written some notes about what was being said about glyphosate at this meeting. And --

A. Where is this?
Q. This would be the last page, the bottom half of the page. Do you see group 1, group 2, group 3, group 4, with listings for glyphosate?
It's going to be the last page of the document.
A. Yes, I do see that.
Q. And there are notes for subgroup 1, which is for exposure data, correct?
A. Correct.
Q. And there's a notation here, "Detectable in water and food."
Do you recall that discussion?
MS. GREENWALD: Objection, form.
A. Not specifically. But it is normal.
Q. And then there is a note for subgroup 2 for human data, correct?
MS. GREENWALD: Objection, form.
A. There appears to be a note on glyphosate in human data under group 2.
Q. And Dr. Ross' notes indicate that subgroup 2 stated that glyphosate was

negative NHL, and then says, "Case control glyph" with an arrow "NHL," and then a notation, "AHS negative data," correct?
MS. GREENWALD: Objection, form.
A. That's exactly what it says.
Q. And "AHS" is referring to the Agricultural Health Study, correct?
MS. GREENWALD: Objection, form.
A. I can't presume that.
Q. Do you recall whether there was discussions at the Agricultural Health Study during this working group meeting?
A. Of course there were discussions of the Agricultural Health Study during this meeting.
Q. With respect to group 3 -- subgroup 3, that is the animal subgroup, correct?
A. That is correct. That's -- if this note pertains to that, yes.
Q. And Dr. Ross wrote down that the animal subgroup said that the animal carcinogenicity data for glyphosate was limited to inadequate, correct?
MS. GREENWALD: Objection, form.

A. It -- he has written a note that says, "Glyphosate - limited to inadequate."
Q. "Limited" and "inadequate" are both defined terms in the IARC preamble, correct?
A. For the animal data, yes.
Q. Do you recall a presentation during a plenary session in working group 112 where the animal subgroup was discussing the animal data for glyphosate as being limited to inadequate?
MS. GREENWALD: Objection, form.
A. I can't recall.
Q. You don't recall one way or the other?
A. No. This is a preliminary -- if he is taking notes from the preliminary meeting, it's just a preliminary meeting. And so I have no clue as to -- I mean, it's typical to have these discussions in plenary midweek.
Q. And just so the record is clear, this would have been a presentation by the animal subgroup after the period of time that it had taken prior to the meeting to

conduct their analysis and then after the first few days of the subgroup meeting, correct?
MS. GREENWALD: Objection, form.
A. In a typical IARC monograph meeting, midway through the week, the animal group would have gone through each of the papers together, discussed problems with the paper, and were beginning to think about where they would go with the call, that is correct.
Q. Do you recall yourself voicing any objections to the animal group's preliminary assessment of the glyphosate data?
A. At this point?
I might have -- I wouldn't have voiced concern at their calling it "limited." But I might have voiced concern at their interpretation of one or two of the studies.
Q. Let me show you another e-mail we received from Dr. Ross.
(Exhibit 15-13, e-mail dated March 11, 2015, marked for

identification, as of this date.)
Q. Dr. Portier, Exhibit 15-13 is an e-mail from Ivan Rusyn initially to -- it doesn't have a "To" line here but it is discussing convening group 4 downstairs in the first coffee break on March 9, 2015.
Do you recall attending a meeting of group 4 -- March 9, just to refresh your recollection, will be the second-to-last day of the IARC working group meeting.
Do you recall attending a coffee break meeting of the mechanism subgroup on March 9, 2015?
MS. GREENWALD: Objection, form.
A. There is no way I could recall a small submeeting at an IARC monograph meeting and whether I was in attendance or not.
Q. Do you recall discussions with respect to whether or not glyphosate should be classified as 2B or 2A under the IARC classification scheme?
A. Could you ask the question again? I want to be clear I got that question right.

Q. Do you recall discussions during the working group meeting with members of group 4 as to whether or not glyphosate should be classified as 2B, possible carcinogen, or 2A, probable carcinogen?

A. I was specifically not allowed to do that.

So the answer to that question is: As an invited expert, I would have not encouraged in one way or the other on any of the -- any of the final listings, but I would have talked about the science and the interpretation of that science.

Q. Would you have talked about whether or not the -- in your opinion, the mechanistic data was strong so as to allow -- and I recognize you wouldn't have continued in the next step -- but so as to allow under the preamble glyphosate to be moved from 2B to 2A?

MS. GREENWALD: Objection to form.

A. I specifically remember the discussions that group had relative to the strength of the evidence for mechanisms for

glyphosate, and I clearly remember keeping my mouth shut. Because I was an invited specialist and that was my job.

Q. Do you recall that as of March 9 -- so this would be three days after the notes we looked at from Dr. Ross -- the animal subgroup had -- was classifying the data -- the animal data as for glyphosate as limited?

MS. GREENWALD: Objection, form.

A. So IARC monographs are owned completely by the entire working group. And so the animal carcinogenicity working group would make a recommendation. However, the entire working group has to agree or conclude or concur with that recommendation. Otherwise, it can change.

As you can see in this case, Ivan Rusyn had concerns about limited evidence in animals, but yes, up to March 9, it appears that the animal working group was going to recommend limited.

Q. Just so I understand the process, the animal subgroup recommended that the animal data was limited, but the full

working group ultimately decided that the animal data was sufficient for glyphosate, is that correct?

MS. GREENWALD: Objection, form.

A. I can't be certain that's the way it actually worked.

Q. You were at the meeting, do you recall that's how it worked?

A. I don't recall. I've seen cases where the entire working group has changed the recommendation in the plenary session before. I can't remember.

Q. Following the working group meeting, the working group's conclusions were published in an article in The Lancet, correct?

A. Very brief summary, abstract more than anything else, yes.

Q. Does IARC have an arrangement with The Lancet to publish abstracts of its meetings?

A. Yes, they do.

Q. This happens shortly after the meetings are concluded, correct?

A. That is correct.

Q. Just so I understand the process, this is not a peer-reviewed article that appears in The Lancet correct?

MS. GREENWALD: Objection, form.

A. I actually do not understand the way in which Lancet reviews this article. So I can't answer the question.

MR. LASKER: Let me mark as next in line 15-14.

(Exhibit 15-14, e-mail dated March 13, 2015, marked for identification, as of this date.)

Q. Here is an e-mail March 13, 2015 to you and other members of the working group from Kathryn Guyton asking for comments on the draft article that was to appear in Lancet about the working group 112 meeting, correct?

MS. GREENWALD: Objection, form.

A. This is an e-mail from Kathryn Guyton sending a draft of the document that will be going into Lancet Oncology and asking for these members of the working group to review it for clarity.

Q. Do you recall if you reviewed the

draft and provided any comments?
A. I'm pretty certain I would have read it. I don't recall if I provided comments.
Q. You agree that your involvement in the IARC working group on glyphosate had the appearance of being a conflict of interest, correct?
MS. GREENWALD: Objection, form. That's not his testimony.
A. The fact is that IARC felt it was a potential or a perceived conflict of interest. That is the fact. My opinion doesn't matter.
Q. Well, my question though is about your opinion.
You do agree that your involvement in the IARC working group on glyphosate has the appearance of being a conflict of interest, correct?
MS. GREENWALD: Objection.
A. I'm having a tough time with the question. I've never really thought about it.
Do I think I had a conflict of

interest? No. But would others potentially see it as a conflict of interest? Of course, yes.
Q. So you do --
A. Some others, not all others. Some others.
Q. So just to be clear, you do agree that your participation in working group 112 on glyphosate has the appearance of being a conflict of interest?
MS. GREENWALD: Objection, form.
A. As I said before, I agree with the statement that some people would perceive it as a conflict of interest.
Q. A few months after IARC reached its causation determination, the issue of whether glyphosate can cause cancer was considered by European regulators, correct?
A. I am sorry, what was the first part of that sentence?
Q. Some months after IARC reached its causation determination, the issue of whether glyphosate can cause cancer was considered by European regulators, correct?
A. Specifically considered by the

European Food Safety Authority.
Q. You registered your company as a lobbyist in Europe so you could lobby against glyphosate reregistration, didn't you?
MS. GREENWALD: Objection, form.
A. No, I did not.
Q. Let's take this in steps.
A. Sure.
Q. You did lobby -- you did register your company as a lobbyist in Europe, correct?
A. No, I did not. At least as far as they told me I did not.
Q. Who is "they"?
A. Go ahead and put it in and I'll explain.
MR. LASKER: This is Exhibit 15-15.
(Exhibit 15-15, printout from LobbyFacts, marked for identification, as of this date.)
Q. Dr. Portier, this is a document put out by LobbyFacts EU, which notes that your company, C. Portier Consultations, was

at least thought to be registered, if not registered, as a lobbyist in Europe in connection with the reregistration decision for glyphosate, correct?
MS. GREENWALD: Objection, form.
A. I -- there are so many parts to that, I have no idea.
Would you like me to tell you what this is?
Q. Let me first go through the document.
On the second page of the document, it talks about a C. Portier Consultations registration on EU transparency register, and the issue was registration of the pesticide glyphosate, correct?
A. It says something like that.
Q. And the office that's listed here is the Office of C. Portier Consultations, correct?
A. It's my home address.
Q. And at least according to this source, your company was registered in Europe to consult on a reregistration of

the pesticide glyphosate, correct?
MS. GREENWALD: Objection, form.
A. That is not my understanding.
Q. What is your understanding?
A. We were asked by the commissioner of health -- four of the scientists who participated in a -- who were coauthors of a letter sent to the commissioner concerning the quality of the review done on glyphosate by the European Food Safety Authority.
The commissioners' staff told us that we could not -- we would have to register to come in and talk to the commissioner because everybody has to register. They gave us a particular space to fill it in on the EC website.
I went to that spot, I filled this in as they asked me to fill it in, since I had to come up with a title for the company, or -- because the thing wouldn't take nothing in that spot, I called it C. Portier Consultations, for lack of a better term.
The day after I entered this, the

staffer called back and said, I have this all wrong. I'm sorry. You can come see the commissioner because all you want to talk about is scientific issues. You're not lobbying on behalf of a company. You're all academics. You don't have to do this, but I had already done it.
Q. Just so I understand, you were told by the staff European -- a staffer on the European Commission --
A. Yes.
Q. -- that you didn't have to register because you were not presenting your views on behalf of any private entity, is that correct?
MS. GREENWALD: Objection, form.
A. They -- they told us we were not lobbyists and this list was for lobbyists, and therefore, we did not need to register. That was the crux of the conversation.
Q. The reason you didn't have to register is because you were not providing information -- or you were not talking to the European regulators on behalf of any private -- other private entity, correct?

MS. GREENWALD: Objection, form.
A. I don't exactly know how to answer that question because I don't know what their rules specifically are. All I did was respond to what the staffer told me I had to do.
Q. In any event, after this discussion, you then did appear and speak with European Parliament, European regulators, about glyphosate, correct?
A. That's too complicated a question for me to answer.
I met with very specific people. The head of the -- the health commissioner for European Commission and several of his staff members. I think one of them was a regulator but I can't be absolutely certain.
There was interaction on my part with EU parliamentary members and there was interaction on my part with other members of parliament and conferences at various other national authorities.
Q. On early November of 2015, you reached out to other members of the IARC

working group to help you in your discussions with the European regulators, correct?
MS. GREENWALD: Objection, form.
A. At some point before that letter went out, I asked other scientists to -- who were interested to join me in writing the letter.
MR. LASKER: Let's mark this as Exhibit 15-16.
(Exhibit 15-16, e-mail chain dated 11/9/2015, marked for identification, as of this date.)
Q. Exhibit 15-16 at the bottom of the first e-mail in the chain is an e-mail that you sent to a number of other scientists dated November 9, 2015 regarding the EFSA review of glyphosate, correct?
A. That appears to be what it is.
MS. GREENWALD: Eric, the Bates is cut off the bottom. Do you know what it is? It doesn't appear on this document.
MR. LASKER: I don't. We will get that for you. I don't have it.

MS. GREENWALD: Thank you.
Q. In this e-mail, you were telling these other scientists that the European Food Safety Agency was going to conclude that glyphosate has no carcinogenic potential, correct?
A. I believe I read that, yes.
Q. And you were telling these individuals that this created two problems in your view: That it might weaken the IARC monograph program, and suggest that the IARC working group did not adequately review all of the data, correct?
MS. GREENWALD: Objection, form.
A. No.
Q. You stated and quoted specifically then, that EFSA's determination that glyphosate had no carcinogenic potential created two problems: One that it weakens the strength of the IARC monograph program to stimulate change in how some of these agents are reviewed and addressed.
And the second is that it suggests we did not do our assessment

adequately and that had we seen all the data they saw, they would have gotten -- we would have gotten a different answer, correct?
MS. GREENWALD: Objection, form. That wasn't what he testified.
A. No, it was not read exactly, but the point of my saying "no" before is you said I said it would weaken the IARC monograph program.
That's not what this says. It says it weakens the strength of the IARC monograph program to stimulate change. That's not weakening the program.
Q. And then the second concern that you had is that it would suggest that the work that we did -- and by "we," you are talking about working group 112, correct?
A. Yes, I guess so.
Q. That if we did not do our assessment adequately, and if we had seen all the data, we would have gotten a different answer, correct?
A. In fact, this suggestion was all over, from EFSA, from PF4, from others as

well.
Q. You state in your e-mail to these scientists, "I do not intend to let this happen." Correct?
A. I do not intend to let the strength of the IARC monograph program to stimulate change in how these agents are reviewed happen, and I do not intend to let it happen that people said we did our estimate wrong.
Q. On November 11, 2015, you sent a follow-up e-mail to a broader group of recipients, again raising the same concern about the EFSA's conclusion that glyphosate does not cause cancer, correct?
MS. GREENWALD: Objection, form.
(Exhibit 15-17, e-mail chain dated November 11, 2005, marked for identification, as of this date.)
A. OK, what is your question now?
Q. On November 11, you sent a follow-up e-mail to a broader group of recipients, again raising concerns about EFSA's conclusion that glyphosate did not cause cancer, correct?

MS. GREENWALD: Objection to form.
A. That would be incorrect.
I raised concerns about scientific flaws in the BFR addendum. I am concerned that the serious flaws of the BFR addendum, if not challenged, can continue to be used by regulatory agencies to dismiss critical science pertinent to regulatory decisions.
Q. You are asking this broader group of scientists to join you in a letter to be sent to the European regulators about glyphosate, correct?
A. That is correct.
MR. LASKER: Why don't we take a break?
MS. GREENWALD: That's up to you. Yeah, OK.
THE VIDEOGRAPHER: The time is 10:19 a.m. We're off the record.
(Recess.)
THE VIDEOGRAPHER: The time is 10:34 a.m. We are on the record.

BY MR. LASKER:
Q. Dr. Portier, before the break, we were talking about some e-mails that you had sent to some scientists in November of 2015.
Do you recall that?
A. Are you -- you're talking about document 15-17?
Q. Yes. And 15-16.
A. Could you read the question again -- restate the question.
Q. All I asked is we were talking about e-mails that you had sent to scientists --
A. We were talking about these two documents.
Q. -- in November 2015.
A. We were talking about these two documents, correct.
Q. As of the time you sent these e-mails, you had been signed on as an expert consultant for plaintiffs' counsel in this litigation for more than seven months, correct?
MS. GREENWALD: Objection, form.

A. I can't be certain of the exact amount of time.
MR. LASKER: Let's mark as the next document in line, which is 15-18.
(Exhibit 15-18, letter dated March 29, 2015, marked for identification, as of this date.)
Q. Dr. Portier, these are documents that you produced to us in response to our requests -- document requests for this deposition.
And as set forth in this cover letter, or this first letter, you signed an engagement letter signing up as an expert consultant with plaintiffs' counsel in this litigation on March 29, 2015, correct?
A. That is correct.
Q. So that would be more than seven months before?
A. I just wasn't sure of the dates. I'm sorry.
Q. So this is about seven months or so before you sent those e-mails out that we were just looking at, correct?
A. Probably, yeah.

Q. You did not disclose in your e-mail to these other scientists asking you to join you in this letter the fact that you were a paid consultant for plaintiffs' counsel in this litigation, did you?
MS. GREENWALD: Objection, form.
A. The draft document has a -- what is it at the end -- the manuscript has a thing at the end that says if anybody has any conflicts of interest, and that was already, as far as I remember, in the draft.
But the letter itself does not disclose that.
Q. Well, let's take this one step at a time.
The e-mail that you sent to these other scientists -- or the two e-mails you sent to these other scientists asking them to join you in this letter does not disclose the fact that you had been working as a paid consultant for plaintiffs' counsel in the litigation, correct?
A. The e-mail had an attachment. The attachment was the draft of the letter.

I believe the attachment had the conflict of interest to it on the draft, but I'm not certain.
Q. Let's look at the letter that you actually sent.
MR. LASKER: We will mark this as Exhibit 15-19.
(Exhibit 15-19, letter dated November 27, 2015, marked for identification, as of this date.)
Q. This is the letter that was ultimately sent -- the open letter that was sent by you and the individuals you had asked to join you to Commissioner Andriukaitis, European Commission?
A. Yes.
Q. This November 27, 2015 letter also does not disclose the fact that you had signed on as a paid consultant with plaintiffs' counsel in this litigation, correct?
A. That appears to be the case.
Q. So neither the e-mails that you sent to these other scientists asking you

to join you in the letter to the European regulators or the letter you actually sent to the European regulators in November of 2015, disclosed the fact that you had been working with plaintiffs' counsel in this litigation for over seven months, correct?

MS. GREENWALD: Objection to form.

A. That is a complicated question. Could you simplify it for me.

Q. We will take it in parts.

The two e-mails that you sent in November of 2015 to the scientists asking you to join you in this letter to the European regulators regarding glyphosate does not disclose the fact that you had been working as a private consultant for plaintiffs' counsel in this litigation, correct?

MS. GREENWALD: Objection, form.

A. Letter 15-17 and 15-16 do not say that I'm consulting with these law firms.

Q. And the open letter that you sent to the European Commission on November 27, 2015, also does not disclose the fact that

you had been working for over seven months as a paid consultant for plaintiffs' counsel in this litigation, correct?

A. That is correct.

Q. You signed on as a private consultant for plaintiffs' counsel nine days -- within nine days of the publication of The Lancet article announcing IARC's 2A classification of glyphosate, correct?

A. Where is the date of that again?

Q. We can show that to you.

A. Here it is, March 29 of 2015. That appears to be the case.

Q. When did you first speak with plaintiffs' counsel about working with them as an expert in this litigation?

A. March 20 -- soon -- before March 29.

I was already working with counsel --

Q. OK, so when were you --

A. -- on something different.

Q. So when did you -- let's ask that.

So this is with Mr. Lundy?

A. I don't know to what degree my discussions with them become confidential, so I'm at a loss here.

Q. I'm not going to ask you about the actual substance of the conversations, although that's a separate issue, not a privilege issue, but my question right now is dates.

When did you --

A. So that was with Mr. Lundy, in answer to your question.

Q. And you had been working with Mr. Lundy on other matters prior to March 2015, is that correct?

A. As far as I recall, yes.

Q. Were you -- for those other matters, have you been disclosed as a testifying expert in connection with those?

A. I'm not a testifying expert in those.

Q. Do you know if your involvement in that litigation has been publicly disclosed?

A. That I do not know.

Q. How long prior to March 2015 had

you been working with Mr. Lundy?

A. I don't know. Maybe two months.

Q. When do you recall -- and obviously, it's going to be sometime -- would it be fair to say sometime between March 20, when the IARC classification was announced, and March 29, when you had a conversation with Mr. Lundy about working as an expert in the glyphosate litigation?

MS. GREENWALD: Objection to form.

A. The answer is that's not correct.

Q. When did you have your first conversation with Mr. Lundy about working as an expert for plaintiffs in glyphosate litigation?

A. Sometime prior to this agreement here. Maybe a few days. I have no idea.

But the IARC monograph finding was announced the day the monograph closed. The publication was later.

Q. Do you recall whether you had your first conversation with Mr. Lundy before or after The Lancet article was published?

A. No.
Q. It could have been before, could have been after, you don't recall?
A. Don't recall.
Q. Is the other matter that you are working with or -- with Mr. Lundy related to a -- and you don't have to identify the substance, but a substance that has been part of an IARC review for carcinogenistic?
A. There have been many substances for review by IARC for carcinogenicity, this one included.
Q. So the other work you're doing for Mr. Lundy also involves an IARC-reviewed substance, is that correct?
A. That is correct.
Q. You had -- in your retention agreement on March 29, 2015, it notes that you will be working both with Mr. Lundy and with Ms. Greenwald for Weitz & Luxenberg, correct?
And her name is specifically mentioned on I think page 3 of the agreement.
A. Yes.

Q. Have you worked with Ms. Greenwald or her firm prior to this time?
A. No.
Q. Just one other question with respect to the other consulting work with Mr. Lundy.
The other matter, is that -- does that involve a substance for which you had served on the IARC working group?
A. Define "substance"?
Q. The issue that you're consulting with them -- the other issue that you are consulting with, does that involve exposures that were reviewed by IARC on a working group that you were part of?
A. Yes.
Q. So pursuant to the terms of your agreement with your March 29, 2015 letter, your engagement with plaintiffs' counsel began on March 29, 2015 and has continued through to the present, correct?
A. Yes.
Q. You were paid a $5,000 retainer by plaintiffs' counsel on or about March

29, 2015, correct?
A. Correct.
Q. You agreed in March 29 -- and this is on page 3 of your engagement letter -- to work under the exclusive direction of three attorneys at the Lundy Lundy law firm, and Robin Greenwald of Weitz & Luxenberg, correct?
MS. GREENWALD: Objection, form.
Q. That's No. 6.
MS. GREENWALD: Objection.
A. No. 6 says I will be working under the exclusive direction of Hunter Lundy, Matthew Lundy and Kristie Hightower with Lundy, Lundy, Soileau & South, and Robin Greenwald with Weitz & Luxenberg.
Q. You agreed on March 29, 2015 -- and this is No. 7 on -- numeral 7 on page 3 -- that any and all work product created by you or on your behalf in whole or in part during the course of this engagement authorized by these attorneys shall be considered a work for hire and the property of the firms, correct?
A. That is correct.

Q. You agreed on March 29, 2015, in -- on page 3, numeral 4, that you would not do any other work related to glyphosate outside the specifics of the litigation without the written consent of the plaintiffs' attorneys, correct?
A. It says, "I will not accept any RoundUp or glyphosate-related engagement with any law firm that is party to RoundUp and/or glyphosate-related litigation without their written consent."
Q. You also agreed on March 29, 2015 -- and this is on page 2 -- that you would not disclose your work for plaintiffs' counsel to media organizations, trade journals, professional publications, members of the public or other purported experts, correct?
MS. GREENWALD: Objection, form.
Q. That's No. 3.
MS. GREENWALD: Same objection.
A. No. 3, sorry.
Now, your question again, please.
Q. You agreed on March 29, 2015, that you would not disclose your work for

plaintiffs' counsel to media organizations, trade journals, professional publications, members of the public or other purported experts, correct?
A. Correct.
Q. You agreed to retain the plaintiffs' lawyers to represent you if anyone sought to compel you to disclose this information, correct?
A. I believe that's what part C says.
Q. And you began billing plaintiffs' counsel for your time as of -- and this is the first invoice attached -- June 17, 2015, correct?
A. Yes.
Q. You had a meeting on June 17, 2015 with Mr. Lundy, and then a second meeting with Mr. Lundy and Ms. Greenwald on June 19, 2015, correct?
A. That is correct.
Q. On October 19, 2015, you sent plaintiffs' counsel an invoice for your work on their behalf from June of 2015 to October of 2015, correct?

A. Yes.
Q. And you have been working as a paid consultant for plaintiffs' counsel throughout the entire time that you have had discussions with regulators in the United States and in Europe about glyphosate, correct?
MS. GREENWALD: Objection, form.
A. Again, I have to get that question in my head here.
Since March 29, 2015, I have been working with counsel.
Q. So during the entire period of time in which you have had conversations with U.S. regulators and European regulators about glyphosate, you have been a retained expert for plaintiffs' counsel in this litigation, correct?
MS. GREENWALD: Objection, form.
A. The e-mails, discussions and everything else that I sent to the regulators is not part of the work I have done for this law firm.
Q. That was not my question.
A. OK, what was your question again.

Q. During the entire period of time in which you have had conversations with U.S. and European regulators about glyphosate, you have been a paid consultant for plaintiffs' counsel in this litigation, correct?
MS. GREENWALD: Objection, form.
A. Yes.
Q. Now, you attached to your expert report some submissions that you have made to European regulators and to the EPA in the United States in opposition to the decisions or findings by those agencies that glyphosate does not cause cancer, correct?
A. The -- if I remember the letters correctly, they are raising scientific concerns about the way in which these particular agencies reviewed the evidence for glyphosate and cancer.
Q. These submissions that you have made to the regulators contain much of the same scientific analyses that you have included in your expert report in this litigation in support of the plaintiffs,

correct?
MS. GREENWALD: Objection, form.
A. I -- it's not correct.
Q. So is it -- let me ask this: In your submissions to the European regulators and U.S. regulators, you represented pooled analyses of animal cancer bioassays, correct?
A. Yes, correct.
Q. And you present those same pooled analyses in your expert report in this litigation, correct?
MS. GREENWALD: Objection, form.
A. No, not correct.
Q. You have revised them over the course of time, correct?
MS. GREENWALD: Objection, form.
A. I have revised the way in which I do the pools analyses over time.
Q. And you have submitted different pooled analyses to the regulators over time, correct?
A. That is correct.
Q. And you have submitted pooled analyses also in your expert report,

correct?
A. That is correct.
Q. And some of the pooled analyses in your expert report you are continuing to use in your submissions to the regulators, correct?
MS. GREENWALD: Objection to form.
A. That isn't correct.
Q. You have not presented any of the information from your -- any of your analyses in the expert report to regulators?
A. You're proposing a sequence of events that is not correct.
Q. Not my question.
A. I know it's not your question, but the answer to the question has to do with the sequence of the events.
Pooled analyses were done for my letters to the regulators and others with these data.
That was done prior to any expert report I prepared for this litigation.
Q. But both those pooled analyses

were conducted after you had been retained as a private expert for plaintiffs' counsel in this litigation, correct?
MS. GREENWALD: Objection, form.
A. What was the term you used for there?
Q. Your pooled analyses that you submitted to the U.S. and European regulators were prepared after the time that you signed on as a paid expert for plaintiffs' counsel in this litigation, correct?
MS. GREENWALD: Objection, form.
A. A paid consultant and/or expert, yes.
Q. The submissions that you made -- strike that.
In your submissions to these regulators, the letters that you submitted, you do not disclose your relationship with plaintiffs' counsel as an expert in private litigation against Monsanto, do you?
MS. GREENWALD: Objection, form.
A. I do not recall in my letters to EPA whether I did such a thing. I can't

answer that part of it.
Clearly in the letter you have given me, that was not in there.
Q. The letter I gave you was the European regulators, correct?
A. The first letter I sent.
MR. LASKER: Let's mark as Exhibit 15-20.
(Exhibit 15-20, attachment to the expert report, marked for identification, as of this date.)
Q. And this was one of the attachments to your expert report in this litigation and a submission that you made to the EPA on October 4, 2016.
A. OK.
Q. You begin your submission to EPA in October of 2016 with a disclaimer, correct?
A. This work was done with my own research and on my own time. Yes.
Q. And you state -- you told the EPA, and anyone else who was looking at your submissions, that you had, quote, received no reimbursement for any of these

comments, correct?
A. That's correct.
Q. And during this same time period, you were publicly proclaiming that, quote, nobody has paid me a cent to do what I am doing with glyphosate. I have no conflict whatsoever, correct?
MS. GREENWALD: Objection, that is not what this says.
Q. Let's look at this document.
MR. LASKER: We will mark this 15-21.
(Exhibit 15-21, document entitled, "Oh Brother, CropLife Questions, Makeup of Glyphosate Panel," marked for identification, as of this date.)
Q. Dr. Portier, this is an article dated October 12, 2016, entitled, "Oh Brother, CropLife Questions, Makeup of Glyphosate Panel."
Do you see that?
A. Yes, I do.
Q. This is discussing the EPA's evaluation of glyphosate, correct?

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MS. GREENWALD: Objection, form.
A. This is an article by Steve Davies discussing CropLife questioning the makeup of the glyphosate panel.
Q. On the second page of this document, at the bottom of the page, there is an -- you have been interviewed and there's some various statements you have made regarding glyphosate, correct, in the panel?
A. I'm sorry?
Q. At the bottom of the second page, there is various discussions, comments that you have made to the reporter in connection with this article, correct?
MS. GREENWALD: Objection, form.
A. This pertains to the work I did part time for the Environmental Defense Fund, and it's conceivable the reporter got this quote out of context.
So I can't -- I can't tell you whether certainly I got it or not. I've been misquoted many times.
Q. The quote in this article that is attributed to you in October of 2016 is,

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"Nobody has paid me a cent to do what I am doing with glyphosate," and "I have no conflict of interest whatsoever," on the bottom of the page.
Do you see that?
MS. GREENWALD: Objection, form.
A. That -- those two sentences are on the bottom of the page.
Q. Did you ever have any follow-up discussion with this reporter telling him you misquoted me?
A. I have no problem -- probably not. I'd never do that.
Q. Prior to your submissions to EPA in October of 2016, you had, of course, in fact, been paid by plaintiffs' counsel to assist them in the glyphosate litigation against Monsanto, correct?
A. Prior to my submissions to EPA in October of 2015 -- yes.
Q. And as of October 2016, when you were quoted in this article as telling the world that you had no conflict whatsoever, you, in fact, had been consulting with plaintiffs' counsel in this litigation for

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more than 18 months, correct?
MS. GREENWALD: Objection, assumes facts not in evidence and form.
Q. You can answer.
MS. GREENWALD: You can answer. I have my objection on the record.
A. Repeat the question now.
Q. As of October '16 -- October 2016, when you were quoted in this article as stating that you had no conflicts whatsoever, you had, in fact, been consulting with plaintiffs' counsel in the glyphosate litigation against Monsanto for more than 18 months, correct?
MS. GREENWALD: Objection. Same objection as before.
A. At the time this quote in this article is written, I was working with counsel, yes.
Q. And had been working with them for more than 18 month, correct?
MS. GREENWALD: Same objection.
A. That is correct.
Q. And when you were quoted in this article as saying nobody had paid you a

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cent for what you are doing with glyphosate, you had by that time sent plaintiffs' counsel three separate invoices for your glyphosate work in litigation against Monsanto, correct?
MS. GREENWALD: Objection, form.
A. The work being referred to here was the analyses and evaluations and reading of the regulatory documents, for which nobody paid me.
Q. So it is your testimony that plaintiffs' counsel did not pay you to review the regulatory documents?
A. They were paying me to provide them with advice and consulting. Until they decided that I would be an expert witness, there was nothing they were requiring me to read or review except an occasional paper they would send me.
Q. Let me ask you to look at Exhibit 15-18. It is the retention agreement and attached exhibits.
A. Yes.
Q. And if you look at page 7 of this document, it's the invoice dated June 30,

2016, correct?
A. Page 7?
June 30, 2016, there is here June 30, 2016.
Q. And this invoice is four months before you submitted -- had your submission to the EPA, correct?
A. Yes.
Q. And in this invoice, you are charging -- or you're billing plaintiffs' counsel for your work in reading and evaluating the EPA's glyphosate documents, correct?
A. That's what it says. I stand corrected from my previous statement.
Q. So plaintiffs' counsel had paid you to evaluate EPA's glyphosate document, correct?
A. That's what it appears to say.
Q. And after being paid by plaintiffs' counsel to evaluate the EPA document, you then made submissions to EPA, correct?
A. But not the evaluation I made for plaintiffs' counsel.

Q. Dr. Portier, let me just ask the question again.
Four months after being paid by plaintiffs' counsel to evaluate the EPA's glyphosate document --
A. I submitted --
Q. -- you made submissions to EPA regarding your evaluation of their assessment, correct?
MS. GREENWALD: Objection, form.
A. Four months after -- I provided an evaluation of EPA's assessment to them, correct.
Q. As of -- just to go back to the question that was pending, as of October of 2016, when you were quoted in this article as stating that nobody had paid you a cent for what you were doing with glyphosate, you had by that time submitted three separate invoices to plaintiffs' counsel billing them for your work on glyphosate, correct?
MS. GREENWALD: Objection, form.
A. The quote that was in that newspaper article that says what you said

it said happened four months, I guess, or so after my being paid by plaintiffs' counsel to evaluate the EPA risk assessment, that is correct.
Q. And by that time, you had, in fact, sent three separate invoices to plaintiffs' counsel for your work in the glyphosate litigation, correct?
MS. GREENWALD: Objection, form.
A. By what time again?
Q. October of 2016?
A. October 2016.
Yes, I had sent three invoices.
Q. As of June 2017, which is the last invoice we have, you have billed plaintiffs' counsel somewhere over $160,000 for your work in preparing your analyses of glyphosate, correct?
MS. GREENWALD: Objection, form.
A. I -- I have no idea what the total is, but maybe. It's a substantial amount of money.
Q. And since -- the last invoice we have is dated, as I said, I guess it's June 18, 2017, through the time -- through June

13, 2017, and then we have a -- one invoice for an airplane ticket.
You have continued to do work on this litigation subsequent to June 13, 2017, correct?
You prepared your rebuttal report?
A. I've done work since then, that is correct.
Q. And I take it you have not yet billed plaintiffs' counsel for that additional work?
A. Is that privileged?
Q. No.
A. No?
No, I have not.
Q. Do you have an approximate amount of time outstanding for your bill for plaintiffs' counsel?
A. Approximate?
No. I mean, I have an exact somewhere.
Q. Have you done more than 20 hours of work on your rebuttal report?
A. Yeah.

Q. Have you done more than 40 hours of work on your rebuttal report?
A. Maybe not.
Q. So we have somewhere on the order of another $15,000 maybe, or is it more?
You don't know?
A. I don't know. I don't really pay much attention to it.
Q. Pursuant to the expressed terms of your engagement letter with plaintiffs' counsel, the work that you did and that you were paid for in evaluating the EPA assessment of glyphosate is "work for hire and the property of the plaintiffs' law firms," correct?
MS. GREENWALD: Objection to form.
A. Let me be clear: I think there is a mistake here -- and this is my mistake, I should have pointed it out earlier -- this is a different EPA glyphosate document than the one that I was complaining about in October. This is a different document.
This was a single, two-page

release from the Clark subgroup of EPA about glyphosate that appeared, I think, in March or June or April of 2016, whereas the comments made later that year were on EPA's draft risk assessment.
Q. Let's go back to the June 30, 2016 e-mail.
You said this was reviewing a two-page document?
A. June 30 --
Q. 2016 invoice.
A. It's a two- or three-page technical document, yes.
Q. You have billed plaintiffs' counsel for 19 hours in reviewing that document, is that correct?
A. Yes.
Q. So you spent 19 hours reviewing a two-page document?
MS. GREENWALD: Objection to form.
A. If you have the document, we can look at that time, but it is a very technical document. It requires that you go back and look at the animal experiment,

experimental evidence. It required me going back to look at the epidemiology experimental evidence. It takes time to give a good scientific response.
Q. So in connection with this work and evaluating the EPA glyphosate document, you spent 19 hours with -- doing an extensive dive into the glyphosate science, is that your testimony?
MS. GREENWALD: Objection to form.
A. It's one memo. I spent 19 hours researching it.
Q. And pursuant to the terms of your engagement letter, this 19 hours you spent in evaluating glyphosate and evaluating the EPA, this EPA assessment was work for hire and the property of plaintiffs' law firm, correct?
MS. GREENWALD: Objection, form.
A. I lost you on that question.
Q. Let's go back to the engagement letter, the beginning of this document, and on page 3, numeral 7, it says, any and all work product created by you or on your

behalf in whole or in part during the course of this engagement authorized by this committee shall be considered a work for hire and the property of the plaintiffs' law firms, correct?
A. This speaks of work product. It doesn't speak of knowledge gained.
Q. Is the work that you were paid for in evaluating EPA assessment of the 19 hours --
A. That wasn't the EPA assessment. It was a memo.
Q. In evaluating, as you say in your invoice, the EPA glyphosate document, that is work for hire and intellectual property of the plaintiff law firm, correct?
MS. GREENWALD: Objection.
That's not his testimony. He asked and answered it.
A. No. The work product from that would be the property of the law firm.
Q. Is it your testimony that the 19 hours that you spent in assessing the scientific data in connection with this EPA document did not play any role whatsoever

in the submissions or the analyses that you presented in your submissions to EPA and to the European regulators?

MS. GREENWALD: Objection, form.

A. Intellectual knowledge gained in any endeavor can obviously carry over into the next endeavor. I can't possibly give you a "no" answer to such a question.

The work product from that evaluation is the property of this firm and it was subsequently given to them.

Q. And the work product that your evaluation, for which you were paid by plaintiffs' law firm in or about June 2016, that work also folded -- was folded into the submissions that you provided to the EPA and to the European regulators, correct?

MS. GREENWALD: Objection, form.

A. No.

Q. Is it your testimony that you did not make use of any of the 19 hours of evaluation that you conducted and were paid for by plaintiffs' law firms in preparing your submissions to the EPA and to the

European regulators?

MS. GREENWALD: Objection, form. Asked and answered.

A. As I said before, intellectual gains from reading documents play a role in anything I ever write or do in the future. Hence, I cannot say "no" to that question.

Q. But in your submission to the EPA, when you submitted your analysis, you did not disclose the fact that you had been paid by plaintiffs' counsel to review the scientific data on glyphosate, correct?

MS. GREENWALD: Objection, form.

A. The document I submitted to EPA about the scientific failures in their evaluation of the scientific evidence for glyphosate did not disclose that I worked for plaintiffs' law firm.

Q. You have been -- you have had a number of conversations with individual EPA officials behind the scenes about glyphosate, correct?

MS. GREENWALD: Objection, form.

A. On what topic?

Q. Glyphosate.

MS. GREENWALD: Same objection.

A. I have spoken with the EPA officials on the glyphosate issue.

Q. And you have had private e-mail communications with Jim Jones about glyphosate, correct?

MS. GREENWALD: Objection, form.

A. I have sent to Jim Jones concern -- my concerns about glyphosate.

Q. In private e-mail communications, correct?

MS. GREENWALD: Objection, form.

A. It was to his EPA e-mail address, which is not a private e-mail address.

Q. Well, the e-mail that you sent was not disclosed publicly. You had a private communication with Mr. Jones on e-mail, correct?

MS. GREENWALD: Objection, form, asked and answered, argumentative.

A. I -- she is right, I answered the question.

Q. So did you publicly disclose -- have you publicly disclosed your e-mail communications with Jim Jones at EPA about

glyphosate?

MS. GREENWALD: Objection, form.

A. I think they did.

Q. And is it your understanding that every communication you have had with Mr. Jones has been disclosed publicly?

MS. GREENWALD: Objection, form.

A. That I don't know. But, of course, you can FOIA them and you will know which ones.

Q. Have you had telephone conversations with Mr. Jones about glyphosate?

A. Not that I recall.

Q. Who is Jim Jones?

A. He was the director of the office of pesticides and toxic substances, the assistant administrator at EPA.

Q. How do you know Mr. Jones?

A. I've known Mr. Jones for years. I was a government official. He was a government official. We were working on environmental issues. That's how I knew him.

Q. In your e-mail communications

with Mr. Jones, did you disclose to him the fact that you were a paid expert for plaintiffs' counsel in this litigation?

A. I don't recall.

MR. LASKER: Mark as Exhibit 15-22 and 15-23 two e-mail communications we have between you and Mr. Jones and others at EPA.

(Exhibit 15-22, e-mail chain Bates stamped EPAHQ6149, marked for identification, as of this date.)

(Exhibit 15-23, e-mail chain Bates stamped PORTIER0000055 through 61, marked for identification, as of this date.)

Q. Dr. Portier, Exhibit 15-22 and 15-23 are two e-mail exchanges, one dated May of 2016, the other dated June of 2016, that include e-mail communications between you and Mr. Jones, correct?

A. Which document are we talking about? Both of them?

Q. Yes.

A. The first document is from Jones -- to Jones from me it appears, and

the second document is from Anna Lowit to me but there is something further down.

Q. If you go to the beginning of the conversation, there's e-mail exchanges. It starts off with an e-mail exchange between you and Jim Jones, and then some further e-mail communications, correct?

MS. GREENWALD: Objection, form.

A. I don't know where the start of that conversation is. I'm sorry.

Q. OK. If you look at Exhibit 15-23, I believe the first e-mail in the chain, and it seems like we got it here twice -- nope. It goes back and forth.

But the first chronological e-mail that I see in this chain is an e-mail at the very end of this on June 23, 2016, from you to Jim Jones correcting an error in the table that you had, I guess, sent to him, correct?

The very last page of the document --

A. I had an area 1 table that I had to correct, new version attached, yes.

Q. And you sent that to Mr. Jones on June 23, 2016, correct?

A. Yes.

Q. And this is at the same time, almost exactly the same time, that you billed plaintiffs' counsel for the 19 hours of work that you had conducted in evaluating an EPA document on glyphosate, correct?

MS. GREENWALD: Objection, form.

A. The dates are going to be close.

Q. So in May of 2016, you spent 19 hours for plaintiffs' counsel reviewing an EPA glyphosate document and were paid by plaintiffs' counsel by that, and then in June of 2016, you made a submission to EPA with at least one table of an evaluation of glyphosate, correct?

A. I don't know. Probably.

Q. You produced this e-mail communication -- at least the June 2016 e-mail communication in response to our document requests, but we did not have the assessment that you actually sent to EPA.

MR. LASKER: So we would request

that that be produced.

MS. GREENWALD: That was produced all PowerPoints supplied by Chris Portier were supplied to you guys.

MR. LASKER: The PowerPoints, yes.

MS. GREENWALD: Correct. That would be --

MR. LASKER: Is this a PowerPoint presentation?

MS. GREENWALD: PPTX is the root of the document attached.

MR. LASKER: Fair enough. We will figure that out.

Q. Although -- so -- in any event, in these communications -- e-mail communications, and particularly the communication in June of 2016, right after you had been paid by plaintiffs' counsel to evaluate an EPA document, you do not disclose to Mr. Jones that you are a paid consultant for plaintiffs' counsel in the litigation, correct?

MS. GREENWALD: Objection, form.

A. In this e-mail right here, I do

not do that. That is correct.
Q. Do you recall other e-mail communications that you had with Mr. Jones during this period of time?
A. I had at least one more, yes.
Q. That has not been produced to us in this litigation.
Do you still have copies of that communication?
A. If you didn't get it, I don't have it.
Q. Do you recall the substance of this other e-mail communication with Mr. Jones?
A. It had to do with errors I saw in the EFSA. It contains much of the stuff I was already sending to EFSA, along with some linkage to problems with some of the things the EPA had done including the memo.
Q. So in June of 2016, you were having a series of e-mails communications with Mr. Jones at EPA based upon issues you had identified through your paid work for plaintiffs' counsel in this litigation, correct?

MS. GREENWALD: Objection, form.
A. It's possible.
Q. You do not have any recollection, sitting here today, of ever disclosing to Mr. Jones that you were working for plaintiffs' counsel during this time period, correct?
A. I don't have a recollection of disclosing or not disclosing. I don't really know.
Q. You also had communications with Ann Lowit at EPA, correct?
A. Yes, that is correct, briefly.
Q. And that would be in this e-mail exchange?
A. This e-mail exchange and then -- I don't know what else is in here.
Q. Do you recall ever disclosing to Ann Lowit that you were a paid consultant with plaintiffs' counsel suing Monsanto?
A. No, I don't recall.
MS. GREENWALD: Objection, form. Go on.
Q. Do you recall having any other conversations with any other EPA employees

about glyphosate?
A. Did I have any conversations -- yes.
Q. What other EPA employees did you have conversations with?
A. I think his name is Steve Johnson, who is in charge of the EPA science advisory panel reviews. I sent him correspondence when I sent him my reviews.
Other EPA employees that I would have spoken to?
I speak with Vincent Cogliano. Sometimes, I might have spoken with him.
Q. Do you recall disclosing to either of these EPA officials the fact that you were a paid consultant for plaintiffs' counsel in this litigation?
A. I don't know about Steve. I don't -- I don't think so.
Q. Have you had any conversations with Tom Burke?
A. I've had lots of conversations with Tom Burke.
Q. About glyphosate?
A. I don't recall.

Q. Can you name for me the individual -- individuals in the European government regulators or government officials with whom you have spoken about glyphosate?
A. There is no way I could remember them all. I'm terrible with names. No. I'm sorry.
Q. Was it more than five people?
A. Yes.
Q. More than ten?
A. I don't know. I can't distinguish between a regulator and a politician in Europe. So I have a difficult time on working out an answer to that question.
Q. Do you recall disclosing to any of those European officials that you were a paid consultant for plaintiffs' counsel in litigation against Monsanto?
MS. GREENWALD: Objection to form.
A. Yes.
Q. Was that in your e-mail -- in your e-mail communications with them or in

your private conversations?
A. I don't know if I used that in my e-mail to Andriukaitis, but it is the first thing we discussed when I walked in his door.
Q. When was that?
A. When we met -- whenever the first time we met after I wrote that letter. I don't know the exact date. I'm sorry.
Q. In your -- you have -- remind me now --
A. Actually, I'll correct that. I'm sorry.
I told him that beforehand. I told his staffer, when we were on the phone when she called to invite me, I said, I have this linkage. Is this a problem?
And they said, no.
Q. You provided testimony in front of the European Commission, is that correct, or you have been invited to?
A. I provided testimony to the German Bundestag, but I did not provide testimony in front of the European Parliament.

Q. In your testimony in Germany, did you disclose that you were a paid consultant for plaintiffs' counsel in this litigation?
A. I can't recall.
Q. Have you worked with a group called the "Health and Environmental Alliance" in connection with their work on glyphosate for registration in Europe?
A. I have advised them now and then. And they have advised me on issues.
Q. We talked earlier about that issue, about whether you should register as a lobbyist or not register as a lobbyist.
In your conversation with the European staffer about whether you should register, did you disclose to him the fact that you were a paid consultant for plaintiffs' counsel in the glyphosate litigation?
MS. GREENWALD: Objection to form.
A. Yes.
Q. There are a number of other organizations that have reviewed glyphosate

during this time period after IARC reaches classification, correct?
MS. GREENWALD: Objection to form.
A. A number of organizations have reviewed the scientific literature on glyphosate following IARC's review of the literature for glyphosate.
Q. And despite Europe's submissions of various analyses, the European Food Safety Agency has continued to reach a conclusion that glyphosate does not pose a risk for cancer, correct?
MS. GREENWALD: Objection, form.
A. That is correct.
Q. And the European Chemical Agency, ECA, has continued to conclude that glyphosate does not pose a risk of cancer in humans, correct?
MS. GREENWALD: Objection, form.
A. ECA has for the first time concluded that glyphosate shows no risk for cancer in humans.
Q. The -- obviously, the German regulators, who you spoke with, they have

continued to conclude that glyphosate did not pose a risk for cancer, correct?
MS. GREENWALD: Objection, form.
A. That's not correct.
Q. The BFR has now concluded that glyphosate causes cancer, is that your testimony?
MS. GREENWALD: Objection, form.
A. There are more than one German agency dealing with glyphosate. BFR has not changed their mind.
Q. That glyphosate does not pose a risk for cancer, correct?
A. Correct.
Q. The Canadian regulators have concluded that glyphosate does not pose a risk for cancer, correct?
A. I don't know.
Q. The World Health Organization, JPMR, has concluded that glyphosate through food does not pose a risk for cancer, correct?
MS. GREENWALD: Objection, form.
A. I'd have to look at their conclusion. It's a little more detailed

and nuanced than that.
Q. Your general understanding though is that the JPMR in conducting its analysis did not raise a concern that glyphosate causes cancer, correct?
MS. GREENWALD: Objection, form.
A. Again, I would have to look at JMPR's document and see.
Q. The Japanese public health regulators have concluded that glyphosate does not cause cancer, correct?
A. I have no idea.
Q. The Australian public health regulators have concluded that glyphosate does not cause cancer, correct?
A. I think I might have read a news article on that, but other than that, I have no idea.
Q. The New Zealand public health regulators have concluded that glyphosate does not cause cancer, correct?
A. I think so. I got some information from one group about that. I don't know if that's concluded or not.
Q. You actually appeared in a radio

program in New Zealand urging the regulators in New Zealand to find glyphosate as a carcinogenic, didn't you?
A. I might have.
Q. In response to our document request for this deposition, you produced a series of slide decks for presentations that you had given to various scientific agencies, correct?
MS. GREENWALD: Objection, form.
A. I have produced a slide deck of any -- exactly what you asked for, any presentation I did on glyphosate.
Q. And at each of those scientific methods you presented some version of the pooled analyses that you conducted on glyphosate that are the same types of analyses you were proffering in this litigation, correct?
MS. GREENWALD: Objection, form.
A. They're not exactly the same.
Q. They are the same type of pooled analyses, correct?
And you have been revising them as you have gone along, correct?

MS. GREENWALD: Objection, form.
A. There are pooled analyses in these slides.
Q. And some of those pooled analyses, in fact, are exactly the same as the analyses you have submitted in this litigation, correct?
MS. GREENWALD: Objection, form.
A. The studies that went into the pooled analyses are exactly the same as the studies in this litigation.
The method by which I pooled them and do a trend test of the overall response from the pooled data is in the slides as well as in this litigation.
Q. Did you make a disclaimer -- well, first of all, none of your slide decks themselves provide a written disclaimer that you are working as an expert for plaintiffs in glyphosate litigation, correct?
MS. GREENWALD: Objection, form.
A. If you say so. I haven't looked.
Q. Did you make a disclaimer at the beginning of each of these scientific

meetings when you presented this data that you were a paid expert consultant for plaintiffs' counsel in private litigation against Monsanto?
A. I can't be certain for every one of them.
Q. You have also given numerous interviews to media outlets and various bloggers commenting on glyphosate issues, correct?
MS. GREENWALD: Objection, form.
A. I've done interviews with all sorts of people on glyphosate issues.
Q. And have you disclosed to each of these media outlets your role as a paid expert consultant for plaintiffs' counsel in this litigation?
A. I can't be certain.
Q. Well, for example -- strike that.
You have also written a number of commentaries about glyphosate in the scientific press, correct?
A. I've written two, I believe.
Q. Well, let's look at one of the first of those.

MR. LASKER: This is -- we will mark this as --

MS. GREENWALD: 24.

MR. LASKER: So it is 15-24. I'm sorry.

(Exhibit 15-24, article from Horizons, dated March 7, 2016 with attachment, marked for identification, as of this date.) marked

Q. Dr. Portier, this is an article you wrote for the Swiss science magazine Horizons, in which you debated that the head of the pesticides unit at the European Food Safety Authority about the safety of glyphosate, correct?

A. This article appeared in a Swiss magazine called Horizons, and yes, there was pro and con, and Jose Tarazona did the con and I did the pro.

Q. This was March 2016, one year after you had signed on as a paid consultant -- paid expert for plaintiffs' counsel in this litigation, correct?

MS. GREENWALD: Objection, form.

A. This is -- yeah, about a year.

Q. And in this article, there is a -- you identify yourself as the former director of the U.S. National Institute of Environmental Health, correct?

A. I certainly would never have identified myself as that. That's incorrect.

Q. There is -- you do not have any disclosure anywhere in this article about the fact that you had been for a year a paid expert for plaintiffs' counsel in litigation against Monsanto, correct?

MS. GREENWALD: Objection, form.

A. There does not appear to be anything on this page that suggests I am a paid consultant for this law firm on glyphosate issues.

Q. And let's look at, as 15-25 -- this is ...

(Exhibit 15-25, article entitled, "Re: Tarazona et al.: Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment," marked for identification, as of this date.)

Q. This is a reply that you published in the journal "Archives of Toxicology," correct?

A. This is a letter to the editor in the journal "Archives of Toxicology."

Q. And in this letter you are again addressing the European Union's assessment of glyphosate and its difference with IARC regarding glyphosate, correct?

A. I don't know if I was talking about its difference with IARC. Give me a moment, please.

No, I don't believe this was discussing the differences with IARC. I believe this was only discussing the scientific problems with the EFSA glyphosate risk assessment and pointing out to the authors of that evaluation, that they missed a number of positive rodent findings.

Q. But this is a -- again, an article or a letter that you had published in the Archives of Toxicology presenting your analysis of the glyphosate science, correct?

MS. GREENWALD: Objection, form.

A. No. It is noting problems with the EFSA risk assessment and some of the analysis I have done for glyphosate.

Q. And this letter was submitted in May of 2017, correct?

A. Probably, yes.

Q. As of this date, you had been working as a paid expert for plaintiffs' counsel for more than two years, correct?

MS. GREENWALD: Objection, form.

A. As of May 2017, I was working for plaintiffs' counsel, correct.

Q. And you had billed plaintiffs' counsel, and we can do the math, but somewhere around $150,000 as of this date for your work on glyphosate, correct, plaintiffs' counsel?

A. I had billed them. That is correct.

Q. And you do not disclose anywhere in this letter to the editor in the journal Archives of Toxicology the fact that you were a paid expert for plaintiffs' counsel in private litigation against Monsanto, do

you?
MS. GREENWALD: Objection to form.
A. This journal doesn't ask for that. I don't know.
Q. Dr. Portier --
A. It's not on the document.
Q. So just so the record is --
A. To answer your question, it is not on the document.
Q. In your letter to the editor that was published in Archives of Toxicology in 2017 -- in June of 2017, you do not disclose the fact that you were -- you are a paid expert for plaintiffs' counsel in litigation against Monsanto, correct?
MS. GREENWALD: Objection, form.
A. In Exhibit 15-25, I do not disclose that I was a paid consultant for this law firm in this litigation.
Q. In 2016, you made a presentation about glyphosate to the Collegium Ramazzini.
A. No, I didn't make a presentation.
MR. LASKER: Let's mark -- this

will be Exhibit 26.
(Exhibit 15-26, article entitled, "The glyphosate saga: an example of influence of unsound science and interest groups in public health decision making," marked for identification, as of this date.)
A. Yes.
Q. This is -- Exhibit 15-26 is a poster presentation that was presented -- it was called "Ramazzini Days."
What is Ramazzini Days?
A. Ramazzini Days is something that Ramazzini Institute holds once a year where -- it is a scientific conference.
Q. At this scientific conference, there was a poster presentation regarding glyphosate, and you are one of the coauthors of that poster presentation, correct?
MS. GREENWALD: Objection, form.
A. The document 15-26, I am one of the coauthors.
Q. That is a poster presentation that was presented at Ramazzini Days,

correct?
MS. GREENWALD: Objection, form.
A. Yes, I guess.
Q. And this presentation, you are listed as an author along with five individuals who are identified as Ramazzini fellows, correct?
A. One, two, three, four, five, that is correct.
Q. As of this date, you are not a Ramazzini fellow, correct?
A. As of this date, I am not -- I was not a -- well, I don't know. I honestly don't know.
Q. You have recently become selected --
A. I am a Ramazzini fellow --
Q. OK.
A. -- yes.
I guess by this date I wasn't because I'm not listed as one.
Q. So it was sometime in the last year that you became a Ramazzini fellow, is that fair?
A. I would think so, yes.

Q. And one of the other scientists that you were -- that you're presenting with here is Philip Landrigan, correct?
A. That is correct.
MS. GREENWALD: Objection to form.
Q. Philip Landrigan actually assisted, helped you, in preparing that open letter that you submitted to the European regulators in November of 2015, correct?
MS. GREENWALD: Objection to form.
A. Philip Landrigan's name is on that letter, I believe. I would have to check to make sure.
And yes, he did provide comments.
Q. What other, if any, collaborations have you had with Philip Landrigan relating to glyphosate?
MS. GREENWALD: Objection to form.
A. Probably a few things. I can't recall.
Q. Have you consulted with

Dr. Landrigan about further research relating to glyphosate?
A. No.
Q. Have you communicated with Mr. Landrigan about European regulators' assessment of glyphosate beyond the open letter in November of 2015?
MS. GREENWALD: Objection, form.
A. Say it again, please.
Q. Have you consulted with Philip Landrigan about the European registration of glyphosate apart from that letter in November of 2015?
MS. GREENWALD: Objection, form.
A. So first, I don't consult with Philip Landrigan.
Q. Communicate?
A. We collaborate or we communicate, so --
Q. That's a better word.
A. -- let me make that clear.
Q. So let me reask it.
Have you collaborated with Philip Landrigan about glyphosate registration in Europe outside of that November 2015 letter

that we have already discussed?
A. Not that I recall.
Q. Have you collaborated with Philip Landrigan related to the EPA's assessment of glyphosate?
MS. GREENWALD: Objection to form.
A. Not that I recall.
Q. Have you collaborated with Mr. Landrigan about assessments of the glyphosate science?
MS. GREENWALD: Object to form.
A. Mr. -- Dr. Landrigan is a cosignatory of the open letter, and that open letter discusses the science around glyphosate.
So I guess the answer to that question is yes.
Q. You said you had a number of other collaborations with Mr. -- with Dr. Landrigan, if I understood correctly, regarding glyphosate --
A. No.
Q. OK.
A. Sorry, none.

Q. In your poster presentation at Ramazzini Days, in the conclusion, you state that -- you talk about economically motivated activities having influenced the glyphosate science, correct?
MS. GREENWALD: Objection, form.
A. I should pay more attention to what my coauthors write sometimes.
That is what it says.
Q. You do not disclose anywhere in this poster presentation your role as a paid expert for plaintiffs' counsel in private litigation against Monsanto, do you?
MS. GREENWALD: Objection, form.
A. Not specific. I list myself as an environmental health consultant.
Q. Again, just so the record is clear, you do not disclose the fact that you were a paid consultant for plaintiffs' counsel in private litigation against Monsanto?
A. That is correct.
Q. Now, you're -- the point you're making in this poster presentation instead

is about what you characterize as an improper influence of corporate money on scientific research, is that correct?
MS. GREENWALD: Objection, form.
A. I don't --
Q. In the conclusion?
MS. GREENWALD: Same objection.
A. That's what the -- I am sorry, let's be clear.
First, I want to make something clear: You asked me if I made a presentation to them. Baur -- Xavier Baur made the presentation. I did not attend this meeting.
Now, you just asked me -- if you could repeat the question.
Q. In the poster presentation -- and you are a coauthor of the poster?
A. Correct.
Q. In the poster presentation, the concern is being raised about potential improper influence of corporate money on scientific research, correct?
MS. GREENWALD: Objection, form.
A. That's one little bit at the tail

end, correct.
Q. And you and the other authors are calling upon the Collegium Ramazzini to take a stand against corporate funding of scientific research --
MS. GREENWALD: Objection to form.
Q. -- as part of this presentation, correct?
MR. SNOO: Objection to form.
A. Actually, no. We encouraged the Collegium Ramazzini to again support an IARC evaluation of carcinogenicity.
Q. In the earlier paragraph, right before where you are reading, you talk about:
"Glyphosate is a one example of inappropriate corporate influence of public health regulation by the use of unsound scientific reviews" --
A. But your question said --
Q. -- "and would call for increased sensitivity, full transparency and implementation of effective rules governing decision-making bodies," correct?

MS. GREENWALD: Objection, form.
A. But we are not calling for the Ramazzini Institute to do that, or Collegium Ramazzini, which was your question to me.
Q. So you are calling for scientists more broadly, is that fair?
MS. GREENWALD: Objection to form.
Q. Or regulators?
MS. GREENWALD: Same objection.
A. We are calling for an increased sensitivity, full transparency and the implementation of effective rules governing decision-making bodies. That's what we are calling for. That's what we said.
Q. Am I correct in my understanding then Collegium Ramazzini does not take money from private corporations for its scientific research?
A. I have no idea.
Q. During your time in government at NTP, you worked on collaborative efforts between the NTP and the Collegium Ramazzini, correct?

A. I don't recall.
We certainly did some work with them trying to help them improve their cancer bioassays. That I do recall.
Q. And in your CV --
MR. LASKER: And you can mark that as 15-27.
(Exhibit 15-27, curriculum vitae, marked for identification, as of this date.)
Q. If you look at the fifth page under your U.S. Government service activities, and it's about three-quarters down the page under U.S. Government service activities, you are listed as an organizer, formal collaborative agreements between NTP and Ramazzini Foundation from 2001 to 2006, correct?
A. That is correct.
Q. And so for this five- or six-year period then, the NTP and Ramazzini Foundation were involved in collaborative agreements relating to toxicological studies?
MS. GREENWALD: Objection, form.

A. It was more related to pathology and the storage of data from toxicological studies.
Q. During this period, you were the organizer of these agreements.
Did the Ramazzini Foundation conduct any research for NTP?
A. I don't believe they did.
Q. During this period, did the Ramazzini Foundation conduct any research that was funded by the U.S. Government?
MS. GREENWALD: Objection, form.
A. They did get some funding from NIEHS or NTP, but, boy, I cannot for the life of me remember. I think they got some funding.
Q. Are you aware that the Collegium Ramazzini has announced that it will be conducting studies on glyphosate with respect to genotoxicity and oxidative stress?
A. Yes, I am aware of that.
Q. Are you involved in that research effort?
A. No.

Q. Have you had any conversations with the folks at Collegium Ramazzini about that research?
A. Yes.
Q. What has been the nature of your conversations?
A. Part of it they were asking me to join them and analyze their data at the end. I declined.
Part of it was just general questions about the science and what's already been done with glyphosate.
Q. And in your conversation with Collegium Ramazzini, did you disclose the fact that you were a paid consultant for plaintiffs' counsel in litigation against Monsanto?
A. It is the Ramazzini Institute. They are different entities.
But yes, I did disclose to them.
Q. Is that the reason that you decided not to participate in their scientific evaluation?
A. Partly. There are other reasons.
Q. What were the other reasons?

A. I'm busy. I'm retired. They wanted me to come down to Bologna and give a talk and other things and I just wasn't interested.
Q. Dr. Portier, you have stated that you do not believe that causality between glyphosate formulations and NHL has been demonstrated, correct?
MS. GREENWALD: Objection, form.
A. What I believe is written in the expert report.
Q. Well, let me just ask this question: It is true that you do not believe that causality between glyphosate formulations and NHL have been demonstrated, correct?
MS. GREENWALD: Objection, form.
A. Causality is an interesting -- it's a spectrum, but if you're using causality to mean 100 percent, absolutely certain, then I would have concern. But my conclusion is it probably causes NHL.
Q. Let's take a look next in line. This is Exhibit 15-20. It is already marked. So it's one of the exhibits in

there.
A. 15-20? Oh, boy. I'm not good at keeping things in order here.
Q. This is your submission to EPA in October of 2016, correct?
A. Yeah, it looks like that.
Q. And then on page 7, about two-thirds down the page, you're talking about whether there is an association between glyphosate exposure and the risk of non-Hodgkins lymphoma.
Do you see that, and that's what starts the summary?
A. Start with "Summary," and how far do you want me to read?
Q. First of all, I'm asking if you see that section, which you obviously do.
The end of that paragraph, you state, with regard to glyphosate in NHL, "So is causality plausible here? Yes, absolutely. Is it demonstrated? No, clearly not."
That was your statement, correct?
A. If you could wait.
This is strictly discussing the

epidemiology data, and the question was whether the epidemiology data, by itself, demonstrates causality, and the answer to the question is no.
Q. And that is your opinion, correct?
MS. GREENWALD: Objection, form.
A. That is only for the epidemiology data, and for the epidemiology data to exhibit clear causality, it would have had to be sufficient instead of limited in the IARC review.
I still believe it's limited and not sufficient by itself to demonstrate causality.
Q. OK, fair enough.
You are a proponent of a principle called the "precautionary principle," correct?
MS. GREENWALD: Objection to form.
A. I have been in debates with others on the precautionary principle where I've had to choose one side or the other.
But I'm not a proponent and I

don't hate it. I'm not clear on what it is in the way it is applied.
Q. Well, let me ask you this -- well, first of all, you were a member of a group called "Critical Scientists Switzerland," correct?
A. Yes, I am.
Q. And one of the goals of Critical Scientists Switzerland is promoting the precautionary principle, correct?
A. I suppose it is, yes.
Q. And in your assessment of glyphosate, you have talked about public protective decisions, correct?
MS. GREENWALD: Objection, form.
A. I have no idea -- I certainly do talk about public protective science -- use of science to protect the public.
Q. And in respect specifically to the glyphosate, and, for example, in your submissions to EPA, you have called upon them to apply this public protective approach in their assessment of the glyphosate science, correct?
MS. GREENWALD: Objection, form.

A. I don't recall that. You would have to show me. I'm sorry.
Q. So we are still on Exhibit 20. And if we could look at page 11.
And here you're talking about your comment on the rat studies, correct?
A. That's what it says, yes.
Q. And then the bottom of the page, the second paragraph on the bottom, the last line, you state that the public protective decision in this case should be to conclude these tumors arose as a function of exposure to glyphosate, correct?
A. It's the purpose of EPA to protect the public and they have to make that decision, and in this case, they should have included these tumors as a function of exposure to glyphosate, yes.
Q. Again, in your discussion with EPA, you're calling upon them to apply this protective approach in their assessment of glyphosate, correct?
MS. GREENWALD: Objection to form.

A. I'm calling them to conclude these tumors arose as a function of exposure to glyphosate.
Q. Based upon the fact that EPA is a --
A. Public health agency.
Q. And should therefore be applying a public protective methodology, or a methodology that is protective of the public in making its assessments about carcinogenicity, correct?
MS. GREENWALD: Objection to form.
A. It's a long question but I will -- I think you were reading way more into this sentence than really is there.
They are a public health agency. It's their job to protect the public. The correct decision here, the public-protected decision, should be to conclude these tumors arose as a function of exposure to glyphosate.
Q. And your understanding, when there is -- if there is uncertainty in the data but there is data that is suggestive,

for a regulator buying -- making a public-protective decision, they should lean in favor of binding an association, is that fair to say?
MS. GREENWALD: Objection to form.
A. No, I don't -- I don't believe that is a general rule I would hold.
Having been a regulator myself, it's -- there are many facets to making a decision. And you worry about public health but decisions are complicated.
Q. With respect to carcinogenicity, you have also stated your belief that it is glyphosate and not the surfactants in the formulated products that are causing the effects, correct?
MS. GREENWALD: Objection to form.
A. I can tell you what I believe.
I believe that glyphosate has an effect, and I believe the surfactants also have an effect, but the effect seen in human epidemiology is clearly partly due to glyphosate.

Q. You have also stated your belief, with respect to carcinogenicity, that it is glyphosate and not the surfactants in the formulated products that are causing the effects, correct?

MS. GREENWALD: Objection, form and asked and answered.

A. There is a lot of evidence here. So you have to break it down for me by the type of evidence you want me to discuss.

Q. We are going to provide you with -- do you recall being interviewed during one of the times that you went to Europe to talk about the European Food Safety Authority's assessment of glyphosate?

A. I've been interviewed dozens of times.

Q. During the break we will ask you to listen to one of those interviews.

MS. GREENWALD: Counsel, it has to be on the record. I'm not going to have him look at something on a break.

That's not the way it works in this litigation. You guys have done it

against us --

MR. LASKER: Well, we have had our people review things during the breaks so they could answer questions after the break.

MS. GREENWALD: Well, that's your choice.

We have also had depositions where we have taken a couple-minute break and then your counsel holds it against our time.

So if you want him to do it, we will do it on the record during your own time.

MR. LASKER: We will get that keyed up in a moment then.

Q. In presenting your opinions in your expert report, you have presented them in the context of the Bradford Hill criteria, correct?

A. Yes.

Q. And the question that a scientist must answer under the Bradford Hill criteria in deciding whether one can reach a causation opinion is "Is there any other

way of explaining the set of facts before us," correct?

MS. GREENWALD: Objection, form.

A. It's a paraphrase probably, or something along those lines, but yes.

Q. You agree that this is the appropriate methodology to be followed in reaching a causation opinion with respect to glyphosate or glyphosate formulations and non-Hodgkins lymphoma, correct?

MS. GREENWALD: Objection to form.

A. The Bradford Hill criteria with modifications have been accepted by many authorities as the way to approach a causality argument.

Q. My question was about you though. Do you agree that the appropriate methodology to be followed in reaching a causation opinion with respect to glyphosate is the Bradford Hill criteria including the question is there any other way of explaining the set of facts before us?

MS. GREENWALD: Objection, form,

asked and answered.

A. I think that quote is in my expert report. And the approach I took in the expert report, I believe, is the correct approach for glyphosate.

Q. You still didn't answer my question.

Do you believe the correct approach, correct methodology in reaching a causation opinion with respect to glyphosate or glyphosate formulations and NHL is to ask the question is there any other way of explaining the set of facts before us?

MS. GREENWALD: Same objection, form, and asked and answered.

A. I believe that the approach I use is the correct approach. That's my answer.

That question is too simple. The approach is much more complicated. Bradford Hill was just using it as a means for people to understand the concept of what he was trying to get through, but this is -- the whole criteria is very complicated and much greater than that one

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sentence.
Q. So in conducting your assessment of the glyphosate science, has it been your methodology to look to see whether there is any other way of explaining the set of facts before us?
MS. GREENWALD: Objection, form.
A. It's -- part of the Bradford Hill criteria is -- the philosophy of Bradford Hill is that question.
I didn't ask that question specifically on every single piece of evidence I looked at.
Q. Did you ask that question with respect to the glyphosate science as a whole?
MS. GREENWALD: Objection to form.
A. Glyphosate --
Q. Science as a whole --
MS. GREENWALD: Objection.
Q. -- with respect to carcinogenicity.
A. As a whole?
MS. GREENWALD: Same objection.

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A. Yes.
Q. Dr. Portier, I would like to ask you about -- let's go back to the question of the interview that you've had, and we will play for you -- this is a televised interview that you had in Europe.
MR. LASKER: And let's get this so the court reporter can hear it.
MS. GREENWALD: Do you have a transcript of it?
MR. LASKER: We have a thumb drive.
MS. GREENWALD: Do you have a transcript?
MR. LASKER: We don't have a transcript. We have a thumb drive.
A. My hearing is not great.
Q. Let's play the videotape.
That's you on the screen, right?

A. Looks like it.
MS. GREENWALD: And, Dr. Portier, if you can't hear it, we should stop it sooner than later.
MR. LASKER: It's pretty short.

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MS. GREENWALD: I don't want to play games here either. So let's see if you can hear it sufficiently, and all of us, actually, in the room.
(Videotape plays.)
MS. GREENWALD: I can't hear it. So you have to start it over.
MR. LASKER: Let's do this after the break.
MS. GREENWALD: We would also like some authentication that this is actually an accurate -- if you could give us the link and we can look at it, we'd just have some confirmation of what it is.
MR. LASKER: We can do that off the record, and then we will put it on the record, too. That's fine.
Q. Dr. Portier, when did you first reach your conclusion that glyphosate probably causes non-Hodgkins lymphoma in humans?
A. When did I first reach that conclusion?
Well, I agreed with the IARC

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monograph conclusion. So I guess it was at the end of the IARC monograph.
Q. And then do you recall when you first reviewed the data tables for the various animal cancer bioassays that you discuss in your report that were provided with the Greim arbitration?
A. Not really. I can't say exactly when I reviewed those supplemental tables.
Q. Was it before or after the date that you submitted the open letter to the European regulators in November of 2015?
A. I think it was probably after that.
Q. Was it before or after the date that you submitted your evaluations or you submitted -- provided submissions to EPA in October of 2016?
A. I can't be certain.
Q. In your expert report, you address the animal cancer bioassays under the Bradford Hill criteria biological plausibility, correct?
MS. GREENWALD: Objection to form.

A. I address it there and in two other places, correct.
Q. And you agree that animal cancer bioassays are intended to test whether glyphosate can cause cancer in mammals, thus supporting the concept that chemicals -- let me strike that.
It is your opinion as set forth in your expert report that animal cancer bioassays are intended to test whether glyphosate can cause cancer in mammals, thus supporting the concept that the chemical could cause cancer in humans, correct?
MS. GREENWALD: Objection to form.
A. That is part of what I believe from animal cancer studies.
There is a second part to that because they can be, under certain conditions, tumor specific for humans.
Q. You would agree that an evaluation of human health risks, sound human data, whenever available, are preferred to animal data, correct?

MS. GREENWALD: Objection, form.
A. In any endeavor, looking at mammalian health, the target population, doing everything you can in the target population that you -- things I can do in the target population are important and should be considered. Things that I can't do in the target populations, I will use other scientific models to look at.
As a general rule, if I have the exact same study and one is in humans and one is in rodents, I'm going to take the human one as more important.
Q. And I think it is consistent with what you just said, animal and in vitro studies are particularly important for you to supply evidence missing from human studies, is that fair?
MS. GREENWALD: Objection, form.
A. In vitro?
Q. Well, let's go with just animal studies.
MS. GREENWALD: Same objection.
Q. Animal studies might provide support for an assessment, but they are

mainly used to supply evidence missing from human studies, correct?
MS. GREENWALD: Objection, form.
A. No.
(Exhibit 15-28, document entitled, "Principles for modeling dose-response for risk assessment of chemicals," marked for identification, as of this date.)
A. I didn't think anybody ever read that document.
Q. One thing that came out of this, right?
A. That's amazing.
Q. So 15-28, this is a report of a committee that you chaired on principles for modeling dose-response for the risk assessment of chemicals, correct?
A. Did I chair it?
Q. Or maybe you served on this committee. I don't remember who chaired, frankly.
A. I don't know either.
Q. You worked on this committee, correct?

A. I worked on this committee that produced this report. That is correct.
Q. And on the beginning of this report -- and I recognize it is a long report, but on page Roman X at the beginning, it is sort of the summary section --
A. Where?
Q. It's Roman X.
A. Yes.
Q. And the final paragraph on that page states:
"In the evaluation of human health risks, sound human data whenever available are preferred to animal data. Animal and in vitro studies provide support and are used mainly to supply evidence missing from human studies."
Do you agree with that?
A. No. I realize I was on the committee but I don't agree with the statement.
Q. There is also a statement in this report at page 31, which is normal 31, not Roman. This is the end of the second full

paragraph under 4.6, the last sentence:
"For dose response analyses based upon laboratory data using animals, there is an additional problem of extrapolating from animals to humans."
Do you agree with that statement?
MS. GREENWALD: Objection, form.
A. This has to do with calculating risk --
Q. And do you agree --
A. -- and in the context of calculating risk, that statement is correct.
Q. And page 34, Section 5.1 is a statement:
"It has always been a challenge to extrapolate from effects observed in experimental animal bioassays to potential effects in humans in order to protect humans from potentially harmful chemical exposures."
Do you agree with that statement?
A. I'm trying to find it.
Q. 5.1, the first paragraph.
A. OK.

Again, this has to do with risk, not hazard. And in the context of risk, not hazard, this is indeed a true statement.
Q. There are certain mechanisms of action with respect to rodent carcinogenicity that do not apply to humans, correct?
MS. GREENWALD: Objection, form.
A. There have been -- the mechanisms apply to humans. The components of the mechanism don't exist in humans.
So there are cases where chemicals have caused cancer in rodents and the mechanism by which they do it does not work in humans.
Q. And there are differences between rodents and humans -- strike that.
These differences between rodents and humans can vary from one type of cancer to another --
MS. GREENWALD: Objection to form.
Q. -- is that fair to say?
MS. GREENWALD: Objection form.

A. As far as I know, there are only three cases of how this happens, so I -- it -- in the three cases, there are different mechanisms.
Q. There are differences in mechanisms of action between rats and mice, and between different strains of mice and rats, that will impact whether or not a chemical could cause cancer in that animal, correct?
A. There are mechanisms which could impact the degree to which the chemical causes cancer in the animal. Metabolism could cause differences. Many things.
Q. And scientists actually use different animal models to try and support the concept that exposure to a chemical can be linked to a specific type of cancer in humans, correct?
MS. GREENWALD: Objection to form.
A. Cancer -- there is numerous models that are used to assess the carcinogenic potential of chemicals in mammals.

Q. And different animal models will be used for different types of cancer, correct?
A. I don't really know that that statement is true.
Which -- different types of cancer in humans? Or different types of cancer in the animals you're going to do the study in?
I don't know the context of your question.
Q. Let's do it either way.
There are animal models that are used to assess whether a substance can cause a specific type of cancer in rodents, correct?
A. Yes.
Q. And there are different rodent models that are used to try and make an assessment as to whether or not an exposure can cause a certain type of cancer in humans, correct?
MS. GREENWALD: Objection, form.
A. Not that I'm aware of as a general screening tool.

Q. OK. Moving -- so moving away from a general screening tool -- let me just back up.

So the cancer bioassays that we are going to be discussing and you discuss in your report are general screening bioassays, correct?

A. That is correct with the exception of one of them.

Q. And there are then other animal models that are used subsequent to a screening study that will focus on potentially specific types of cancer, correct?

MS. GREENWALD: Objection, form.

A. You are talking about in rodents?

Q. Yes.

A. After exposure to the chemical?

So let me see if I am -- I am going to talk a little bit so I can get this straight in my head. Excuse me.

So the chemical gets done in a screening and an animal in the screening gets the tumor. Why would a scientist move from the, let's say, Wistar rat I saw a

tumor in to a different animal when I'm already getting tumors in the Wistar rats?

In answer to the question, I don't think there are that many cases where they switched off for a specific reason for a specific tumor.

Q. In your expert report, you cite to a number of articles regarding the current state of play with respect to identifying rodent models that could be used to analyze the possibility of NHL in humans, correct?

MS. GREENWALD: Objection to form.

A. I see what your question is about. Now, that's the difference. OK.

The rodent models for NHL are developed to get therapies for NHL for humans. They are not developed for the purpose of identifying tumors that arise in humans from exposure to chemicals.

They induce the NHL in the animal and then try to fix it.

Q. So with respect to mice, you cite to a 2009 book chapter by Herbert Morse

called "Mice models of human B lymphoid neoplasm," correct?

A. I believe I do. Yes.

(Exhibit 15-29, article entitled, "Mouse models of human B lymphoid neoplasms," marked for identification, as of this date.)

Q. In this book chapter, specifically at page 3 -- and this will be on the left column at the end of the column -- Dr. Morse states that species-specific differences in the immune system and molecular circuitry required for transformation make it difficult to model NHL in mice, correct?

MS. GREENWALD: Objection, form.

A. This is the last paragraph --

MS. GREENWALD: I can find it for you.

Q. End of the --

MS. GREENWALD: I found it. It's right here.

A. "Could thus make it difficult to model some human diseases in mice."

He is talking about genetically

modified mice here, yes.

Q. And Dr. Morse, if you turn to page 2 and then carry over to page 3, one of the issues that Dr. Morse notes is that the murine leukemia virus can cause lymphomas in mice through a mechanism that has no direct parallel to NHL in humans, correct?

MS. GREENWALD: Objection, form.

A. Everything he has written here is correct.

Q. So there are -- just to be clear, so I'm clear, the murine leukemia virus can cause lymphomas in mice through a mechanism that has no direct parallels to NHL in humans, correct?

MS. GREENWALD: Objection, form.

A. It's -- there is a parallel in humans. It just doesn't happen with that virus in humans.

Q. So what Dr. Morse says is these contributions to disease pathogenesis -- that's the cause of disease in the mouse -- have no direct parallels in human B lymphomas, correct?

MS. GREENWALD: Objection to form.
A. He is talking specifically about the murine leukemia virus, but the mechanism by which the murine leukemia virus causes NHL in -- causes these B lymphomas in the mice exist in humans. It's just not activated by this particular pathogen.
Q. Dr. Morse also notes -- and this is the first full paragraph on that left column on page 3, starting "Second," that there are significant differences between mouse and human immune systems in their development, structure, phenotype and function?
A. Correct.
Q. And this is significant because NHL in humans has been associated with immune system disorders, correct?
MS. GREENWALD: Objection, form.
A. I'm not absolutely certain.
Q. Are you not aware of an association between HIV and non-Hodgkins lymphoma?

A. Yes, I am.
Q. So it is correct that HIV in humans has been associated with immune system disorders, correct?
MS. GREENWALD: Objection, form.
A. It is true that NHL in humans -- correct.
Q. And there are significant differences between mouse and humans' immune systems, correct?
MS. GREENWALD: Objection to form.
A. There are differences between mouse and human immune systems, that is correct.
Q. And Dr. Morse further states, that same paragraph, that the spleen is the major secondary lymphoid organ in the mouse, whereas lymph nodes fill that niche in humans, correct?
A. That I don't know.
Q. You don't know one way or the other?
A. No. I'm sorry.
Q. And Dr. Morse also states in the

following paragraph, starting "Finally," that the genetic and epigenetic alterations required for neoplastic transformation sometimes differ for mouse and human, correct?
A. They do sometimes differ, yes.
Q. So when we are talking about alterations, we are talking about genetic changes that are required for cancer to form, correct?
A. Are you talking about epigenetic and genetic?
Q. Right. So these are genetic and epigenetic changes that are required for cancer to occur, correct?
MS. GREENWALD: Objection to form.
A. I'm not certain what he is saying here because neoplastic transformation can mean transformation of a carcinoma into a metastatic tumor, it could mean transformation from an adenoma to carcinoma.
So I'm not exactly certain what he is talking about here, but there are

genetic and epigenetic alterations that are required for both of those processes, and sometimes they differ for mice and humans.
Q. And it is also genetic and epigenetic alterations that would be required for a normal cell to be mutated that would sometimes differ from mouse and human, correct?
MS. GREENWALD: Objection to form.
A. Sometimes differ, yes, correct.
Q. And now Dr. Morse states in this paper that you cite in your report that the best-studied mouse strains -- and this is on page 2 -- for potential use as models for human B-cell lymphomas are the NFS.V congenic mice and the AX -- I'm sorry -- AKXD recombinant inbred strains, correct?
MR. LASKER: On the phone, can you put your phone on mute?
Thank you.
Q. I will state that again.
On page 2, Dr. Morse states that the best-studied mouse strains for potential uses --

MS. GREENWALD: Hey, guys, if you're not going to go on mute, we're going to have to disconnect the line.

Q. OK, we'll try that one more time.

Dr. Morse states that the best-studied mouse strains for potential use as models for human B-cell lymphomas are the NFS.V plus congenic mice and AKXD recombinant inbred strains, correct?

MS. GREENWALD: Objection to form.

A. Technically, these are not strains. These are transgenic mouse models. They derive from certain strains. I don't know what strains they derive from.

But he says these two mouse entities or types are the best models. He would know.

Q. Now, none of the glyphosate studies that we are going to be talking about were conducted in either of these mice strains?

A. Again, you are mistaken with what this means.

Q. I'm not asking what it means.

A. No one would ever test in these strains because these congenic and transgenic mice all get NHL. You could never detect NHL or any type of tumor like that if you use these because these are not -- they have already been produced to induce the tumors.

Q. Can you cite to any -- again, this is a document that you cited in your expert report with respect to mouse models for non-Hodgkins lymphoma.

Can you cite to any publication that points to CD1 or Swiss Albino mice as appropriate mouse models for human non-Hodgkins lymphoma?

MS. GREENWALD: Objection, form.

A. For the production --

Q. Yes.

A. -- of lymphomas from exposure to a chemical?

Q. No. Can you cite to any source document, any published document, that suggests that CD1 or Swiss Albino mice are appropriate mouse models for assessing the potential for a substance to cause NHL in

humans?

MS. GREENWALD: Objection, form.

A. No, probably not.

I -- I'm hesitating because the problem is OECD says these mice, CD1 mice, are good mice for studying chemicals for producing cancer. Hence, that document in essence is recommending if you are going to look for cancer, NHL is a cancer, then that's the right model.

That's why I am hesitating. That's not what he is talking about here, but that's why I was hesitating. Sorry.

Q. But specifically, can you cite to any publication that suggests that CD1 mice or Swiss Albino mice are appropriate mouse models for human non-Hodgkins lymphoma?

MS. GREENWALD: Objection, form and asked and answered.

A. I just answered that.

I can point to OECD and their guidance that this is an appropriate model for screening for cancer, and NHL is a cancer.

Q. Beyond the OEC document talking

about cancers generally, can you point to any document that is talking about non-Hodgkins lymphoma in particular --

MS. GREENWALD: Objection --

Q. -- with respect to CD1 mice or Swiss Albino mice?

MS. GREENWALD: Objection to form. Asked and answered.

A. I can't cite a single publication for any cancer where a specific mouse model is proposed to evaluate a chemical effect to cause cancer because of the mouse model.

So the answer to your question is I cannot cite anything specific to those mouse models producing malignant lymphomas and being the best model around.

Q. Dr. Morse includes a chart in his chapter on page 2 that identifies potential parallel neoplasm or cancers in human and mice, correct?

A. Yes.

Q. Dr. Morse does not suggest that any tumors in mice other than certain B-cell lymphomas would have a potential relationship to the development of

non-Hodgkins lymphoma in humans, does it?
MS. GREENWALD: Objection to form.
A. Yeah, you've lost me. Sorry.
Q. Dr. Morse does not suggest that there are any types of tumors in mice other than certain B-cell lymphomas that have a parallel to NHL in humans?
MS. GREENWALD: Objection, form.
A. His article is about B-cell lymphomas. This table was all about B-cell lymphomas.
Q. Dr. Morse does not suggest, for example, that there is any relationship between venal tumors in mice and the development of NHL in humans, correct?
A. Renal tumors in mice? Is that what you were questioning me?
I didn't understand that at all.
Does he suggest that kidney tumors would -- kidney tumors in the mouse would predict or be directly related to this tumor in humans? No.
Q. And would you -- with respect to different types of tumors in different

organs, would you agree that evidence of renal tumors in a mouse would not be directly relevant to the development of non-Hodgkins lymphomas in humans, correct?
MS. GREENWALD: Objection to form.
A. I'm not sure.
We did a paper on this, and I thought it came out recently, but I can't -- I can't tell.
And we looked at whether this tumor in this mouse seems to associate with this tumor and this human. And I don't remember if that particular case popped out or not.
So I can't answer the question very well. Sorry.
Q. So if I understand correctly, you have done an assessment of certain tumor types in mice to determine whether or not they are predictive of certain tumor types in humans?
MS. GREENWALD: Objection to form.
A. We have done a paper that looks

at all of the known human carcinogens from the IARC list, 101 chemicals minus -- I think it is about 86, 85 chemicals.
So these are chemicals that we know they cause cancer in humans and we know where they cause cancer in humans, so each of them had cancer bioassays also done -- well, some of them didn't, so we had to throw those out.
But most of them had cancer bioassays and so we could see what cancers arose in animals, what cancers arose in humans, and we could just look at the frequency of agreement.
Q. Are you aware of any published article that conducts an analysis to test whether the development of renal tumors in mice is predictive of NHL in humans?
MS. GREENWALD: Objection to form.
A. Um, no.
THE VIDEOGRAPHER: I'm approaching the end of the videotape.
MR. LASKER: We will take a break.

THE VIDEOGRAPHER: The time is 12:32 p.m. We are off the record.
(Luncheon recess)

AFTERNOON SESSION
1:20 p.m.
THE VIDEOGRAPHER: The time is 1:20 p.m. We are on the record.
BY MR. LASKER:
Q. Good afternoon, Dr. Portier.
A. I hope you enjoyed your lunch.
Q. Wonderful.
Before the break, we were discussing when you first looked at the data tables for the animal cancer bioassays that were provided with the Greim publication.
Would I be correct in my understanding that you would have reviewed those data tables prior to your submission to EPA in which you presented a pooled analysis of the data from those animal studies?
MS. GREENWALD: Objection, form.
A. If I remember correctly, all of the pooled analysis in the data I submitted to EPA were the mouse lymphomas and the hemangiosarcomas and the kidney tumors and

the answer to your question is no, I'd probably not reviewed it before then because all those came from EFSA review.
Q. When you, in your pooling of data with respect to -- let's actually show him the October 4, 2016. It has already been marked.
It is 15-20, you can look at 15-20.
MS. GREENWALD: They are not all here.
THE WITNESS: It's the bottom one because I reordered them just now.
A. Yes, OK. Let's see what pooled analyses I did. OK, so EPA's -- I did not pool the rat studies here.
Q. So is it your recollection then that you would have first reviewed or if we were trying to get to the day where you first reviewed the Greim supplement, it would be at the time that you had pooled analysis for some of the rat studies?
A. That's when I seriously got into looking at Greim's very carefully because in order to do the pooling in any of these

studies, I have to pull in nonsignificant findings from the other studies and none of the regulatory agencies provide nonsignificant findings.
So when I decided to pool the rat studies, that's when I really had to dig in there.
Q. I don't know if we have three copies of this now.
MR. LASKER: Let's go off the record for a minute.
THE VIDEOGRAPHER: The time is 1:25 p.m. We are off the record.
(Recess)
THE VIDEOGRAPHER: The time is 1:27 p.m. We are on the record.
Q. Dr. Portier, you note in your expert report that because of the large number of evaluations that have been done -- the large number of glyphosate rodent studies that have been done, that raises a concern that false positives could be exaggerated, correct?
A. Let me break down your sentence for a second. Exaggerated I think is the

wrong term.
Q. Why don't we mark the revised report. This is next in line.
(Exhibit 15-30, expert report of Christopher J. Portier marked for identification, as of this date.)
Q. Just for the record, Dr. Portier, Exhibit 15-30 is your revised expert report that was provided to us on or about June 27, 2017, and on page 50 of your report, that second paragraph, midway through, you state, "Because of the large number of evaluations done in an individual animal carcinogenicity study, there is concern that the false positive rates could be exaggerated." Correct?
A. That's what I said. Surprised I used exaggerated.
Q. Well, the point, in any event, that you're making there is that if 20 evaluations are done and a finding is deemed significant at a p-value of less than .05, then you would expect that one of those evaluations would report out as being positive simply due to chance, correct?

MS. GREENWALD: Objection, form.
A. That's what I wrote and that is correct.
Q. So a false positive then is when an individual test or trend meets the p less than .05 standard, but it is, in fact, due to chance rather than a carcinogenicity effect of a tested compound, correct?
A. A false positive is when there is no effect and you falsely declare it's positive either by statistical evaluation or whatever. That would be a false positive.
Q. And the point you're making here and, in particular, you state, for example, that there were -- on page 50, you list 329 total sites for rats and 16.5 that would be expected. Do you see that?
A. That is correct.
Q. And that again, that is the same point you're making that you would expect 1 out of 20 of those tests to report with a p less than .05 simply due to chance, correct?

A. Correct.
Q. And the reason that complicates the analysis of the glyphosate data is because there are so many evaluations that have been conducted in the animal studies, correct?
MS. GREENWALD: Objection to form.
A. The problem of false positives affects every study. But where you have, for example, with glyphosate, hundreds of analyses that can be conducted, you're going to be expecting to have a number of findings p less than .05 simply due to chance, correct.
MS. GREENWALD: Objection to form.
A. "Expectation" is the important word there. You expect to see it. That doesn't mean you necessarily saw it but you do expect it.
Q. So you're making the point here on page 50 is you have 329 total sites as you set forth on table 15 that could be examined or in the rat studies, and from

that, by chance alone, you would expect 16 or 17 to report out with a p less than .05, correct?
A. I'm -- that's correct. You know this table changed --
Q. I do understand that. I understand.
A. Thank you.
Q. You have further broken this down, down test by sex and by strain to look at what you would expect -- how many trends you would expect to see with ps less than .05 by chance and then comparing them to what you actually observe in the data, correct?
A. That is correct.
Q. And let's pull out your rebuttal report. And we will mark this as 15-31.
(Exhibit 15-31, Rebuttal Report of Christopher J.Portier marked for identification, as of this date.)
Q. And I think this statement is the same in both your initial report and in your rebuttal report, but it appears at page 7 on your rebuttal report.

You are discussing the number of trends that you see in the data or that you report in the data as compared to the number of trends that you would expect simply by chance. Correct?
MS. GREENWALD: Objection, form.
A. At the bottom of page 7, I discussed the new modified table 15 which discusses what we were discussing earlier. Same table.
Q. And what you state with respect to the rats -- and I want to focus on that now -- is with the exception of male Sprague Dawley rats, the observed number of tumors are at or near the expected number for the different sex strain groups in mice, correct?
A. That's correct.
Q. For female Sprague Dawley rats, you observed the number of trends that would be expected due to chance, correct?
A. I believe so, yes.
Q. For male Wistar rats, you found or observed the number of trends p less

than .05 that you expect to see due to chance, correct?
A. That is correct.
Q. And for the male Wistar rats, likewise, you observe the number of trends of p less than .05 you would expect due to chance, correct?
A. That is correct.
Q. But you nonetheless opine, based upon your analysis, that the data shows that glyphosate causes hepatocellular adenomas and skin keratoacanthomas in male Wistar rats and it causes mammary gland adenomas and adenocarcinomas in female Wistar rats, correct?
MS. GREENWALD: Objection to form.
A. I don't know about opining, but I certainly discuss those tumors and come to a conclusion that they are probably caused by glyphosate.
Q. So your conclusion is that the tumors that you identified for Wistar rats that have trends less than .05, which is the same number you would expect due to

chance, is, in fact, evidence of causation, correct?
MS. GREENWALD: Objection to form.
A. In fact -- they are part of the evaluation of causation. The skin keratoacanthomas were also seen in the Sprague Dawley rats which is the reason I did not decide that they were just random chance and the mammary gland carcinomas and adenomas and carcinomas, because it's the same progression of tumor, there is greater evidence that it remains.
So a decision to argue for a positive finding is not just statistical. It's also tied to the actual biology.
Q. Well, Dr. Portier, that wasn't my question.
You observed the number p less than .05 trends for Wistar rats that would be expected due solely to chance, correct?
MS. GREENWALD: Objection, asked and answered.
A. I observed the same number as expectation.

Q. Due to chance?
A. Due to chance.
Q. But your opinion is, in fact, this is evidence that glyphosate caused those tumors in those rats, correct?
MS. GREENWALD: Objection, form.
A. What is "this"? What is "this is evidence"?
Q. The trends that you observed of p less than .0.5 for Wistar rats which are the same trends you would expect to see due to chance, in your opinion, is evidence that glyphosate caused those tumors in Wistar rats. Correct?
MS. GREENWALD: Objection, form.
A. It's part of the evidence. Yes.
Q. You reached your rat causation opinions through the application of a pooling methodology, correct?
A. Yes, I did.
Q. And you agreed that methods for combining analyses of multiple animal cancer bioassays are not available in the

scientific literature, correct?
MS. GREENWALD: Objection, form.
A. Say again.
Q. You agree that methods for the combined analysis of multiple animal cancer bioassays are not available to the scientific literature?
MS. GREENWALD: Same objection.
A. I believe I wrote that, but it is now incorrect.
Q. At the time that you drafted your revised expert report, it was your understanding that methods for the combined analysis of multiple animal cancer bioassays are not available in the scientific literature, correct?
A. That is correct.
Q. And because of that, you developed the pooling methodology that you used for the purposes of your glyphosate analysis, correct?
A. Oh, I can't take credit for developing it, no.

Q. Can you cite -- first of all, have you ever published a paper in which you used this pooling methodology that you use in this case?
A. I'd have to go back and look. The pooling methodology is simply taking information from multiple laboratories or multiple experiments and putting it together and doing one analysis, and I believe I have, using the same technology, taken data from multiple experiments and done the analysis.
So I can't take credit for it, nor can I say I never did it.
Q. Let me ask you again. Can you cite to my -- first of all, have you ever published a paper in which you use this pooling methodology?
MS. GREENWALD: Objection, asked and answered.
A. I think I have.
Q. Can you cite to which paper that is?
A. I would have to go look at the papers.

Q. Can you cite, sitting here today, to any published paper by any scientist using this pooling methodology in analyzing animal cancer bioassay data?
A. Yes.
Q. Which article?
A. The someone asked me to look -- so Mike Dourson is going to be the new assistant administrator for EPA and I was asked to look at some of his papers and he does it in two of his papers.
Q. Can you say the name again?
A. Mike Dourson, D-O-U-R-S-O-N.
Q. Let's take a look at how you applied the pooling methodology in this case.
Now, we already talked about the fact that you opine, based upon your pooling analysis, that glyphosate causes mammary gland tumors in female Wistar rats, correct?
A. Wistar rats, I think so, yes.
Q. We can look at your expert report at page 28. And this is 15-30. Starting at page -- 15-30, you're talking about the

Brammer study.
A. Yes.
Q. And then you have on the next page, 28 is Brammer, 30 is Suresh, and 31 is -- I'm sorry, it bounces around a little bit. 32 is Wood, correct?
A. Yes.
Q. Those are the three studies in Wistar rats, correct?
A. Yes.
Q. So in the Brammer study reported on page 28, there were more mammary tumors found in the female Wistar rats that were not treated with glyphosate than were found in any of the three treated groups individually, correct?
A. More mammary grand adenomas and carcinomas in the control group than the treated groups, yes.
Q. And then the second Wistar study is Suresh. That's reported in page 30 of your expert report, correct?
A. Yes.
Q. In that study, the data finds a statistically significant inverse trend or

negative trend for mammary tumors with increased doses of glyphosate, correct?
MS. GREENWALD: Objection, form.
A. I don't actually know. I just see the p trend. I don't know what the slope was.
Q. But the p-value, if you have a p-value of .970 for a positive trend, that translates also to a trend of .03 for a negative trend. That's the way the math works, right?
A. Probably. I would want to look at the statistic to be sure, but probably, yes.
Q. So with that understanding, the Suresh study found an inverse trend, a negative trend for mammary glands that would be significant to p equals .03, correct?
MS. GREENWALD: Objection, form.
A. I am not sure.
Q. The Suresh study found more mammary gland tumors in the controls than

in the highest dose group, correct?
A. That is correct.
Q. And if the p trend for mammary gland adenomas and carcinomas in Suresh is an inverse trend, p equals .03, that would mean that the incidence of mammary gland tumors in female Wistar rats decreased as the dose increased by a statistical measure, correct?
MS. GREENWALD: Objection, form.
A. Because of the high response in the control, yes, that's probably the case.
Q. The third study you have for Wistar rats is the Wood study and that is a study that found a -- you report a statistically positive trend increasing tumors for mammary gland tumors, correct?
A. For mammary gland adenocarcinomas and mammary gland adenocarcinomas and adenomas combined. Yes.
Q. So for the three Wistar rat studies for mammary tumors, we have one study, the first one study we looked at, by Brammer, where there were more tumors found

in the controls than in any of the treated groups.
We have a second study by Suresh that reported what appears to be a statistically significant negative trend, meaning less tumors, less mammary gland tumors as the dose increases. And we have a third study that shows an increased trend of more tumors with more dose. Correct?
MS. GREENWALD: Object to the form.
A. We have the Brammer study which is negative; the Suresh study which is negative; and the Wood study which is positive.
Q. Just to be clear again, the Suresh study appears to be statistically significant negative, correct?
A. Correct.
Q. Now, when you pooled these studies together, and you report that -- I think on page 33 -- when you pooled the three studies together, you did not find any increased risk of mammary tumors in female Wistar rats, correct?

A. OK, say the question again.
Q. When you pooled the three Wistar rat studies together, you did not find any increased risk of mammary tumors in female Wistar rats with treatment for glyphosate, correct?
A. Yes, I got a p-value well above .05.
Q. To reach your causation opinion -- and you did reach an opinion that glyphosate causes mammary tumors in Wistar female rats. We just talked about that. To reach that opinion, you removed Suresh from your pooling analysis, correct?
MS. GREENWALD: Objection to form.
A. First, I want to check the conclusion. So I'm very clear on what I said.
Q. On page 52, you state that glyphosate causes mammary gland adenomas and adenocarcinomas in female Wistar rats, right? That's your opinion in your expert report, correct, Dr. Portier?
A. Yes, yes. It should have said

limited. I'm sorry, that was a -- that was a mistake. That's in this paragraph on page 33.
Q. To reach your opinion to support the idea that there is a causation with mammary tumors in Wistar rats, you dropped the Suresh study from your pooling analysis completely, correct?
A. I did a sensitivity analysis in which I removed the one study that might have not matched the other two. And I did a separate pooling. That is correct.
Q. So by removing the statistically significant negative trend, decreasing tumors with increasing glyphosate use, in Suresh, you were able to pool the two other studies to opine that there was a positive trend for mammary tumors in Wistar rats with glyphosate, correct?
MS. GREENWALD: Objection to form.
A. When, with justification, I removed the Suresh study, I could see a significant finding; and, hence, I said there was limited support for that tumor.

Q. Well, you're stating that now.
A. No, it's right there.
Q. In your expert report?
A. Page 33.
Q. Page 52.
A. Page 33, "Given the mixed results for the pooling from this tumor, I conclude there is limited support for the notion that glyphosate can cause mammary gland adenomas and adenocarcinomas in Wistar rats."

I've already conceded that in the final conclusion I should have used the word "limited" for that tumor.

Q. If you had instead removed the Wood study from your analysis and pooled instead the Suresh study and the Brammer study, you would have reported a statistically significant protective effect of glyphosate against mammary tumors, wouldn't you have?

MS. GREENWALD: Objection, form.

A. That, I do not know.
Q. You didn't conduct that

sensitivity analysis?

A. I had no reason to believe the Wood study was different from the Animoto study, or whatever we are talking about. Wood and -- Wood and Animoto was the two I pooled, correct? Wood and Brammer, Wood and Brammer.

I had no reason to believe that Wood was different than Brammer. But I had reason to believe that Suresh was different than the other two.

Q. With respect to mammary tumors, what was your basis for concluding that Suresh was different than Wood and Brammer?

A. When a -- when a strain of animals shows any tumor, whether it's the adenocarcinomas or the liver tumors, at a rate which is incredibly different than the others, it suggests that the strains are not -- they are not exactly operating the same.

The hepatocellular adenomas and carcinomas in the Suresh data set -- I believe it was the hepatocellular adenomas and carcinomas were substantially larger in

the control population, substantially, than either of the other two studies. That raises a flag that suggests that those studies are not replicates of each other and one should be careful when combining them.

Q. In the mammary gland tumors, you had, in the Wood study, eight out of 51 with tumors in the high dose group and that is significantly different than what you found in the other two studies, in Suresh and Brammer, correct?

MS. GREENWALD: Objection, form.

A. There were different doses. That's -- they are not equivalent connections and I don't know if they were statistically significant or not. They were different. There is no doubt about it.

Q. You used a similar pooling methodology to reach your opinion that glyphosate causes hepatocellular adenomas in male Wistar rats, correct?

A. I believe I did.

Q. Neither the Suresh study or Wood study found any increased incidence of hepatocellular adenomas in male Wistar rats, correct?

A. OK, let's see here. I was looking at the wrong ones. The first paragraph under joint analysis.

Q. It might be easier to look at the tables, 28, 30 and 32. Neither the Suresh study nor the Wood study found any increased incidence in hepatocellular adenomas in male Wistar rats, correct?

A. No statistically significant increased incidence, that is correct.

Q. And when you pooled the results of the three Wistar rat studies, you likewise did not find a positive trend for hepatocellular adenomas, correct?

A. I'm trying to find where I did the pooling and talked about whether it is significant or not.

I didn't pool all three studies. I'm sorry, I didn't pool them here. I don't see an analysis of the pooled three studies because the hepatocellular adenomas

seen in the Suresh study were 48 percent in controls; whereas the other two studies, the hepatocellular adenomas were down in the 0 to 1 percent to 2 percent range. Hence, pooling all three of them would be a mistake from the start. So I never even bothered.

Q. You reach your causation opinion based on a pooling that dropped the Suresh study out of the analysis, correct?

MS. GREENWALD: Objection, form and asked and answered.

A. I didn't drop the Suresh -- I didn't drop the Suresh out of the analysis, I never put it in.

Q. And in your discussion of that analysis, or your reasoning there for not including or -- in your evaluation, the hepatocellular adenomas, you state that, to reject a finding based upon only one in three being positive is the same as rejecting a coin being fair if, in three flips of the coin, the result is one head and two tails, correct?

MS. GREENWALD: Objection,

form.

A. I do write that in here.

Q. And you -- so you state that to reject causation based upon the findings of one positive trend and two null findings for hepatocellular adenomas, then it is the same as rejecting a coin as being fair if in three flips of the coin, the result is one head and two tails, correct?

A. Yes. The rest of it says you can't -- it simply is not possible and there is a better way to address these findings.

Q. And your pooling methodology for the glyphosate animal studies then seeks to determine whether the data is sufficient to reject a finding of causation for glyphosate and cancer in rodents, correct?

A. No. The pooling is there to evaluate whether, for this tumor, having seen a positive in one or two studies, does that positive stay when you group it with all the rest of the studies that it should be appropriately grouped with.

Q. And the analogy you are talking

about is rejecting a coin being fair, correct?

MS. GREENWALD: Objection to the form.

A. No, the rejection of a coin being fair here is that it's impossible to do it with only three flips.

Q. Right.

A. It's not that I can't reject a coin being fair. Of course I can if I do a large enough sample size.

So it's the concept that you can't do this that is being brought up there.

Q. In scientific analyses, you start off with a null hypothesis and then you try to reject that hypothesis, correct? That's the scientific methodology?

A. Correct. Well, you don't try to reject the hypothesis. If the data pops that way, it rejects the hypothesis.

Q. So for a coin toss, is the null hypothesis that the coin is fair and you are trying to reject that, correct?

MS. GREENWALD: Objection,

form.

A. If that's your hypothesis, yes.

Q. For glyphosate and the animal studies, the null hypothesis is that glyphosate does not cause tumors, correct?

MS. GREENWALD: Some objection, form.

A. The null hypothesis is that it does not cause an increase in tumors, that is correct.

Q. And your assessment, though, is looking to see whether the data is sufficient to reject the possibility that glyphosate does cause tumors, correct?

MS. GREENWALD: Objection, form.

A. No, the test is to see whether the rejection of the null hypothesis from the one study is -- remains or is -- goes away when I pool the data.

Q. So you are pooling the data to see if you can support -- strike that.

So you are pooling the data of those two studies without the third study to see if you can then reject the finding

in the third study, is that correct?
MS. GREENWALD: Objection, form, asked and answered.
A. No.
Q. You also exclude the Suresh study from your pooling analysis to support your opinion in your rebuttal report that there is a suggestion that glyphosate causes pituitary tumors in -- strike that.
I want to get that right. Yes. At page 6 of your rebuttal report, you also exclude the Suresh study from your pooling analysis to support your opinion that there is a suggestion that glyphosate causes pituitary tumors in female Sprague Dawley rats, correct?
MS. GREENWALD: Objection to form.
A. I did not include -- I don't know if I did the three. I don't think I -- I'm -- yes, that is -- I believe that's correct.
Q. Now, you used that same pooling methodology to conclude that there was a statistically significant positive trend

for skin keratoacanthomas in male Wistar rats, correct? And that's initially your revised report at page 32.
A. Page 32?
Q. I'm sorry. Page 31.
A. That is correct.
Q. So for skin keratoacanthomas, pooling the Wood and Brammer studies alone did not result in a statistically significant positive trend for male Wistar rats, correct?
A. It resulted in a p-value for trend of 0.053 which was barely not statistically significant.
Q. So for your skin keratoacanthoma causation opinion, you did pool, include the Suresh study in your pooling analysis to come up with a statistically significant finding, correct?
MS. GREENWALD: Objection, form.
A. I believe I wasn't that marginal. Let me look at my summary.
Q. Page 35.
A. I've got you. I'm sorry, I'm

just checking my -- yes. That must be what I used in my table 8.
Q. So you dropped or did not include Suresh for your pooling methodology when it resulted in a finding of no increased trend for mammary glad or hepatocellular tumors, but then included Suresh in your pooling analysis to calculate a positive trend for skin keratoacanthomas, correct?
MS. GREENWALD: Objection to form.
A. No.
Q. Did you not include Suresh in your analysis for skin keratoacanthomas?
A. In all of them, maybe all of them except hepatocellular adenomas, I did analyses with Suresh included and without Suresh included. All of those analyses play a role in my decision about whether this is a real tumor finding or a chance tumor finding and how much support there is.
Q. And in your finding of a positive trend, as you reported in your final opinion, to find a positive trend for

mammary gland tumors and hepatocellular adenomas, you used a pooling only of the Wood and Brammer study, and to reach your opinion with respect to keratoacanthomas, you used a pooling of all three studies, correct?
MS. GREENWALD: Objection, form.
A. I used all of the analyses that it had done to that time.
Q. For mammary gland tumors and the hepatocellular adenomas, to find a statistically significant positive trend, you found that only when you pooled just the two studies, Brammer and Wood, correct?
A. As I mentioned before, I saw an almost statistically significant p equals p.053 in the combined analysis.
I do not characterize it as negative. I characterize that as almost significant.
Q. Just to be clear, we are talking about mammary gland tumors and hepatocellular adenomas. Is it your testimony now that you found an almost

significant trend with those two tumors when you combined the three studies? I think you are confusing it now for skin --

A. I am sorry, for skin keratoacanthomas.

Q. No, let me -- for mammary gland adenomas and hepatocellular adenomas -- I am sorry, for mammary gland tumors and for hepatocellular adenomas, you opined to a statistically significant increased trend by pooling just Wood and Brammer, correct?

MS. GREENWALD: Objection, form.

A. For mammary gland adenomas and adenocarcinomas combined.

Q. And hepatocellular adenomas for those two tumors, you reported a -- or you opined to a statistically significant increased trend by pooling Brammer and Wood and not including Suresh, correct?

MS. GREENWALD: Objection, form.

A. For those two tumors, I saw -- not for -- for hepatocellular adenomas, I did not pool the three. So I do not know

what the result of that pooling would be.

When I pooled the two, yes, I saw significant p-value. For that tumor.

Q. And for mammary gland tumors, when you pooled the three, you didn't see a statistically significant trend, but when you pooled the two, you did?

A. That is correct.

Q. And that was the basis for your opinion with respect to mammary gland tumors, correct?

MS. GREENWALD: Objection, form.

A. That's the basis for my opinion that there is limited support for the notion that glyphosate can cause mammary gland adenomas and adenocarcinomas in Wistar rats.

Q. And for skin keratoacanthomas, where you report a statistically significant trend on your table, that is based upon the pooling all three of the studies, correct, including Suresh?

A. As I said before, it's based upon everything that went on in that evaluation.

Q. All three of the studies were pooled to get that statistically significant trend, correct?

A. No. The statistically significant -- you're confusing my decision to say this is glyphosate-related with any given one test or not. If you look through here, you will see is that there are subtleties involved in this.

In this case, when pooled with the Suresh study, it was highly -- it was highly -- no, it was statistically significant for the keratoacanthomas, and when it was not pooled, it was almost statistically significant for the keratoacanthomas. Therefore, I decided that there is a -- there is fire here and there is probably something going on. And that's why I made the decision to say that it was causal.

Q. And you reported that trend as statistically significant in your tables, correct?

A. In the table 8, I put three dots for the triple. I should have put one.

Q. Let's look at your pooling methodology for Sprague Dawley rats in your rebuttal report and this is page 6.

You opine that the Sprague Dawley rat study suggests a potential for glyphosate to cause adrenal cortical tumors in female rats, correct? That's page 6.

MS. GREENWALD: Objection, form.

Q. Second paragraph, first full paragraph on page 6, returning to table 2.

A. So ask your question again, please.

Q. Through -- in your rebuttal report, you opine that the Sprague Dawley rat studies suggest a potential for glyphosate to cause adrenal cortical tumors in female rats, correct?

MS. GREENWALD: Objection, form.

A. That is correct.

Q. When you pooled the results for the four Sprague Dawley studies, your pooling methodology reported a statistically significant negative trend for glyphosate and adrenal cortical tumors,

correct?
A. That is, I believe, correct.
Q. So in other words, you found, by pooling the studies, that there was a decrease in the incidence of adrenal cortical tumors with an increased dose of glyphosate and that was statistically significant, correct?
A. No. What I found was that the -- because of the hypothesis rates of this tumor in Lankas, et al., 1981 and the lower rates in the others, you end up with a negative trend because of that high rate of tumors. And that's why you have the negative trend. I would never have called that pooled analysis a negative trend because it was clear to me that that pooled analysis was flawed.
Q. OK. But just to be clear, page 10 of your rebuttal expert report, you present the data the -- your pooled analyses for adrenal cortical carcinomas in female Sprague Dawley rats -- correct? Adrenal cortical carcinomas?
A. I'm sorry, I'm kind of slow, yes,

I present that, yes.
Q. In your original pooled analysis, you have a p of .-- 0.997 which translates to an inverse trend with a p of .003. That's statistically significant, correct?
A. For negative, it has a negative trend. That is correct.
Q. And despite the fact that your pooling analysis finds this statistically significant inverse trend with p equal to .003, your ultimate opinion is that these studies suggest a potential for glyphosate to cause adrenal cortical tumors, correct?
MS. GREENWALD: Objection, form.
A. I concluded that because the Lankas study is 26 months instead of 24 and because the tumor rates seen in that study far exceed the others, that it doesn't belong in that pooled analysis and I made my conclusion based upon pooling the other three studies.
Q. Well you talk about dropping the Lankas Sprague Dawley study. You used that same approach to reach an opinion with

respect to kidney adenomas in male rats. Correct?
MS. GREENWALD: Objection, form.
A. Again, the Lankas study was 26 months and the rest were 24. That is reason to exclude it.
Q. And, in fact, though, if you looked at the four Sprague Dawley rat studies and that would be on pages 26 to 27 of your expert report -- I am sorry.
A. Wistar rats. It starts on 24 -- anyway, OK.
Q. So for Lankas, we were going to talk about the kidney adenomas, you did not find increased instance of kidney adenomas with increased dose of glyphosate, correct?
A. That is correct.
Q. And then if we look at the Stout and Reucker study, the second Sprague Dawley study, it's a 24-month study you do not find an increased incidence of kidney adenomas with increased dose of glyphosate, correct?
A. That is correct.

Q. If you look at the Atkinson study which is the third study for kidney adenomas in male Sprague Dawley rats, you did not find an increased incidence of kidney adenomas with increased exposure to glyphosate, correct?
A. That is correct.
Q. So three of the four. And in fact, three of the four Sprague Dawley studies did not find any kidney adenomas whatsoever in either the middle or highest glyphosate dose groups tested, correct?
A. I'm looking for the fourth study. I'm sorry.
Q. The fourth study would be table --
A. Table 6, and I wanted to look at that.
That would be correct. Three of the four did not have, by themselves, a positive finding for this tumor.
Q. Well, my question was a little bit different. Three of the four Sprague Dawley studies did not find any kidney adenomas whatsoever in either the high dose

or middle dose glyphosate group, correct?
A. I believe that is correct. This is a very rare tumor.
Q. But using your methodology, you opined that that data proves that glyphosate caused kidney adenomas in male Sprague Dawley rats, correct?
A. I believe that's what I said and I believe that is the case, yes.
Q. So now you dropped Lankas from your analysis for adrenal cortical tumors and kidney adenomas, but you highlight the findings of Lankas with respect to other tumors that were seen in that study?
A. In the Lankas study. Other tumors that were seen in the Lankas study.
Q. Yes.
A. That is correct.
Q. So for example, with thyroid C-cell tumors in female rats and in testes interstitial tumors in male rats, those tumors were found in the Lankas study but not found in the other three studies, correct?
A. That is correct.

Q. And in your expert report, you state that Lankas might be informative on causation with respect to these tumor types because there was a 26-month study while the other three studies were for 24 months, correct?
A. That is correct.
Q. You also opine, in your expert report, that glyphosate causes thyroid C-cell tumors in male Sprague Dawley rats, correct? You can look at page 52 if you want.
A. Thank you.
Thyroid C-cell adenomas and carcinomas combined in male Sprague Dawley rats.
Q. So the answer is yes, you do opine that glyphosate causes thyroid C-cell tumors in male Sprague Dawley rats, correct?
MS. GREENWALD: Objection to form.
A. That's what it says, correct.
Q. Now, let me mark for you your initial expert report. We will make this

32.
(Exhibit 15-32, Original Expert Report of Dr. Christopher J. Portier marked for identification, as of this date.)
Q. So Exhibit 32 is the expert report you submitted in this case in May of 2017, correct?
I'll represent to you it was May 1, unless there is some disagreement there.
You revised this expert report in your July report, correct?
A. That is correct.
Q. Now, at page 53 of your May -- your first expert report. I'm sorry, not 53. 34, of your May 2017 expert report, you're talking about the findings for thyroid C-cell tumors, correct?
A. That is correct.
Q. And at that point in time, you didn't have data from the Lankas study, correct?
A. That is correct.
Q. And you concluded, based upon

your analysis of the three other studies, that there was -- the evidence is weak that glyphosate causes thyroid C-cell tumors in male Sprague Dawley rats. Correct?
A. That is correct.
Q. And if we go now to your revised expert report, that same page on Exhibit -- page 34 on your revised expert report, here you now have data from the Lankas study and you note that pooling all four studies yields a significant trend of p equals .041. Correct?
A. I have to find it. I'm sorry.
That appears to be correct.
Q. So you're no longer saying that the evidence is weak, correct?
A. That is correct. But --
Q. And that is because you're now including the Lankas study --
MS. GREENWALD: He was finishing a sentence.
A. That is correct. But you are right, that is an error. This should remain weak. This is -- this is not my intention, I'm -- you have -- you're

correct.
Q. So you are now opining that you should not have included the Lankas study in this pooling analysis?
A. No, I should not have concluded that this was evidence -- that it should have been weak or limited evidence that glyphosate causes thyroid C-cell tumors. I should have put that in there.
Q. In your revised report, to reach a statistically significant finding for thyroid C-cell adenomas, you included the Lankas study in your pooling methodology, didn't you?
MS. GREENWALD: Objection to form.
A. I had done both since I did it in my previous one. But here, it seems I pooled all four. That is correct.
Q. You had pooled all three in your May report and, then to reach a statistically significant finding in your July report, you pool all four, correct?
MS. GREENWALD: Objection, form.

A. No, no.
Q. You didn't pool all four studies in your July expert report?
A. I did, but I didn't do it to achieve statistical significance.
Q. In your rebuttal report, you also discuss pooled analysis in Sprague Dawley rats for skin keratoacanthomas and basal cell tumors. I think this is based on page 6 of your report.
A. Which one are we looking at?
Q. I am sorry, your rebuttal expert report. So this is 15-31.
A. Page 6?
Q. Yes.
A. I -- OK, what are we looking at here.
Q. So you report that for skin keratoacanthomas, you are reporting a pooled finding of an increased trend for increased skin keratoacanthomas for Sprague Dawley rats, correct? On page 6 of your rebuttal report, on the bottom, the second paragraph from the end.
Page 6, second paragraph from the

bottom, pooling the remaining new findings in Sprague Dawley rats. Do you see that?
A. It seems that's what I did, that's correct.
Q. Which of the four Sprague Dawley rat studies did you pool for your positive -- reported positive reports in skin keratoacanthomas?
MS. GREENWALD: Objection to form.
A. It does not say.
Q. I know it does not say. That's why I am asking you.
A. I would have to go back.
Q. Basel cell tumors, you also report a pooled finding. Which of the four Sprague Dawley rat studies did you include in your pooling analysis for basal cell tumors?
A. Again, I don't know. I would have to go back and look.
Q. Basal cell tumors, those in mice are the sames basal cell tumors in humans? Is that a similar tumor?
A. It's -- it arises from the same

place.
Q. And basal cell tumors, as I know all too well, in humans are generally caused by exposure to sunlight, correct?
MS. GREENWALD: Objection to form.
A. Can I go back to your previous question about what was pooled and correct that?
Q. Sure.
A. Thank you. All four studies were pooled for that evaluation.
Q. Is that for both the evaluations?
A. What was the skin keratoacanthomas -- and what was the other one?
Q. Basal cell.
A. Actually -- I did both poolings. OK, like I did before, three and four.
Q. Where is your --
A. Table 2, page 10.
Q. OK. What is 3 and what's 4?
A. So Lankas, Ekemoto, Atkinson and Stout and Reucker is Sprague Dawley rats, the first big block that's pooling all

four. Oh, no, I didn't show the pooled three here, I'm sorry.
Q. You are looking Wistar rats I think?
A. I was looking at Wistar rats.
Q. Just so the record is clear --
A. I don't have anything here that says when I pooled -- just one minute.
I don't say here when I pooled only three instead of the four, so I can't answer the question.
Q. At least as reported in table 2, you are relying upon a pooling analysis of all four of the Sprague Dawley rat studies including Lankas for those two tumor types?
A. I can't answer the question.
Q. Fair enough.
A. I thought I could. Sorry.
Q. Basal cell tumors, those are caused primarily by exposure to the sun, correct?
MS. GREENWALD: Object to form.
A. I don't know. Skin cancers are -- certain skin cancers are caused

primarily by the sun, but I don't know if that is a basal cell -- is the same thing.
Q. Do you know of any evidence or can you cite to any publication that states that an oral ingestion, eating study, of any substance can result in a basal cell tumor? Can cause a basal cell tumor?
A. Probably. It's well known that rats and mice, after they eat, lick their skin, and so it's well known that you get some degree of absorption on the skin in these types of studies.
Q. So your sense then would be to the extent that there are skin tumors reported in these studies that might be attributed to the glyphosate, it would be because of rats licking their skin?
A. You couldn't rule it out. It could be either one and to give you an example, we saw an increase in skin tumors from oral ingestion of dioxin.
Q. And was that an oral gavage or a feeding study?
A. It was an unusual study. I just don't remember. It was probably an oral

gavage.
Q. That would be a liquid ingestion as opposed to a solid ingestion of the chemical?
A. Yes, and forced into the stomach of the animal so it would not be licking itself and putting it on the skin.
Q. With respect to this potential licking of the skin, you would not be able to actually determine what the dose was for any of the animals in these studies, correct?
MS. GREENWALD: Objection, form.
A. You could figure out with some degree of accuracy an estimate of how much was going on the skin from studies people have done in looking at the issue. Nobody has done that, but you probably could.
Q. But as of today, nobody has conducted the study that would allow you to determine what dose of glyphosate might have been licked on to the skin of these mice in the various treatment groups, correct?

A. That is correct.
Q. So you would not be able to come up with any trend based upon dose of glyphosate applied to the skin using these studies, correct?
A. No, that's not true. Almost certainly the dose to the skin is going to be concentration dependent because the animals will, on average, all do the same amount of grooming. And so as you double the dose, you're going to probably double the amount that gets on the skin. So I could do a trend test for that.
Q. Do you have any evidence of your review of the studies that looked at the grooming habits of these rats with respect to whether the grooming habits were the same across treatment groups?
A. There is no evidence either way in almost any study about grooming habits, it's not recorded.
Q. Let's turn to the mice, mouse studies, mice studies, mouse studies.
You used the same pooling methodology that you applied with the rat

studies in reaching your causation opinions in mice, correct?
A. Yes.
Q. In your rebuttal report -- again, if you look at page 7, you state that the observed findings of p less than .05 in Swiss Albino mice, both male and female, and female CD-1 mice would be consistent with what would be expected due solely to chance, correct?
A. I'm not sure where you are reading at.
Q. At the bottom of page 7 in your rebuttal report. Yeah.
A. Now, what's the question?
Q. So you state in your rebuttal expert report that the observed findings of p less than 0.05 trends in Swiss Albino mice, both male and female, and female CD-1 mice are consistent with what would be expected due solely to chance, correct?
MS. GREENWALD: Objection to form.
A. That's not what I said.
Q. You state that in female CD-1

mice and Swiss Albino mice, the expected and observed numbers are approximately equal, correct?
A. That is for the expected and observed number of p values less than 0.05, that is correct.
Q. Right. Just to be clear then, you state in your rebuttal expert report that the observed findings of p less than 0.05 trends in Swiss Albino mice and female CD-1 mice are consistent with what would be expected due solely to chance, correct?
MS. GREENWALD: Objection to form.
A. No, that's not what I wrote. I wrote what I wrote. It says they are approximately equal. That is all it says.
Q. So the number of observed trends that you saw in female CD-1 mice and in Swiss Albino mice are approximately equal to what you would expect to see due to chance, correct?
MS. GREENWALD: Objection, form, asked and answered.
A. I answered it.

Q. Is that correct?
MS. GREENWALD: Objection, same two objections.
A. I answered the question already.
Q. I am going to ask it again because I don't believe you did.
In female CD-1 mice and Swiss Albino mice, the number of trends you would expect to see due to chance and the number of trends you, in fact, did see are approximately equal, correct?
MS. GREENWALD: Objection, form.
A. That is correct.
Q. Now, based upon your pooling methodology, you opine that glyphosate causes a number of tumors in CD-1 mice, correct?
A. Due to the data I'm looking at, which includes the pooling analysis and the individual analysis and other things, I am convinced that a number of tumors in the CD-1 mouse are positive.
Q. So your causation opinion with respect to CD-1 mice is looking at four

studies, correct?
MS. GREENWALD: Objection, form.
Q. The four mouse studies?
MS. GREENWALD: Objection, form.
A. There are four mouse studies that were acceptable for use in the causation evaluation, that is correct.
Q. And two of the studies were 18 months in duration and two of them were 24 months in duration, correct?
A. That is correct.
Q. In your pooling analysis, you conduct pooling of the two 18-month studies and then you conduct pooling of the two 24-month studies and you also conduct pooling of all four studies combined?
MS. GREENWALD: Objection to form.
A. I don't know that I did all four studies combined all the time, but I probably pooled them all the time in all four as well.
Q. If your pooling methodology

reported a positive trend for tumor type in any one of those three pooled analyses, you ultimately opined that the glyphosate causes that type of tumor in CD-1 mice, correct?

MS. GREENWALD: Object to form.

A. No.

Q. Are there any tumor types that resulted in a positive trend in either the 18-month studies or 24-month study or the four studies combined that you do not opine was caused by glyphosate?

MS. GREENWALD: Objection, form.

A. You've lost me a little bit there. I would have to look. I'm sorry. I'd have to look carefully.

My guess would be, looking at it -- no, I'd have to look. I'm sorry, I can't guess.

Q. Now, in connection with -- strike that.

When you look at the 24-month study through your pooling methodology, you

did not find an increased trend for any type of tumor in CD-1 mice, correct?

A. I would have to look at it and make sure of that.

Q. So why don't we look at page 11 of your revised expert report.

A. OK.

Q. I am sorry, not your revised. Your rebuttal.

A. Rebuttal.

Q. We were on the same page physically and mentally.

A. So looking at the mouse studies here, none of them reached a level of statistical significance. That is correct. They -- one of them is marginally, two of them are marginally -- no. One, one is marginally significant.

Q. For example, for malignant lymphoma in male CD-1 mice, your pooling methodology reports a positive trend when the two 18-month studies were pooled, correct?

A. That is correct.

Q. There is no positive trend when

the two 24-month studies are pooled, correct?

A. That is correct.

Q. And there is no positive trend when all four studies are pooled, correct?

A. It's a marginal trend, but it's not statistically significant at the .05 level.

Q. And you opine through this analysis that the data establishes that glyphosate causes malignant lymphoma in male CD-1 mice, correct?

MS. GREENWALD: Objection to form.

A. My opinion is glyphosate causes malignant lymphoma in male CD-1 mice.

Q. When you applied your pooling methodology so the data on hemangiosarcomas in male CD-1 mice from the two 24-month studies, you likewise do not find an increased trend, correct?

A. It doesn't reach the level of statistical significance, that is correct.

Q. Now, in your expert report -- and this is at page, your initial expert

report, the revised one, 15-30, at page 48, you suggest another approach in analyzing those two studies for hemangiosarcomas and first I want to make sure that you are on page 48?

A. Yes, I am.

Q. The top for hemangiosarcomas in male and pooling the two 18-month studies and then pooling the two 24-month studies, correct?

A. That's correct.

Q. And you note, again, pooling the two 24-month studies did not result in a statistically significant increased trend for hemangiosarcomas, correct?

A. That is correct.

Q. Then you state if you were to remove the findings in the high dose group in one of the 24-month studies and then pool the two 24-month studies without the high dose group, then your pooling of the 24-month studies would be a statistically significant increased trend, correct?

A. I note that there is an aberrant result in the highest dose of the Knezevich

and Hogan study and I looked at the sensitivity of the pooled analysis to removal of that aberrant result.

Q. And now if you followed the same methodology and ignored the findings of hemangiosarcoma in the highest dose group of the highest dose group of the Atkinson study or the Wood study your pooling methodology would not have resulted in any trend for hemangiosarcomas in the 18-month study, correct?

MS. GREENWALD: Objection to form.

A. That's possibly true, yes.

Q. You also conducted -- you don't present that data though in your expert report?

A. This is a -- this is the pooling evaluation here. There is reason -- that's just simply an observation on my part. That is all it is. This is not used as part of my overall evaluation.

Q. It was important enough for you to put it in your expert report?

A. Because I did it.

Q. But you didn't do the same analysis removing the high dose group from either Atkinson or Wood studies, correct?

A. I saw no reason to do it.

Q. That would not have resulted in a positive trend, would it have?

MS. GREENWALD: Objection, form, asked and answered.

A. I do not know, but I saw no reason to do it.

Q. In fact, it would have removed a trend that you wanted to rely upon, wouldn't it?

MS. GREENWALD: Objection, asked and answered, form.

Q. You don't know?

A. I -- first, I don't know if it would remove the trend. Probably it would. But that's not the point here. The reason for pooling -- for looking at it here is the classic things you do. It's a sensitivity analysis to see how sensitive the findings are to what appears to be an aberrant result. That was all that was done here. And it seemed to be very

sensitive to that high dose point.

Q. You conducted a historical trend analysis for hemangiosarcomas in male mice in the Sugimoto study, correct? That's page 42 of your initial or July 2017 report, 15-30.

A. Yes, it starts on page 41. OK.

Q. So you calculated that while the concurrent control trend -- you calculated that while the concurrent control trend analysis for hemangiosarcomas in male mice in Sugimoto is not statistically significantly increased, you did find a significant increase in your historical trend analysis, correct?

A. For hemangiosarcomas, the trend test was marginally significant and historical control evaluation was significant.

Q. That p trend, that p hist. trend is listed as one of your statistically significant trends in your table 15, correct?

MS. GREENWALD: Objection, form.

A. Yes, that is correct.

Q. Now, hemangiosarcomas are one of those types of tumors that you have stated must be combined as systemic tumors, correct?

A. Yes, that is correct.

Q. So whether hemangiosarcomas in the liver or kidney or in the spleen, for the purposes of the trend analysis, they are all grouped together, correct?

A. No, they -- from what I understand, they group it slightly differently than that. I'm sorry. I have to go and try to figure it out myself, but I don't know exactly.

But they tend not to pool liver and kidney hemangiosarcomas with the other hemangiosarcomas, I think it has something to do with the origin of the cells for the hemangiosarcoma.

Q. So is it your understanding then, in reporting hemangiosarcomas, you would separately analyze, for trend analysis, liver and kidney -- I am sorry, which one did you say it was?

A. I think it is liver and kidney, but I would ask my pathologist first. I would trust him to tell me how to combine these things.
Q. For the Sugimoto study then, is it your understanding that the hemangiosarcomas that you found were not in the liver or kidney?
A. I don't honestly know. I -- I can't be absolutely certain. You asked me about systemic tumors and combining them. But in this case, I have no clue.
Q. So for the purposes of the historical trend analysis then for the Sugimoto study for hemangiosarcomas to find a historical incidence of hemangiosarcomas then, you would look at all the hemangiosarcomas in controlled animals in the historical database?
A. That you -- yes, you look at all the historical hemangiosarcomas in the historical controlled database, that is correct.
Q. Now, you note in your report that the historical control rate for

hemangiosarcomas based on Giknis and Clifford is zero out of 1424, correct?
Actually, you have two different numbers. Zero, 1424 on your footnote, and I think you have zero out of 1149 in your text. One of those two, right?
A. Yeah, it's one of those two. I'm sorry.
Q. The key point that you're making here is the fact that hemangiosarcomas was never seen in historical controls should strongly support any positive finding as in the Sugimoto study as being significant correct?
A. Biologically significant, that is correct.
Q. Let's take a look at the Giknis and Clifford report.
(Exhibit 15-33, report entitled, "Spontaneous Neoplastic Lesions in the Crl:CD1 Mouse" marked for identification, as of this date.)
Q. This is the source of your information on historical control for hemangiosarcomas, correct?

MS. GREENWALD: Objection to form.
A. This is the Giknis and Clifford paper that I referenced, yes.
Q. Let's take a look at table 5 on page 21 and 22. Actually, first of all, just to set the stage, on page 5 of this report they have a summary of the individual studies and information, correct? So this identifies the 18-month study and 24-month studies, correct?
A. That is correct.
Q. So studies 1 through 26, those are the 18-month studies, correct?
A. That -- yes, that is correct.
Q. And those are the -- that's the data set we would be looking at for this historical control?
A. I believe so, yes.
Q. If we looked at pages 21 and 22, this has the instance of neoplasm by study for selected organs in males, correct? So these are the male historical database? Historical controls?
A. That is correct.

Q. And you, in coming up with your statement that there were no hemangiosarcomas in these historical controls, you were looking at the whole body, multiple organ line, third from the bottom, correct?
A. That is correct.
Q. There is another line item for hemangiosarcomas in the liver, correct?
A. That is correct.
Q. And there were, in fact, 12 historical control animals in the 18-month studies with hemangiosarcomas in the liver, correct?
A. That is correct.
Q. And again, you don't know with Sugimoto whether the hemangiosarcomas were in the liver or other organs, correct?
MS. GREENWALD: Objection, form.
A. Typically it's whole body hemangiosarcomas, but I can't be certain exactly what they did.
Q. So for determining what the historical control instances of

hemangiosarcomas, we should be looking -- including these 12 hemangiosarcomas in the liver, correct?

MS. GREENWALD: Objection, form.

A. No. I would not recommend that. The typical pathological approach is whole body hemangiosarcomas, and from my understanding, that is what we were analyzing.

Q. And you would not include liver hemangiosarcomas. Is that your understanding?

MS. GREENWALD: Objection, asked and answered.

A. That is my understanding, but the only way to verify that is if I have the individual animal pathology data.

Q. You don't have that for Sugimoto?

A. Is that a Monsanto study? No, I don't have it.

Q. Are there any other organs where hemangiosarcomas would not be included in the historical control rate?

A. You really have to ask that

question of the pathologist.

Q. Let's look at table 3 in the Giknis and Clifford report. And specifically at page 12.

Now, this has data for all 46 of the studies, it doesn't break it out, but for the spleen, there are 28 hemangiosarcomas in these studies, correct?

A. That's what it says.

Q. Just to put this in context, page 9, they report the data for liver hemangiosarcomas, correct?

A. Yes, they do.

Q. So there were 29 hemangiosarcomas in the liver in the control animals in the 46 studies, correct?

A. That's what it says.

Q. And we know from table 5 that 12 of those were in the 18-month studies, correct?

A. Twelve of the 29 were in the 18-month studies, that is correct.

Q. And with the spleen, we know we have 29 hemangiosarcomas among all 46 studies, but we don't know how many of them

were in the 12-month study -- I'm sorry, the 18-month study and how many were in the 24-month study, correct?

A. That is correct.

Q. Is it your -- to the extent that there were spleen hemangiosarcomas in 18-month historical controls, should that -- those hemangiosarcomas be included in your historical control incidence for Sugimoto?

MS. GREENWALD: Objection to form.

A. You would really have to ask a pathologist.

Q. So you don't know one way or the other?

A. I don't know one way or the other what Sugimoto did. All I know, he characterized it the way he characterized it.

Q. In the Giknis paper, Giknis and Clifford paper also reports on hemangiosarcomas in other tissues. It reports hemangiosarcomas in the testes, in the skin, in the pancreas, and in the lymph

nodes. And if you want you can go through the page 11, 12, and 13, you will see listings of the other hemangiosarcomas.

To the extent that those hemangiosarcomas appeared in the 18-month studies, do you know if those should be included in your historical control rate for Sugimoto?

A. I can't know how many of those appeared in the 18-month studies from this document. So I can't -- I can't answer the question in reality.

Q. And so then would it be fair to say that you, without additional information that you do not have, cannot state what the appropriate historical control rate for hemangiosarcomas should be for the Sugimoto study?

MS. GREENWALD: Objection, form.

A. No, I can tell you what is characterized -- we can look up what OECD requires for this tumor, for this combination, if they require something for this combination, and that could be looked

at here assuming that Sugimoto followed OECD guidelines.

I don't -- I know he followed the OECD guidelines. I just haven't looked at the issue.

Q. Do you know if the hemangiosarcomas in Sugimoto were in the liver or spleen or testes or the pancreas or any other tissues where hemangiosarcomas were found in the control animals?

MS. GREENWALD: Objection, asked and answered.

A. The hemangiosarcomas were characterized as whole body hemangiosarcomas which is the same characterization in this document for a specific class of tumors.

Q. I asked a different question.

Do you know if the hemangiosarcomas in the Sugimoto study, the two hemangiosarcomas, do you know in what tissue of the animal they occurred?

MS. GREENWALD: Objection, form, asked and answered.

A. Again, they were characterized as

whole body hemangiosarcomas. I do not know what tissue they came in, but they fell in that general category.

Q. If they were in the liver --

A. They wouldn't be a whole body hemangiosarcoma.

Q. That's your understanding?

A. That's my understanding. Since Giknis and Clifford come from a contract lab that does these types of things all the time, I'm assuming that is a common classification for a category of tumors, multiorgan -- multiorgan hemangiosarcoma.

Q. You separately opine that glyphosate causes these hemangiomas in female CD-1 mice, correct?

MS. GREENWALD: Objection, form.

A. The data supports a finding of me hemangiomas in female whatever it was.

Q. CD-1 mice?

A. CD-1 mice. I'm sorry there is so many things here.

Q. Let's walk through the findings for this tumor type for the four CD-1 mouse studies. The first is Knezevich study,

page 38 of your report.

A. Page 38. Knezevich and Hogan.

Q. So now we are talking about hemangiomas in female CD-1 mice and the first question is for the Knezevich study, there was no finding of an increased trend in hemangiomas in female CD-1 mice, correct?

A. That's correct.

Q. In fact, the trend is above .5 so it actually leans in the negative direction, correct?

MS. GREENWALD: Objection to form.

A. Hard to say.

Q. The Atkinson study, and this is reported on page 39, likewise does not find evidence of an increased risk of hemangioma in female CD-1 mice, correct?

A. That is correct.

Q. The Wood study on page 41, likewise, does not find evidence of an increased trend in hemangiomas in female CD-1 mice, correct?

A. The Wood study, given the

historical controls, I would say it does show --

Q. On page 41?

A. I don't have -- you're right, you're right, my mistake. There is no significant trend here, positive trend. That is correct.

Q. So the one study in CD-1 mice that you find with an increased trend and what forms the basis of your pooled analysis finding is the Sugimoto study which you report on page 42, correct?

A. The Fujimoto study when --

Q. Sugimoto.

A. Sugimoto, when combined with the Wood, et al., study has a significant increase in hemangiomas combined. And then the Wood study itself is also significant for hemangiomas.

Q. You mean the Sugimoto?

A. Sugimoto, God. Sorry, long day.

Q. Three of the four CD-1 mice studies do not find any evidence of an increased risk of hemangiomas in CD-1 female mice, correct?

A. The 24-month studies have to be handled differently than the 18-month studies. So in the 18-month studies, you have one positive study and one study without a positive trend.

The study without the positive trend has a lower exposure and the highest exposure group. The study with the positive trend has higher doses.

When you combine them together with the doses and the responses, you maintain a significant response. That's what the data tells you.

Q. Dr. Portier, that was not my question.

There are four CD-1 mouse studies, correct?

A. There are four CD-1 mouse studies.

Q. The two 24-month studies do not report any positive trend with hemangiomas in female mice, correct?

A. That is correct.

Q. The Wood 18-month does not find any increased trend in hemangiomas in

female CD-1 mice, correct?

A. It -- it found some, but not an increase, that is correct.

Q. So the only CD-1 mouse study that found any increased trend of hemangiomas in female CD-1 mice was the Sugimoto study, right?

A. That is correct.

Q. And using -- if you had followed that same methodology that you followed in doing your sensitivity analysis for hemangiosarcomas and you knocked off the aberrant finding in that high dose group in one of the studies, you would not have found any increased trend for hemangiomas in any of the CD-1 mice studies, correct?

MS. GREENWALD: Objection, form.

A. If, individually, one study at a time, I had knocked this off, then this significant finding might go away probably. No, it would go away, it would not be there.

Q. So if you followed the same sensitivity analysis methodology that you

used for hemangiosarcomas, you could look at the hemangiomas and conclude there was no increased trend for hemangiomas, correct?

MS. GREENWALD: Objection to form.

A. That is not true.

Q. Did you do a sensitivity analysis knocking off the high dose group in Sugimoto the way that you knocked out the high group in Knezevich for hemangiosarcomas?

MS. GREENWALD: Objection to form.

A. I have done that analysis. For some of the presentations I had where the regulatory agencies were saying that the doses were too high. And I believe I have an example in there where there is -- well, this is hemangiomas, they didn't have them at the time. I haven't done the analysis, no.

Q. You opine that glyphosate causes kidney tumors in male CD-1 mice, correct?

A. I believe, yes. That is correct.

Q. Now, neither of the 24-month CD-1 mouse studies reports a statistically significant increased trend for kidney tumors in male CD-1 mice, correct?

A. OK, let's see. That would be tables 9 and 10. Kidney hemangiomas, kidney sarcomas, the 24-month studies?

Q. Yes, that would be Knezevich and Atkinson.

A. Knezevich using historical control test is significant.

Q. We are going to go to concurrent control. We will get to historical control in a second.

My question is with respect to statistically significant trends which would be p less than .05, neither of the 24-month CD-1 studies report a statistically significant increased trend for kidney tumors in male CD-1 mice, correct?

A. If significance is defined as 0.05, that is correct.

Q. In its monograph for working group 112, the IARC working group stated

that the finding for Knezevich was statistically significant to the p equals .05 level, correct?
A. I'd have to look. I'm sorry.
Q. Do you recall that there was a calculation that was conducted using the approximate trend test?
A. That, I do recall. The decision was twofold, but yes.
Q. And the IARC monograph, the IARC working group, using the approximate trend test, reported that the findings for kidney tumors in Knezevich was statistically significant at p equals .05, correct?
A. For the trend test, yes, that is correct.
Q. Your analysis now is that the Knezevich study does not have a p less than 0.05 trend for kidney tumors, correct?
MS. GREENWALD: Objection, form. That's not his testimony.
A. It -- could you say it again? I don't know --
Q. Your expert analysis now is that the Knezevich study for renal tumors does

not report a p less than .05 finding, correct?
MS. GREENWALD: Same objection.
A. The p-value is reported in that study from the exact test and that p-value is not less than 0.05. But I do report the p-value.
Q. Yes, I understand.
the -- you've been talking about the historical trend analysis for Knezevich, for renal tumors. Just mentioned that, correct?
A. Correct.
Q. And in your p hist. analysis for the Knezevich study, you again rely upon the data from that 2000 report by Giknis and Clifford, correct?
A. I would have to look.
Q. It's page 37 of your --
A. Give me a moment, please.
So 36 onward on to 37?
Q. Yes. We were talking about historical control data and you use Giknis and Clifford?

A. That's not true.
Q. I'm sorry. Top of page 37, I am reading, "I will use the study by Giknis and Clifford 2000 since it best covers the range of studies we have for CD-1 mice, correct?
A. It says that. But before that, it says, "These studies have virtually identical rates for the important tumor seen in CD-1 mice," which refers to not one historical control but three.
Q. OK, but for the purposes of your historical trend analysis, for the Knezevich and Hogan study, for kidney adenomas and carcinomas, you used a historical rate from Giknis and Clifford, correct?
A. That is for kidneys?
Yes, that is correct.
Q. And you agree that in any analysis using historical controls, the data should be from studies in the same time frame, for the same animal strain, preferably from the same laboratory or same supplier, and preferably reviewed by the

same pathologist, correct?
MS. GREENWALD: Objection, form.
A. If possible. And when possible, that would be assuming that the historical control data set is a valid and useful data set, that would probably be the best approach.
Q. You also agree that historical control data should be taken from studies that are of the same duration as the study in interest, correct?
A. Where possible, absolutely.
Q. And as a general matter, you would expect a higher incidence of tumors in historical controls as the duration of the study increases, correct?
A. On average, yes.
Q. So all things being equal, you would want to use 24-month study, historical control data, to compare to a 24-month study, correct?
A. All things being equal, yes, if you could get it.
MS. GREENWALD: When there is

a natural breaking point, I need a comfort break.
MR. LASKER: This would be right now is fine.
MS. GREENWALD: I don't want to -- is now OK?
MR. LASKER: Now is perfectly fine.
THE VIDEOGRAPHER: The time is 3:03 p.m.
(Recess)
THE VIDEOGRAPHER: The time is 3:18 p.m. We are on the record.
BY MR. LASKER:
Q. Dr. Portier, let's go back to that Giknis and Clifford 2000 report. It's right on the top of your pile there. Left hand. There it is.
And this, again, is the source of the historical control data that you used for your p-hist. analysis of the Knezevich kidney tumor findings, correct?
A. This is the source of the mean historical control response that was applied in the analysis that appears in the

paper.
It's not the only historical controls group I looked at.
Q. But just to be clear, this is the source of the data that you used for your p-hist. analysis of the kidney tumors in Knezevich, correct?
A. That -- in the published document, yes, that is correct.
Q. Where did you get, by the way -- strike that.
The Charles River posts its historical trend data on its website, correct? That's where you got this?
For example, this 2000 report is right on their website, correct?
A. Whatever it says in my references is where I got this from. It is a website.
Or does it even say? Let's see. Giknis and Clifford, which one is that?
But anyway, I believe it is their website, that is correct.
Q. So this report provides historical control data, and it's on page 1 from 51 studies initiated between January

1987 and December of 1996, correct?
That's by a common study parameters on the top on page 1?
Page 1, common study parameters, the 51 studies included?
A. Oh, yes, there it is. Thank you.
Q. Were initiated between January 1987 and December of 1996, correct?
A. That is correct.
Q. So this is -- the Knezevich study was a two-year study, completed report in 1983, so these studies in this 2000 report for the historical control data were all initiated maybe 6 to 16 years after the Knezevich study, correct?
MS. GREENWALD: Objection, form.
A. They were after the Knezevich and Hogan study, that is correct.
Q. Between 6 and 16 years after, correct?
A. Probably, yes.
Q. And if it was available, you agree that it would be more reliable to use historical control data for studies conducted closer in time to Knezevich,

correct?
MS. GREENWALD: Objection, form.
A. Not necessarily correct.
Q. If you had a choice between historical control data in CD-1 mice for Charles River, for example, that was closer in time to the Knezevich study, you would like to look at that historical control data, correct?
A. I would look at it, but I would have to evaluate whether I thought it was better or worse than this particular dataset.
Q. Have you looked at any Charles River data to determine whether they have data on historical controls for a time period closer to Knezevich?
A. I didn't find them.
If I had, I would have used them probably.
Q. In fact, in your submission to regulators --
A. I will point out that the regulators use this as well, as well as your expert.

Q. In your submission to regulators, you have stated that attempting to compare animals ranging over 16 years for historical control data is inappropriate because of the known drift in strains over time, correct?
A. I probably said something like that, that is correct.
Q. Now, the historical control data that you use in your analysis, your p-hist. analysis in your expert report is listed on page 10 of the Giknis and Clifford paper, 1533, correct?
A. What are we looking at here?
Q. This is the kidney historical control data. It's the third tumor typed down on page 10, kidney.
A. I'm sorry, I have to make sure that kidney is not one of the one where they give the individual tumor incidence? They do not.
Yes, that is it.
Q. And if you look at this data, you have .37 for kidney adenomas and .16 for adenocarcinomas, total is .43. And that

is, I believe, the historical control data that you used for your p-hist. analysis or the number that you use for your historical controls, correct?
A. I use .27 for the kidney adenomas, .15 is what it says here for the kidney carcinomas --
Q. We will give you that one.
A. -- and then the joint historical rate is .44 percent.
Q. Now, for this historical control data, that would be a mix of 24-month and 18-month studies --
A. That is correct.
Q. -- from the Giknis paper?
So to the extent it includes the 18-month study -- well, you would agree if you had the data broken down, it would be more reliable to use historical control data drawn solely from 24-month studies, correct?
MS. GREENWALD: Object to form.
A. If the -- this is a 24-month study, I would prefer to have 24 month only historical controls.

Q. Now, the Charles River website, I've gone to that website and it does have an earlier report.
MR. LASKER: So let's mark that as the next in line.
(Exhibit 15-34, Charles River report dated March of 1995, marked for identification, as of this date.)
spontaneous neoplastic lesions in the CD-1BR mouse marked for identification, as of this date.)
Q. This is a report dated March 1995 prepared for Charles River Laboratory by Dr. Lang, correct?
A. That seems to be what it says.
Q. If you look at page 4, it has a listing of the different studies -- CD-1 mouse studies used to obtain historical control data, correct?
A. That is correct.
Q. And there are ten 24-month studies in CD-1 mice that were used in generating historical control data, correct?
A. That is correct.

Q. The ten studies were initiated between 1981 and 1990, correct?
A. No, 1983 --
Q. Look at --
A. I am sorry. Yes, 1981 and 1990, correct.
Q. So these studies were initiated between 1981 and 1990, correct?
A. That is correct.
Q. So this covers the time period of Knezevich and then forward a period of years, correct?
A. That is correct.
Q. And on page 23 of this report, we have data broken down just for the 24-month CD-1 mice studies, correct?
A. This might not cover Knezevich. I'm sorry, I want to correct my previous answer.
It partially covers Knezevich, but because of the length of time it takes to run a study, Knezevich probably started in 1979 or so.
Q. These studies are closer in time to Knezevich certainly than the studies in

the Giknis and Clifford 2000 report, correct?
A. Correct.
Q. And on page 23, the Lang report sets forth historical control data specifically for the 24-month CD-1 mouse studies, correct?
A. That's what table C1 says.
Q. And on page 24, they report the historical control data for kidney tumors, correct?
A. Renal adenomas and renal cell carcinomas are reported, that is correct.
Q. And the historical control data reported in these studies, 24-month studies, closer to time to the Knezevich study, report a mean historical control rate for kidney tumors, adenomas and carcinomas combined, of 2.3 percent, correct?
MS. GREENWALD: Objection, form.
A. Maybe. When you combine them, you could have multiple adenomas and carcinomas in the same animal, so you would have -- the highest it would be would be

2.3 percent. It could be as low as 1.34 percent for the combined.
Q. The data that you used from the 2000 Giknis report to get your combined data, you added the incidence from the adenomas and the carcinomas in the 2000 Giknis and Clifford report.
We just went through that, correct?
A. Yes, I did it -- correct.
Q. For this data, using the same methodology that you used to come up with a historical control rate for your Knezevich paper, the historical control rate is actually about five times greater than the control rate that you used for your p-hist. trend analysis, correct?
A. It is 2.3 percent.
Q. Compared to .42 or .44 percent, correct?
A. Right. Yeah.
Q. So the actual -- or I am sorry, the historical control incidence of kidney tumors -- the mean historical control incidence from these 24-month studies

closer to time to Knezevich is more than five times greater than the historical control rate that you used for your p-hist. trend analysis, correct?
MS. GREENWALD: Objection, form.
A. That were used by me and the EPA and EFSA, and that is correct.
Q. And to be fair, EPA and EFSA did not conduct a p-hist. trend analysis, correct?
A. That is correct.
Q. You are the only one who has conducted a p-hist. trend analysis, correct?
MS. GREENWALD: Objection to form.
A. For these data, that is correct.
Q. And the historical control rate that you used to conduct that p-hist. analysis is five times lower than the historical control rate reported in this Lang 1995 study that covers CD-1 mouse studies of the same duration and closer in time to the Knezevich study, correct?
MS. GREENWALD: Objection, form.

A. Yes, that's correct.
Q. You also agree that the historical control rates for kidney tumors in CD-1 mice may not even apply to the Knezevich study because additional sections were taken of the kidney tumors in that study, correct?
A. I retract that statement actually. I thought about that when I was rereading it.
The thing is the extra sections produced nothing. There were no new tumors. There were no new findings at all. And so since it's still based upon the original findings, I would say this historical control set is applicable.
Q. If there had been additional sectioning of the -- first of all, when you say you retract that statement, you are retracting a statement that appears in your expert report, correct?
A. Whatever I'm doing, the statement that says because of the taking of three liver slices, these historical controls may not be appropriate, I'm now saying I

believe these historical controls are appropriate because the three extra sections did not change anything.

Q. So just so we are clear, in your expert report, which is 1530 on page 37 -- so this is your expert report.

A. Um-hm.

Q. You state, with respect to your P trend analysis for Knezevich for kidney tumors, and it's about one-third down the page:

"These historical control rates may not apply to this analysis because a reevaluation of the kidney tumors considered additional sections and no information is available on how additional sections affect historical control rates in this strain of mice. Differences have been seen in other settings."

Correct?

A. That is correct.

Q. And that is a statement that you are now retracting today, correct?

A. I'm certainly not retracting the statement that says this has been seen in

other settings. These historical -- what I am retracting is "may not apply."

Q. And for -- just so I understand, the point that you were making in your expert report is that if the historical control animals had been -- there had been additional sections taken of those animals, there might have been additional tumors found in those animals, correct?

A. Correct.

Q. And if you were then doing an apples-to-apples comparison of studies with similar numbers of sectioning, you would want to compare the findings in Knezevich after those multiple sections with control -- historical controls after the multiple sections, correct?

MS. GREENWALD: Objection, form.

A. If the multiple sections had altered the numbers, I would want to do that. Failing to alter the numbers then means that they are appropriate against the original pathology, which is the final pathology. Therefore, they are appropriate.

Q. If it was the case that multiple sections of historical control animals found additional kidney tumors, is it your testimony that those additional tumors should not be considered as relevant historical controls to the Knezevich study?

A. You have lost me a little bit. I'm sorry.

Q. I'll say it again.

If the historical control animals -- those studies where you got the historical control data -- had undergone additional sectioning and found additional tumors -- you got that part?

A. Um-hm.

Q. In trying to identify what the historical control rate was as compared to the Knezevich study, would you have considered those additional tumors found in the historical control animals?

A. I certainly would have looked at it.

Q. And that was the basis of your original statement that you have in your expert report as to why the historical

control rates that you have from Charles River might not apply, because you don't know that there was additional sectioning of those animals, correct?

MS. GREENWALD: Objection to form.

A. I assume -- in fact, I'm certain that under OECD guidelines, there is guidance on how to section kidney tumors. And the kidney tumors that were done in Giknis and Clifford were certainly done under OEC guidelines because of the nature of that laboratory.

The previous ones I don't know about because it was earlier. But they are all done the same way.

Q. And they are just -- there wouldn't be additional sectioning?

A. There wouldn't be additional sectioning because they would be doing whatever the guidelines say.

Q. The 24-month Atkinson study -- and this is in your report at page 39 -- it reports -- and you report in your expert report -- a statistically significant

negative trend for kidney tumors in CD-1 mice with increased dose of glyphosate, correct?

A. Yes, I would guess that's the case.

Q. And the -- you recently told a blogger by the name of Carey Gillam that when the findings for renal tumors in these two 24-month mouse studies, Knezevich and Atkinson, are combined, there is a statistically significant increased trend, correct?

MS. GREENWALD: Objection, form.

A. I don't know. I would have to see.

(Exhibit 15-35, e-mail chain dated June 7, 2017, marked for identification, as of this date.)

Q. For the record, Exhibit 15-35 is an e-mail exchange that you provided to us between you and Carey Gillam, correct?

A. What's the question again? I finally got to read it.

Q. You told Ms. Gillam in June of 2017 that when the results of these two

24-month mouse studies are combined, there is a statistically significant increased trend, correct?

A. Correct, but I think that is wrong. I think I probably intended the two 18-month studies.

Q. OK.

A. Or she might have --

Q. In looking at your revised report -- and this is in connection -- just to be clear, you're talking about the 1983 study, which is the Monsanto study, correct?

A. The first sentence is definitely talking about the 1983 Knezevich and Hogan study.

Q. That is a 24-month study, correct?

A. That is a 24-month study.

Q. That is the context in which you are telling Carey Gillam that when the two 24-month studies are combined, meaning the Monsanto study and the Atkinson study, the kidney tumors are statistically significant, correct?

A. Yeah, that seems to be the case, yes. That's correct.

Q. But that was a mistake, correct?

A. That when they are combined, they are marginally statistically significant, not -- without the term "marginally," they are just marginally statistically significant.

Q. They are not statistically significant, correct?

A. They are marginally statistically significant.

Q. Your statement to Ms. Gillam was incorrect?

A. It seems it's not as correct as I would like it to be.

Q. Now, with respect to the 18-month studies, neither of the two 18-month CD-1 mouse studies are reported a statistically significant increased trend for kidney tumors against concurrent controls, correct?

A. That was a marginal statistical increase in the Sugimoto study.

Q. Correct, not statistically

significant at P equals .05, correct?

A. That is correct.

Q. The Wood study did not find kidney tumors at any dose group, correct?

A. That is correct.

Q. And the Sugimoto study did not find any kidney carcinomas at any dose group, correct?

A. It found kidney adenomas, that is correct.

Q. So just so we are clear, the Sugimoto did not find any kidney carcinomas at any dose group, correct?

A. That is correct -- well, I don't have kidney carcinomas here. So I would have to look back at the original study to make sure there were none because I don't have them here.

Q. In your methodology, your goal at least was to list kidney carcinomas findings in all these studies, correct?

MS. GREENWALD: Objection, form. I missed that. Sorry.

A. Say the question again, please.

Q. When you had kidney carcinomas

data for these studies -- these animal studies, you reported that in these tables, didn't you?
A. When I had them, yes.
Q. But now --
A. In some of them, I'm not absolutely certain. The Atkinson, et al., study, I don't think they separated them at all. I don't think I had a chance to see the difference. So I can't answer the question.
The intent for kidney tumors was to talk about the combined -- if the combined could be made.
Q. But you actually report on kidney adenomas and then you separately report on kidney carcinomas and then you separately report on kidney adenomas and carcinomas combined?
A. Because I had that from Knezevich and Hogan.
Q. So for the four CD-1 mouse studies that you have one study finding a statistically significant negative trend for kidney tumors and no studies finding a

statistically significant positive trend, correct?
A. Marginally significant positive trend.
Q. I'll ask the question again.
From the four CD-1 mouse studies, the P equals .05 is the statistical significance. You had one study finding a statistically significant negative trend, meaning less tumors with more glyphosate for kidney tumors, and no studies finding a statistically significant positive trend, correct?
MS. GREENWALD: Objection, form, asked and answered.
A. The overall evaluation included both the trend test and the historical controls, but yes, when just looking at the trend test and not using anything to do with the historical controls, there are two marginal statistically significant findings that are not at the .05 level.
Q. And there is one finding at the 05 level, statistically significant, showing a lower incidence of kidney tumors

with increased dosing of glyphosate. That's the Atkinson study, correct?
A. Let me look at it again.
Yup, that is probably significant at the 05 level.
Q. In your pooled analysis though, you conclude that glyphosate causes kidney tumors, correct?
MS. GREENWALD: Objection, form.
A. Kidney tumors?
So pooling the 18-month studies is significant. Pooling the 24-month studies is marginally significant. Pooling all four is significant. That is what I -- that is what it says.
Q. What data did you use in this pooled analysis? Did you use data for kidney adenomas, kidney carcinomas or for both kidney adenomas and carcinomas combined?
A. It's for kidney tumors, which is adenomas and/or carcinomas.
Q. So for the Sugimoto study then, where you had only data for adenomas, what data did you use for the carcinomas to pool

for combined total?
MS. GREENWALD: Objection, form.
A. I'd have to go back to the original Sugimoto study to be able to address that, the Greim study.
Q. But am I correct for the pooling, you would want to put in -- assuming that there were no kidney carcinomas in that Sugimoto, you would want to include 0000 for the kidney carcinomas in your pooled analysis for Sugimoto, correct?
MS. GREENWALD: Objection, form.
A. I didn't do a pooled analysis of kidney carcinomas alone. So I can't answer the question because you -- I didn't do such an analysis.
Q. No, I'm talking about for combined, when you do a combined analysis, would you include the data for the kidney carcinomas in that pooled analysis?
A. Yes, I would.
Q. Now, your pooling methodology for renal tumors did result in what you have described here today as marginally significant -- a marginally significant

increased trend for renal tumors in the two 24-month studies, correct?

And if you look at page 11 of your rebuttal report, where you have your pooled analysis -- if you go in your rebuttal report, you have the table. It is just a little bit easier to find.

Table 3 on page 11 of your rebuttal report has all your pooled analysis.

A. OK. Got it.

Q. So for the two 24-month studies, when you pooled them for kidney adenoma and carcinoma, you report what you have been describing as a marginally significant increased trend, correct?

A. For the 18-month studies?

Q. No, the 24-month studies.

A. 24-month studies.

That is correct.

Q. So based upon your pooling methodology then, your opinion that the renal tumors and the combined data for Knezevich and Atkinson show an increased trend of tumors, that's almost significant,

correct?

MS. GREENWALD: Objection, form.

A. The combined pooled analysis of Atkinson and Knezevich, that shows a marginally significant P value which is almost significant, correct.

Q. For an increased trend in tumors with increased --

A. For an increased trend in tumors.

Q. If you can go to your report -- your initial report at page 38, so we can look at the data.

For the Knezevich study, you have 1 tumor in the control animal, 0 in the low-dose group, 1 out of 50 in the high-dose group, and 3 out of 50 in the -- I'm sorry, let me state that again.

For Knezevich, for kidney adenoma and carcinoma combined, you report 1 out of 49 tumors in the control animals, 0 out of 49 in the low-dose group, 1 out of 50 in the mid-dose group, and 3 out of 50 in the high-dose group, correct?

A. That's what EPA reported, that's correct.

Q. And for the Atkinson study, which is the next page, on 39, you have 2 out of 50 kidney adenomas and carcinomas in the control animals, correct?

A. That is correct.

Q. You have 2 out of 50 in the low dose, correct?

A. That is correct.

Q. You have 0 out of 50 in the mid dose and 0 out of 50 in the high dose, correct?

A. That is correct.

Q. And so if you look at these two studies combined, you have 3 renal tumors out of 99 control mice in the control animals, correct?

A. That's correct.

Q. You have 2 renal tumors out of 99 in the low-dose groups, correct?

A. Correct.

Q. You have 1 renal tumor out of 100 in the mid-dose group, correct?

A. These are terribly different doses. You can't just combine them that way. That's not how it's done. I'm sorry.

Each individual group and its dose is fed into the pooled analysis exactly like it is in the study.

So the pooled analysis would have 1 out of 49 in control and 2 out of 50 in control. Then at a dose of 190 mgs per kilo per day, it would be 0 out of 49. At 102, it would be 2 out of 50. At 298, it would be 0 out of 50. At 955, it would be 1 out of 50. At 1,000, it would be 0 out of 50. And at 5,874, it would be 3 out of 50.

Q. So the trend analysis then, if I understand your testimony correctly, that you conducted for the purposes of your expert report here did a trend analysis using each of the different dose levels as a different point in the trend analysis over the combined studies, is that correct?

MS. GREENWALD: Objection, form.

A. The individual doses are attached to the chemical. You don't just haphazardly pool high and low dose.

If that's what you just said, then that's correct.

Q. Let me just be clear, in your earlier submissions to EPA and to the European regulators, you did combine doses into a control, a low dose, a mid dose and high dose for your trend analysis, correct?

MS. GREENWALD: Objection, form.

A. No, I didn't. I combined them into that form for an illustration of what the dose response trend looked like, because when you put the individual dose response points up there, it's very difficult to see a trend just simply because of the nature of that type of data, but by grouping doses that were close together, you got a better chance.

The pictures also included a confidence interval side to side and up and down.

Q. Let me make sure I'm clear on your methodology.

A. That's not what's here.

Q. I understand that.

In your methodology, when you submitted a pooled analysis to the EPA, did you conduct your P analysis based upon 4

different combined dose groups or did you conduct your pooled analysis based upon 8 or 16 or 12 different dose levels as the case may be?

MS. GREENWALD: Objection, form.

A. The analyses submitted to EPA included both simply for completeness. The individual dose group studies are the one which are the clearest and correct way to do this.

Q. And just so I understand then, for your pooled methodology, while you have three tumors -- real tumors in control mice in Knezevich and Atkinson and three tumors in the high-dose group in Knezevich and Atkinson, that data under your pooled methodology results in an almost statistically significant increased trend in tumors with increased dose, correct?

MS. GREENWALD: Objection, form.

A. There are other doses in that dose response range which all play a role in the statistical significance of that trend. And all of those doses combined in the pooled analysis gave a statistically

significant trend.

The reason it's statistically significant is because the three out of control are at low doses, which also have very low response as well, and remember, it's not 3 out of 50, 49 in control, or 99, it's 1 and 2. But they are matched with other dose groups that are 0, 0, 2, 0, 0, 0, 0. That pushes that down in the low exposure range and the upper exposure range picks up the trend.

That is why you see a statistically significant trend.

Q. And just so we are clear, if you look at the different tumor levels in these two studies, there were five renal tumors found in the controls and the lowest dose group studied, and that there were four tumors found in the three highest dose groups studies, correct?

A. Again, over a very broad range, that is a statement of fact.

Q. So through your pooling methodology with two studies where you have 5 tumors out of 200 in the lowest -- in the

controls at the lowest dose studied and 4 tumors out of 200, if you will, in the highest doses studied, you have an almost statistically significant increased trend, is that correct?

MS. GREENWALD: Objection, form.

A. I'm sorry, you have -- you have lost me. What am I doing?

You're trying to make me pool something new?

Q. I'm not making you pool anything. You have done the pool.

In pooling these two studies, you have -- the data shows that you have 5 kidney tumors in the 150 animals where you have control animals and the lowest dose studied, correct?

A. I have what appeared in the lower dose groups, that is correct.

Q. And so you have -- and you have 4 tumors out of 150 in the highest doses studied?

A. There are doses with 0, 0, 1 and 3.

Q. I understand that. But if you

look at the data combined and you're pooling this data --
A. I'm not going to look at the data combined. The data is what it is. The data is 0, 0, 1, 3.
Q. It's actually 1, 0, 1, 3 --
A. 1, 0, 1, 3, whatever.
Q. -- and 2, 2, 0, 0, correct?
A. It is whatever it really is. So it is 1, 2, 2, 0, 1, 0, and 3.
Q. And that distribution under your pooling analysis results in an almost statistically significant increased trend, correct?
MS. GREENWALD: Objection, form.
A. That distribution under the use of the scientifically verifiable and methodologically sound Armitage linear trend testing proportions shows a P value which is statistically significant.
So does the analysis using the logistic regression approach suggested by your expert.
Q. We can talk about that later because our expert wouldn't agree to that.

Let's talk about -- I take it that you have your code for your pooling analysis -- various pooling analyses that you conducted over time, correct?
A. Let me correct something here. You keep calling it "my pooling analysis." The pooling analysis I did is the more accurate statement. Again, because I told you Dourson has already done it, by all technical reasons, I would have to reference him now that I know it's there, and so it should be his pooling algorithm, not mine.
But the point is it is just the pooling algorithm I used.
Q. The pooling algorithm you used, you still maintain that?
A. Yes.
Q. And has that pooling algorithm changed over time for glyphosate?
A. I'm going to try to break it down to make it clear.
There is pooling of the data, and then there is analysis of data by the Armitage linear trend test, and then there

are three ways you can calculate P values in the Armitage linear trend test.
So the choice of which datasets to pool has not changed. So the pooling has not changed. The analysis by the Armitage linear trend test in proportions has not changed. The only thing that has changed has been the way in which I calculate the P values for those tests.
Q. Understood.
The -- let's talk about the modified table 15 in your rebuttal report.
A. OK.
Q. So your table 15 in your listing of total sites, that is, as I understand it, a calculation of the total sites for which three or four tumors were found in the glyphosate data, correct?
A. With exception. The rare tumors in kidney and hemangiosarcomas are also included in this table.
Q. That wasn't my question. My question is the total sites column.
A. The hemangiosarcomas only have two tumors.

Q. I understand that.
A. I am sorry.
Q. My question is, if you look at modified table 15, you have a calculation of total sites.
Do you see that?
And it's a column -- the fourth column on modified table 15.
A. Yes, I see it.
Q. It has a footnote, footnote 1, correct?
A. Yes.
Q. And total sites is based upon the sites with three or more tumors, correct?
MS. GREENWALD: Objection, form.
A. Actually, it's described directly in the text of the document. On page 4 first full paragraph, this also includes joint analyses and some room for joint analyses and other things.
Q. I understand that.
I'm looking again just at the total sites column.
A. Correct.
Q. And you have a footnote that

describes that the total sites are taken from an analysis done by a Dr. Haseman, correct?

MS. GREENWALD: Objection, form.

A. It's a suggestion from Dr. Joseph Haseman in his EPA testimony.

Q. And Dr. Haseman in his EPA testimony is quantifying the number of sites in the glyphosate data for which three or more tumors were found, correct?

A. He is quantifying the number of sites which he felt would be relevant in a statistical evaluation of how many sites were actually evaluated in the study.

Q. Well, for this column though he is actually just doing an addition. He's adding up the number of sites for which three or more tumors were found in this column?

A. No, in this column is me adding up three or more tumors --

Q. OK.

A. -- and adding, like Dr. Haseman did, some room for joint analyses of tumor findings.

Q. Is it your testimony that the total sites calculation that you use in your report includes sites where less than three tumors were found?

A. Yes.

Q. So that is your understanding of table 15 for the total sites column?

MS. GREENWALD: Objection to form.

A. Table 15 includes enough room to cover all of the analyses that were done.

Q. Well, that's -- I don't know what "enough room" means.

A. Enough numbers of tumors to incorporate all of the analyses that are relevant for these data.

Q. To get these numbers that you have listed here, you have a footnote that states:

"Numbers of sites is based upon suggestions by Dr. Haseman in his written testimony to the EPA with female rats modified for fewer sites with three or more tumors. Male mice, 10.5 sites. Female mice, 15 sites. Male rats, 21.5 sites.

And female rats, 26."

Correct?

A. That's what the footnote says.

Q. In Dr. Haseman's analysis, these numbers, at least 10.5, 15 and 21.5, are the numbers he calculated for tumors with -- for sites with three or more tumors, correct?

A. That's not what he says as far as I know. He was just looking for sites that would be likely.

But I'd have to see his EPA testimony again to make sure that that is the case.

Q. OK. So --

A. That is -- that is probably what he did. That's probably the case. I don't know if he said it.

Q. OK. But you now testify that you think it probably is the case that the numbers in this table for total sites are the number of sites for which three or more tumors were found?

MS. GREENWALD: Objection, form.

A. The numbers in this table --

Q. For total sites.

A. -- are consistent with what I found in evaluating the numbers of sites with three or more from the data in these studies.

Q. OK, fair enough.

The total sites then is used as your -- as one of the -- well, total sites is then used to calculate the expected number of sites you would see at P less than .05, correct?

If you take the total sites and multiply it by .05, correct?

A. Correct.

Q. That's your expected number of less than .05, which is the column on table 15 right next to the total sites column, correct?

A. That is correct.

Q. And you also use that total site column -- total site number to calculate the expected sites P less than .01, correct?

MS. GREENWALD: Objection, form.

A. I used the total sites,

multiplied it by .01 to get the expected less than .01 in that last column -- third column -- third-from-last column.

I should note just for the record while we are here, I have an addition error. I put 19 on both sexes for rats when it is really 18.

Q. And the --

A. The sum is the same.

Q. 30 should be 29?

A. No, the 30 is 30. That 19 is just wrong.

Q. That should be 18?

A. 18.

Q. So 11 and 6 equal 18?

A. Let's see here.

Q. If you have 11 male and 6 female, you add up to 18?

A. The 12 -- the first one is 12. If I count the tumors themselves, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 1, 2, 3, 4 5, 6, it should be 18.

I don't know why the counts in the tumors are incorrect for the rats.

Q. OK. So now for your observed

tumors, which you have next to your expected, you also include trends that you calculate based upon your p-hist. analysis, correct?

A. I'm sorry, say that again.

Q. For your observed trends of less than .05, and for less than .01, you use -- you report the numbers that you find for a concurrent control trend test and also add to that the numbers of -- that you observed through your p-hist. analysis -- historical trend analysis?

A. No, of course not. That would be terribly methodologically flawed.

Q. So is it your testimony then that you do not include in your observed count in table 15 findings that are only significant based upon the historical trend analysis?

A. No, the -- this -- I should be clear in the text, but I'll make it clear now, what I'm putting in here is the P value observed for the trend test, because the correct control to use is the control for the trend test, except in the cases of

very rare tumors, which are the two mouse tumors we were talking about earlier, and those P values are put in here from the historical trend test, not from the typical trend test.

Q. So let me make sure I understand correctly.

In your table 15, for your expected, you have the number of tumors you would expect based upon total sites with three tumors or more, and then you have your expected and then you have your observed column, and your observed column also includes tumors that you observed -- or trends that you observed based upon your historical trend analysis, correct?

MS. GREENWALD: Objection, form.

A. I -- I'm -- I'm not understanding the question. It's --

Q. OK. Your -- through your historical trend analysis --

A. Let me try -- let me try something --

Q. Let me just ask the question this way: For your historical trend analysis,

for example, you calculated statistically significant trends at two sites where there are only two tumors, correct?

A. Rare tumors at rare sites.

Q. Right. And those sites would not be part of the total sites that you have listed in your column on total sites because there is only two tumors there, correct?

A. No. This is not -- as I pointed out before, this is for the typical types of analyses that would be done. Enough extra counts were put in there to cover the counts for the two rare tumors that we looked at.

Q. OK, let me go back to that, because I'm misunderstanding. I thought we had established this.

In your total sites, footnote 1 shows how those total sites were calculated based upon what Dr. Haseman had calculated. Those were the sites for which three or more tumors were found, correct?

A. No --

MS. GREENWALD: Objection, form.

A. -- I'm sorry, that's not the case.

If you look at table 1 in the report -- in my rebuttal report, table 1 tells you how many tumors of each type were in each -- were in each of the studies.

Q. Right. And you have each individual site, and then for you total sites, you also include combined tumors, correct, where you had three or more tumors in the combined data, correct?

A. If they are even done or not done.

But I have -- in this table, I have more than -- I have somewhere around, I believe, 100 more observe -- more -- I have the possibility of 100 more evaluations being done than the total number of eval -- of sites with three or more tumors.

So I've left 100 open spots for analyses that might have been done rather than just the three or more tumors.

Q. Dr. Portier, the numbers that you have in your report for total sites are

numbers that Dr. Haseman reported, correct, that's where you got those numbers?

MS. GREENWALD: Objection, form.

A. With a modification, and those numbers are very conservative.

Q. The modification you made was to reduce the number of sites for female rats as -- from what Dr. Haseman had reported and you made it lower, correct?

A. Yes.

Q. And Dr. Haseman --

A. And I explained why I did that.

Q. And Dr. Haseman, in adding up those sites that you use, he added the number of sites, either with individual or combined analyses, that had three or more tumors, correct?

A. No, he was -- he was just roughly looking at two of the -- three of the studies, I believe -- I'd have to see his writeup, if you have it.

Q. Sitting here today, you don't recall one way or the other whether those total site numbers from Dr. Haseman that you use in your table 15 were for sites

with three or more tumors?

MS. GREENWALD: Objection, form, asked and answered.

A. I would have to see Dr. Haseman's comments to be able to answer that question for you.

Q. Well, would you agree if those numbers for total sites only include sites with three or more tumors, for your analysis, since you also looked at historical trends and rare tumors, you would have to provide some additional bump up for the total sites to account for the possibility of trends, the sites with fewer than three tumors, correct?

MS. GREENWALD: Objection, form.

A. That bump up, as you put it, is already incorporated in these sets of numbers such that there are sufficient numbers in each of the sex species groups that I feel I've probably put a number in here which is more than the number of evaluations which were actually done.

Q. OK. And in your calculation of your adjustment for p-hist. -- first of

all, in deciding which studies or tumor sites to conduct historical analyses for, you did not do historical analyses for all rare tumors in these studies, correct?

MS. GREENWALD: Objection, form.

A. Yeah, I -- I don't -- I don't understand the question. I am sorry.

Q. In deciding which tumor sites to conduct a p-hist. analysis, you base that on your review of where there were sites that were -- where there had been one finding of a statistically significant trend in a concurrent control, correct?

MS. GREENWALD: Objection, form.

A. Yeah, I'm -- again, you have lost me in the question. I am sorry.

Q. Let me ask this: Through your p-hist. analysis, you can calculate statistically significant trends at sites with one or two tumors, correct, for rare tumors?

A. An analysis using that approach could potentially find a positive finding for just two tumors, that is correct.

But the two I chose -- the

tumors -- let -- the tumors I chose to evaluate were identified by regulatory agencies as a concern because those tumors were different than the historical controls.

I didn't go back and look at every single site and get historical controls for every single site because I didn't analyze every single site with two tumors in it. So that just -- it would never have occurred except that this was flagged already by the regulatory community.

Q. So in your --

A. And I will add, because I still don't understand -- I guess I don't have to understand the relevance of your questions.

Q. So for your historical trend analysis, you didn't conduct -- you only did historical trend analysis for tumors that had been flagged as potential issues, correct?

MS. GREENWALD: Objection, form.

A. I did -- for every tumor where EPA or some other authority flagged it as

falling outside of the range of historical controls, and arguing that it could go away, I did the historical control analysis to illustrate the importance of doing something correct with historical controls.

However, as I say at the beginning, the best control to use for any of these studies is the concurrent control, except in the case where there are rare tumors. So in those cases, I used the P value from historical control for this table that you're looking at.

Q. If you were to determine the number of P trends that you might find by chance in a historical trend analysis of rare tumors -- so you would have -- as you have already testified, if you conduct 20 tests, you would find one by chance, correct?

MS. GREENWALD: Objection, form.

A. You would not find any by trend analysis. I'm sorry, two -- two tumors -- I must have missed your question.

Q. I'll ask it again.

For tumors where you can do

historical trend analysis, where you could calculate a p-hist., the rare tumor, and you have two tumors, so there's enough with rare tumors, two tumors with a historical trend analysis is enough to find a historical -- to find a trend, correct?

A. With the right historical control dataset, yes.

Q. And if you were to look at 20 rare tumors where you have historical control data and run a p-hist. analysis, you would expect by chance that one of them would report a P less than .05, correct?

MS. GREENWALD: Objection, form.

A. No, I can't say that. You're in a realm of behavior of the statistical methods that are dependent upon both the historical control dataset and the concurrent dataset, and to be quite honest, I'd have to sit down and do some analyses to figure out what this type of analysis you are suggesting would be done.

But I don't understand why you're suggesting the analysis because typically you flag something as a rare tumor based

upon the advice of the pathologist involved.

Q. I understand. But in your table 15, you're comparing what you observe to what would be expected by chance.

And what I'm trying to understand is what you -- what number of sites you would expect to see by chance for rare tumors or through historical trend analysis versus the number of trends you found with a historical trend analysis?

MS. GREENWALD: Objection, form.

A. But this table, 15, is only for the number of analyses done. It's not -- not a theoretical number of analyses. It is for analyses done.

Q. That may be why I misunderstood.

So your table 15 is comparing only the analyses you did as total sites, and then calculating an expected number of sites and an observed number of sites, is that correct?

A. No. It's calculating the number of potential sites.

I didn't calculate exactly how

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many analyses I did. I guess I can go and do that but I haven't, because what you're looking at is -- I looked at all the EFSA studies and EPAs.

So it wouldn't be correct for me to put in here the total sites that I personally evaluated, because those other documents guided me to sites, and those other documents had evaluated sites in a standard statistical way. But they didn't tell me how many they did.

So I technically can't give you an exact number for the total sites. This is the way it is sometimes with practical science. What I can do is create a logical, reasonable estimate for the total sites that had been reviewed, had been analyzed. And that's what this is.

Q. Just so I'm clear, if your total sites number did not include the numbers that would account for both individual tumor types with three or more tumors for adenomas and carcinomas and combined total sites with three or more tumors and the rare tumors for which you might find a

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statistically significant finding --

A. The two rare tumors.

Q. OK, so all of those possibilities, for your modified table 15 to make sense, would have to add up to the total sites that you have listed in your total tumor sites?

MS. GREENWALD: Objection to form.

A. Or in this case, I've been conservative enough that I'm pretty certain that total sites is larger than that number of the sites that you have evaluated, which makes it somewhat conservative.

Q. And you can, in fact, just add up the number of sites in these studies with three or more tumors, correct, you have got all the data?

A. I've done that.

Q. Have you looked at all the sites combined and separately?

Because you report both of those in your table.

MS. GREENWALD: Objection, form.

Q. So you have kidney adenomas,

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kidney carcinomas, kidney adenomas and carcinomas combined?

MS. GREENWALD: Objection to the form.

A. I've allowed sufficient numbers in the total sites to cover those.

Q. Have you added up all the sites in the studies with adenomas more than three, carcinomas more than three, and adenomas and carcinomas combined more than three?

MS. GREENWALD: Objection to form.

A. You wouldn't always do the combined analysis. That's not standard methodological practice in toxicology. You do the combined analysis only sometimes.

So adding up that number, creating that number that you just made up -- you just suggested would not reflect the number of sites that would actually be done.

Q. Have you gone through the exercise of adding up the sites that you think should be combined so you actually

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have the total number of sites with adenomas, with carcinomas, and adenomas and carcinomas combined where you believe that's appropriate?

MS. GREENWALD: Objection to form.

A. You can't do that evaluation sort of in isolation. So no, I have not done that.

Q. So sitting here today, do you know the total sites -- total number of sites for which you could have done a trend analysis for -- I'm sorry, for adenomas, for carcinomas, and as you think it appropriate, adenomas and carcinomas combined in this dataset?

MS. GREENWALD: Objection to form.

A. You can't -- again, you can't look at it that way. If carcinomas are zero, for example, you would only do the adenoma evaluation. If adenomas are zero and you have carcinomas, you would only do the carcinoma evaluation. There are other similar situations where you do those site

types of evaluations.
Unless I sat with EPA and they gave me every test they did, or I sat with EFSA and they told me every test they did, I cannot figure that number out. All I can do is give you an approximation.
Q. OK, I'm not asking about the number of analyses that were done. I'm asking you about the number of analyses that could be done, because that's what your total sites column is, correct?
MS. GREENWALD: Objection to form.
A. No, the total sites column should be an estimate of the number of sites that were done. That is what it's attempting to give you.
Q. I understand.
MR. LASKER: Let's take a break.
THE WITNESS: I'm happy to go on.
Q. In your report for female CD-1 mice, you have listed an observed trend that you identify as "SL."
Do you see that?
It's on mice tumors P less than

05.
A. Mice tumors P less than 05 SL. Yes.
Q. And you have SL listed as skin lymphoma?
A. Yes, it is.
Q. Now, I don't find any skin lymphoma in any of the studies. There was a SL trend in the Knezevich study that you report for spleen lymphomas.
A. Oh, that's correct, that's the splenic lymphomas. Thank you. Yes, that is the splenic lymphomas.
Q. You include spleen lymphomas as one of your observed trends in your table 15?
A. It is an observed trend, that is correct.
Q. OK.
A. That is correct.
Q. Now, the spleen lymphomas, I think in your rebuttal report, you state should be combined with all the lymphomas for a combined lymphoma number in doing a statistical analysis?

MS. GREENWALD: Objection to form.
A. They're not -- they're not -- I'm sorry, give me a minute to look this up, please.
Splenic lymphosarcomas. They are not lymphomas. They are lymphosarcomas.
Q. So in your testimony, lymphosarcomas do not need to be listed with lymphomas?
I'm trying to understand.
A. That's correct, you wouldn't combine sarcomas with lymphomas.
Q. Do you know how many lymphosarcomas were analyzed in Knezevich, given tissue types?
A. By whom.
Q. By the investigators in Knezevich?
A. I'm not able to see the full report from them, so I wouldn't know that.
Q. And you have the data table from --
A. But I don't have the report of what analyses they did, therefore, I can't

answer the questions.
Q. You have data presented for a number of different tissue type lymphosarcomas in the Knezevich study, correct?
A. I have -- yes, I have data tables that show lymphosarcomas in several different tissues.
Q. And in your response to Dr. Corcoran, you testify that Dr. Corcoran improperly calculated trend analyses reporting out all of those different lymphosarcoma sites and that they should be combined in your opinion, correct?
MS. GREENWALD: Object to form.
A. I noted that he had done multiple analyses about lymphosarcomas and there only should be one lymphosarcoma analysis. However, I can't do that myself but I did report the one.
Q. But the multiple lymphosarcoma sites that are separately calculated, those would not be separately listed as total sites because the total sites in your table 15 combines systemic tumors, correct?

MS. GREENWALD: Objection, form.
A. They were listed in the total site that Dr. Corcoran had done --
Q. Not Dr. Corcoran's, I'm talking about yours.
A. Let me finish -- and the table 15 has one site for lymphosarcomas. One, it takes up one site and it was evaluated, so it is put into this table. And it had a P value associated with it, which also goes into this table.
This is a table of what evaluations were done.
Q. So the total sites column then does not -- in table -- modified table 15 does not include the other lymphosarcomas sites that were analyzed in the Knezevich study, just the splenic lymphosarcoma, correct?
MS. GREENWALD: Objection, form.
A. In my table 1 on page 9 of the rebuttal reports, the three-or-more-tumors column only allows one spot for lymphosarcomas. So when lymphosarcomas were found, whether it was five organs or

one organ, I collapsed it down into a single entry into this table.
Q. So in the Knezevich study then, for the purposes of your analysis, you have one total site where there could be a calculation conducted and one tumor site being splenic lymphosarcoma where you observed a trend, is that correct?
A. That is -- for each study, there is sufficient room for that type of evaluation to be done, and in this case, there was one evaluation of that type, and that is included.
Q. And the other however many other sites that were evaluated are not included in the total sites column?
MS. GREENWALD: Objection, form.
Q. For lymphosarcoma. I'm sorry.
MS. GREENWALD: Same objection.
A. I can't know that. I don't know how many other sites were evaluated. As I pointed out before, that information is not available to me, so I can't answer the question.
Q. Just to be clear, the Knezevich

study is the Monsanto 1983 mouse study, correct?
A. The splenic lymphosarcomas?
The rows are the Knezevich and Hogan study, that is correct.
Q. So you have that full report -- study report, correct?
A. I have that study report, but the study report is presented with groups of -- the part I have is presented with groups of animals by organ. So I -- it gives me the numbers for spleen and gives me the numbers for wherever, say, kidney.
But because this tumor can appear quite often in multiple organs in the same animal, and I'm interested in incidents, I cannot back those numbers out and make the correct -- what I would consider the correct classification.
Q. In your modified table 15, you also include listing of four observed sites for -- and these are actually as opposed to the skin and bone.
You have four sites for skin tumors. You have three, I think, skin

keratoacanthomas and one basal cell carcinoma in your table for the rat studies, correct?
A. I have skin keratoacanthoma for the rat studies, I have three, and one basal cell, that is correct.
Q. Now, let me show you -- you talked about the NTP is sort of the gold standard for these cancer bioassays, correct?
A. For the way they are done and the way they are presented and the way they are analyzed, that is correct.
Q. And the NTP combines different skin tumors into one category, correct?
A. That I don't know for certain.
MR. LASKER: Let's mark this.
A. Of course, NTP uses a different strain of animals.
Q. They use many different strains of animals, but I'm talking about -- let me ask you this: When NTP combines tumor types, does it combine different tumor types for different strains of animals?
So, for example, you --

A. Oh, they might, yes, they might.
Q. For skin tumors, do you know one way or the other whether NTP combines tumor types for any different type of rodent?
A. No, I don't.
(Exhibit 15-36, report entitled "NTP historical controls, report all routes and vehicles, Wistar-Han rats, August 2016, marked for identification, as of this date.)
Q. This is Wistar rats, and I'll refer you to page 32 of this report.
MS. GREENWALD: I am sorry, what page?
MR. LASKER: Page 32.
Q. As reflected at least for this rodent, the NTP combines I think it is something like 12 different types of skin tumors to report an overall combined instance for skin tumors, correct?
A. On the previous -- 12?
On the previous page, it gives the individual historical control data for basal cell adenoma or basal squamous tumor benign, basal cell adenoma, basal squamous

benign or trichoepithelioma, basal cell carcinoma, basal cell carcinoma with basal squamous tumor, malignant or not otherwise specified, and then it provides a category for all of these things combined in one table, yes --
Q. For purposes of --
A. -- and there is no skin keratoacanthoma in this listing.
Q. Actually, page 32, just so we are clear, the listing -- the second listing includes keratoacanthoma, correct?
A. Yes, there it is, correct.
Q. And that is grouped together with basal cell or squamous cell carcinoma, carcinoma, basal squamous tumors M or B, basal cell adenomas, adenomas, papillomas, squamous papillomas, keratoacanthoma and trichoepithelioma, correct?
A. That's correct. It doesn't mean they would analyze it that way, but that is what's on this paper.
Q. For the purposes of your total site analysis -- or total site numbers in modified table 15, did you have counts for

different sites for the skin or was skin just one site for your total site calculation?
A. I'm sorry, when I counted up all the numbers of tumors greater than three tumors, it could easily have two skin sites or three.
Q. Do you recall right now whether you had more than one skin site for your total sites or not?
A. I would have to go back to the original tables and read through and see how many of them were greater than three and/or skin.
I don't have that recollection. I can't remember that much detail on -- with so many numbers around.
MR. LASKER: Now I would like to take a break. Thanks.
THE VIDEOGRAPHER: The time is 4:36. Off the record.
(Recess.)
THE VIDEOGRAPHER: The time is 4:48 p.m. We are on the record.

BY MR. LASKER:
Q. Dr. Portier --
A. Before you ask me a question, during the break, I took the time to look over this Charles River Laboratory document you gave me. And I would like to correct my reaction to it a little bit on the record.
Q. Which document is that?
A. 15-34.
MR. LASKER: Let's go off the record for a second, just because I want to find out if you are going to be asking questions, but if you will, we will save it.
THE VIDEOGRAPHER: Did you say go off the record?
MR. LASKER: Yes.
THE VIDEOGRAPHER: The time is 4:49 p.m. We are off the record.
(Recess.)
THE VIDEOGRAPHER: The time is 4:50 p.m. We are on the record.
MS. GREENWALD: I would like the record to reflect Dr. Portier asked

Mr. Lasker if he could have a minute or two to clarify his answer to the document 15-34, which he admitted during his testimony before he had never seen before, and during the ten-minute break, Dr. Portier used that to familiarize himself very briefly with it.

He did not use that time at all during the time Mr. Lasker was asking him questions. He asked for one or two minutes to clarify and correct his answer, and Mr. Lasker right now is not letting him do that.

MR. LASKER: Just so the record is clear, Dr. Portier will have the opportunity to clarify that before the end of the deposition here today.

MS. GREENWALD: I have made my peace. He can do it on your time.

Q. Dr. Portier, let's turn to your opinions regarding mechanism of carcinogenicity in your report.

You mentioned ten key characteristics of carcinogens, and I think

it is part of the Smith publication, correct?

A. That is correct.

Q. And is it your opinion that there is only sufficient evidence for glyphosate with respect to two of those characteristics, correct?

A. I do not believe that is what I said.

Q. Let me look at your report on page 53.

And on page 53 you're talking about the ten characteristics of mechanisms for carcinogenicity, correct?

And it's the top of the page where you cite to Smith.

A. That is correct.

Q. And you say, "There is limited evidence on glyphosate for most of the key characteristics," but then you identify two characteristics, genotoxicity and oxidative stress, which you believe have sufficient evidence, correct?

A. To warrant a full review. I reviewed all of the other evidence but it's

limited and not -- doesn't warrant a full review.

Q. OK, that's fine.

Now, you have stated that we don't know for sure if glyphosate is genotoxic, correct?

MS. GREENWALD: Objection, form.

A. Where would you -- where is this in here?

Q. First of all, that's a general question and then I can do a follow-up.

But I want to know if you recall having made the statement that we don't know for sure if glyphosate is genotoxic?

MS. GREENWALD: Objection, form, and the witness asked you to please identify where you think he made that statement.

A. I can't -- I -- my expert statement is right here and I believe my conclusions on genotoxicity are quite clear. So if you want to ask me about that, please ask me about it.

Q. Well, I'm asking you whether or not you have made the statement "we don't

know for sure if glyphosate is genotoxic."

If you don't recall, that is fine.

MS. GREENWALD: Objection, asked and answered. My objection stays the same.

A. I seriously don't recall.

Q. OK. Can you state here today that you have not made the statement that we do not know for sure if glyphosate is genotoxic?

MS. GREENWALD: Objection, asked and answered, argumentative.

A. I don't recall. It's still the answer.

Q. Let's mark as -- I will have to make this as two documents. This is an article that appeared in a German news site, so we have had it translated.

So we will have the German document as the next in line, and then the English translation as 38?

MS. GREENWALD: Can you please tell us who translated it?

MR. LASKER: It is set forth on

the document.
MS. GREENWALD: Was it a certified translator?
MR. LASKER: It is. You will see it in a second.
(Exhibit 15-37, German article, marked for identification, as of this date.)
(Exhibit 15-38, translation of German article, marked for identification, as of this date.)
Q. So, Dr. Portier, 15-38, which will be more useful for us to look at since it is the translation to English -- first of all, the record can reflect that it is a certified English translation as set forth on the bottom of page 1.
MS. GREENWALD: So, Mr. Lasker, if I can just ask for the record whether this was a certified translator. I'm not seeing that reference here, that she is a certified translator.
She is certifying that she translated it. Is she a certified

translator?
MR. LASKER: We will get that information for you if it is not on the document. I apologize right now.
MS. GREENWALD: It's not.
Q. Dr. Portier, in -- do you recall being interviewed in July, which would be about a month and a half ago, about the European Union assessment of glyphosate?
MS. GREENWALD: I just want to -- I'm objecting to all these questions.
You can answer them, but I'm objecting to all the questions on the grounds that we have no idea if this is an accurate translation.
MR. LASKER: That's fine.
A. I was interviewed by Martin Forter and Stephanie Fuchs.
I don't believe it was July 18. I think it was before that.
Q. OK, but then it would appear in an article after you were interviewed, that makes sense?
A. Of course.
Q. OK. And if you can look at

page 4 on the English translation, this is -- just so the record is clear, and you can look through this -- this document sets forth a series of questions to you and your answers on various issues with regard to the EFSA and ACA review of glyphosate, correct?
MS. GREENWALD: You have to give him a chance to look at this, Mr. Lasker.
A. Now, what is your question.
Q. This -- in your interview with Mr. Forter and Ms. Fuchs, they asked you a series of questions, and you provided answers. That's normal interview format, correct?
MS. GREENWALD: Objection, form.
A. In this case, they asked questions, we had a discussion, that is correct.
Q. And one of the questions they asked you, as reflected on page 4 of the English translation, was is glyphosate genotoxic, correct?
MS. GREENWALD: Objection, form.

A. That is what they give -- your translator has said what they say, and that is what they say.
I can't tell you if they asked me that question in this frame in the interview.
Q. And if you look at the -- well, do you speak German?
A. That still wouldn't solve the problem because I don't know if they asked me that question verbatim as they put it here.
Q. That's not my question. My question is: Do you speak German?
A. I speak some.
(German phrase.)
Q. If you can also look at Exhibit 15-37, the German article on the bottom of page 3, there is a question that I'm going to butcher in German, but it "Ist Glyphosat genotoxisch?" is the question.
MS. GREENWALD: Hold on.
Don't guess. I said don't guess.
If he is not fluent in German, he can't guess on what this means.

MR. LASKER: OK.
A. Again, the -- there is a two-stage process here. The first is did they ask me the question? And the second is did your translator get it right from what they wrote?
I can't tell you if they asked me this question verbatim. But I can tell you that "Ist Glyphosate toxicisch" is the question that they have -- you have converted to English.
Q. And the conversion "Is glyphosate genotoxic" is an accurate translation of that question, correct?
A. That is correct.
Q. The answer that they have -- you can read it in German as well as in English from you -- is, "We don't know for sure. The data of 50 percent of the studies argues for genotoxicity, 50 percent against it."
First of all, do you see that statement in the article?
MS. GREENWALD: Object to form.
A. I see it in the translation,

that's clear. I have --
Q. You have to turn the page for the German.
A. No, it's right here. But I'm not good enough in German to look at this.
Q. Can you state, sitting here today, that you did not state to this reporter, in answer to the question "Is glyphosate genotoxic," "We do not know for sure"?
MS. GREENWALD: Objection to form.
A. I can't tell you. They could have easily taken it out of context or something along those lines. I have no idea. What I -- I can't answer "yes" or "no" to that question.
Q. OK, so sitting here today, you can't state that you didn't make this statement, and you can't say that you did, you just don't recall, correct?
MS. GREENWALD: Objection, form.
A. My current opinion on the genotoxic data for glyphosate is in the expert report. This does not match what's

in the expert report.
Q. I understand that.
Are you saying that you did not say this in the interview or are you saying you can't recall whether you said it?
MS. GREENWALD: Objection, asked and answered.
A. It was answered. I'm sorry, yes. She is right.
Q. Do you recall whether you said to these reporters, we don't know for sure whether glyphosate is genotoxic?
MS. GREENWALD: Objection, asked and answered now several times.
A. I do not recall.
Q. Do you recall whether you said, in the interest of public health, we should therefore classify glyphosate as genotoxic, in my opinion?
MS. GREENWALD: Objection, form.
A. I cannot possibly answer the question. No.
Q. You don't recall?
A. Don't know.
Q. You don't recall one way or the

other?
A. No. It was a long interview. It was over an hour.
Q. The -- you do -- you agree that just because a chemical can damage DNA, that does not mean it will cause mutations, correct?
MS. GREENWALD: Objection, form.
A. Say it again, please.
Q. Just because a chemical can damage DNA, that does not mean it will cause mutations, you agree with that statement, correct?
MS. GREENWALD: Same objection.
A. In general, that is correct. I would state it slightly different, but as a general, broad sweep, that's good enough.
Q. And just to be clear, if you can look at your expert report on page 53, I thought I quoted you, but maybe I did not.
Page 53 in your expert report on genotoxicity, the second full paragraph starting "Just because a chemical can damage DNA does not mean it will cause mutations," correct?

A. Yeah.
Q. That's your statement?
A. That's my statement.
Q. You agree with that, correct?
A. I would have liked to have written it slightly differently and more nuanced, but that's good enough.
Q. You agree that not all chemicals are mutagens, correct?
A. Who defines what the geno -- it's going to depend on a lot of different things. Who's making the call, who's doing the evaluations, et cetera.
But in looking at NTP studies with NTP evaluations, not all genotoxic substances cause tumors in male and female rats and mice.
Q. And just to be clear also, not all chemicals that are reported to be genotoxic are found to be mutagenic, correct?
A. Not all chemicals that are reportedly genotoxic are found to be mutagenic?
I can't answer that question.

It's too broad. I'm sorry.
Q. OK. I am correct that if a genotoxic chemical does not cause mutations, then it cannot cause cancer through a genotoxic mechanism, correct?
A. The assays -- this is all dependent upon what you look at.
The assays that are done for mutations are very limited assays looking at a very small number of genes and a very small number of mutations.
So to answer your question, I can answer it this way: There are some chemicals that are genotoxic that do not appear to be positive in the toxicological assays that have been done to evaluate them.
Q. I appreciate that. I was trying to ask a different question. I didn't word it correctly.
This is not in an individual study that tests one way or another. This is a broader, mechanistic question.
If a substance is genotoxic but it does not cause mutations, just as a

matter of fact, then it cannot cause cancer through a genotoxic mechanism, correct?
A. It can do it through a side -- to really think it through -- through side activities.
Genotoxic compounds are very reactive. They can damage other parts that could lead to oxidative stress or other things that will cause the mutations and the cancers.
So it's complicated.
Q. OK. And again, I didn't word this correctly, so I apologize, but for a chemical to cause cancer through a genotoxic mechanism, cause of action, it would have to progress to a mutagen -- a mutation -- I'm sorry -- correct?
A. The -- in a theoretical sense, if such a compound were not interacting with anything else, then in a theoretical sense, in a multi-stage model, you would expect a mutation to occur. If you could find it, that may not be possible. But you would expect a mutation to occur.
Q. And all of us sitting in this

room, we constantly have DNA damage to our cells in the ordinary course, correct?
MS. GREENWALD: Objection, form.
A. All living organisms have repair capacity and -- because they always have problems with their DNA during replication.
Q. And in the ordinary course, we are having DNA damage in our cells probably millions of times each day, correct?
MS. GREENWALD: Objection, form.
A. I couldn't give you an exact number.
Certainly not millions of times each day in each cell, because the DNA damage only really has any value during the time the cell replicates, and many of the cells in humans simply don't replicate that often.
Q. Every time there is a replication though, in the ordinary course, it is not uncommon for there to be DNA damage, correct?
A. That is correct.
Q. As you said, the human body has repair mechanisms that respond to DNA

damage so that it doesn't cause further damage, correct?
MS. GREENWALD: Objection, form.
A. The body has DNA repair capacity through several processes for different types of DNA damage, yes.
Q. And you would also agree that not all chemicals that test positive for mutagenicity cause cancer in humans, correct?
A. Not all chemicals that have been tested for genotoxicity --
Q. For mutagenicity.
A. -- for mutagenicity, and the evaluation is done by reputable groups, like the NTP, then I wouldn't be surprised if some of those that were mutagenic were not also carcinogenic, but I couldn't give you one right now.
Q. Now, in your expert report, you opine that the evidence is sufficient to classify glyphosate as genotoxic, correct?
A. Yes.
Q. In your expert report, you do not opine that the evidence is sufficient to

classify glyphosate as a mutagen, correct?
MS. GREENWALD: Objection, form.
A. The -- there is -- the evidence is insufficient to classify the mutagen because of the reasons I gave earlier.
There aren't that many tests, and they are very specific to very genes -- very few genes, not the entire human genome.
Q. And you do agree though that both glyphosate and glyphosate formulations have consistently tested negative in the Ames mutagenistic test, correct?
A. They have consistently with the exception, I believe, of four studies -- but there were a lot of studies -- consistently tested negative for the reverse mutation assay of a specific gene in salmonella typhimurium. So yes, the Ames test.
Q. And as you note in your expert report, there is a wide diversity of different types of genotoxicity tests, correct?
A. There are a wide diversity of

tests looking at effects of chemical on the gene, yes.
Q. And you state in your report, "Genotoxicity is a complicated area from which to draw a conclusion due to the diversity of studies available," correct?
A. It is, yes.
Q. And that is the case certainly with glyphosate in your opinion, correct?
MS. GREENWALD: Objection to form.
A. If I said it in here, you would have to tell me where it is again.
Q. I'm just asking you, would you agree that for glyphosate, genotoxicity is a complicated area from which to draw a conclusion due to the diversity of studies available?
MS. GREENWALD: Objection to form.
A. In general, genotoxicity is complicated to make decisions because there are so many different possibilities of how people do it. They use different animals. They use different cell lines. They use

different links of time for the exposure, et cetera.
So that is a usual case. I think I said that here but I'm not certain so I can't own up to that for this compound.
Q. But whether or not you said it in your expert report, you agree that that applies to glyphosate, correct?
A. Yes, when compared to something like the animal cancer studies where you have pretty much standardized designs on everything.
Q. Let me ask you about your opinions with regard to oxidative stress.
A. OK.
Q. You agree that oxidative stress is not unique to cancer induction, correct?
MS. GREENWALD: Objection, form.
A. Not unique to cancer induction. I'm not sure what you mean.
MR. LASKER: Let's mark the Smith publication.
(Exhibit 15-39, article entitled, "Key Characteristics of Carcinogens as a Basis for Organizing Data on

Mechanisms of Carcinogenesis," marked for identification, as of this date.)
A. Yes.
Q. And that paper -- this is a paper you were coauthor on, correct?
A. Correct.
Q. And page 715, talking about characteristic five induces oxidative stress, correct?
A. Characteristic five induces oxidative stress, that is correct.
Q. And you and your coauthor state, about halfway through that first paragraph, "Oxidative stress is not unique to cancer induction," correct?
A. "And is associated with a number of chronic diseases and pathological conditions."
Yes. That is correct.
Q. And so -- and you agree with that, correct?
A. That is correct.
Q. And the fact that a substance causes oxidative stressor is bound to cause oxidative stress in human cells in vitro,

or mammals in vitro, does not establish that that substance can cause cancer, correct?
MS. GREENWALD: Objection, form.
A. For any of the key characteristics, seeing a key characteristic does not establish that that -- by itself does not establish that that compound can cause cancer.
Q. So that would apply to oxidative stress and to genotoxicity, correct?
A. That is correct.
Q. Can you cite to any scientific publication or analysis that looks at the percentage of substances that have been shown to cause oxidative stress to see what percentage of them have been shown to cause cancer?
MS. GREENWALD: Objection, form.
A. Yes. We looked at it in the paper that we just did on monograph 100, but I have no idea if it is published yet or not.
Q. In that same paper did you look at scientific data that sets forth

noncarcinogens and look to see whether they are reported to cause oxidative stress?
A. Noncarcinogens.
Q. Noncarcinogens.
A. This was known human carcinogens. The entire analysis was known human carcinogens.
And I'm not certain because it is a separate analysis from the one I was thinking of. I can't be certain it's only the known human carcinogens.
Q. Are you aware of the fact that there are medicines that are used to treat cancer that cause oxidative stress?
A. Yes, I am.
Q. And oxidative stress has also been recognized as potentially acting to block carcinogenicity by inducing a -- I say this apoptosis or cell death, correct?
MS. GREENWALD: Objection to form.
A. At high enough levels, oxidative stress in some cells will kill them through an apoptotic or necrotic mechanism, but different cells get different exposures so

it depends on the level of exposure as to whether they get to that point.
Q. Oxidative stress is happening in our body all the time, correct?
A. It's part of the energy system that drives our ability to move.
Q. So exercise causes oxidative stress, correct?
A. Of course.
Q. And having a cold would cause oxidative stress, correct?
A. That's correct.
Q. Oxidative stress is happening all the time in every cell in the human body just through normal cell operations, correct?
A. What you're measuring in these studies is increased oxidative stress. It's not yes, no. It's increased oxidative stress.
Q. Well, just to be clear, exercise causes an increase in oxidative stress, correct?
A. Very marginally.
Q. And being sick can cause an

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increase in oxidative stress, correct?
A. Very marginal for a very short period of time.
Q. And sunlight can cause an increase in oxidative stress, correct?
A. That I'm not so certain of but it wouldn't surprise me.
Q. What other non-exposure type activities have caused an increase in oxidative stress?
A. I ---I don't quite recall. I'd have to consult a couple of good textbooks or articles.
Q. And the body has repair mechanisms that are constantly responding to cellular damage caused by oxidative stress, correct?
MS. GREENWALD: Objection, form.
A. Not correct. They are responding to cellular damage regardless of the source.
Q. OK. But they would -- in responding to cellular damage, they would respond to cellular damage caused by oxidative stress, correct?

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MS. GREENWALD: Objection, form.
A. If that damage was aimed at DNA, that is correct.
Q. And you cite a number of studies in your expert report that you cite as support for your opinion that glyphosate can cause oxidative stress, correct?
A. I'm sorry.
Q. You cite to a number of studies in your expert report that you believe support your opinion that glyphosate can cause oxidative stress, correct?
A. That's correct.
Q. Have you conducted any analysis to determine whether the concentrations of glyphosate in those studies could ever occur in human cells from the use of a glyphosate-based herbicide?
MS. GREENWALD: Objection, form.
A. Me personally? No.
Some of the studies did that. But not me personally.
Q. And is it your opinion that you rely upon studies -- strike that.
Do you believe that some of the

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studies that you cite to have compared the doses they use with the dose levels that would occur in human cells from the use of glyphosate-based herbicides?
MS. GREENWALD: Objection, form.
A. As I said, some of them I believe might have done that.
The -- these are in vitro studies we are talking about, right?
Q. These are the studies you relied upon.
A. But you're asking me questions about in vitro studies or are you asking me questions about in vivo studies?
Because it actually makes a difference. They are both -- they are both in there.
Q. In your expert report -- let me ask you this: Whether in vitro or in vivo, is it your recollection any of those studies conducted an analysis to determine whether the dose that they use is at a level that is possible for the human cell to have as a result of the use of a glyphosate-based herbicide?

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MS. GREENWALD: Objection, form.
A. I already answered that. I said I thought some of them might have done that and talked about how large it was compared to humans.
But I can't be absolutely certain.
Q. In your assessment of genotoxicity, you state in your expert report that you give the heaviest weight to the in vivo studies in humans, correct?
So there's three studies you talk about, two by Paz-y-Mino and one by Bolognesi, correct?
MS. GREENWALD: Objection, form.
A. The evaluation has different language than that. Because in the context of just talking about the human studies, the Bolognesi is the strongest, I think is what I said, but I don't know if I said I give the most weight.
I am sorry, you would have to point it out in here.
Q. In your revised report on page 54, you state that seeing genotoxicity

in humans is more important than seeing genotoxicity in other mammals, which is more important than seeing genotoxicity in non-mammalian systems, correct?
A. All else being equal, that is correct.
Q. As you said, the study in humans that you believed to be the strongest study is the Bolognesi study, correct?
A. Correct, but that does not make it the major weight of my determination.
Q. I understand.
A. OK.
Q. And let's take a look at the Bolognesi study.
MR. LASKER: We will mark that as...
(Exhibit 15-40, article entitled, "Biomonitoring of genotoxic risk in agricultural workers from five Colombian regions," marked for identification, as of this date.)
Q. And just for the record, this is the study you were talking about -- we were just talking about just previously,

correct?
A. Yes, I believe it was.
Q. The investigators in Bolognesi at page 994, at the bottom of the second column, state that, overall, these data suggest that genotoxic damage associated with glyphosate spraying as evidenced by the NM test is small and appears to be transient, correct?
MS. GREENWALD: Objection, form. That wasn't read right.
A. Overall, these results suggest that genotoxic -- I am sorry.
"Overall, these results suggest that genotoxic damage associated with glyphosate spraying as evidenced by the micronucleus test is small and appears to be transient" is what it says.
Q. Do you agree with the Bolognesi investigators' assessment of their study and findings?
A. I have to look to see the context in which they're making the statement.
I'm not sure I agree with the "small."

Q. The Bolognesi study on page 995, the first column, about half the way down that first paragraph, there is a sentence that starts "Evidence indicates that the genotoxic risk."
Do you see that?
A. Um-hm.
Q. The Bolognesi investigators conclude from their study that evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the area where the herbicide is applied for eradication of cocoa and poppy is of low biological relevance.
Do you see that?
A. I see it.
Q. Do you agree with the Bolognesi investigators' assessment, this assessment of their study findings?
A. I don't know how they could possibly come to that conclusion. So I don't disagree or agree. I can't imagine where they got that from this data.
Q. The Bolognesi investigators found that there was no association between

self-reported exposure to glyphosate and in-transit genotoxic impacts, correct?
A. Not correct.
Q. Let's look at page 994.
A. They -- they ask specific questions about where you were when the spraying occurred. And so that's not self-chosen exposure. That's self-chosen where were you.
Q. Well, let's look actually at page 994 again. The second column on the right, the second paragraph from the bottom, the sentence starts, "There was no significant association between self-reported direct contact with eradication sprays" --
A. Which page are we on?
Q. I'm sorry. Page 994.
A. Right hand --
Q. Second column, second paragraph from the bottom, it starts, "There was"?
A. Yes, now I see it. Sorry. I was second from the top.
Q. The Bolognesi investigators report that there was no significant association between self-reported direct

contact with eradication sprays and frequency of BNMN, correct?

A. That's what they write, but self-reported is an incorrect description of what that was.

Q. There was a -- on the preceding page, 993, there is a table that -- table 4 presents their analysis for self-reported exposure to the glyphosate sprays.

Do you see that?

A. That's what it says in the title, but what it is is a report of where you sort of -- whether you had it in the air, on your skin, or you entered the spraying field.

That's not asking someone did you think you were exposed to this, which would be a self-reported exposure. So not exactly that.

Q. In your understanding, Bolognesi -- the Bolognesi study did not conduct an analysis that asked individuals if they were exposed to the glyphosate spray?

A. It's not here. That's clear to

me.

And my understanding of this study is these are the three things they used, but had they asked the question, do you think you were exposed? People who ate things from the field might have answered yes.

So it's hard from this to jump to self-exposure arguments. But they -- they do point out that it does not seem to be correlated with these things.

Q. And with respect to the analysis of where they were located -- where the individuals in this study were located, the Bolognesi investigators looked at impacts five days later after the alleged spraying -- glyphosate spraying, and then again four months later, correct?

A. That is correct. In certain cities, not in all of them.

Q. And the findings with respect to genotoxic impacts do not continue or are not present four months after the exposure, correct?

MS. GREENWALD: Objection, form.

A. That would not be correct.

Q. In the Narino Province, where there was the highest spraying of glyphosate, the findings four months after the spraying was unchanged from before the spraying, correct?

A. In the Narino Province, that is correct.

Q. If a genotoxic effect does not persist or is not present four months after exposure, it's fair to say that cannot be a cause of cancer, correct?

MS. GREENWALD: Objection, form.

A. Not correct.

Q. So is it your testimony that if there is a genotoxic impact that does not result in genotoxic damage four months after exposure, they can still lead to that can cause cancer?

MS. GREENWALD: Objection, form.

MR. LASKER: I agree with that. Actually, I'm going to state that again.

Q. If a chemical exposure does not cause a genotoxic effect that persists for

four months, can that effect be a cause of cancer?

A. Yes.

And there is a chemical that's a classic example of that in humans, but I don't know it off the top of my tongue.

It's banned. It was a drug.

MR. LASKER: I am maybe done. I may have a chance to have him answer that one question and a few more things, but let's take a break and talk to this guy.

THE VIDEOGRAPHER: The time is 5:29 p.m. We are off the record.

(Recess.)

THE VIDEOGRAPHER: The time is 5:33 p.m. We are on the record.

MR. LASKER: I am going to mark as 15-41 the notice of deposition for Dr. Portier's deposition in this case.

(Exhibit 15-41, notice of deposition, marked for identification, as of this date.)

BY MR. LASKER:

Q. And, Dr. Portier, there is

attached to this notice a list of document requests, request for production of documents, and you have produced some documents here today.

MR. LASKER: I'm going to mark that. That's what this is, 15-42, as the documents that we received from your counsel, Robin Greenwald, in response to the notice of deposition.

(Exhibit 15-42, letter dated August 29, 2017, with attachment, marked for identification, as of this date.)

MS. GREENWALD: You didn't give me a copy of that, did you?

No, I don't want them. That would kill too many trees. No, no, no.

Q. First question, and you can take a moment to leaf through them if you need to, but am I correct in my understanding what we marked as Exhibit 15-42 are the documents that you have that you believe were responsive to the document requests which have been marked as 15-41?

A. If these are documents, they

are -- that were passed on to you, then they are responsive.

Q. And am I correct in my understanding that, at least as far as you believe, you do not have any other documents that are responsive to our document requests?

MS. GREENWALD: Objection, form.

A. As -- I don't know what's in here, what they gave you. So I can't answer that question.

Q. We have not received any electronic data reflecting any of your work product in preparing your various analyses of glyphosate.

I take it you do have that data somewhere, correct?

MS. GREENWALD: Objection, form.

A. By -- I'm not sure what you mean --

Q. You have files on your computer --

A. The data that I used is in this expert report and the data was in spreadsheets.

Q. Do you have those spreadsheets in your computer?

A. Yes, I do.

Q. And do you have the calculations that you conducted on the data in your computer?

A. Probably some of them. The programs I use spit out an answer, I'd write it down, but they weren't always kept.

Q. So you have some data and some you have and others you don't have and you don't know sitting here today?

MS. GREENWALD: Objection, form.

A. I have all of the data. I can't guarantee I have all the results of the runs on the computer.

Q. OK.

And which programs did you use in conducting your analysis?

A. MATLAB.

Q. That was for all of your analyses?

A. No. I used a program by the German Cancer Research Center on animal

bioassays, the exact test, to check it against the MATLAB program for the exact test. I wanted to make sure they were both working right.

And did I use any other programs?

I -- I might have programmed one or two things in the spreadsheet itself.

Q. In your invoices -- or on your invoices to plaintiffs' counsel, you have listed an address 4224 Midvale Avenue -- or North Midvale Avenue in Seattle, Washington?

A. Yes.

Q. Is that a residence that you maintain in the United States?

A. Yes, it is.

Q. Dr. Portier, you had wanted to make a comment about the 1995 Charles River report.

A. That's correct.

Q. Just for the record, what is the exhibit number? Because I don't remember it.

A. 15-34.

So I have some concerns with this

one being the correct historical controls. First, I don't know what a CRL CD-1 13R mouse is and I can't find it. So I'd have to find out if that strain is relevant.

The 13R could indicate some sort of genetic transformation or something, I just don't know what it is.

The other problem in looking at these, I realize these are fairly small numbers of studies groups, and when you go back to the beginning, it turns out this is a companion paper to go with a different paper that provides the historical control database.

So I wouldn't use just this, I'd need the companion paper that goes with it.

MR. LASKER: I pass the witness and reserve the remaining time.

MS. GREENWALD: We are going to go to your room. And just we need one minute.

THE VIDEOGRAPHER: Off the record at 5:38 p.m. We are off the record.

(Recess.)

THE VIDEOGRAPHER: The time is

5:53 p.m. We are on the record.

EXAMINATION BY

MS. GREENWALD:

Q. Good afternoon, Dr. Portier. It is now my turn to ask you a couple of questions and we will call it a day.

I want to ask you one question -- just a couple of questions, the first one being: IARC does not use expert summary articles, is that correct?

A. That is correct.

Q. Can you tell us why?

A. Yes. Expert summary reports sometimes cannot cover the topic completely. It is always much better to go to the source material and work with the source material or the source report.

A good example of that is the Greim study. If all we had used was to read the Greim study to talk about the carcinogenicity of the 12 studies that were included in the appendix of the Greim report, we would have missed a lot of tumors because Greim only had roughly half or even maybe less than half of the total

tumors seen in these studies listed in his report.

And what I mean by seen in these studies is they had a positive Armitage linear trend testing proportions, which is the standard for how people analyze these data.

Q. OK. Thank you.

In biomedical research, is it generally accepted to perform sensitivity analyses?

A. Oh, definitely. It's a -- it's a common tool. The tool is used to judge how sensitive your finding is to slight modifications.

We saw a good example of that with the meta analysis -- meta analyses that were done for this where certain studies were added in, certain studies were taken out, and you look at the overall effect on that and then it gives you a better chance for making the correct judgment about whether you believe the finding you're looking at is positive or negative.

Sometimes it can make you more confused but sometimes it can clarify things for you.

In addition, any time you have got something that you feel not only doesn't -- not that it drives the result, but that maybe shouldn't be included in the evaluation, then you would do a sensitivity analysis to exclude and -- you do both to look and see how important that concept is, and then if you find it's very important, you have to decide which way was the most important way to go.

So that's a normal technique in biomedical research.

MS. GREENWALD: Can I have an exhibit, I think we are on.

(Exhibit 15-43, screen shot from LobbyFacts.eu, marked for identification, as of this date.)

Q. I'm going to show you, Dr. Portier, what I am marking as Exhibit 15-43.

This is a two-page document that we took off the internet today called

"LobbyFacts.eu."

And if you recall earlier today, Mr. Lasker asked you questions about C. Portier Consultation being a registered lobbyist in the European Union.

Do you remember those questions?

A. Yes, I do.

Q. And I believe you testified -- and I'm going to ask you to explain it again -- why you ever -- why you ever registered in the first place with the EU?

A. Because the staffer for the commissioner of health at first thought in order for us to talk to the commissioner of health, we had to register as lobbyists, but then after I think two days -- it wasn't very long, a couple of days -- came back and said, no, I got that wrong, you're not representing anybody, you're representing your academic background and standards, and as such, it would be inappropriate for you to do this. So you don't have to do it.

Q. And what does 15-43 show?

A. Under the little red triangle in

the top half of the page, it says, organization not currently on the register -- registration as it was on 21 December 2015.

Q. And what do you understand that to mean?

A. They have taken the registration off the register, which they told me they would do.

Q. That was as of the 21st of December 2015, right?

A. That's what it looks like, yes.

Q. Now, Mr. Lasker also asked you questions earlier about your consultation with the Environmental Defense Fund, correct?

A. That's correct.

Q. In fact, that was quite a bit of the questions this morning, wasn't it?

A. The --

Q. Early in the morning.

A. A lot of them, yes.

MS. GREENWALD: I'm going to mark 15-44.

(Exhibit 15-44, screen shot from

the EDF website, marked for identification, as of this date.)

Q. And this is a from a blog that was taken off of -- actually, Reuters. Oh, yeah, I'm so sorry, my eyesight is so bad, forgive me. It says, "Off the EDF website." It is a three-page printout from the EDF website, and it is titled, "Growing returns, a coalition of uncommon bedfellows is bringing sustainable agriculture to scale."

Do you see that?

A. Yes, I do.

Q. What is this article about?

A. I'll have to take a look at it real quick here. Sorry.

Q. Is this a description -- let me ask a different question: Is this a description of work that Monsanto is currently doing with the Environmental Defense Fund?

A. Yes, it appears to be. It says, "Founding members of the MRCC include cargo, environmental potential, and General Mills, Kellogg Company, Monsanto, PepsiCo,

and others.

Q. And it actually talks about partnership between Monsanto and the Environmental Defense Fund, correct, on page 2?

A. Yes.

Q. And the date of this article is August 31, 2016, is that correct?

A. Yes, it is.

Q. And I'm going to show you one more document.

MS. GREENWALD: I'm marking it 15-45.

(Exhibit 15-45, document entitled, "Monsanto joins Environmental Defense Fund, others, in Sustainable Agriculture Coalition," marked for identification, as of this date.)

Q. It is a one page document, and it is taken from the Genetic Literacy Project. And it is entitled, "Monsanto joins Environmental Defense Fund, others, in sustainable agriculture coalition."

Do you see that?

A. Yes, I do.

Q. Dated September 1, 2016?
A. Yes, I do -- yes, it does.
Q. What is this?
A. It looks like a news article about the same Midwest Row Crop Collaborative that the other one was on but this is a news item on it.
Q. It is also, again, talking about Monsanto --
A. Whatever Genetic Literacy Project does.
Q. Again, it's talking about Monsanto's work with the Environmental Defense Fund, is that correct?
A. Yes, it is.
MS. GREENWALD: OK, thank you.
Q. Dr. Portier, can you pull out 15-32?
MR. LASKER: That's the original expert report with attachments?
MS. GREENWALD: Yes.
Q. If you can look at the appendices, the first appendices, it is entitled "Document 1." It is sort of towards the back?

A. Yes, I see it.
Q. It says, "Difference in the carcinogenic evaluation is glyphosate between the international agency for research on cancer (IARC) and the European Food Safety Authority (EFSA.)" Do you see that?
A. Yes, I do.
Q. What is the date of this article?
A. August 2016, Volume 7, No. 8 in the Journal of Epidemiology and Community Health.
Q. If you go to page 744 of that article, please.
And if you look at -- there is a loke a lock with an open key, and it says, "Open access."
Do you see that?
A. Yes, I do.
Q. If you go right above that, it says, "Competing interest."
Do you see that box?
A. Yes, I do.
Q. Isn't it the case in this article, you and others provided

information that you were providing advice to a U.S. law firm involved in glyphosate litigation?
"CJP also works part time for the Environmental Defense Fund on issues not related to pesticides."
Do you see that?
A. Yes, that is correct.
Q. Who is "CJP"?
A. That is me, Christopher Jude Portier.
And it refers to the initials used in the author's list at the beginning of the document, wherever that is.
But if you look at the authors list in the beginning of the document, I'm listed as Christopher J. Portier and I'm the only CJP.
MS. GREENWALD: Thank you, Dr. Portier. I don't have any other questions. I appreciate your patience today.
MR. LASKER: I have a couple of follow-ups, but just a couple.

EXAMINATION BY
MR. LASKER:
Q. The Greim publication included supplemental tables with the data for all of the tumors that were analyzed in each of the animal studies -- or glyphosate cancer bioassays, correct?
A. No, not correct. It contained summarized data.
Q. The supplemental materials provided the data on tumor types and tumor counts that you have used in your analyses in this case, correct?
A. For most of the analyses, that is correct.
Q. And every finding that you report as showing significance can be obtained from the supplemental data tables that were provided with the Greim publication, correct?
MS. GREENWALD: Objection, form.
A. The question I was asked by counsel had to do with the use of expert summary -- expert summaries, and so while the data is there, the expert summary is

the written words of Greim.

Q. That's not my question.

The data tables that were provided with the Greim publication in the supplemental materials that were publicly available contains all the data that you would need to generate every one of the calculations in your report --

MS. GREENWALD: Objection, form.

Q. -- except for historical controls?

MS. GREENWALD: Objection, form.

A. Given six months -- and I'm going to have to take some minor reservations, because I can't be absolutely certain, but given six months and that data, I could have done what I wanted -- what I did here.

Q. And that data became publicly available because an author, a scientist at Monsanto, who is a coauthor on the Greim publication, and the other coauthors published the Greim publication and made those data tables available on the internet, correct?

MS. GREENWALD: Objection, form.

A. 30 days before the IARC meeting, that is correct.

MR. LASKER: I have no further questions.

THE VIDEOGRAPHER: This concludes today's deposition. The time is 6:06 p.m. We are off the record.

____

CHRISTOPHER JUDE PORTIER, Ph.D.

Subscribed and sworn to
before me this day
of MO , 2017.

____

CERTIFICATE

STATE OF NEW JERSEY)
)ss:
COUNTY OF UNION)

I, MARY F. BOWMAN, a Registered Professional Reporter, Certified Realtime Reporter, and Notary Public within and for the State of New Jersey, do hereby certify:

That CHRISTOPHER JUDE PORTIER, Ph.D., the witness whose deposition is hereinbefore set forth, was duly sworn by me and that such deposition is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage and that I am in no way interested in the outcome of this matter.

In witness whereof, I have hereunto set my hand this 6th day of September, 2017.

____

MARY F. BOWMAN, RPR, CRR

NAME OF CASE:
DATE OF DEPOSITION:
NAME OF WITNESS:
Reason Codes:
1. To clarify the record.
2. To conform to the facts.
3. To correct transcription errors.
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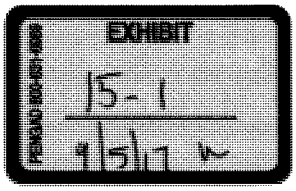
WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

INTERNAL REPORT 05/001

Report of the Advisory Group to Recommend Updates to the *Preamble* to the *IARC Monographs*

4–6 MAY 2005



LYON, FRANCE
2005

Report of the Advisory Group to Recommend Updates to the *Preamble* to the *IARC Monographs*

Lyon, France: 4–6 May 2005

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Report of the Advisory Group to Recommend Updates to the *Preamble* to the *IARC Monographs*

Lyon, France: 4–6 May 2005

Introduction

In February 2003 an Advisory Group to determine priorities for future evaluations within the *IARC Monographs* programme (2003 Advisory Group) made several suggestions for revising the Preamble to the series and recommended that a special group be convened to discuss these (IARC, 2003). As a result, a special Advisory Group to recommend amendments to the Preamble met in Lyon on 4–6 May 2005.

This Report summarizes the discussions of the 2005 Advisory Group in response to issues raised by the staff of the *IARC Monographs* programme or the 2003 Advisory Group. Several other issues were added by the 2005 Advisory Group. The opinions and recommendations of the 2005 Advisory Group follow each issue statement. For convenience, the Report is organized according to the sections of the Preamble.

1. Background

This Advisory Group recommends that the description of the historical context for development of the *IARC Monographs* programme be expanded. Reference could be made to emergence of the Programme as a response to a request that IARC provide a 'list of carcinogens'. At that time, no adequate criteria were available to generate such a list, and scientists advising the IARC recommended that documentation of all available evidence in relation to potential carcinogens be regarded as the only adequate basis for identifying the carcinogenicity of particular agents.

2. Objective and scope

Background. The *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* is an international programme on carcinogenic hazard identification that is achieved by the consensus of experts. The long-term objective is to review critically and evaluate the published scientific evidence on carcinogenic hazards to which humans are exposed. These include chemicals, complex mixtures, occupational exposures, lifestyle factors, and physical and biological agents. Each volume of *IARC Monographs* is the product of an international, interdisciplinary working group of expert scientists, who meet for 8 days at IARC to complete their critical review of the scientific literature and develop a consensus evaluation of the weight of the evidence of the carcinogenic hazard for each agent being considered.

Issue 2a. The 2003 Advisory Group recommended that the relationship of *IARC Monographs* evaluations to public health principles and implementation of public health measures should be addressed in the Preamble.

This Advisory Group agrees with the 2003 Advisory Group and suggests that IARC focus on the fact that cancer is preventable: the major use of the *Monographs* series was and still is the implementation of preventive measures to lower the global cancer burden. As a result of the *Monographs* evaluations, measures to reduce exposure to occupational carcinogens, tobacco smoke, ultraviolet light, ionizing radiation and other recognized causes of cancer could be justified on scientific grounds.

Prevention of cancer begins with the recognition of causal factors, which must be followed by the identification of communities or individuals at risk and the implementation of appropriate preventive measures. Such measures may range from the elimination of the causal agent by regulation to the encouragement of change of behaviour or lifestyle that could avoid exposure.

To date, more than 900 agents, exposures or mixtures have been evaluated, which has offered a wide spectrum of opportunities for initiatives in cancer prevention.

Complete knowledge of the mechanisms of carcinogenesis is not always necessary to achieve a reduction in or the elimination of exposure to a carcinogenic agent. However, such knowledge can strengthen the scientific basis of risk reduction, especially for susceptible subpopulations.

Consideration may be given to presenting these statements as the opening section of the Preamble (i.e. before the present Section 1. Background) under the heading 'Monographs in the context of cancer control', or similar phraseology.

Issue 2b. The 2003 Advisory Group considered that 'risk assessment' should be included as a discussion topic in a broad meeting to assess strategic developments of the *IARC Monographs* programme.

This Advisory Group recommends that, while quantitative information on carcinogenic risks can be useful, a cautious approach should be adopted in including quantitative risk assessment (QRA) in the *IARC Monographs*. Some applications of QRA may require certain assumptions in order to extrapolate from results of high-dose exposure to low doses, from those in animals to humans or from those of occupationally exposed populations to environmentally exposed populations. When information on carcinogenic risks is available from epidemiological studies on the populations of interest, extrapolation outside the range of the available data may not be required. This Advisory Group recommends that IARC confine its potential involvement in QRA to areas where unverifiable assumptions are not required or very limited.

This Advisory Group considered several ways in which the *IARC Monographs* Programme might implement the cautious approach to QRA recommended above. These include (i) the systematic incorporation of quantitative analysis of carcinogenic risk that do not involve extrapolation outside the range of the available data (this is currently provided for within the Preamble), (ii) the inclusion of a new section in future *Monographs* that would summarize data on carcinogenic risks (which would focus on results that involve minimal or no unverifiable assumptions, and could include standardized measures of risk for comparison with other carcinogenic hazards such as summary relative risks from meta-analyses), (iii) the

development of a handbook on cancer risk assessment that would provide guidance on practical aspects of QRA and (iv) the use of a separate group of experts to develop a supplement to a specific *Monograph* that would deal with quantitative risk assessment. (Such supplements would only be prepared in cases where the data were sufficient to assess carcinogenic risks in quantitative terms, and where there was a potential benefit of conducting a detailed, quantitative assessment of risk.) This Advisory Group suggests that these options might be explored more fully in a future Workshop on quantitative assessment of risks for cancer.

Regardless of which of these approaches is adopted, this Advisory Group emphasizes that any initiatives taken by the *IARC Monographs* Programme in the area of quantitative assessment of risks for cancer should be firmly based on science. This Advisory Group also notes that the development of a programme in QRA will require specialized expertise and a significant commitment of resources.

Issue 2c. The 2003 Advisory Group recommended that a paragraph be added in the Preamble to outline the limitations of risk assessment statements, which — in contrast to hazard evaluations — pertain to specific populations, regions and exposure conditions.

This Advisory Group notes that characterization of risk, which combines information on dose–response relationships with levels of human exposure, can vary between populations and with exposure conditions, making an overall characterization that would be applicable globally difficult to achieve.

This Advisory Group notes that the limitations and uncertainties in all aspects of carcinogenic risk assessment, including risk estimation and hazard identification, should be documented as fully as possible. This Advisory Group recommends that variation in risk among subgroups of populations (defined in terms of susceptibility, region and exposure conditions) be described.

Issue 2d. The 2003 Advisory Group proposed consideration of appropriate changes to the Preamble to address the relationship of evaluations in *IARC Monographs* with those of other organizations. The 2003 Advisory Group also noted that the organization of a meeting on this topic with other evaluating authorities would be useful.

Note. The May 2005 meeting included scientists from several of these organizations (NTP, US EPA, California EPA, German MAK, and EC European Chemicals Bureau), and points to include in these statements were developed at the meeting.

This Advisory Group considers that no changes to the Preamble are needed to clarify the relationship of IARC evaluations with those of other organizations, since it falls outside its scope. This Advisory Group agrees with the 2003 Advisory Group that convening a meeting on this topic could be useful. A meeting of representatives from the different organizations involved to discuss and compare their various systems would provide insights into and may lead to the improvement of carcinogen evaluation, and perhaps move toward harmonization where warranted. The development of a paper for publication in a scientific journal that compares and describes the various classification systems for carcinogens would

also be of interest to users of the *Monographs* and other available programmes that identify cancer hazards.

3. Selection of topics for the Monographs

Background. Agents are selected for evaluation based on (i) evidence of human exposure and (ii) some evidence or suspicion of carcinogenicity. Agents and exposures can be re-evaluated if significant new data become available. Periodically, IARC convenes Advisory Groups to advise on priorities for future evaluations or re-evaluations. These Advisory Groups consist of scientists from national and international health agencies and research institutions, and include scientists from as many countries as possible. Seeking such advice is designed to ensure that the *IARC Monographs* reflect the current state of scientific knowledge and remain relevant to national health agencies and to the research and public health communities. Between Advisory Group meetings, additional guidance may be received from the IARC Scientific Council and the IARC Governing Council. Suggestions for new topics are welcome at any time.

Issue 3a. As the list of agents reviewed by the *IARC Monographs* continues to expand, there will occasionally be a need to clarify some particular aspect of the carcinogenic hazard of an exposure (e.g. specific to a given route, such as through water, or a particular population, such as children). How should the IARC determine when to choose to evaluate such studies and how should they be presented? Should this be mentioned in the Preamble in this Section?

This Advisory Group had considerable discussions on this issue, and tried to clarify when the IARC should undertake such restricted evaluations. The general conclusion of this Advisory Group is that reviews by the IARC should be as complete as possible, using all available data for a given monograph. However, this Advisory Group recognizes that, on occasion, the IARC may need to clarify one aspect of the carcinogenicity of an agent and concluded that this type of monograph, on a limited basis, would be useful and informative. However, when summarizing the results of such a review in the 'List of agents evaluated by the *IARC Monographs*', this Advisory Group cautions having separate entries for each sub-review. The basis for this caution is the concern that, by listing the carcinogenicity for a specific route or for susceptible subgroups of the population, inference would be drawn that other routes or subgroups may be considered to be free of a cancer hazard, which is generally not the intent. This Advisory Group feels that this type of evaluation could be mentioned in the Preamble in Section 3 as an evaluation that will occur 'on a limited basis'.

4. Data for the Monographs

Background. The monographs include a critical review of each pertinent epidemiological study and long-term carcinogenesis bioassay, plus a summary of selected significant information on human exposure and mechanisms of carcinogenesis. Scientific articles published or accepted for publication are eligible for consideration. Reports and documents from national and international government agencies are considered if they are available publicly. Consensus reports in the published literature are also considered, subject to the same scrutiny as other articles, including consideration of the compo-

sition and balance of the panel that produced the consensus. Research that is not available publicly, including articles in preparation or under review, is not considered.

Issue 4a. Should working groups continue to consider only publicly available scientific literature, plus articles accepted for publication?

Note. From time to time the Programme receives consultant reports and draft manuscripts that support a particular view. Sometimes the submitter wants to send these directly to Working Group members. The Programme has discouraged these efforts and has asked Working Group members to disregard papers that are not in the public domain.

This Advisory Group supports the general principle that publicly available scientific literature is the predominant source of information considered in the *Monographs*. Raw data that have not been published should not be used.

Issue 4b. Should there be an explicit, general statement regarding abstracts and PhD theses?

Notes. The Preamble does not mention abstracts, and working groups have used abstracts on a case-by-case basis.

In most cases, abstracts do not provide enough unique information to contribute to an evaluation. Most abstracts are only summaries of posters or talks that appear in the proceedings of a meeting but are not published in peer-reviewed journals. In contrast, some abstracts contain detailed information, and sometimes an abstract provides the first credible indication of a possible cancer hazard.

The criteria for exceptions described in the Preamble should include detailed abstracts and PhD theses that are exceptionally needed for an evaluation.

Issue 4c. It is difficult to evaluate properly agents for which some pertinent studies have not been published in the scientific literature.

Note. Recent disclosures have revealed cases of pharmaceuticals and pesticides for which pertinent positive studies were not published and not disclosed. An evaluation of carcinogenicity or a summary of other toxic effects may be misleading if important positive studies are not available. Unlike the question of 'publication bias' (which refers to whether non-positive studies are less likely to have been published), there are no statistical methods to analyse whether missing positive studies are likely to be important. The Programme invites discussion on how to conduct credible evaluations of these agents.

With respect to proprietary or confidential data presented in documents published by other institutions, *Monographs* working groups should judge the appropriateness of their use on an ad-hoc basis. The IARC may specify the criteria for inclusion or exclusion of publications in the openly available scientific literature further and find ways in which the use of proprietary or confidential studies may also be considered.

Issue 4d. The 2003 Advisory Group recommended that the need to refer 'post-evaluation' literature references to the IARC should be emphasized in the Preamble more prominently and specifically than is presently the case.

Notes. A question is whether to make a list of post-evaluation literature available on the IARC website. This could be useful information, but there is also the potential for abuse if one party submitted articles that support only one side of an issue. The Programme does not have the resources to do independent literature searches on agents that have been evaluated in the past.

An intermediate position would be to list only newer studies from sources generally recognized as authoritative, e.g. from the NTP.

Another use of submitted post-evaluation literature would be to keep them for IARC's consideration in future decisions about whether to re-evaluate the agent.

This Advisory Group feels that maintaining an up-to-date, publicly available literature review of all publications on every agent evaluated in the *IARC Monographs* Programme would be burdensome and of little immediate value. This Advisory Group supports the procedure of archiving submitted post-evaluation literature to be available for IARC's consideration on future decisions regarding re-evaluations.

5. The Working Group

Background. Two principles govern the selection of working groups: (i) to invite the best-qualified experts and (ii) to avoid real or apparent conflicts of interests. Consideration is also given to demographic diversity. Members are chosen on the basis of knowledge and experience, which can come from research into the specific agents to be evaluated or from general experience in conducting or evaluating epidemiological or experimental studies. The working groups are international in nature; a typical working group comprises approximately 20–25 expert scientists from 8–12 countries. To promote consistent evaluations and efficient meetings, some effort is made to include a few scientists who have had prior experience at *Monographs* meetings.

Issue 5a. The 2003 Advisory Group recommended that the procedure to select and invite *Monographs* meeting participants be described in detail in the Preamble.

Note. The IARC proposes incorporation into the Preamble of some text from Cogliano *et al.* (EHP 2004), which explains that working groups are selected to invite the best-qualified experts and to avoid real or apparent conflicts of interests. It also discusses the roles of Invited Specialists, Observers, Representatives of national and international health agencies, and the IARC secretariat. The Preamble would also mention that participants' names are listed on IARC's website before each meeting and would stress that participants should not be contacted or lobbied.

This Advisory Group recommends inclusion in the Preamble of text from Cogliano *et al.* (EHP 2004), which explains that working groups are selected to invite the best-qualified experts and to avoid real or apparent conflicts of interest. This would include a definition of the roles of Members, Invited Specialists, Observers, Representatives of national and inter-

national health agencies and the IARC Secretariat. A description in the Preamble of the recently adopted procedure of listing participants' names on the IARC website before each meeting (together with the statement that participants should not be contacted or lobbied) is supported. However, as this procedure is relatively recent, the subsequent Preamble meeting (December 2005) may wish to consider any additional experience gained by the IARC in the intervening period. This Advisory Group also feels that the term 'Invited Specialist' is confusing since all Working Group Members are invited and specialists and suggests that IARC consider an alternative name.

Issue 5b. Should Invited Specialists be permitted to write text on mechanisms and other relevant data (Section 4)?

Notes. An Invited Specialist is an expert with critical knowledge and experience who is recused from certain activities because of a real or apparent conflict of interests. These activities include serving as meeting Chair or Subgroup Chair, drafting text that discusses data on cancer or contributes to the evaluations (Sections 2–4 and 5.2–5.5) and participating in discussions on the evaluations. Invited Specialists are present during Subgroup and Plenary discussions to contribute the benefit of their knowledge and experience.

Allowing Invited Specialists to write Section 4 would be a relaxation of this policy. In the case of agents for which most of the mechanistic research has been supported by an industry that has an interest in the outcome of the meeting, many of the experts who had published these results would be designated as Invited Specialists. Under current policy, this leaves fewer experts to write working papers. If an Invited Specialist were needed to write part of Section 4, this could, perhaps, be accepted on an exceptional basis, with an explanation in the List of Participants discussing the circumstances.

On the other hand, the use of mechanistic data to raise or lower an overall evaluation can be a major source of controversy. Working Group members who are not experts on mechanisms, as well as most readers of the Monographs, rely on Section 4 as a comprehensive and balanced review of the subject. If someone linked to the affected industry wrote this review, there could be a loss of public confidence in the impartiality of the *Monographs*.

This Advisory Group supports the practice of 'Invited Specialists'. An Invited Specialist is a person with critical knowledge and experience who is recused from certain activities because of a real or apparent conflict of interest. To allow invited specialists to write text for Sections 2, 3 or 4 would be a relaxation of current policy. This Advisory Group recommends that IARC continue its current policy not to allow invited specialists to write any section other than Section 1.

Issue 5c. The 2003 Advisory Group recommended that the issues of 'bias of opinion' and 'conflict of interests' be discussed in the Preamble.

Note. IARC proposes the incorporation into the Preamble of some text from Cogliano *et al.* (EHP 2004) to discuss the WHO *Declaration of Interests* and its use in determining appropriate limitations on an expert's level of participation. It also discusses the importance of identifying the pivotal issues in advance and

convening a Working Group that includes a balanced representation of all scientific views.

This Advisory Group recommends the incorporation into the Preamble of some of text from Cogliano *et al.* (2004) that deals with conflict of interests and apparent conflict of interests, and refers to the WHO Declaration of Interests procedure and its use in determining appropriate limitations on an expert's level of participation. This should not be too detailed, because consistency with WHO procedures (currently under revision) needs to be maintained.

Issue 5d. Should *Monographs* working groups continue to include scientists who have done research on the topic being evaluated?

Notes. Some people have claimed that the inclusion in a Working Group of authors of papers that are being evaluated is a scientific conflict of interests, and that these authors should not be permitted to judge and vote on the validity of their own hypothesis. In addition, it was claimed that the mere presence of such authors would have a chilling effect on any critical discussion of their findings by other Working Group members.

IARC notes that allowing the experts themselves to write the critical reviews and consensus evaluations is often regarded as one of the strengths of the Programme and distinguishes the *IARC Monographs* from some other programmes on carcinogen identification.

One strength of the *Monographs* process is that reviews are written and evaluated by experts of worldwide standing who have done research on the agent being considered; this practice should continue. The inherent difficulty of a real or perceived bias caused by Working Group members being involved in the evaluation of their own data is recognized. This Advisory Group considers that it would be inappropriate for individual members both to draft initially and then review text discussing their own work, which could detract from the essential peer-review status of *Monographs* evaluations. However, this Advisory Group considers that specification in the Preamble of a particular restriction may not be appropriate and could lead to reduced expert input into the *Monographs* evaluation process. The lack of such a restriction does not preclude action being taken by the IARC to ensure that bias is prevented and scientific peer review is maintained. The Agency may wish to clarify further measures that could be adopted to reduce any perception of bias as discussed above.

Issue 5e. Should there be public nominations of potential *Monographs* Working Group members? If so, how?

Note. A member of the IARC Governing Council suggested this change. The programme is interested in a discussion of how this could be achieved while avoiding a public debate on Working Group membership.

This Advisory Group considered the desirability of calling for public nominations for potential *Monographs* Working Group members. At present, Working Group members are selected by IARC on the basis of their relevant scientific expertise and lack of conflict of interests. The current selection process has resulted in past *Monographs* Working Groups being comprised of leading scientific authorities in areas of critical importance to the successful evaluation of the carcinogenic potential of the agent in question.

This Advisory Group notes that the receipt of public nominations for *Monographs* Working Group members offers may potentially broaden the selection process, either through a targeted call for nominations from knowledgeable organizations worldwide or through an open call for nominations posted on the IARC website (both options could also be implemented simultaneously). This Advisory Group feels that seeking outside nominations could reduce the possibility of perceptions of bias in the selection process. However, it was not clear to this Advisory Group whether a fully open public nomination process, which could involve a not insignificant addition to the workload in screening the nominations received, would substantially enhance the quality of Working Group membership. If a public nomination process were adopted, this Advisory Group recommends that it not be exclusive and that IARC be allowed to make the final decisions on the choice of *Monographs* Working Group members drawn from internally identified experts as well as public nominations.

In the light of the preceding considerations, this Advisory Group does not recommend that the procedure of a call for public nominations be incorporated into the Preamble at this time. However, this Advisory Group suggests that IARC consider the possibility of incorporating public nominations into the selection process for *Monographs* Working Group members on a non-exclusive, trial basis. This Advisory Group is also concerned that a call for public nominations could result in a large number of biased or less qualified persons applying.

6. Working procedures

Background. The *IARC Monographs* are published as a series of volumes. Each volume is developed by a separate Working Group at an 8-day *Monographs* meeting. A volume can contain one or more monographs, which can cover a single agent or a group of related agents. Each monograph generally includes the following sections:

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Other data relevant to an evaluation of carcinogenicity and its mechanisms
5. Summary of data reported and evaluation
6. References

Before each meeting, Working group members critically review the literature and write first drafts of Sections 1–4. IARC formats these first drafts for review at the meeting.

The objectives of the meeting are review and consensus. The first days of the meeting are devoted to Subgroup work. Four Subgroups, each responsible for one section, peer-review the individual members' drafts, develop a joint revised draft and then write the summaries that become Section 5. During the final days of the meeting, the Subgroups come together in plenary session. The entire Working Group peer-reviews and reaches consensus on the critical reviews in Sections 1–4 and discusses and reaches consensus on the summaries and partial evaluations proposed by the Subgroups. The Working Group then develops and reaches consensus on an overall evaluation of each agent.

After the meeting, IARC scientists review all data cited by the Working Group in their final draft to ensure scientific accuracy and clarity. IARC then publishes and distributes the finished volume.

Issue 6a. The Preamble suggests that participants are selected approximately one year in advance and that *Monographs* are published 6 months after a meeting.

Note. For many years, these time estimates have not been realistic. The Programme would like to achieve more timely publication of the *Monographs*, but proposes replacing the specific time estimates with less precise but more accurate phrases such as 'before the meeting' and 'after the meeting'.

This Advisory Group agrees with the current time frame (approximately 1 year in advance) used by the IARC as guidance in selecting participants for a *Monographs* Working Group meeting. This Advisory Group also feels that it is appropriate to provide some aspect of this time frame in the Preamble. However, given the historical publication time frame for the *Monographs*, the Group feels that the current Preamble is too prescriptive in describing when a volume will appear following a *Monographs* Working Group meeting; this Advisory Group therefore suggests that this limit be changed to a more reasonable time frame or be dropped completely. This Advisory Group recommends that IARC make an effort to return to a prompt (approx. 6 months) publication time frame.

Issue 6b. The Preamble states that industry sources may assist in preparing sections on production and use. The IARC has received letters from some parties who claim that the Preamble requires interested industry sources to assist in developing opinions on adverse health effects.

Note. The programme would like to clarify that industry involvement (i) is not required and (ii) is limited only to sections on production and use.

The Preamble clearly states that scientists from industrial associations 'may assist' in the preparation and does not imply this is a requirement. However, there is some room for clarification in this part of the Preamble and IARC is encouraged to do some modest re-writing of this text. This Advisory Group suggests expanding representation to be inclusive of not only industrial sources but also other directly interested parties such as environmental groups and national authorities.

Issue 6c. Peer review

Notes. The *IARC Monographs* can be described as a peer review of the publicly available scientific literature on a topic. All text in sections 1–4 is peer-reviewed at the *Monographs* meeting. Section 5 is the consensus expert opinion of the peer reviewers who have discussed the scientific literature throughout the 8-day *Monographs* meeting.

It should be noted that WHO regulations specify, "The text of an expert committee report may not be modified without the committee's consent."

This Advisory Group acknowledges and affirms that peer review is the primary criterion and standard for scientific integrity. In its most widely used scientific context, peer review typically involves assessment of manuscripts submitted for publication in scientific journals. This normally necessitates that 2–3 scientists review a manuscript, and there is no requirement for agreement between such referees.

IARC Monographs evaluations are the outcome of scientific discussions among 15 or more scientists and each stage of the process may involve consultation and agreement between various members of the Working Group or the Working Group as a whole. Sub-groups of the Working Group produce evaluative documents that are discussed and reviewed at length in plenary by the other members of the Working Group. Subsequently, IARC staff (who have not otherwise drafted the material in question) review the final drafts to ensure the quality of the information in each monograph.

In as much as the content and evaluations reached in the course of *IARC Monographs* Working Group meetings are totally dependent on the outcome of deliberations by many Working Group members, the Monographs attain, and indeed exceed, the standard normally required for peer review. The status of the *Monographs* as a peer review document is hereby asserted by an independent group of experts not convened for the purpose of making a *Monographs* evaluation. This assessment is not that of the IARC staff or of the organization as a whole, but is itself a peer review made by the present Advisory Group, which is a group of international scientists owing no allegiance to IARC except for an implicit commitment to maintain the excellence of the *Monographs* Programme. The convening of such a Group maintains the Agency's tradition of seeking external input for all aspects of the Programme.

Literature search and retrieval processes are sufficiently rigorous that it is highly unlikely that important studies are missed.

Finally, the exceptional nature of the development and deliberative process of the *Monographs* goes far beyond the usual peer review process used by scientific journals. This Advisory Group does not recommend that IARC undertake any further peer review of the draft than already occurs through the *Monographs* process, and does not recommend that the Preamble be modified to discuss peer review.

Evaluations are open to peer-review and other criticism, but it is not practicable to re-convene any *Monographs* Working Group to respond to disputed evaluations. Strictly speaking, peer review of a *Monographs* evaluation would require the deliberation of a comparable group of international experts, as distinct from any individual evaluation. It is arguable, therefore, that 'totally independent' peer review of *Monographs* evaluations is not feasible. This constraint, in the view of this Advisory Group, does not detract from or qualify its conclusion that *Monographs* evaluations are correctly regarded as outcomes of a peer-review process.

7. Exposure data

Background. Each monograph begins with a section that describes the agent's physical or chemical properties, its production and uses, analytical methods for its detection and measurement, its occurrence in the environment and in the workplace and existing national regulations that are applied to it. This information does not contribute to the evaluation of its potential carcinogenicity. Unlike the sections on cancer in humans and cancer in experimental animals, this section does not need to be a comprehensive review of the literature but should give a good representation of all WHO regions.

Issue 7a. Information on exposure is sometimes difficult to find, especially from developing countries.

Note. The programme invites suggestions on how to increase the comprehensiveness of this section.

This Advisory Group notes the existence of several national databases that may prove useful in assessing and placing bounds on the range of environmental exposures. Such databases are generally limited to chemicals, and contain little or no information on exposure to biological or physical agents.

A list of databases maintained by the United States Environmental Protection Agency (US EPA) is available. Data related to agents in air, water, food and soil can be useful in the estimation of individual exposures and in some cases those of populations. Other countries have compiled similar databases that could be consulted. The IARC is encouraged to solicit such information from Participating States and pursue the identification of these resources. This Advisory Group especially emphasizes the importance of obtaining data from developing countries, where high exposures that occur may be overlooked. Such exposure data may also prove useful to epidemiologists in the planning of future studies.

The IARC is also encouraged to collaborate with other UN agencies such as WHO/IPCS, UNEP and ILO.

8. Studies of cancer in humans

Background. Cohort studies, case–control studies and ecological studies of cancer are generally the major contributors to the evaluation of human evidence. Studies of preneoplastic lesions and measurements of biological markers (e.g. DNA or protein adducts) and markers of early stages of carcinogenesis (proto-oncogene mutations) are also reviewed.

Issue 8a. Given the development of the field of molecular epidemiology since the last update of the Preamble, should there be guidance on consideration of these data? If so, what?

Note. This is a new and evolving field for which no standard approaches to evaluation have been developed. Specific guidance may be useful for promoting consistent approaches by different working groups.

Molecular epidemiology uses molecular biomarkers of exposure, genetic susceptibility and intermediate end-points. Most of these data should be mentioned in Section 8 (c) of the Preamble 'Inferences about mechanism of action', which already includes similar statements, and contribute to Section 4, 'Other data relevant to an evaluation of carcinogenicity and its mechanisms' in a monograph.

Uses of molecular epidemiology for hazard identification and evaluation include:

- the use of biomarkers of internal dose (e.g. DNA adducts) that can reinforce exposure assessment and comparison with animal data;
- the use of end-points markers of intermediate (also known as early-effect biomarkers) such as mutations, chromosomal aberrations or genomic instability that

help to clarify the mechanistic pathways and increase comparability between animals and humans;

- genetic susceptibility (through, e.g. Mendelian randomization and the study of gene–environment interactions) that can increase the biological plausibility of associations by showing that its modulation of risk is consistent with the expected causal pathway; and
- other markers relevant to the study of infectious agents involved in carcinogenesis and markers of inflammatory or immunological responses.

This Advisory Group suggests that a special meeting be organized to explore the potential use of newer markers such as gene expression, promoter methylation and proteomics/metabonomics in the evaluation process. It is stressed that the contribution of such tools should be evaluated with the same degree of stringency as that used for the evaluation of the epidemiological and animal data. The meeting could update recent Workshops held at IARC on biomarkers, with a specific focus on carcinogen identification and evaluation.

Molecular epidemiological data that identify populations that are more susceptible than others to the agent(s) to be evaluated may be important for the identification of carcinogenic hazards to humans. It should be noted, however, that data on genetic susceptibility usually originate from multiple comparisons arising from subgroup analyses. This can generate false-positive results and inconsistencies across studies, and such studies therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent to be evaluated, these data can serve as additional evidence for causality.

Issue 8b. Where is the best place to report preneoplastic lesions and markers: Section 2 (Cancer in humans) or Section 4 (Mechanistic and other relevant data)?

Note. The Preamble suggests that these data can appear in Section 2, but in practice they generally appear in Section 4.2 (Toxic effects). The rationale is that data on preneoplastic lesions and markers provide indications of mechanisms but do not generally contribute to the evaluation of evidence in humans. If understanding has evolved to the point that preneoplastic lesions and markers can affect the evaluation of evidence in humans, perhaps these data should appear in Section 2. If not, this statement in the Preamble should be changed to be consistent with current practice.

Studies of preneoplastic lesions (such as colorectal adenomas or oral lesions in humans) that have clearly been associated with the development of malignancies may be — and have been — considered in Section 2 (Cancer in humans) and may serve — and have served — in the evaluation of human data. With regard to molecular epidemiological data, markers of internal dose can be included in Section 1 when they are measured in the context of exposure assessment, in Section 2 ('Studies of Cancer in Humans') when they are measured in the context of an epidemiological study of cancer or in Section 4 ('Mechanistic and other relevant data') when the main focus is on their role in mechanisms of carcinogenesis. Similarly, markers of intermediate end-points and studies on genetic susceptibility could be included both in Section 2 when they are studied in the context of epidemiological studies of cancer and in Section 4 when the main focus is on mechanisms.

Issue 8c. Meta-analysis of population-based studies

Repeated population-based studies of the same agent may lead to results that are ambiguous. Combined analyses of data from multiple studies have been proposed as a means of resolving this ambiguity.

Two types of combined analysis can be conducted: the first involves combining summary statistics such as odds ratios from individual studies and the second involves a pooled analysis of the raw data from the individual studies. The former approach will be referred to as a meta-analysis and the latter will be referred to as a pooled analysis.

The main advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore interactions and modifying effects that may explain heterogeneity among studies in more detail. The main disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, data collection procedures, measurement methods and effects of unmeasured co-variates that may differ among studies. Despite these limitations, combined analyses, when conducted wisely, can provide a firmer basis for drawing conclusions about potentially carcinogenic agents than individual studies.

It is recommended that the Preamble encourage the use of combined analyses within the Monographs. However, it is important that the same criteria for data quality as would be applied to individual studies be applied to combined analyses, and that such analyses take heterogeneity between studies into account.

Meta-analyses may occasionally be conducted by Working Group members during the course of preparing a monograph, and are identified as original calculations by placing the results within square brackets [...]. These may be de-novo analyses or updates of previously conducted analyses that incorporate the results from new studies. Whenever possible, however, it is preferable that such analyses be conducted prior to the Working Group meeting, either by members of the Working Group or under contract with an expert in this area. Publication of the results of such meta-analyses prior to or concurrently with the *Monographs* Working Group meeting is encouraged for purposes of peer review.

9. Studies of cancer in experimental animals

Background. Two-year carcinogenesis studies in rats and mice are generally the major contributors to the evaluation of evidence in animals. Studies of administration with co-carcinogens, studies of pre-neoplastic lesions and studies of metabolites and other chemical derivatives are also reviewed.

Depending on the outcome of issue 12d, it may be appropriate to expand this section to include additional study designs.

Issue 9a. Meta-analysis of animal experiments

Meta-analyses of animal experiments are conducted less frequently than those of population-based studies, largely because of differences in animal species and strains. Because of the use of high doses, experiments on animal carcinogenesis tend to exhibit less ambiguity than population-based studies, and thus the need for meta-analyses to resolve ambiguities is reduced. These observations do not preclude the use of meta-analytical methods to interpret

animal data; however, if such analyses are conducted, they should meet normal standards for data quality.

10. Other data relevant to an evaluation of carcinogenicity and its mechanisms

Background. The evaluation also considers mechanistic and other relevant data. These include toxicokinetics (absorption, distribution, metabolism and excretion), acute and chronic toxic effects other than cancer, reproductive and developmental effects, genetic and related effects, and information on potential mechanisms for the observed carcinogenic responses.

Issue 10a. Given the increased understanding of mechanisms of carcinogenesis since the last Preamble update, should there be additional guidance? If so, what?

Note. This is an area requiring considerable judgement, and specific guidance is useful for promoting consistent approaches by different working groups. In contrast, the field is still evolving, and too much detail will soon become outdated. Historically, the Preamble has discussed general principles that are expected to be applicable for many years.

This Advisory Group finds that no definitive guidance can be specified on interpretation of data, because of the wide spectrum of possible mechanisms and the degree to which they may or may not be understood, the relatively rapid developments in the field and the expanding nature of the mechanistic data available. The scientific judgements made by a Working Group during a *Monographs* meeting should reflect the state-of-the-art at the time. Section 4 of the *Monographs* should discuss critically the evidence on mechanisms of carcinogenicity as it pertains to the overall evaluation of carcinogenesis, in the perspective of and in parallel with the discussion of animal and human data in Sections 2 and 3. Section 4 provides the basis for the evaluation of other relevant data in Section 5 in terms of whether there is strong, moderate or weak evidence that any carcinogenic effect observed is due to a particular mechanism; evaluations may also include judgements of whether the mechanisms are similar or different in animals and humans, and within the human population. It is therefore essential that Section 4 provide a critical review of the data on which to base such evaluations. In this regard, this Advisory Group recommends that the guidance given in section 10 of the Preamble for developing the section on 'Other relevant data' in the Monographs (Section 4) be more extended.

This Advisory Group recommends that the procedures for *Monographs* evaluations be modified to provide for a statement regarding evidence of a carcinogenic mechanism (that is, evidence presented in Section 4). The scope of such evidence is unlimited, and the type of studies that may be deemed relevant is continually expanding. Such evidence would at least include toxicokinetics, cellular changes such as DNA binding or induction of DNA damage , alterations in gene expression, such as changes in the expression of tumour suppressor genes and oncogenes, and enhancing effect of the agent on cell proliferation. Where relevant, the literature cited in Section 4 and used to evaluate mechanisms may include studies initially cited in earlier sections, such as molecular epidemiological findings.

For the evaluation of data on mechanisms of carcinogenesis, no elements are available to provide definitions analogous to the categories of sufficient and limited used in Sections 2

and 3. Therefore, it is suggested that these terms should not be used in the process under discussion in Section 4. However, agreement may be reached on the strength of evidence that establishes the mechanism(s) by which a particular agent causes or is likely to cause cancer. It is suggested that the evaluation statement refer to strong, intermediate or weak evidence that a carcinogenic process(es) is induced by the agent under evaluation.

A wide spectrum of possible mechanisms of carcinogenesis has been identified but is still subject to expansion. Some well-recognized pathways to malignant transformation have given rise to widely used terminology such as 'genotoxic' and 'epigenetic'. While the use of such terms may allow unification of many different types of investigation, they should be employed with caution. For example, reference to genotoxicity could include exposures, agents and their metabolites that do not modify DNA *per se* but may result in genomic changes through the production of secondary DNA-reactive intermediates (e.g. reactive oxygen species). Some guidance on how to specify mechanisms clearly would be useful in the Preamble.

The evaluation statement may be made in terms of strength of evidence either for or against a specific mechanism. It may also refer to evidence that the mechanism(s) of carcinogenesis is similar or different in animals and humans, and even within the human population.

This Advisory Group notes that availability of an evaluation of mechanistic data may potentially provide different means to reach the overall evaluation. The overall evaluation may be reached by a comprehensive consideration of all three evaluations (i.e. those related to human carcinogenicity, animal carcinogenicity and mechanism) rather than the present process in which a default evaluation is upgraded or downgraded on the basis of conclusions reached on the mechanism.

Issue 10b. In order to put more emphasis on relevant mechanistic considerations (Section 4.5), should the sections on toxicokinetics (Section 4.1), toxic effects other than cancer (Section 4.2), reproductive and developmental effects (Section 4.3) and genetic effects (Section 4.4) be shortened to resemble review articles?

Note. Many readers use the *Monographs* as a general reference on toxic effects, and the programme has historically had an interest in covering toxic effects other than cancer, especially reproductive and developmental effects. Nevertheless, Sections 4.1–4.4 have been growing and sometimes constitute more than half of the references and pages of a monograph, although the evaluation is determined by the studies of cancer in humans (Section 2) or experimental animals (Section 3). This leads to two problems. (i) At the meeting, the lengthy review of Sections 4.1–4.4 leaves little time for discussion and joint development of Section 4.5. (ii) In the published monograph, the lengthy presentation of Sections 4.1–4.4 may create a misleading impression of the relative importance of the different lines of evidence and hinder a reader from identifying the key studies among the many reported. What are the benefits of an encyclopaedic study-by-study review of other relevant data? Should some effort be made to reduce the number of studies reviewed or the level of detail reported for each study?

Data on reproductive, developmental and other toxic effects are summarized in a monograph in Section 4 'Other data relevant to an evaluation of carcinogenicity and its mechanisms'. These data are included even when the observations have no apparent relevance to

the cancers observed in epidemiological studies or cancer bioassays. Although the *IARC Monographs* may be a convenient source of such data for some users, the development of these reviews for the *Monographs* can be distracting and may consume more time and resources than are justified by its relevance to the evaluation. The literature for the section must be found and compiled, the section must be written and, at the meeting, the IARC Working Group must review, discuss and agree to its content. The section also has to undergo fact and data quality checking by IARC staff. A related point is that data for certain types of genetic and related effects were found in the consensus report of an IARC symposium to be unsuitable for classifying or predicting carcinogenic hazard, even though they are commonly summarized in the *Monographs* (McGregor *et al.*, 1999). This Advisory Group recommends that IARC need the advice given by this symposium, together with more recent knowledge, and consider limiting the scope of the review to those tests that are considered to be potentially relevant to cancer hazard identification.

This Advisory Group recommends restructuring Section 4 to focus on those data that are critical to the evaluation of carcinogenicity. As an example for monographs on chemical substances (to be discussed by IARC), this Advisory Group considered the following outline for the section on 'Other relevant data', and emphasizes that this is provided as an illustration of an approach, and not an endorsement of any specific outline.

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms
4.1 Pharmacokinetic data
4.2 Mechanistic data
4.3 Data on susceptible individuals, populations and life stages
4.4 Relevant data on toxicity
4.5 Additional relevant data

As in current *Monographs*, Section 4.1 would describe the available basic information on absorption, distribution, metabolism and excretion in animals and humans, and could include more specific information on the saturation of such processes, cross-placental transfer and other issues pertinent to interpretation of the studies and the evaluation of carcinogenicity. However, this section would no longer include a detailed study-by-study description. Instead, it would emphasize features that are critical to the interpretation of human and animal carcinogenicity studies and to the overall evaluation of carcinogenicity for the agent in question, and would take the form of a critical review of the data.

Similarly, Section 4.2 would provide a critical review of the mechanistic data relevant to the evaluation of carcinogenicity. In addition to genetic and other data, Section 4.2 may also include, among others, data on gene expression, alterations in tumour-suppressor genes, oncogenes and growth-controlling pathways, modulation of DNA repair, epigenetic effects, alterations in post-translational modification of proteins, apoptosis, cell immortalization, angiogenesis, metastasis and stroma interaction (see Hanahan & Weinberg, 2000). Certain types of genetic and related effects that are generally felt to be unsuitable for classifying or predicting carcinogenic hazard (see e.g. McGregor *et al.*, 1999) would not be included.

Section 4.3 would be reserved for a critical review of data that have a bearing on the identification of susceptible populations — both animal and human — for example, with respect to genetic effects, age, disease status or other factors. When data are available, these may elucidate further the interpretation of results reported in Sections 2 and 3.

Section 4.4 would provide a critical review of toxicological data that are relevant to the evaluation of carcinogenicity such as information on systemic exposure, possible target organs, immunotoxicity (which may also be relevant to Section 4.2) and endocrinal effects.

To the extent that effects on reproduction, teratogenicity and other developmental effects may be informative for a particular evaluation, they may be noted.

Section 4.5 would review any other additional relevant data that are not included under the earlier sections.

Issue 10c. Should there be a new sub-section (Section 4.6?) on biologically susceptible populations and life-stages?

Note. National health agencies have become interested in identifying susceptible populations and life stages. Mechanistic data are increasingly available to suggest which populations and life stages may be particularly susceptible to the carcinogenic activity of an agent.

The recent monograph on human papillomaviruses (Volume 90) included the following evaluation that refers to a susceptible population: "There is *limited evidence* in humans for the carcinogenicity of HPV genus-beta types in skin (squamous-cell carcinoma). In the rare case of epidermodysplasia verruciformis patients, there is compelling evidence for the carcinogenicity of HPV genus-beta types 5 and 8 in skin (squamous-cell carcinoma)."

As outlined above, Section 4.3 would address this issue. This Advisory Group notes that the field is undergoing extensive research and the data presented in Section 4 should emphasize cases where there is evidence of defined populations or individuals at increased risk. See also Issue 8a.

11. Summary of data reported

Background. At the meeting, Sections 5.1–5.4 are written to summarize the information reviewed in Sections 1–4.

Issue 11a. Should the summaries include a limited number of key citations?

Note. The Preamble does not mention this practice, but summary sections have traditionally not included citations. For example, a typical sentence might read, "Several case–control studies and two cohort studies reported increases in risk for oral cancer." The intention is to make the summaries easy to read. The current practice could be improved by including enough additional information to allow a knowledgeable reader to identify the study specifically without giving the reference (for example, "a cohort study of electronics workers in New York"). In contrast, a citation is unambiguous to the knowledgeable and non-knowledgeable reader alike.

One of the reasons for including key citations in the Summaries is to provide more transparency regarding the basis on which the Working Group reached its conclusions. However, this Advisory Group notes that Section 5, which summarizes the relevant human, animal and other pertinent data and provides the IARC overall and specific summary evaluations, is easily readable. The language is clear and in a form that is easily perused. Section 5 can therefore be used to communicate the findings of an IARC monograph to the public, and provides some general background on the basis for the IARC findings. Addition

of references will make the summary less readable for the general public. Nevertheless, when data sets are large and complicated, it can be difficult to determine from the summaries which studies were pivotal to the conclusions of the Working Group, and which received less weight. Further, nowhere does a Monograph give the full logic of the Working Group's considerations in weighing data and deciding on the different categories of evidence. This Advisory Group recognizes the value in providing greater explanation and transparency on the Working Group's deliberations in the monograph, and recommends that this be done. This should be done without including citations in the final summary.

This Advisory Group discussed different ways of describing and presenting the Working Group's evaluation and weighing of the evidence. One approach would be to include new subsections at the end of Sections 2, 3 and 4, which would provide summaries and integrative evaluations of the data presented. In this subsection, the data would be summarized with references and an explanation given of how the Working Group reached its decision. An alternative possibility would be to provide a detailed overall summary of the evidence, with references, together with the weighing of the evidence, in a section preceding the current Section 5.5. Such a section could be part of the existing Section 5, or included in a section possibly entitled 'Considerations of the Working Group'. This Advisory Group does not endorse either of these but provides them as examples for IARC's consideration. This point is discussed further under issue 12d.

12. Evaluation

Background. The Working Group reaches a consensus evaluation through a stepwise process that reveals the weight given to each line of evidence. There are separate evaluations of the evidence for cancer in humans and cancer in experimental animals, each choosing one of the descriptors *sufficient evidence*, *limited evidence*, *inadequate evidence* or *evidence suggesting a lack of carcinogenicity*. The evaluation of human evidence is based on whether a causal interpretation is credible and whether chance, bias and confounding can be ruled out with reasonable confidence. The evaluation of evidence in experimental animals is based on whether positive findings were observed in multiple test systems or indicate an unusual result. The partial evaluations are combined into a default evaluation that the agent is *carcinogenic to humans* (Group 1), *probably carcinogenic to humans* (Group 2A), *possibly carcinogenic to humans* (Group 2B), *not classifiable as to its carcinogenicity to humans* (Group 3) or *probably not carcinogenic to humans* (Group 4). The mechanistic and other relevant data are then considered to determine whether the default evaluation should be raised or lowered.

Issue 12a. Clarify whether National Toxicology Program (NTP) studies in male and female rats and mice should be regarded as independent studies capable of providing *sufficient evidence.*

Note. Some Working Group members recently refused to recognize these as 'independent studies' because they were carried out at the same time in the same laboratory using similar protocols.

This Advisory Group recommends that the Preamble be updated so that the finding of carcinogenicity in both sexes of the same species tested in a good laboratory practive (GLP) study that satisfies internationally accepted guidelines or a study of comparable validity could

be treated as providing sufficient evidence. The emphasis should be on whether the body of animal data as a whole supports a finding of causality in animals. Currently, a finding of sufficient evidence of carcinogenicity in animals usually requires unequivocal findings of carcinogenicity in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. This statement is unclear as to whether studies of both genders conducted concurrently in the same laboratory should be treated as independent.

The criteria for sufficient evidence for carcinogenicity in experimental animals were adopted before the current, very extensive GLP studies were devised. GLP studies that adhere to internationally accepted guidelines are well designed and well conducted, and the findings are carefully reviewed. National Toxicology Program (NTP) studies meet these criteria. The NTP Technical Reports and findings are subjected to expert peer review in a public forum and are exposed to formal public comment. Considerable confidence should therefore be placed in findings of clear evidence from NTP studies, as much, for example, as in a single bioassay with a finding of unusual tumours. This Advisory Group therefore recommends that IARC update its criterion on reproducibility for sufficient evidence of cancer in experimental animals and state clearly that GLP studies in both sexes of a single species may be considered as independent.

In addition, given the increased quality of bioassays today, this Advisory Group recommends that IARC expand cases in which a single, well-conducted study provides the basis for an evaluation of sufficient evidence to include strong findings of tumours at multiple sites. Currently, a single study in one species might be considered to provide sufficient evidence when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset. The category 'multiple sites' could be added to this list. The use of unusual findings is discussed in the Preamble as an exceptional case. However, the language 'to an unusual degree' is sufficiently restrictive to limit the use of findings in single studies and denoting it as an exception does not appear to be necessary.

Issue 12b. Should there be additional guidance regarding unusual tumours in experimental animals or, more generally, on the use of historical control information to evaluate unusual tumours?

Note. A recent evaluation stalled on the questions of what the Preamble means by 'unusual' and whether a particular tumour type should be considered as unusual.

The proper use of historical control data in interpreting the results of animal carcinogenesis bioassays has been a subject of some controversy. When historical control data are highly variable, it has been argued that treatment-related increases in tumour incidence that fall within the historical control range are within the limits of experimental variability, and thus do not necessarily constitute evidence of increased risk for cancer. However, the large variation seen among historical studies may be attributed to factors that affect between-study variation but not within-study variation, which represents the appropriate error term for interpreting a current experiment.

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a current experiment. These methods assign the appropriate weight to historical and concurrent controls, on the basis of the extent of between-study and within-study variation. When historical control data demonstrate a high degree of variability, these methods assign little weight to the historical data in the assessment of dose–response

within a current experiment. When the historical data exhibit little variability and demonstrate tumour-response rates similar to those in the concurrent control, these methods assign much greater weight to the historical data by effectively increasing the size of the concurrent control group.

Because of the potential for misinterpretation of information on historical controls, it is recommended that the Preamble provide guidance on the proper use of historical control data in interpreting the results of laboratory experiments. These methods can be particularly useful in interpreting rare outcomes.

Issue 12c. The definition of *evidence suggesting lack of carcinogenicity* states that this conclusion is inevitably limited to the "species, tumour sites and levels of exposure studied." Should "age at exposure" be added to this list?

Note. Several studies and analyses have shown that age at exposure is a factor in carcinogenesis, especially during perinatal development.

This Advisory Group agrees that 'evidence suggesting lack of carcinogenicity' should include restrictions regarding the limits set on the interpretation of this finding. While 'age at exposure' could be added, so could a number of other items such as susceptible groups studied (in humans and genetically modified mice) or route (in both humans and animals). The IARC is encouraged to add 'age at exposure' as an element to consider in evaluating both human and animal data and to choose careful rewording to note that other limitations apply to the data set as well.

Issue 12d. In the time since the Preamble was last updated, an *IARC Scientific Publication* has recommended that mechanistic information be considered in evaluating the evidence of carcinogenicity in experimental animals.

Notes. The consensus report of *IARC Scientific Publication* No. 146 (McGregor *et al.*, 1999) concluded [page 5]:

"Many of the assays described above contribute to the assessment of carcinogenicity in experimental animals. In the absence of data from conventional long-term bioassays of carcinogenesis or from assays with neoplasia as the end-point, consistently positive results in several models addressing several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals."

The Programme invites discussion on updating the definitions of *sufficient evidence* and *limited evidence* in experimental animals to characterize better an agent that displays the hallmarks of a carcinogen in mechanistic studies, but for which lifetime bioassays have not been conducted (and may never be conducted). This could allow pertinent mechanistic information (reviewed in Section 4) to contribute to the evaluation of evidence in experimental animals when long-term bioassays are not available (reviewed in Section 3).

The consensus report of the *IARC Scientific Publication* on the use of data from short- and medium-term bioassays and genetic effects studies in carcinogenicity evaluation (McGregor *et al.*, 1999) noted the following:

> "The numbers of adequately designed, executed and described rodent carcinogenicity tests... have been falling in recent years, and experiments performed and published by academic investigators are now unlikely to be so-called standard two-year bioassays. Thus, the traditional source of experimental evidence for carcinogenicity on which the *Monographs* Programme has historically relied is beginning to disappear, while advances in understanding chemical carcinogenesis have led to the use of short- and medium-term assays with end-points of neoplasia or lesions that are precursors to neoplasia."

This report reviewed various animal models that use neoplasia or preneoplasia as the end-point (transgenic and knock-out mice, non-mammalian systems) and assays for cell proliferation and cell death. Some types of study were found to provide greater evidence of carcinogenicity than others. The symposium concluded that, "in the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models addressing several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals." The group also concluded that for established models of initiation–promotion, the appearance of tumours after exposure to a chemical that was used as an initiator provided evidence of carcinogenicity in rodents. Further, certain other established models in which preneoplastic lesions were produced were considered to be highly predictive of rodent carcinogenicity, and the additional observation of promoting activity was deemed to make the evidence compelling.

The IARC symposium mentioned above was convened in 1997 and further scientific developments that have occurred since that time have increased the body of test systems that provide evidence of possible carcinogenicity in humans. However, data from new bioassays of carcinogenesis in mammalian and non-mammalian species cannot be accommodated within the current IARC classification scheme. This Advisory Group recommends that IARC consider modification of this scheme to accommodate such data.

New whole-animal test systems could be described in Section 3 (Studies of cancer in experimental animals) and given a preliminary evaluation by the subgroup that discusses animal data. Further general guidance on the inclusion of such data and subsequently on how the more varied body of data might lead to an evaluation of sufficient evidence of carcinogenicity in experimental animals would be needed in the Preamble.

In addition to the evidence from whole-animal studies, various *IARC Scientific Publications* and other authoritative reviews support the notion that possible carcinogenicity can be assessed on the basis of other relevant data. For example, the US NTP Report on Carcinogens allows the classification of an agent as 'reasonably anticipated to be a human carcinogen' on the basis of mechanistic and structure–activity data alone. Similarly, an agent for which there is 'less than sufficient evidence' from animal studies (including inadequate evidence) and strong evidence from other relevant data could potentially be classified by IARC in Group 2B if the Preamble were modified. This Advisory Group recommends that IARC consider changing the Preamble to reflect this possibility, also taking into account issues discussed in 10a.

Issue 12e. The 2003 Advisory Group recommended that information on the target organ for cancer be included when possible in future evaluation statements. They recommended that this issue be addressed in the Preamble, specifically with reference to the evaluation of epidemiological data and the use of a specific format for the statement of such information.

Note. The format endorsed by the 2003 Advisory Group would provide a general sentence on the epidemiological evaluation, followed by a separate sentence to specify the target organ(s) or tissue(s), as in the statement for solar radiation (Volume 55):

"There is *sufficient evidence* in humans for the carcinogenicity of solar radiation. Solar radiation causes cutaneous malignant melanoma and nonmelanocytic skin cancer."

This Advisory Group endorses the recommendation made by the 2003 Advisory Group.

Issue 12f. The 2003 Advisory Group proposed that the specific criteria for re-evaluation of agents to a category of higher or lower concern — which are outlined in various *IARC Scientific Publications* — be included in the Preamble.

This Advisory Group disagrees with the 2003 Advisory Group on this issue. It is felt that, in most cases, a re-evaluation of an agent by IARC would be conducted in the context of a new monograph on that agent and the criteria set forth in the Preamble would apply. Adding specific criteria from *IARC Scientific Publications* would unduly burden the Preamble with a number of issues that would possibly be revised by future IARC workshops and scientific publications and would warrant more frequent changes to the Preamble. This Advisory Group considered that a general statement suggesting that, where appropriate, *Monographs* working groups that review agents for which data are available that may include topics that are also covered in an *IARC Scientific Publication* will be provided appropriate guidance from that publication, would be sufficient.

Issue 12g. Do the evaluations (Section 5.5) provide enough discussion to explain how the Working Group reached its conclusions?

Notes. A typical evaluation section is a series of statements in the form:

There is *limited evidence* in humans for the carcinogenicity of [agent].

There is *limited evidence* in experimental animals for the carcinogenicity of [agent].

[Agent] is *possibly carcinogenic to humans (Group 2B).*

The Preamble does not specify how much discussion to provide, but standard practice has been rather uniform across *Monographs*. The choice between *sufficient evidence*, *limited evidence*, *inadequate evidence* and *evidence suggesting lack of carcinogenicity* is almost never explicitly discussed. The choice between Groups 1, 2A, 2B, 3 and 4 is generally not discussed if the final evaluation is the default evaluation. If the final evaluation is either raised or lowered after consi-

deration of mechanistic and other relevant data, then an explanation is added. The explanation is generally between two and 15 lines long.

When an agent is re-evaluated, there is generally no comparison of the previous and new evaluations. For example, in Volume 88, formaldehyde, was judged to have *sufficient evidence* in humans for the first time. Without an explicit comparison of the old and new evaluations, there has been some misunderstanding and mischaracterization of the basis for the new evaluation. In another example, in Volume 60, the classification of styrene was raised from Group 3 to Group 2B because styrene is metabolized to styrene-7,8-oxide, which was found in the blood of exposed workers together with DNA adducts, haemoglobin adducts, DNA damage and chromosomal damage, but a re-evaluation in Volume 82 does not mention why these other relevant data did not affect the later classification into Group 2B.

This Advisory Group is of the opinion that the *Monographs* would be improved if information describing the manner in which evaluations were derived with respect to carcinogenicity in humans, carcinogenicity in animals and any evidence of a mechanism were added. Information provided in this context should not necessarily be limited to a specific line of argument favouring the overall evaluation reached, but should, where relevant, indicate differences of scientific view that became evident in the evaluation process. To that extent, the relevant text would have to be drafted and approved by the Working Group after the overall evaluation was reached.

It is proposed that a summation of the Working Group deliberations should not involve detailed argument, but a broad statement of the principal line(s) of argument that emerged. No specific language or terminology is proposed. The section should be brief but should include significant statements and a reasonable indication of the key arguments.

The text proposed for inclusion could follow the evaluation statements in Section 5.5 and might be part of that Section, or might merit a new subheading immediately preceding the evaluations.

The heading 'Overall evaluation' should be immediately above, and should include the overall evaluation statement only.

Issue 12h. When there are strongly held differences of opinion on the overall evaluation, should the evaluation section present only the majority position?

Note. The title page of each volume states, "This publication represents the views and expert opinions of an IARC Working Group..." and the Preamble does not mention this practice. The majority opinion is generally the only one presented, regardless of whether it represents a unanimous consensus or a sharp division decided by one vote. This practice provides for clear-cut classifications with no distinction between, e.g. strong 2As and weaker 2As. In contrast, the state-of-the-science sometimes includes more than one opinion. Some Working Group members have objected to the inclusion of 'minority reports', while other Working Group members have complained when alternative scientifically reasoned views are not mentioned.

This Advisory Group feels that the current practice of presenting only the majority opinion in the overall evaluation is the best approach in virtually all cases and that the

Preamble should not be changed substantively. It is anticipated that, when minority views exist, they will be discussed in the integrative section outlined under issues 11a and 12g. This Advisory Group also feels that it is important that IARC provide some guidance on how to describe the extent of disagreement, if any.

Issue 12i. Is additional characterization needed to clarify what is meant when an agent is classified in Group 3?

Notes. Group 3 is a broad classification, covering agents with positive results that are not adequate for Group 2B, agents with negative results that are not adequate for Group 4, agents that have not been studied adequately for any hint of a conclusion and agents that have been studied adequately to form a conclusion that the mechanisms of carcinogenicity in experimental animals do not operate in humans. Does the Group 3 classification need further discussion in the Preamble? In the individual monographs?

Nevertheless, some clarification is needed to ensure that a Group 3 classification is not mistaken for a determination of non-carcinogenicity or overall safety. For example, several internet pages have appeared with titles such as "IARC scientists confirm safety of mineral wool insulation." A picture of a bare-skinned baby lying on a roll of pink insulation accompanies one such page, suggesting that IARC found no concern even for skin irritation. The Programme proposes the addition of a paragraph to explain that an evaluation of *not classifiable* is not a determination of safety for either cancer or effects other than cancer, and that further testing for carcinogenicity may be needed, especially when exposure is widespread.

This Advisory Group does not feel that additional clarification is needed in the Preamble to explain the broad range of reasons why agents appear in Group 3. However, the Group feels that some clarification could be provided to indicate that categorization into Group 3 is not equivalent to overall safety and the IARC is encouraged to make these changes in both the Preamble and the individual volumes (e.g. in the Note to the Reader).

Other issues

Issue 13a. Should the title be changed to "*IARC Monographs on the Evaluation of Carcinogenic Hazards to Humans*"?

Notes. It is a major matter to change the title of a serial publication. The current title is well known, and frequent title changes can be disruptive to library indexing systems. Nevertheless, over the years since the *IARC Monographs* began, the term 'hazard' has evolved to mean a qualitative assessment of whether an agent can cause cancer at some dose, while the term 'risk' has come to mean a more quantitative assessment that considers hazard, dose–response and exposure.

The title has been changed twice in the past. Volumes 1–16 were entitled '*IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man*'; Volumes 17–42 were entitled '*IARC Monographs on the Evaluation of the Carci-*

> *nogenic Risk of Chemicals to Humans*'; and Volumes 43–90 were entitled '*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*'.
>
> The *IARC Monographs* have evaluated carcinogenic hazards, not carcinogenic risks, so the current title can be misleading. Conversely, if there is a strong possibility of including some elements of quantitative risk assessment in the near future [taking into account the outcome of the discussion of Section 2 of the Preamble on objective and scope], then the current title would be descriptive of these expanded monographs.

The *Monographs* series is widely referred to and known as a series on hazard evaluation although the title, '*IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*', indicates risk. In the vernacular of public health professionals, 'carcinogenic risk' is a quantitative term, and means the chance or probability that an individual will develop cancer under defined conditions. In general usage, 'risk' can be a qualitative term that refers to the possibility of harm, both in English and when translated into different languages.

This Advisory Group does not feel there is sufficient justification to change the title of the *Monographs* at this time. While the use of 'hazard' in the title would be more precise technically, it would also be somewhat disruptive. For example, it would require that libraries change their indexing of the series. There are a few instances in which a quantitative dose–response assessment was published in a monograph, and there is the possibility that IARC may include more such characterizations in the future. This is discussed under Issue 2b above. The *Monographs* also contain a section on exposure, another component of the risk-assessment process.

Issue 13b. Terminology

> **Notes.** Some text in the Preamble still refers to 'chemical compounds', which reflects the programme's origins in evaluating chemicals. The Programme proposes substituting the word 'agent' where appropriate.
>
> Over the years since IARC first used the term, 'strength of evidence' has taken on a negative connotation that is often used pejoratively to depict an evaluation that considers only positive studies and not the non-positive or negative studies. This is not what IARC intended, and it is not what IARC does. The Programme proposes to change 'strength of evidence' to 'weight of evidence' as a generally recognized term that more clearly reflects IARC's evaluation process.
>
> The Programme would also be interested in advice about whether the phrases 'evidence of carcinogenicity' and 'evidence for carcinogenicity' are perceived as equivalent, or whether one phrase is more likely to be interpreted as meaning the evidence from positive studies only.

This Advisory Group supports the use of the term 'agent' in place of 'chemical compound', since there are numerous examples of carcinogens (such as viruses and radiation) that are not chemicals.

This Advisory Group discussed the terms 'strength of evidence' and 'weight of evidence' at some length, but was unable to establish a preference for either of the two terms. This Advisory Group recommends that IARC review the scientific and possibly common use

of these two terms, and other similar terms, to determine which is best suited to the *Monographs*.

This Advisory Group does not see any substantive difference in meaning between the phrases 'evidence of carcinogenicity' and 'evidence for carcinogenicity'.

Issue 13c. Research needs

> **Note.** The Preamble [Section 2] "The *Monographs* may also indicate where additional research efforts are needed." In practice, this generally does not happen. The Programme intends to ask future working groups to identify research needs and would be interested in some discussion about where to present this information and in what form.

This Advisory Group feels that the wording used in the current Preamble is adequate. In discussing where to place research recommendations, this Advisory Group considered that these were implicit in the overall evaluations and did not feel that there was a need for a separate section on this issue. Considering the magnitude of the effort needed to complete a *Monographs* evaluation, this Advisory Group suggests that IARC continue to treat inclusion of research recommendations as an option.

References

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Discussion of Changes in the Draft Preamble

Prepared by the staff of the *IARC Monographs* programme
31 August 2005

This paper describes the major changes that appear in the draft Preamble that will be reviewed by an Advisory Group during 5-9 December 2005. Most changes have been made in response to the recommendations of the Advisory Group to recommend updates to the Preamble (May 2005) or in response to comments from recent meeting chairs and subgroup chairs (March-April 2005). These earlier reports are available on the *Monographs* website (http://monographs.iarc.fr).

1. Background

An expanded section describes the programme's origin, historical development, and current role in assisting national and international health agencies to reduce the global burden of cancer. [Advisory Group recommendations 1 and 2a]

2. Objective and scope

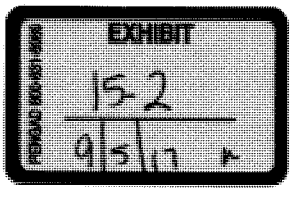
New text explains the difference between hazard and risk in the context of the risk assessment paradigm. The *Monographs* are described as an exercise in hazard identification. For several recent *Monographs*, however, the important public health questions have been both qualitative and quantitative. Accordingly, the draft Preamble allows a *Monograph* to address questions of dose-response assessment, in some cases through a subsequent publication prepared by a separate working group with expertise in quantitative dose-response analysis. [Advisory Group recommendation 2b, comments by several recent chairs]

Previously, a carcinogen was defined as an exposure that can increase the incidence of malignant neoplasms. This definition has been expanded to include exposures that can reduce the latency or increase the severity or multiplicity of malignant neoplasms. This is consistent with the current practice of other health agencies. It also makes explicit what is meant in epidemiology by an increase in the age-specific incidence of cancer, a concept that covers a reduction in latency or an increase in the proportion of tumours that are malignant.

This section also explains that IARC can convene international scientific conferences to develop consensus principles on how mechanistic data can be used in an evaluation of human carcinogenicity. The results of these conferences will be reported in IARC Scientific Publications. *Monograph* Working Groups may cite these publications as long as they still reflect the current state of scientific knowledge. [Advisory Group recommendation 12f]

3. Selection of topics for the *Monographs*

New text explains the circumstances under which a *Monograph* would review only the new data published since a prior evaluation. This can be useful for updating a database or identifying new tumour sites associated with a carcinogenic agent. This may become an



important activity in the future, as the programme strives to keep more than 900 past evaluations up to date. [Advisory Group recommendation 3a]

In 1996 IARC stopped producing the directory of agents being tested for carcinogenicity and the directory of on-going research in cancer epidemiology. Accordingly, references to these series have been dropped. [Chair comments]

4. Data for the *Monographs*

This section now explains that the *Monographs* intend to include all pertinent epidemiological studies and cancer bioassays in experimental animals. For mechanistic and other relevant data, however, *Monographs* may cite only those studies that are relevant to an evaluation of carcinogenicity. [Chair comment]

The section also explicitly mentions abstracts and doctoral theses as reports that can be considered in exceptional cases. It is expected that this will happen only when the abstracts or doctoral theses contain detailed information and provide a unique indication of a potential cancer hazard. [Advisory Group recommendation 4b]

5. Meeting participants

This section now includes a discussion of the roles of Working Group Members, Invited Specialists, Representatives of national and international health agencies, Observers, and the IARC Secretariat. Accordingly, the title of the section is being changed to cover all meeting participants, not just the Working Group. The section explains that IARC uses literature searches to identify most experts and gives consideration to the balance of scientific findings and views. [Advisory Group recommendations 5a and 5c and comments by many recent meeting chairs and subgroup chairs]

The section also includes a description of the procedure IARC uses to assess conflicts of interests. It cites the WHO Declaration of Interests, which provides definitions and guidance about what constitutes a real or apparent conflict. IARC now requires all participants to submit their declaration before invitations are extended. The declarations are updated and reviewed again at the opening of a meeting. A participant with a real or apparent conflict of interests may participate only in a limited capacity, and all relevant interests are disclosed at the meeting and in the published *Monograph*. [Advisory Group recommendation 5c and comments from many recent meeting chairs and subgroup chairs]

There is also a description of the recent practice of disclosing the names of participants before each meeting, together with a statement that participants should not be contacted or lobbied. Such information appears on the *Monographs* website (http://monographs.iarc.fr). [Advisory Group recommendation 5a]

IARC is not expanding the role of Invited Specialist to allow them to write text on mechanistic and other relevant data. Strong mechanistic data can sometimes lead to a conclusion that *sufficient evidence* in experimental animals is not relevant to human carcinogenicity. To assure public confidence in the impartiality of such determinations, the mechanistic sections, like the sections on studies in humans and studies in experimental animals, are written by experts with no links to the parties that have a financial interest in the evaluation. [Advisory Group recommendation 5b]

The new practice of issuing a public call for experts is not being incorporated into the Preamble at this time. IARC is currently exploring this on a trial basis. When the draft Preamble is reviewed in December 2005, IARC will report the results of three separate trials for volumes 93, 94, and 95. [Advisory Group recommendation 5e]

Advisory Group recommendation 5d has been addressed by changes to Preamble Section 6 that are described next.

6. Working procedures

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The pre-meeting time schedule has not been changed. Beginning with volume 95, which will meet in October 2006, IARC will generally announce meeting topics 12 months in advance. This information will appear on the *Monographs* website (http://monographs.iarc.fr). The staff thanks the Advisory Group for its insistence on this goal. [Advisory Group recommendation 6a]

In a similar spirit, the post-meeting goal of publishing *Monographs* within 6 months after a meeting has been retained, although the programme does not anticipate being able to return to this schedule in the foreseeable future. There is still a backlog that was created by the 2-year period required to check the large amount of text, tables, and pages for volume 83 on tobacco smoke and involuntary smoking.

This section now describes the division of a *Monograph* meeting into subgroup sessions and plenary sessions and identifies the objectives of each activity. [Chair comment]

No specific restrictions had prevented Working Group Members from drafting and then reviewing text discussing their own work. The staff, however, believes it is a good idea to discourage his practice. Accordingly, some new text in Section 6 states, in a non-restrictive manner, that care is taken to ensure that each study summary is written or reviewed by someone not associated with that study. [Advisory Group recommendation 5d]

7. Exposure data

This section includes several minor changes that reflect the evolution of current practice over the past several years. [Chair comments]

Two new sentences note the availability of exposure data from national agencies and UN agencies. The section encourages future Working Groups to obtain data on exposures in developing countries. [Advisory Group recommendation 7a]

8. Studies of cancer in humans

A new section (labelled 8(c)) was inserted to discuss meta-analyses and pooled analyses of population-based studies. These have been cited or developed for several recent *Monographs*. Such combined analyses can provide a firmer basis than individual studies for drawing conclusions, especially when the individual studies report ambiguous or conflicting results. Some points to consider and limitations of these analyses are listed. [Advisory Group recommendation 8c and comments from recent chairs]

The section on inferences about mechanisms (now 8(d) but formerly 8(c)) was updated to include more detailed guidance on mechanistic biomarkers and the use of molecular epidemiology data on susceptibility. [Advisory Group recommendation 8a and comments from several recent chairs]

There are also some minor wording changes to make the guidance more clear or to reflect prevailing practice. [Comments from several recent chairs]

9. Studies of cancer in experimental animals

Some text was added to include studies of cancer in non-laboratory animals (for example, livestock or companion animals). This reflects current practice for a few viral and chemical agents. [Chair comment]

In Section 9(c) a new paragraph was added to discuss the use of historical control data, which have been considered by several past *Monographs*. Comparisons to historical controls can aid in the interpretation of unusual tumour types, provided careful attention is paid to between-study and within-study variability. [Advisory Group recommendation 12b]

A new paragraph mentions combined analyses of animal studies as an aid in interpreting animal data. [Advisory Group recommendation 9a]

There are also some minor wording changes to make the guidance more clear or to reflect prevailing practice.

10. Mechanistic and other relevant data

The discussion of mechanistic data has been expanded and now appears earlier in the section, immediately after the discussion of toxicokinetics. This gives mechanistic data more prominence and provides a closer link between toxicokinetics and mechanisms. Accordingly, the title of the section is being changed to put mechanisms first. Future Working Groups will attempt to identify the possible mechanisms of carcinogenesis that might be operating, review the data that are consistent or not consistent with each alternative mechanism, and identify significant data gaps and data that may suggest the operation of other mechanisms. Mechanisms can be discussed at several levels, from structural changes at the molecular level to changes at the organism level. [Advisory Group recommendations 10a and 10b, plus comments from many recent chairs]

Future *Monographs* will also include a new section on susceptible individuals, populations, and life-stages. This section builds on the knowledge of toxicokinetics and mechanisms discussed in earlier sections. Several examples of factors that can lead to susceptibility are listed in the draft Preamble. [Advisory Group recommendation 10c]

The draft Preamble does not prescribe a standard outline for *Monograph* Section 4 (which reviews mechanistic and other relevant data), but the order in which topics are discussed suggests the following outline [Advisory Group recommendation 10b]:

4 Mechanistic and other relevant data

4.1 Toxicokinetic data (absorption, distribution, metabolism, excretion)

This section reviews the potential for the agent and its metabolites to be distributed to various organs and tissues.

4.2 Mechanistic data
This section identifies the possible mechanisms of carcinogenesis that might be operating, reviews the data that are consistent or not consistent with each alternative mechanism, and identifies significant data gaps and data that may suggest the operation of other mechanisms.

4.3 Susceptible individuals, populations, and life-stages
This section builds on the knowledge of toxicokinetics and mechanisms to identify those who might be more susceptible. This includes, for example, susceptibility that arises from polymorphisms of metabolism, from the presence of disease, from exposure to the agent at a critical period of development (for example, infancy, puberty, or old age), and from exposure to other agents that can alter the kinetics or dynamics of the agent being evaluated.

4.4 Other forms of toxicity that are relevant to carcinogenicity
This section reviews toxicological effects that are relevant to the evaluation, including developmental and reproductive toxicity. It is not an encyclopaedia of chronic toxic effects, but should focus on, for example, toxic effects that confirm distribution and biological effects at the sites of tumour development, or toxicity that alters physiology in a way that could lead to tumour development.

4.5 Additional relevant data
This section reviews structure-activity relationships, the toxicological implications of physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

11. Summary and integration

Future *Monographs* will include an integration section that presents and discusses the reasoning the Working Group used to reach its evaluation. This new section is a significant addition to the *Monographs*, because it is the only place that the Working Group can explain the full logic of how it weighed data and drew conclusions. (The critical reviews in *Monograph* Sections 1-4 and the summaries in *Monograph* Sections 5.1-5.4 are factual reviews with minimal interpretation, and the evaluations in *Monograph* Section 5.6 can be as short as three simple sentences that state the standard categories chosen to describe the evidence of cancer in humans, in experimental animals, and the overall evaluation.) IARC receives many requests for information about how a Working Group reached its evaluations, and the *Monographs* will be improved by including this explanation of the Working Group's deliberations. Accordingly, the title of the section is being changed to include the word "integration." [Advisory Group recommendations 11a and 12g, plus comments from several recent chairs]

The integration section will be the place to report minority views. This new practice should not be abused to discuss every conceivable interpretation of the data. It will be reserved for cases where the Working Group tried but could not reach consensus, and the minority strongly believes that their differing views should be presented. [Advisory Group recommendations 12g and 12h, plus comments from several recent chairs]

The Advisory Group suggested several alternative locations for the new integration section. The draft Preamble places the integration section after the separate summaries (*Monograph* Sections 5.1-5.4) and before the evaluations (to become *Monograph* Section 5.6). This ordering best reflects the sequence in which these items emerge during a *Monograph* meeting. The new Section 5.5 will integrate the separate lines of evidence that are summarized in Sections 5.1-5.4 and discuss the reasoning that leads to the evaluations that are stated in Section 5.6. Thus, the draft Preamble implicitly suggests the following outline for *Monograph* Section 5:

5 Summary, integration, and evaluation [new title]
5.1 Exposure data
5.2 Human carcinogenicity data
5.3 Animal carcinogenicity data
5.4 Mechanistic and other relevant data
5.5 Integration [new section]
5.6 Evaluation [formerly Section 5.5]

Because *Monograph* summaries should not introduce data that were not discussed earlier, most of the detailed text on mechanistic data that previously appeared in Preamble Section 11 has been updated and moved to an expanded Preamble Section 10.

There are also some wording changes to make the guidance more clear or to reflect prevailing practice. [Comments from several recent chairs]

12. Evaluation

The general philosophy in making changes in this section was to maintain stability in the evaluation criteria whenever this is consistent with the current state of the science. Accordingly, substantive changes were made only when recommended by the Advisory Group. Comments from recent meeting chairs and subgroup chairs were incorporated where they would clarify the Preamble to better reflect prevailing practice or to reduce the possibility of misinterpretations that had occurred in the past. Other comments that would have substantively altered the evaluation criteria were not incorporated, as the intent of the Preamble amendment process is not to toughen or relax the evaluation criteria.

The evaluation criteria for human data (Section 12(a)) now instruct Working Groups to identify the target organ(s) or tissue(s) where there is *sufficient evidence of carcinogenicity* in humans. This reflects the prevailing practice over the past several years. [Advisory Group recommendation 12e and chair comments]

Clarifying text has been added to reiterate (from Section 8) the characteristics of epidemiological study results that would lead to a finding of *evidence suggesting lack of carcinogenicity* in humans. [Chair comment]

The evaluation criteria for animal data (Section 12(b)) have been changed to reflect the Good Laboratory Practices (GLP) that emerged after the original text was written. As discussed in both the Advisory Group report and the chair comments, considerable confidence can be placed in findings of clear evidence from GLP studies, such as those conducted by the US National Toxicology Program. As recommended by the Advisory

Group, the draft Preamble now states that positive results in both sexes of a single species in a GLP study can provide *sufficient evidence of carcinogenicity*. In addition, "strong findings of tumours at multiple sites" was added to the list of results in a single study that might be considered to provide *sufficient evidence*. "Exceptionally" was removed from the "single study" sentence in response to the Advisory Group's recommendation that the phrase "to an unusual degree" was already sufficiently restrictive in limiting the use of single-study findings. [Advisory Group recommendation 12a]

"Age at exposure" is now mentioned in the list of conditions that limit a conclusion of *evidence suggesting lack of carcinogenicity* in animals. "Conditions of exposure" was also added to cover other factors such as exposure route. [Advisory Group recommendation 12c]

The evaluation criteria for mechanistic and other relevant data (Section 12(c)) discuss several factors that may strengthen a conclusion that a particular mechanism is operating in experimental animals. There was some discussion at the May 2005 Advisory Group meeting about replacing the term "mechanism" by "mode of action" and citing the IPCS framework for considering mode of action. The Advisory Group did not support this, calling "mechanism" the scientific term that is appropriate for *Monograph* evaluations while recognizing that national regulatory agencies may prefer to use the less specific concept of mode of action to make pragmatic decisions. Accordingly, the term "mechanism" has been retained in the Preamble and some key relevant concepts of the IPCS framework are discussed. The draft Preamble stresses the importance of considering the possibility that multiple mechanisms might contribute to tumour development, a key concept of the IPCS framework.

There is also a reiteration of the Preamble's intent that the conclusion that a mechanism does not operate in humans is not based on exposure or risk levels. *Monograph* evaluations are a determination of hazard, not risk.

The expert workshop that developed IARC Scientific Publication 146 recommended in their consensus report that, in the absence of cancer bioassays in experimental animals, strong mechanistic data could be used in an evaluation. This reflects the increasing ability of mechanistic data to provide an indication of carcinogenic potential. Accordingly, the Advisory Group recommended that an agent can be characterized as *possibly carcinogenic to humans* based solely on strong mechanistic data. The overall evaluation criteria (Section 12(d)) have been updated to follow this advice. [Advisory Group recommendation 12d]

Clarifying text has been added to explain that the terms "*probably carcinogenic*" and "*possibly carcinogenic*" have no mathematical significance. [Chair comment]

Some commercial entities have claimed that classification of their product in Group 3 was a determination of safety by IARC. A statement has been added to discourage this erroneous interpretation. [Advisory Group recommendation 12i]

Advisory Group recommendations 12b, 12g, and 12h were addressed by changes to other sections of the Preamble, as described above.

Other changes

The title *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans* is not being changed to substitute the word "hazard" for "risk." Several reasons are discussed in the Advisory Group report. A discussion of "hazard" versus "risk" now appears in Preamble Section 2, with specific mention of how this relates to the title. [Advisory Group recommendation 13a]

The Advisory Group discussed the terms "weight of evidence" and "strength of evidence." The draft Preamble continues the previous use of "strength of evidence" as a matter of historical continuity. It should be understood that *Monograph* evaluations have always considered both studies that support the finding of a carcinogenic hazard and those that do not. [Advisory Group recommendation 13b]

The term "chemical compound" has been replaced by "agent" to reflect the broader scope of the programme. [Advisory Group recommendation 13b and chair comments]

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

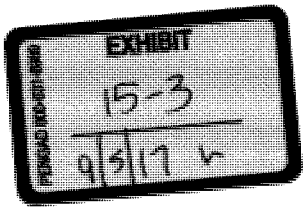
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

INTERNAL REPORT 06/001

Report of the Advisory Group to Review the Amended Preamble to the *IARC Monographs*

6–8 December 2005

LYON, FRANCE
2006



FOREWORD

During 2005, IARC amended the Preamble to the *IARC Monographs*. The Preamble describes the principles and procedures used in developing *IARC Monographs*, including the scientific criteria that guide the evaluations. The objective was to reflect scientific developments and procedural changes that have occurred since the Preamble was last amended in 1991.

The process began in March 2005, when IARC asked meeting chairs from the previous 10 years and subgroup chairs from the previous 5 years for suggestions on which parts of the Preamble should be revised, based on their experience. Their suggestions were considered by an international Advisory Group that met in May 2005 to recommend updates to the Preamble. The report of the May Advisory Group discussed a series of issues and made several recommendations (IARC Internal Report No. 05/001).

The recommendations of the May Advisory Group and the earlier suggestions formed the basis of a draft Preamble prepared by IARC staff. In August 2005, IARC made available the draft Preamble and other materials on the *IARC Monographs* programme website (http://monographs.iarc.fr) and invited the general public, the scientific community, national health agencies and other organizations to comment. Comments received after a two-month period were considered by a larger Advisory Group that met in December 2005 to review the amended Preamble.

Herein is the report the December 2005 Advisory Group. Its recommendations have been incorporated into the amended Preamble, which was given a final review by that Advisory Group. The amended Preamble will be used from the February 2006 *Monographs* meeting onwards.

IARC thanks the German Federal Ministry of Health and Social Security for financial support for the May and December Advisory Group meetings. IARC also thanks the Members of the May and December Advisory Groups, the meeting chairs and subgroup chairs who made useful suggestions, and the individual and institutional commentors who submitted valuable suggestions and perspectives. These contributions have all helped to enhance and renovate the *IARC Monographs* programme.

Report of the Advisory Group to Review the Amended Preamble to the *IARC Monographs*

Lyon, France
6–8 December 2005

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[1] Advisory Group members serve in their individual capacities as scientists and not as representatives of their government or any organization with which they are affiliated. Affiliations are provided for identification purposes only.

[2] Also served on the May 2005 Advisory Group to recommend updates to the Preamble.

[3] Receives some research support and equipment from IARC.

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Acknowledgement

IARC thanks the German Federal Ministry of Health and Social Security for financial support for this Advisory Group meeting.

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Organizations
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CONCAWE (Oil Companies' European Association), Belgium
European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Belgium
International Institute of Synthetic Rubber Producers (IISRP), USA
International Union, United Automobile, Aerospace and Agricultural Implement Workers of America (UAW), USA
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[7] Serves on review panels for the US Environmental Protection Agency and the Minnesota Department of Health, for which compensation will be received through Versar and Eastern Research Group, respectively. (These agencies sometimes use private contractors to convene review meetings).

Report of the Advisory Group to Review the Amended Preamble to the *IARC Monographs*

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General comments

The Advisory Group (AG) was generally impressed with the new version of the Preamble and commended the Secretariat on a document that addressed the deficiencies seen in the previous version while maintaining the integrity of the *Monographs* Programme. The Secretariat had done an excellent job of considering and including the comments suggested by previous Working Group Chairs, the May Advisory Group (MAG) and others who offered advice in advance of the development of a draft Preamble. In addition, the solicitation of outside comments prior to the meeting of the AG provided a broad perspective of the issues that are of concern to interested parties in the draft Preamble and will definitely lead to an improved Preamble and improved *Monographs* Programme.

The majority of the AG comments were focused on clarification of the intent of the wording in the draft Preamble rather than substantive changes in the outlined process. However, there were a few issues that the AG wished to highlight as important modifications suggested for the final Preamble. These include:

1. Restructure to two basic sections – General Principles and Procedures, Scientific Review;
2. Changes to the tone and tenor of the levels of evidence used to evaluate carcinogenicity data from laboratory experiments;
3. The use and utility of mechanistic data in modifying both degrees of evidence and the final classification in Working Group deliberations;
4. Clarification of the role of invited experts and representatives in the Working Group evaluations; and
5. Balance and conflict of interest.

Each of these issues were discussed within the context of the recommendations of the AG that are given below and are broken down into sections that follow those of the draft Preamble.

Structure of the Preamble

In essence, the first six sections of the draft Preamble refer to procedural issues related to the formation, composition and management of a *Monographs* Working Group and could be captured as subheadings under the title 'Part A: General Principles and Procedure'. The core of the scientific review conducted by the Working Group and guidance for the final evaluations are given in Sections 7–12. These could also be grouped under a single title of 'Part B: Scientific Review and Evaluation'. Subsequently, by numbering the sections of Part B, a structure is created in which the Sections of the *Monographs* relate to the numbering in the Preamble. Thus, the new Preamble would have the following structure:

Part A: General Principles and Procedures

1. Background
2. Objective and Scope
3. Selection of Topics for the Monograph
4. Data for the Monographs
5. Meeting Participants
6. Working Procedures

Part B: Scientific Review and Evaluation

1. Exposure Data
2. Studies of Cancer in Humans
3. Studies of Cancer in Experimental Animals
4. Mechanistic and Other Relevant Data
5. Summary and Integration
6. Evaluation

1. Background and brief introduction

This text is fairly short and enhances the historical perspective through which one can view the development of the *Monographs* Programme. In the one-paragraph introduction, the word 'scientific' should be inserted before 'principles' to emphasize that the Preamble defines both the processes used and the scientific principles that support these processes in making decisions for any one agent, mixture or exposure circumstance. In addition, it was suggested that the following text be added to the end of the introductory paragraph:

> The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The working procedures through which any IARC Working Group implements these principles are not specified in detail, remain predominantly the prerogative of any individual Working Group and usually involve operations that have been established as being effective during previous *Monographs* meetings.

The AG also recommends that the Secretariat develop a more detailed informational document describing the Preamble and its overall objectives and how it is employed in making Working Group decisions. This document does not need to be part of the formal Preamble but could exist on the IARC web server or as a short document for distribution to interested parties.

2. Objective and Scope

In Section 2, the term 'consensus' is used to describe the final evaluations of the Working Group. In common with three of the public comments (Huff, ECETOC, IISRP), the AG felt this term could lead to confusion. The AG discussed the terminology that might best be used to describe the decision-making process. While the word 'consensus' was considered to be a useful term, it was evident that no single word would adequately cover all options that a

Working Group might legitimately use in arriving at an evaluation. In the light of these considerations, the following was suggested:

> IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The Working Group Chair may elect to call a vote on issues when consensus is not readily achieved to determine the diversity of opinion among Working Group Members.

Also in Section 2, the public comments (NRDC, Melnick, Huff, ECETOC, IISRP) highlighted concerns regarding the definition of a carcinogen. The AG felt the definition was adequate with a minor exception noted below:

> In these *Monographs*, an agent, mixture or exposure circumstance is termed 'carcinogenic' when it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may, in some circumstances (see Section 9), contribute to the judgement that the exposure is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

By placing the *IARC Monographs* into their proper context in the overall process of risk assessment, others may understand clearly what part of the process is being addressed. However, members of the AG noted that the process of risk assessment is described differently from country to country. To avoid confusion, the AG suggested that the third and fourth paragraphs of Section 2 be replaced with the following text:

> For the *Monographs*, a cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating a hazard, despite the historical presence of the word 'risk' in the title.
>
> The *Monographs* critically review and evaluate the published scientific evidence in order to assess whether an agent can alter the age-specific incidence of cancer in humans. The long-term objective is to publish up-to-date information on each carcinogenic hazard to which humans are exposed.

While the last paragraph of Section 2 covered the use of the *IARC Monographs* in risk assessment and regulatory decisions, the AG felt there was a broader use and this should be noted. The following modifications to the last paragraph suggest the changes that are needed:

> The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning any necessary preventive measures, provide effective cancer control programmes and decide among the myriad of options that govern a public health decision. The evaluations of IARC Working Groups are scientific, qualitative judgements about the evidence for or against carcinogenicity based on the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country, and relate to many factors including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of the individual governments and/or other international organizations.

Additional public comments pertained to various parts of Section 2. The AG felt that the remaining text used by the Secretariat in the draft Preamble was clear and concise and did not need additional modification.

3. Selection of Topics for the *Monographs*

Only a few public comments related to this section and the AG felt that none of them warranted a change in the draft Preamble. The AG accepted the text as written.

4. Data for the *Monographs*

In the third paragraph of Section 4, the Draft Preamble discusses the inclusion of government reports and limits them to those that have undergone peer-review. The AG felt this wording was too restrictive and suggested that it should be removed from the Preamble. Instead, the AG suggested this wording:

> Government agency reports that are publicly available may be considered.

One public comment (Grilli) noted the existence, in some cases, of data on agents being reviewed in the *Monographs* that could not be included due to the requirement that they be publicly available. Most notably, this could pertain to toxicological information on pharmaceuticals and/or pesticides which has historically been labelled as proprietary and not subject to public disclosure. While it was recognized that the restriction of data to be considered to published scientific research has the potential to preclude consideration of information that is confidential or of otherwise restricted availability but which might impact the evaluation, the AG felt that the strength of the *Monographs* series would be reduced if evaluations were made using data that may not be shared with other scientists and the public at large. Thus, while the AG was concerned that such data are not in the open scientific literature, it fully supported the Secretariat in their use of only 'publicly available' data in the evaluations. That said, prior to each *Monographs* meeting, the AG encourages IARC to seek actively data from different sources (published and unpublished) using multiple mechanisms such as a call for data through the IARC website, to request submission of publications from developing countries, to prepare review articles from publications in local journals and to request data from government agencies. If necessary, during a Working Group meeting, unpublished data could be reviewed and/or analysed by the Working Group Members.

The third sentence of paragraph 3 in Section 4 has too much detail and inappropriately elevates the utility of abstracts (public comment by ECETOC, IISRP). While the AG supported the use of any information, including abstracts, by a Working Group if it is critical to their evaluations, a better wording of this sentence was considered to be:

> Exceptions may be made on an ad-hoc basis to include doctoral theses and other material that are in their final form and publicly available, if their inclusion is considered pertinent to making a final evaluation (see Section 12).

Several other public comments were provided on Section 4, but the AG felt that these were not appropriate for the Preamble.

5. Meeting Participants

There was general support by the AG on the clarification in the Preamble of the roles of the meeting participants. With only minor suggestions (see below), the AG endorsed the description and restrictions given in this section.

Two public comments noted a lack of clarity in the roles of and restrictions placed on Invited Specialists. The AG recognized the importance of using Invited Specialists as a resource for technical information that may assist a Working Group in its deliberations. However, because of the potential for conflict of interest, the AG recommends that Invited Specialists continue to be used by IARC in a limited capacity, and that their involvement be structured in such a way so as not to influence the evaluations. In this context, the AG felt that the role of Invited Specialists in drafting text for the Working Group should be restricted to non-influential issues in exposure such as a general description of data on production and use.

Three public comments suggested (ACC, ECETOC, IISRP) that meeting participants with conflicts of interest simply be required to state these conflicts and not be limited in their role in the Working Group. The AG disagreed with this position and fully supported the limits outlined in the draft Preamble.

Four public comments (Greenberg, Melnick, ACC, UAW) mentioned balance as a key issue in developing a Working Group. The AG agreed that balance of perspectives is an important consideration, but noted that conflict of interest does not necessarily imply prejudice. The restriction of the role of Observers to that of participants who only observe and do not attempt to influence the meeting reduces significantly the concern about balancing conflicts of interest among this category of participant. In contrast, Invited Specialists play an important and critical role by bringing their knowledge and experience to the subgroup and plenary sessions. The data that they emphasize, the particular interpretations they present and the lines of research that they may have explored naturally reflect the particular experience and employment of the Invited Specialists and may also reflect the interests and perspectives of their employers. For these reasons, IARC should consider the evenness of Invited Specialists in certain situations, for example, when the volume and nature of the information that they contribute could appear to influence the evaluation. IARC should re-evaluate the issue of whether or not to balance Invited Specialists or Observers after gaining experience with the new procedures that are currently in place.

For clarity, the AG suggested that the wording regarding Observers be changed to note that they are "... admitted by IARC to a meeting...".

One public comment (Huff) suggested that the role of Representatives be restricted with regard to both numbers and manner of participation similarly to that of Observers. The AG partially agreed and suggested that the Preamble include the sentence:

> Representatives may not serve as Meeting Chair or Subgroup Chair, draft any part of a monograph or participate in the discussions on the evaluations.

The number of Representatives should be decided by the IARC and the AG had no opinion on this issue.

The definition used for the IARC Secretariat appeared to be too restrictive and could prevent temporary visitors to IARC from being included in the list of Working Group Members. The AG suggested the following wording for the first sentence:

> The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise.

The possibility that members of the IARC Secretariat be obliged to make a Declaration of Interest was discussed by the AG, and it was concluded that IARC should consider this possibility.

The AG felt that all other public comments were either dealt with appropriately in the draft Preamble or were too detailed to be included.

6. Working Procedures

Two public comments (ECETOC, IISRP) requested that the first drafts of the *IARC Monographs* be made available for public comment [repetition]. The AG noted that, although the draft Preamble refers to the initial write-ups as first drafts, this is a mischaracterization. The initial write-ups of the scientific reviews are in the form of draft working papers, which contain initial compilations and reviews of data that are designed to initiate the discussions and deliberations of a Working Group at the start of a *Monographs* meeting. The working papers typically undergo several cycles of deliberation, review and revision before they achieve a form that could be considered as draft sections of a monograph. Public release of working papers ahead of the meeting would therefore be inappropriate as it could frequently lead to misconceptions regarding the ultimate review and characterization of the evidence by a Working Group and politicize the development process of the *Monographs*.

One reason to release material early is the possibility that data that were not being considered by the Working Group may be identified. The AG felt that a better approach to addressing gaps in data would be a call for relevant data prior to the development of the working papers, coupled with careful selection of experts for the Working Group. In a related comment (Huff), it was noted that, if draft working papers are provided to observers prior to the meeting, they should be made available to others who cannot afford to attend the meeting but who are interested in the issue. The AG noted this as a concern, and recommends that working papers not be sent to Observers ahead of the meeting. Should this occur, public release of working papers or other more restricted releases should be considered. Nevertheless, the AG did not believe release of pre-deliberational drafts to be in the best interest of the *Monographs* programme.

A number of other comments were provided to IARC regarding Section 6. Some related to mixing disciplines in the various breakout groups during a Working Group meeting (UAW, ECETOC). The AG felt that these issues should not be included in the Preamble but recommends that IARC consider them when forming Working Groups. The remaining public comments pertaining to Section 6 were felt to be inappropriate for the Preamble.

Sections 7–10

The AG felt that the core of the scientific review conducted by a Working Group will receive major guidance from Sections 7, 8, 9 and 10. In view of the many public comments on these sections and the subtle changes in language that the Group wanted to incorporate, the AG decided to provide IARC with a modified draft of these sections rather than comments on what should be changed. In many cases, the changes the AG made to these sections address public comments, but not all public comments were deemed appropriate and many were therefore not included in the changes. Where appropriate, the AG inserted commentary enclosed in square brackets ([]) into the draft text to explain some changes or support individual passages. The AG did not provide further commentary on these sections and felt that the new drafts provide an ample description of their intent. The suggested wording for Sections 7–10 is given in the Appendix.

11. Summary and Integration

There was broad support within the AG and from the public comments for an integration section that explains the basis for the conclusion. It was felt that this section will improve the transparency of the evaluations and increase public confidence and understanding. In general, the AG felt that the language used in the draft Preamble was clear and concise. One comment (Tomatis) suggested a change in the title was needed to replace 'Integration' with 'Rationale'. The AG agreed that this would be an improvement.

Finally, this section should not provide new data and the last sentence of section (c) should therefore be altered to read:

> Dose–response and other quantitative data may be summarized when available.

12. Evaluation

Several comments (IISRP, Grilli, Huff) suggested that the actual names and/or numbers of categories be altered to provide greater flexibility in and/or clarity of interpretation. The AG felt that the current categories used by the IARC were adequate, had stood the test of time and should remain effectively the same.

In the evaluation process, consideration of mechanistic data in their entirety occurs at the final stage of the evaluation. However, specific mechanistic findings may be taken into account in determining the confidence that should be vested in particular epidemiological or experimental studies. Hence, although mechanistic information is not excluded from the determination of *sufficient* or *limited evidence*, these determinations are primarily expressions of the outcome from epidemiological and experimental studies, respectively.

One public comment (Tomatis) suggested that the identification of target organ(s) in the description of the levels of evidence of carcinogenicity in humans could mislead readers into believing that other organs have been deemed to be free of agent-induced cancers. The AG recognized this possibility and suggested the following sentence be added to the end of the paragraph on "***Sufficient evidence of carcinogenicity***":

> Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

There was considerable debate in both the AG and the public comments (Huff, NRDC, UAW, ACC, CONCAWE, ECETOC, IISRP] regarding the proposed change to include positive findings in both sexes in a single species from a Good Laboratory Practice study as providing '*sufficient evidence* of carcinogenicity'. The AG supported the recommendation of the MAG and suggested that IARC keep this designation in the Preamble. The debate centred around the issue of the quality of studies versus the independence of laboratories. The AG felt that, if a study of males and females in a single experiment was very well conducted and provided significant detail on the characterization of the animal exposures, care and feeding in the laboratory and the evaluation of pathogens together with a high quality of pathology with external review, then positive results in both males and females could satisfy the criterion of a causal inference in two experiments. The Working Group would still be expected to use their best scientific judgement in making a decision on whether there was sufficient evidence, but the AG felt that the clarification of this issue in the Preamble was warranted.

Given the historical relevance of the two examples listed as (a) and (c) in the draft Preamble, the AG felt that (b) should be included as a separate sentence and that the reference to the NTP be removed. The following language was suggested:

> ***Sufficient evidence of carcinogenicity***: The Working Group considers that a causal relationship has been established between the agent or mixture and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.
>
> A single study in one species and sex might be considered to provide *sufficient evidence* of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or at an increased incidence at multiple sites.

There was a suggestion to delete "certain neoplasms which may occur spontaneously in high incidences in certain strains," from the category for '*limited evidence* of carcinogenicity' in animals (Huff) because statistical significance would be achieved only with an incidence that was considerably increased. The AG agreed and suggested that this text be removed, noting that the Working Group may still reduce the degree of evidence if, for a specific agent, the results warrant such a reduction.

The AG also spent a considerable amount of time discussing the use of specialized toxicological studies and the potential categories under which they may be included. Of particular interest were initiation–promotion studies and studies in genetically modified animals. This discussion was initiated due to difficulties associated with the classification of these types of data that had been encountered in recent *Monographs* meetings. The AG felt that the descriptions given for *limited* and *sufficient evidence* do not provide adequate guidance to ensure some degree of consistency in the evaluations made by Working Groups from one *Monographs* meeting to another. However, the AG did not wish to add multiple new examples to the degrees of evidence used for animal experiments. It was felt that the best solution would be to include a single additional description of the weakest level of evidence one might accept as providing *limited evidence* of carcinogenicity from the special studies into this category and expect that reasonable scientists who evaluated other special studies would act accordingly. Agents that only show promoting activity in one or more well-conducted initiation–promotion study, while showing a causal inference for increased carcinogenic activity, would need additional mechanistic data or data from other sources to conclude that this causal inference was *sufficient evidence* of carcinogenicity. Examples of other types of data that may raise this degree of evidence could include multiple initiation–promotion studies in several species and several different organ systems that consistently demonstrate promotional activity, an initiation–promotion study that shows a causal increase in the initiating capacity of the agent or a single two-year carcinogenicity study in a single sex of a single species that demonstrates a causal association. A more detailed discussion of these issues is provided in *IARC Scientific Publications No. 146* and Working Groups may wish to consult this volume when faced with special studies. Hence, it was proposed to add this case to the list of circumstances enumerated under *limited evidence* of carcinogenicity.

In addition, the AG felt that it would be useful to include explicitly these types of study in the list of those to be considered when evaluating the evidence in experimental animals. It

was suggested that the following wording be added to the beginning of Section 12(b) together with a reference to the discussion of the use of these data in *IARC Scientific Publications No. 146*:

> Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis.

In the light of these recommendations, the AG drafted new text to describe the evaluation of evidence in experimental animals as follows:

> ***Limited evidence of carcinogenicity*:** The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent or mixture increases the incidence of benign neoplasms or lesions of uncertain neoplastic potential only; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Several comments (Huff, Tomatis, ECETOC, IISRP, UAW) noted that the second to last paragraph under 12(c) beginning with "Current or anticipated..." needed to be clarified and/or revised. The AG agreed in principle that this paragraph could be expanded, but did not provide any specific language.

Several public comments related to the proposed change to allow a classification of *possibly carcinogenic to humans* (Group 2B) solely on the basis of strong evidence from mechanistic and other relevant data. The AG supported this clarification by IARC and noted that there is increasing confidence in our understanding of mechanisms which is supported by the science. Other public comments suggested this should be based on the full statement regarding use of mechanistic data given in *IARC Scientific Publications No. 146* (IISRP, ECETOC). The AG encouraged the IARC to consider this possibility.

One public comment (Melnick) supported extending this concept to allow mechanistic data to place a compound into Group 2A. The AG felt that this was possible, but only when the compound is clearly a member of a mechanistic class for which one or more members of the class have *sufficient evidence* of carcinogenicity that places some members in Group 1 or Group 2A.

The IARC Secretariat was encouraged to define a strategy to address situations in which unanimity on an overall evaluation cannot be reached. The AG recommends that the portion of Section 11 that refers to integration be moved to the end of Section 12 as a new topic (e). In cases of differing scientific interpretation, the AG felt that the overall evaluation should reflect the majority view but that the minority view be provided an opportunity to present a brief summary of the alternative position and the scientific rationale for this position. In establishing the majority view, the Working Group Chair may elect initially to take a non-binding poll of the Working Group to establish the extent of agreement and/or disagreement among the Members. The AG discussed the actual wording of this paragraph and proposed an alternative wording which is given below:

> The reasoning that the Working Group used to reach its [consensus] evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals and mechanistic and other relevant data. It includes general statements

of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions and an explanation of the reasoning of the Working Group in weighing data and making evaluations (see Section 12). When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale.

APPENDIX

7. Exposure data

The scope of the *IARC Monographs* has expanded beyond chemicals to include complex mixtures, occupational exposures, lifestyle factors, physical and biological agents and other potentially carcinogenic exposures. In respect of the various classes of agent, the specification and use of appropriate indicators of exposure are undertaken by the Working Group and may be outlined in the General Remarks of the relevant *Monographs* volume.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are included at the beginning of each monograph.

Most monographs on chemical agents include sections on chemical and physical data, analysis, production and use, occurrence and human occupational and environmental exposures. Monographs on biological agents have sections on taxonomy, structure and biology, methods of detection, human exposures, epidemiology of infection and clinical disease other than cancer. Those on physical agents that are forms of radiation include sections on energy, range of the radiation and on source and routes of exposure. Those on foreign bodies, fibres and respirable particles include sections on sources and routes of exposure and size range and relative dimension of the particles. Whenever appropriate, a monograph may include other sections such as historical perspectives or the description of an industry or habit.

For chemical agents, the Chemical Abstracts Services Registry Number, the latest Chemical Abstracts Primary Name and the IUPAC Systematic Name are recorded; other synonyms are given, but the list is not necessarily comprehensive. For biological agents, taxonomy and structure are described, and the degree of variability is given, when applicable.

Information on chemical and physical properties that are relevant to identification, occurrence and biological activity are included. A description of technical products of chemicals includes trades names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients. For biological agents, mode of replication, life cycle, target cells, persistence and latency and host response are given.

The purpose of the section on analysis or detection is to provide an overview of current methods, with emphasis on those widely used for regulatory purposes. Methods for monitoring human exposure are also given, when available. No critical evaluation or recommendation of any of the methods is meant or implied. For biological agents, methods of detection and exposure assessment are described, including their sensitivity, specificity and reproducibility.

The dates of first synthesis and of first commercial production of a chemical or mixture are provided when available; for agents which do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

Information on the occurrence of an agent or mixture in the environment and information on human exposures is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases (ref. NHANES). In order to understand more fully the carcinogenic risk of an agent, it is important to obtain a full range of data on human exposure. Information on exposure should include relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccines and therapy, are described.

8. Studies of cancer in humans

This section includes all epidemiological studies. Studies of biomarkers included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of studies considered

Several types of epidemiological study of cancer contribute to the assessment of carcinogenicity in humans—cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent, mixture or exposure circumstance under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs, as exemplified by exposure to arsenic in drinking-water (IARC, Vol. 84).

In some instances, case reports and case series have provided important information about the carcinogenicity of agents [response to one of the public comments]. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events—that is, a particular exposure and occurrence of a cancer—has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship is present.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed by the Working Group. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between disease and an agent, mixture or exposure circumstance. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or to appear weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, the Working Group considers a number of aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration should be given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case-control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken into account — in the study design and analysis —other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of disease frequency among individuals at different levels of exposure are also desirable in cohort studies, since they minimize the potential for confounding related to difference in risk factors between an external reference group and the study population.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case-control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case-control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well-conducted analyses can be considered by the Working Group. There are two types of combined analyses. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (ref).

Advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, data collection procedures, measurement methods and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

Meta-analyses relevant to a particular monograph may be available as published studies and hence be available for consideration by the Working Group. Alternatively, meta-analyses may be undertaken prior to a *Monographs* meeting, and may occur as a consequence of the topic of the *Monographs* volume being publicized on the IARC website. Publication of the results of such meta-analyses prior to a *Monographs* meeting is a requirement for their consideration. IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monographs* meeting. Finally, as a means of gaining insight from the results of multiple individual studies, ad-hoc calculations that combine data from different studies may be conducted by the Working Group in the course of a *Monographs* meeting. The results of such original calculations, which would be specified in the monograph by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful

in making causal inferences. In addition, such analyses may suggest whether a carcinogen acts early or late in the process of carcinogenesis, although at best they allow only indirect inferences about the mechanism of action.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004; Bonassi *et al.*, 2005). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses of individual susceptibility and/or host responses and inference of a mechanism. This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies (see Section 10).

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites thought to be the basis of susceptibility can be taken as evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons arising from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent to be evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent, mixture or exposure circumstance in question is carcinogenic for humans. In making their judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or using different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in amount of exposure), and results of studies judged to be of high quality are given more weight than those of studies judged to be methodologically less sound.

If the risk of the disease in question increases with the amount of exposure, this is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship. Demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

A number of scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the

overall database are also considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires first of all that the studies giving rise to it meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (*a*) be consistent with an estimate of effect of unity for any observed level of exposure and, when considered together, (*b*) provide a pooled estimate of relative risk that is at or near unity and (*c*) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency for relative risk of cancer to increase with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained in this way from several epidemiological studies can apply only to the type(s) of cancer studied and to dose levels and intervals between first exposure and observation of disease that are the same as or less than those observed in all the studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

9. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilboestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents and mixtures that cause cancer in experimental animals also cause cancer in humans, nevertheless, in the absence of adequate data on humans, it is biologically plausible that agents and mixtures for which there is *sufficient evidence* of carcinogenicity in experimental animals (see Section 12) present a carcinogenic hazard to humans. In the absence of additional scientific information, these agents or mixtures are considered to pose a carcinogenic hazard to humans. An example of additional scientific information would be data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Section 12).

The Working Group considers all available long-term studies on cancer in experimental animals with the agent under review. In all experimental settings, the nature and extent of impurities or contaminants present in the mixture or agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, exposure route, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported.

Other studies summarized may include: experiments in which the agent or mixture was administered in conjunction with known carcinogens or factors that modify carcinogenic effects (initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility of changes in the physicochemical properties of the individual substances during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar structures or similar viruses) to the one being evaluated in the monograph is also considered. Such results may provide biological and mechanistic information relevant to the understanding of the process of carcinogenesis in humans and may strengthen the plausibility of a conclusion that the agent that is being evaluated is carcinogenic in humans.

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route and schedule of exposure, species, strain (including genetic background where applicable), sex, age, duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

As mentioned earlier (see Section 4), the *Monographs* intend to summarize all pertinent published studies. Those studies in experimental animals that are judged irrelevant to the evaluation or judged to be inadequate (e.g. too short a duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have recently been published (e.g. OECD reference).

Considerations of importance to the Working Group in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported adequately.

When benign tumours occur together with and (a) originate from the same cell type in an organ or tissue as malignant tumours in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response

observed. If an agent or mixture induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, it should nevertheless be suspected of being a carcinogen and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, the dose of the carcinogen and the route, timing and duration of exposure. Evidence of an increased incidence of neoplasms with increased level of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted into their reactive intermediates, both metabolic and pharmacokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce non-linearity in the dose–response relationship (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analysis of long-term experiments in animals

Factors considered by the Working Group include the adequacy of the information given for each treatment group: (i) the number of animals studied and the number examined histologically, (ii) the number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailar, 1989; Beiler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour is discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: the time of death provides an indication of the time of tumour onset for rapidly fatal tumours, and can be evaluated using life-table methods; non-fatal or incidental tumours that do not affect survival can be evaluated using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Methods, such as the Poly-K test, that do not require information on tumour lethality, which is often difficult to determine, can also be used. When data are available on the number and/or size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through NMR [?nuclear magnetic resonance]), other more complicated statistical procedures may be needed (Kopp-Schneider & Portier; Dunson *et al.*).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from an experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: little less weight to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent

controls by arguing that it falls within the range of the historical controls, particularly when historical controls show high between-study variability and are, thus, of little relevance to the current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender, and strain, as well as other factors such as the basal diet and general laboratory environment that may affect tumour–response rates in control animals (Haseman *et al.*, 1984; Greim; Fung; ...).

Although meta-analyses and combined analyses of animal experiments are conducted less often than are similar analyses of epidemiological studies due to differences in experimental protocols, both meta-analyses and combined analyses of animal experiments can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

10. Mechanistic and other relevant data

Mechanistic and other relevant data provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and humans. The nature of the assessment of mechanistic and other relevant data to be evaluated depends on the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important. Thus, in Section 4 of a monograph, not every available study is typically cited. Relevant topics to be addressed may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations, life stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive, thus the same studies may be discussed in multiple subsections. For example, a mutation in a gene coding for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanistic data and individual susceptibility if it also exists as an inherited polymorphism. To assess these topics, data on dose, duration and life-stage relationships of carcinogenic effects and on their contribution to the natural history of cancer are considered. For example, consideration is given as to whether the mechanism may act early or late during tumour development.

(a) Toxicokinetics

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect the dose–response relationships include tissue half-life, uptake, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of cancer development

To narrow the focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to data gaps and to data that may suggest the operation of other mechanisms. The relevance of the mechanism to humans is discussed, in particular, when

mechanistic data are derived from experimental model systems. Changes in the micro-environment of the affected cells, tissues or organs can be divided into three, non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of physiological changes include mitogenesis, compensatory cell division, evasion of apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal estrogens and/or androgens and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities for enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in the cytokines that govern movement of cells through the cell cycle, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis should be given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal mutation/aneuploidy to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999; refs). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically by phylogenetic group according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether use of an exogenous metabolic system *in vitro* affected the test result. These data are listed in tabular form.

Positive results in tests using prokaryotes, lower eukaryotes, insects and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information about the

types of genetic effect produced and about the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations and chromosomal aberrations), while others are to a greater or lesser degree associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for tumour-promoting activity, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of greater relevance than that in other organisms. The demonstration that an agent or mixture can induce gene and chromosomal mutations in mammals *in vivo* indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents or mixtures that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression and calculi and other deposits that cause chronic irritation), that evidence is presented critically and reviewed in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. IARC Scientific Publication 147).

(c) Other data relevant to mechanisms

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, molecular biology (integration and expression of viruses, and any genetic alterations seen in human tumours) and other observations that might include cellular and tissue responses to infection, immune response and the presence of tumour markers.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to include foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities rather than from degradation products. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(d) Activity classes

A description should be provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of

the agent's physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from the evaluation of hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to over-interpret changes in individual end-points (e.g. changes in expression in one gene) without evaluating the consistency of that finding in the broader context of the other end-points evaluated (e.g. other genes with linked transcriptional control). High-output data can be used in evaluating mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data where the number of observations far exceeds the number of end-points measured, the utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but have a consistent pattern of carcinogenic response across entire classes of related compounds.

(e) Individual susceptibility

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on knowledge of the toxicokinetics and mechanisms of carcinogenesis of that agent and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of metabolic genes of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and focus the linkage of in-vivo and in-vitro laboratory studies to humans.

(f) Other adverse effects

Finally, data on acute, subchronic and chronic adverse effects other than cancer are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is evaluated by the same criteria as are applied to epidemiological studies of cancer, but giving fewer details.

Posted on 19 January 2006

Evans, Sharon L (NIH/NIEHS) [E]

From:	Birnbaum, Linda (NIH/NIEHS) [E]
Sent:	Wednesday, October 21, 2015 8:10 AM
To:	Evans, Sharon L (NIH/NIEHS) [E]
Subject:	Fwd: FYI
Attachments:	Wristband USA Today.jpg; ATT00001.htm; Final Press Release_ Oct 2015.pdf; ATT00002.htm

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GEN
Birnbaum/orig
c/
EDF File
ES
10/21

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S
Director, National Institute of Environmental Health Sciences
and National Toxicology Program
phone: 919-541-3201
fax: 919-541-2260
e-mail: [redacted]

Begin forwarded message:

> **From:** Chris Portier [redacted] (b) (6)
> **Date:** October 21, 2015 at 12:06:21 AM EDT
> **To:** "Birnbaum, Linda (NIH/NIEHS) [E]" <[redacted]>
> **Subject: Re: FYI**
>
> Hi Linda,
>
> I am good and enjoying my life these days. Too many trips to the US this year, but EDF has been busy on a number of fronts and I am enjoying helping them set some new and interesting directions. (b) (6) [redacted] I am also having a bit of fun pushing the IARC Glyphosate finding into the European decision on re-regigistration. I am not sure it will have any impact other than to make EFSA uncomfortable, but I am trying. There have been a few national Parlimentary hearings I have testified in and several letters to various governments. This is fascinating and something I would never have done as a Fed.
>
> If you noticed, in the article, we are building a registry of people interested in having a wristband analysis done. We are thinking about maybe trying to do something nationally (see attached). So, feel free to share; the more people interested, the more likely we can find the funds to do something big and the better the scientific outcome. We will probably be contacting you in a few months for some guidance and direction on this as we further develop our ideas.
>
> I hope all is well with you and your family.
>
> C.

EXHIBIT
15-4
9/5/17

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Report

Chemical Detection Project: New Technology Sheds Light on Chemicals in Our Environment

Chemical Detecting Wristbands Show Americans Can't Avoid Toxic Chemicals

A simple looking wristband can shed new light on the previously invisible problem of toxic chemicals in our midst. Environmental Defense Fund (EDF) conducted a pilot project asking 28 individuals to wear the wristbands for one week. The project's findings make clear the power of this technology to detect the presence of chemicals in our everyday lives and to advance our understanding of the health effects of exposures.

Thousands of chemicals are used in the products that surround us every day—from our couches, to our carpets and even the clothes on our backs. Chemicals are used to make 96% of all products sold in America, and some 85,000 chemicals are available for use on the market.

Scientific research is increasingly linking chemicals in common use to some cancers, infertility, diabetes, Parkinson's and other illnesses. Pregnant woman, infants, and children are especially vulnerable. National CDC studies routinely detect hundreds of chemicals in the blood and urine of virtually all Americans tested, and many babies are born with hundreds of chemicals already in their bodies.

Key findings from 28 wristbands

- *100% detected PBTs.*
- *86% detected flame retardants chemicals.*
- *93% detected one or more pesticides.*
- *100% detected the fragrance galaxolide.*

Yet, we still have a very limited understanding of the chemicals in our own lives and little assurance of their safety.

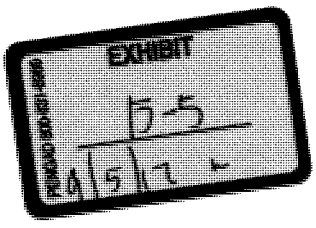
Harnessing a new technology to overcome an environmental health challenge

A cutting edge monitor from MyExposome, Inc., developed by researchers at Oregon State University (OSU), promises to transform our understanding of environmental exposures to chemicals—to make the invisible, visible—and, in so doing, open up new opportunities for reducing exposures.

The monitors are surprisingly simple: Silicone wristbands, like the ones worn in support of various causes, are specially prepared to act as a sponge to absorb hundreds of different chemicals (current analytic methods detect over 1,400) in our environment—the air, water, and even personal care products. (Detailed background on the wristbands is at myexposome.com.)

The simplicity of this new technology opens a range of opportunities to empower individuals with information about what chemicals are present in the environment. They also offer the possibility to explore important questions about the efficacy of interventions to reduce exposures.

To better understand the potential and limitations of this technology, EDF conducted a small pilot project to engage individuals to become "environmental sensors" for a week. Detailed findings follow.



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Key Findings

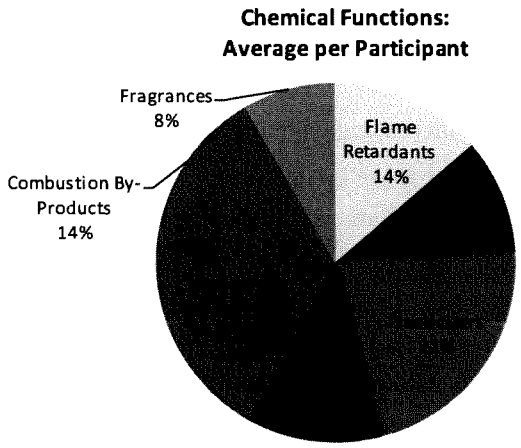
Summary Results

- **28** people participated in this project.
- The wristbands were analyzed for a total of **1,418** chemicals.
- A total of **57** chemicals were detected in all the wristbands.
- Each wristband detected an average of **15** chemicals (range: **10-27**).
- All of the wristbands detected persistent, bioaccumulative and toxic chemicals ("**PBTs**").
- **86%** of the wristbands (24 of 28) detected one or more flame retardants.
- **93%** of the wristbands (26 of 28) detected one or more pesticides.
- Every wristband detected **galaxolide**, a common fragrance used in cleaning and beauty products.

Where might these chemicals be found?

The wristbands detected chemicals used in a wide variety of consumer products – from plastics and personal care products to furniture. The primary functions of the chemicals detected in this project include:

- **13** combustion by-products
- **12** pesticides
- **9** plasticizers
- **7** flame retardants
- **4** chemicals in personal care products*
- **4** fragrances

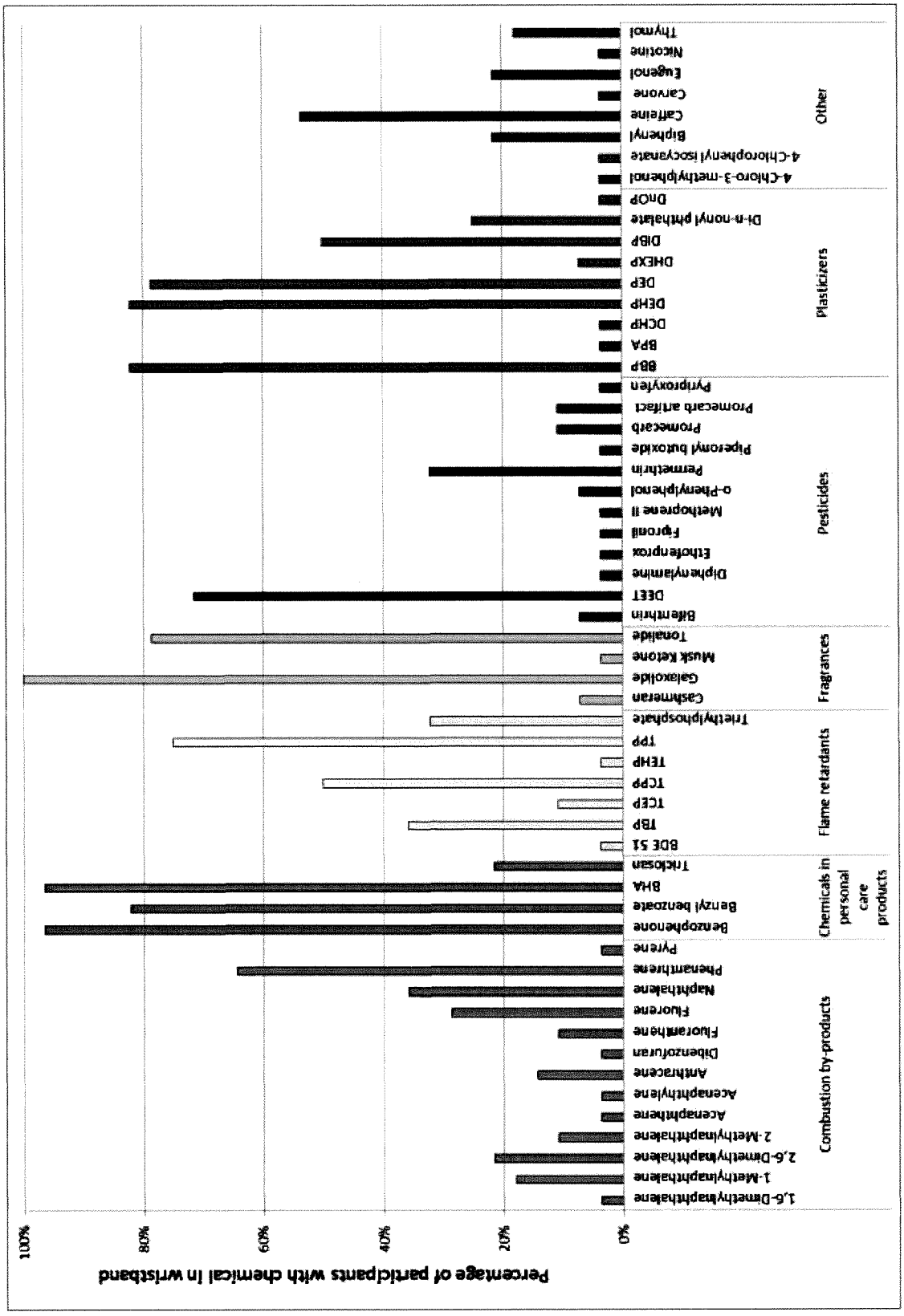


Are any of these chemicals hazardous**?

- The most common hazards associated with the **57** chemicals detected in this project are **cancer** (35%), **developmental** and/or **reproductive effects** (28%), **endocrine disruption activity** (61%), **respiratory effects** (28%) and **skin sensitization** and/or **skin irritation** (42%).
- Of the **8** phthalates detected, **2** (**DEHP** and **BPP**) have been permanently banned by Congress for use in toys and certain children's products due to their adverse effects on the male reproductive system. Bans are pending for **3** additional phthalates detected: **DCHP**, **DIBP**, and **DHEXP**. These phthalates remain legal for many other uses.
- Several hazardous flame retardant chemicals were detected, including **TCEP**, banned in the EU due to its toxicity to the reproductive system.
- A number of polycyclic aromatic hydrocarbons (PAHs) detected are persistent in the environment and associated with health effects such as cancer, including **naphthalene**, **phenanthrene**, and **anthracene**.

* The chemicals in personal care products category includes preservatives, antimicrobials, UV filters and fragrance enhancers. Plasticizers and fragrances may also be found in personal care products.

** The hazard of a chemical refers to its intrinsic ability to cause harm or induce a toxic effect. Risk is a function of both hazard and exposure, the amount of the chemical substance that enters a person's body.



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Appendix

I. Definitions

Hazard – The hazard of a chemical refers to its intrinsic ability to cause harm or induce a toxic effect, such as those listed below in "Chemical Hazard Types." Risk is a function of both *hazard* and *exposure*, the amount of the chemical substance that enters a person's body. Assuming a constant exposure, chemicals will differ in the type and magnitude of toxic effect(s) that they may induce.

Persistent bioaccumlative toxic chemicals ("PBTs") – Chemicals that do not break down readily from natural processes, accumulate in organisms – concentrating as they move up the food chain, and are harmful in small quantities.

Chemical Hazard Types[1]

Cancer (i.e., carcinogenicity) – Can cause or increase the risk of cancer.

Developmental effects – Can harm the developing child; effects may include birth defects, low birth weight, and biological or behavioral problems that appear as the child grows.

Reproductive effects – Can disrupt the male or female reproductive systems, changing sexual development, behavior or functions, decreasing fertility, or resulting in loss of the fetus during pregnancy.

Endocrine disruption activity – Can interfere with hormone communication and production, which controls metabolism, development, growth, reproduction, and behavior.

Respiratory effects – Can result in high sensitivity such that small quantities trigger asthma, rhinitis or other allergic reactions in the respiratory system.

Skin sensitization – Can trigger allergic reactions on the skin.

Skin irritation – Can irritate or seriously damage the skin.

Functions & Uses

Chemicals in personal care products – Chemicals added to personal care products (e.g., lotions, soaps, and cosmetics), such as preservatives and antimicrobials. Plasticizers and fragrances (see below) are excluded from this category.

Combustion by-products – Chemicals formed from the incomplete burning of coal, oil, gas, garbage, or other organic substances. Most chemicals included in this category are polycyclic aromatic hydrocarbons (PAHs).

Flame retardants – Chemicals added to a variety of materials, including textiles, electronics, plastics, and foam to reduce flammability.

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[1] Chemical hazard type definitions are based on the Pharos Project, available here: https://www.pharosproject.net/

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Fragrances – Chemicals with an inherent odor. These chemicals are often added to personal care products, cleaning products, food products, and more.

Pesticides – Chemicals designed to kill, repel, or mitigate any pest (insects, rodents, weeds, fungi, and microorganisms). This category excludes antimicrobials designed for use in personal care products.

Plasticizers – Chemicals used to provide plasticity and flexibility to plastics, such as polyvinylchloride (PVC). This category includes phthalate chemicals, which are added to a variety of items, including construction materials, personal care products, toys, food packaging, medical devices, and more.

Other – The "Other" category includes food additives, tobacco derivatives, chemical intermediates, and chemicals that cannot be classified due to many overlapping functions.

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II. Full List of Chemicals Detected

1,6-DIMETHYLNAPHTHALENE *(CASRN: 575-43-9)*
Specific Hazards:[2] No data
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of:[3] Air
Government Resource: http://toxnet.nlm.nih.gov/ (search term: 1,6-dimethylnaphthalene)

1-METHYLNAPHTHALENE *(CASRN: 90-12-0)*
Specific Hazards: Little human data available; harmful if swallowed
Primary Function(s): Combustion by-product, chemical intermediate
Found in or Used in the Manufacture of: Air; pesticides (inert ingredient); food packaging and additives; ink, pigments, and dyes
Government Resource: http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=43

2,2',4,6'-TETRABROMODIPHENYL ETHER (BDE 51) *(CASRN: 189084-57-9)*
Specific Hazards: Medium hazard for endocrine disruption activity
Primary Function(s): Flame retardant
Found in or Used in the Manufacture of: Building materials; fabric, furniture, and upholstery; electronics
Government Resource: http://www.toxtown.nlm.nih.gov/text_version/chemicals.php?id=79

2,6-DIMETHYLNAPHTHALENE *(CASRN: 581-42-0)*
Specific Hazards: No data
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air; food packaging and additives
Government Resource: Not available

2-METHYLNAPHTHALENE *(CASRN: 91-57-6)*
Specific Hazards: Little human data available; harmful if swallowed
Primary Function(s): Combustion by-product, chemical intermediate
Found in or Used in the Manufacture of: Air; pesticides (inert ingredient); building materials; ink, pigments, and dyes; petroleum products/fuels
Government Resource: http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=43

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[2] Chemical hazards data is based on the Pharos Project database, available here: https://www.pharosproject.net/
[3] Chemical uses data is based primarily on EPA's CPCat database (http://actor.epa.gov/cpcat/faces/home.xhtml), ATSDR's Substance List (http://www.atsdr.cdc.gov/substances/indexAZ.asp), and EPA's InertFinder database (http://iaspub.epa.gov/apex/pesticides/f?p=101:1).

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4-CHLORO-3-METHYLPHENOL *(CASRN: 59-50-7)*
Specific Hazards: High hazard for skin sensitization; medium hazard for endocrine disruption activity, skin irritation
Primary Function(s): Preservative in personal care products (antimicrobial), antiseptic, pesticide (industrial preservative) ("Other")
Found in or Used in the Manufacture of: Personal care products; pesticides; food packaging and additives; cleaning products; building materials; fabric, furniture, and upholstery; ink, pigments, and dyes; pharmacological products
Government Resource: Not available

4-CHLOROPHENYL ISOCYANATE *(CASRN: 104-12-1)*
Specific Hazards: High hazard for skin irritation; medium hazard for cancer, respiratory effects, organ toxicity
Primary Function(s): Chemical intermediate in manufacture of pesticides and pharmaceuticals ("Other")
Found in or Used in the Manufacture of: Pesticides (inert ingredient); pharmacological products
Government Resource: http://toxnet.nlm.nih.gov/ (search term: 4-Chlorophenyl isocyanate)

ACENAPHTHENE *(CASRN: 83-32-9)*
Specific Hazards: PBT; high hazard for cancer
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air; pesticides (manufacture); building materials; ink, pigments, and dyes; pharmacological products
Government Resource: http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/pahs.pdf

ACENAPHTHYLENE *(CASRN: 208-96-8)*
Specific Hazards: PBT; high hazard for cancer
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air
Government Resource: http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/pahs.pdf

ANTHRACENE *(CASRN: 120-12-7)*
Specific Hazards: PBT; high hazard for cancer, skin sensitization; medium hazard for endocrine disruption activity, respiratory effects, skin irritation
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air; pesticides (manufacture); building materials; manufacture/maintenance of vehicles; ink, pigments, and dyes; pharmacological products
Government Resource: http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/anthrace.pdf

BENZOPHENONE *(CASRN: 119-61-9)*
Specific Hazards: High hazard for cancer; medium hazard for endocrine disruption activity
Primary Function(s): UV filter and fragrance enhancer in personal care products, food additive
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); food packaging and additives; cleaning products; building materials; fabric, furniture, and upholstery; paper products; ink, pigments, and dyes; toys and children's products; electronics; cigarette chemicals; pharmacological products
Government Resource: http://hpd.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=570&query=119-61-9&searchas=TblChemicals

BENZYL BENZOATE *(CASRN: 120-51-4)*
Specific Hazards: Little human data available; harmful if swallowed
Primary Function(s): Fragrance fixative and preservative in personal care products, food additive, antiparasitic (treats scabies), pesticide, solvent, plasticizer
Found in or Used in the Manufacture of: Personal care products; air fresheners; pesticides (inert ingredient); food packaging and additives; cleaning products; building materials; manufacture/maintenance of vehicles; cigarette chemicals; pharmacological products
Government Resource: http://hpd.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=2881&query=120-51-4&searchas=TblChemicals

BIFENTHRIN *(CASRN: 82657-04-3)*
Specific Hazards: PBT; high hazard for organ toxicity; medium hazard for cancer, endocrine disruption activity, respiratory effects, skin irritation
Primary Function(s): Pesticide
Found in or Used in the Manufacture of: Pesticides
Government-Academic Collaboration: http://npic.orst.edu/factsheets/biftech.pdf

BIPHENYL *(CASRN: 92-52-4)*
Specific Hazards: High hazard for skin irritation; medium hazard for cancer, endocrine disruption activity, respiratory effects, organ toxicity
Primary Function(s): Chemical intermediate ("Other")
Found in or Used in the Manufacture of: Air; personal care products; pesticides (inert ingredient); food packaging and additives; building materials; paper products
Government Resource: http://www.epa.gov/ttnatw01/hlthef/biphenyl.html

BIS(2-ETHYLHEXYL)PHTHALATE (DEHP) *(CASRN: 117-81-7)*
Specific Hazards: High hazard for cancer, developmental effects, reproductive effects; medium hazard for endocrine disruption activity, respiratory effects, organ toxicity, skin irritation; potential concern for neurotoxicity
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Air; personal care products; pesticides (inert ingredient); food packaging and additives; cleaning products; building materials; fabric, furniture, and upholstery; manufacture/maintenance of vehicles; ink, pigments, and dyes; arts, crafts, hobby materials; toys and children's products; electronics; pharmacological products
Government Resource: http://www.atsdr.cdc.gov/phs/phs.asp?id=376&tid=65

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BISPHENOL A (BPA) *(CASRN: 80-05-7)*
Specific Hazards: High hazard for developmental effects, reproductive effects, skin sensitization; medium hazard for endocrine disruption activity, respiratory effects, organ toxicity, skin irritation
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Food packaging and additives; building materials; manufacture/maintenance of vehicles; paper products; ink, pigments, and dyes; arts, crafts, hobby materials; toys and children's products; electronics; petroleum products/fuels
Government Resource: https://www.niehs.nih.gov/health/assets/docs_a_e/bisphenol_a_bpa_508.pdf

BUTYL BENZYL PHTHALATE (BBP) (CASRN: 85-68-7)
Specific Hazards: High hazard for developmental effects, reproductive effects; medium hazard for cancer, endocrine disruption activity, respiratory effects, skin irritation
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Air; personal care products; pesticides (inert ingredient); food packaging and additives; building materials; manufacture/maintenance of vehicles; paper products; ink, pigments, and dyes; arts, crafts, hobby materials; toys and children's products
Government Resource: http://www.epa.gov/oppt/existingchemicals/pubs/actionplans/phthalates.html

BUTYLATED HYDROXYANISOLE (BHA) *(CASRN: 25013-16-5)*
Specific Hazards: High hazard for cancer, skin sensitization; medium hazard for developmental effects, reproductive effects, endocrine disruption activity
Primary Function(s): Preservative (antioxidant) in personal care products and food
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); food packaging and additives; building materials; toys and children's products; pharmacological products
Government Resource: https://ntp.niehs.nih.gov/ntp/roc/content/profiles/butylatedhydroxyanisole.pdf

CAFFEINE *(CASRN: 58-08-2)*
Specific Hazards: Medium hazard for endocrine disruption activity
Primary Function(s): Food additive ("Other")
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); food packaging and additives; cigarette chemicals; pharmacological products
Government Resource: http://www.fda.gov/downloads/UCM200805.pdf

CARVONE *(CASRN: 99-49-0)*
Specific Hazards: Little human data available; harmful if swallowed
Primary Function(s): Preservative (antimicrobial) in personal care products, food additive, fragrance, pesticide (insect repellent) ("Other")
Found in or Used in the Manufacture of: Personal care products; pesticides; food packaging and additives; cleaning products; cigarette chemicals
Government Resource: http://toxnet.nlm.nih.gov/ (search term: carvone)

CASHMERAN *(CASRN: 33704-61-9)*
Specific Hazards: Medium hazard for endocrine disruption activity
Primary Function(s): Fragrance
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); cleaning products
Government Resource: Not available

DIBENZOFURAN *(CASRN: 132-64-9)*
Specific Hazards: PBT
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air
Government Resource: http://www.epa.gov/ttnatw01/hlthef/di-furan.html

DICYCLOHEXYL PHTHALATE (DCHP) *(CASRN: 84-61-7)*
Specific Hazards: High hazard for reproductive effects; medium hazard for endocrine disruption activity, respiratory effects
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Food packaging and additives; building materials; ink, pigments, and dyes
Government Resource: http://www.cdc.gov/biomonitoring/DCHP_BiomonitoringSummary.html

DIETHYL PHTHALATE (DEP) *(CASRN: 84-66-2)*
Specific Hazards: High hazard for reproductive effects, skin sensitization; medium hazard for endocrine disruption activity, respiratory effects, skin irritation
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); food packaging and additives; cleaning products; building materials; manufacture/maintenance of vehicles; ink, pigments, and dyes; toys and children's products; pharmacological products
Government Resource: http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=112

DIISOBUTYL PHTHALATE (DIBP) *(CASRN: 84-69-5)*
Specific Hazards: High hazard for developmental effects, reproductive effects; medium hazard for endocrine disruption activity, respiratory effects
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Food packaging and additives; building materials; fabric, furniture, and upholstery; manufacture/maintenance of vehicles; paper products; ink, pigments, and dyes; toys and children's products
Government Resource: http://toxtown.nlm.nih.gov/text_version/chemicals.php?id=24

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DI-N-HEXYL PHTHALATE (DHEXP) *(CASRN: 84-75-3)*
Specific Hazards: High hazard for reproductive effects; medium hazard for developmental effects, endocrine disruption activity, respiratory effects
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Pesticides (inert ingredient); food packaging and additives; building materials; manufacture/maintenance of vehicles; toys and children's products
Government Resource: http://toxtown.nlm.nih.gov/text_version/chemicals.php?id=24

DI-N-NONYL PHTHALATE *(CASRN: 84-76-4)*
Specific Hazards: Little human data available; harmful if swallowed
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Data unavailable
Government Resource: http://toxtown.nlm.nih.gov/text_version/chemicals.php?id=24

DI-N-OCTYL PHTHALATE (DnOP) *(CASRN: 117-84-0)*
Specific Hazards: High hazard for skin sensitization; medium hazard for developmental effects, endocrine disruption activity, respiratory effects; low hazard for reproductive effects
Primary Function(s): Plasticizer
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); food packaging and additives; building materials; manufacture/maintenance of vehicles; arts, crafts, hobby materials; toys and children's products; electronics; pharmacological products
Government Resource: http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=204

DIPHENYLAMINE *(CASRN: 122-39-4)*
Specific Hazards: High hazard for skin sensitization; medium hazard for cancer, developmental effects, reproductive effects, organ toxicity
Primary Function(s): Pesticide (antioxidant)
Found in or Used in the Manufacture of: Pesticides; food packaging and additives; building materials; manufacture/maintenance of vehicles; ink, pigments, and dyes; petroleum products/fuels
Government Resource: http://www.epa.gov/opp00001/reregistration/REDs/factsheets/2210fact.pdf

ETHOFENPROX *(CASRN: 80844-07-1)*
Specific Hazards: High hazard for developmental effects; medium hazard for endocrine disruption activity
Primary Function(s): Pesticide (used to repel bed bugs)
Found in or Used in the Manufacture of: Pesticides
Government Resource: http://householdproducts.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=2105&query=80844-07-1&searchas=TblChemicals

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EUGENOL *(CASRN: 97-53-0)*
Specific Hazards: High hazard for respiratory effects, skin sensitization; medium hazard for skin irritation
Primary Function(s): Fragrance, food additive, antiseptic, analgesic ("Other")
Found in or Used in the Manufacture of: Personal care products; air fresheners; pesticides (active and inert ingredient); food packaging and additives; cleaning products; building materials; manufacture/maintenance of vehicles; pharmacological products; petroleum products/fuels
Government Resource: http://householdproducts.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=1925&query=97-53-0&searchas=TblChemicals

FIPRONIL *(CASRN: 120068-37-3)*
Specific Hazards: PBT; high hazard for organ toxicity; medium hazard for reproductive effects, endocrine disruption activity; potential concern for neurotoxicity
Primary Function(s): Pesticide
Found in or Used in the Manufacture of: Pesticides
Government-Academic Collaboration: http://npic.orst.edu/factsheets/fipronil.html

FLUORANTHENE *(CASRN: 206-44-0)*
Specific Hazards: PBT; high hazard for cancer; medium hazard for endocrine disruption activity
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air; building materials
Government Resource: http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/pahs.pdf

FLUORENE *(CASRN: 86-73-7)*
Specific Hazards: PBT; high hazard for cancer; medium hazard for endocrine disruption activity
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air; pesticides (manufacture); building materials; ink, pigments, and dyes
Government Resource: http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/flourene.pdf

GALAXOLIDE *(CASRN: 1222-05-5)*
Specific Hazards: PBT; high hazard for developmental effects[4]; medium hazard for endocrine disruption activity
Primary Function(s): Fragrance
Found in or Used in the Manufacture of: Personal care products; air fresheners; pesticides (inert ingredient); cleaning products; building materials; manufacture/maintenance of vehicles
Government Resource: http://cfpub.epa.gov/si/si_public_record_report.cfm?dirEntryID=245534

[4] Evidence for reproductive/developments effects for galaxolide is based on preliminary studies. The majority of research demonstrates that galaxolide exerts its toxic effects on the environment; there is limited data to indicate that this chemical is toxic to humans.

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METHOPRENE II *(CASRN: 999045-03-3)*
Specific Hazards: Medium hazard for endocrine disruption activity
Primary Function(s): Pesticide
Found in or Used in the Manufacture of: Pesticides
Government-Academic Collaboration: http://npic.orst.edu/factsheets/methogen.html#whatis

MUSK KETONE *(CASRN: 81-14-1)*
Specific Hazards: PBT; medium hazard for cancer, endocrine disruption activity
Primary Function(s): Fragrance
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); food packaging and additives; cleaning products
Government Resource: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+7694

N,N-DIETHYL-M-TOLUAMIDE (DEET) *(CASRN: 134-62-3)*
Specific Hazards: High hazard for skin irritation
Primary Function(s): Pesticide (insect repellent)
Found in or Used in the Manufacture of: Personal care products; pesticides;
Government Resource: http://www2.epa.gov/insect-repellents/deet

NAPHTHALENE *(CASRN: 91-20-3)*
Specific Hazards: PBT; high hazard for cancer, organ toxicity, skin sensitization; medium hazard for endocrine disruption activity, skin irritation
Primary Function(s): Combustion by-product, chemical intermediate (manufacture of plastic and moth repellants)
Found in or Used in the Manufacture of: Air; pesticides (inert ingredient); cleaning products; building materials; fabric, furniture, and upholstery; manufacture/maintenance of vehicles; ink, pigments, and dyes; petroleum products/fuels; pharmacological products
Government Resource: http://www.epa.gov/ttnatw01/hlthef/naphthal.html

NICOTINE *(CASRN: 54-11-5)*
Specific Hazards: High hazard for developmental effects; medium hazard for reproductive effects, endocrine disruption activity; potential concern for neurotoxicity
Primary Function(s): Tobacco derivative ("Other")
Found in or Used in the Manufacture of: Cigarette chemicals; pharmacological products
Government Resource:
http://www.fda.gov/TobaccoProducts/default.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=tobacco&utm_content=1

O-PHENYLPHENOL *(CASRN: 90-43-7)*
Specific Hazards: High hazard for cancer, skin irritation; medium hazard for endocrine disruption activity, respiratory effects, organ toxicity
Primary Function(s): Pesticide
Found in or Used in the Manufacture of: Personal care products; pesticides; food packaging and additives; cleaning products; building materials; fabric, furniture, and upholstery; paper products
Government Resource: http://www.cdc.gov/biomonitoring/Orthophenylphenol_BiomonitoringSummary.html

PERMETHRIN *(CASRN: 52645-53-1)*
Specific Hazards: High hazard for respiratory effects; medium hazard for endocrine disruption activity, organ toxicity, skin sensitization, skin irritation
Primary Function(s): Pesticide
Found in or Used in the Manufacture of: Personal care products; pesticides; building materials; fabric, furniture, and upholstery; paper products; pharmacological products
Government Resource: http://www.epa.gov/oppsrrd1/reregistration/REDs/factsheets/permethrin_fs.htm

PHENANTHRENE *(CASRN: 85-01-8)*
Specific Hazards: PBT; high hazard for cancer, skin sensitization; medium hazard for endocrine disruption activity
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air; pesticides (manufacture); building materials; ink, pigments, and dyes; pharmacological products; explosives
Government Resource: http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/phenanth.pdf

PIPERONYL BUTOXIDE *(CASRN: 51-03-6)*
Specific Hazards: Medium hazard for endocrine disruption activity, skin irritation
Primary Function(s): Pesticide (synergist)
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); pharmacological products
Government-Academic Collaboration: http://npic.orst.edu/factsheets/pbotech.pdf

PROMECARB *(CASRN: 2631-37-0)*
Specific Hazards: Little human data available; harmful if swallowed
Primary Function(s): Pesticide
Found in or Used in the Manufacture of: Pesticides
Government Resource: Not available

PROMECARB ARTIFACT [5-isopropyl-3-methylphenol] *(CASRN: 485106)*
Specific Hazards: Little human data available; harmful if swallowed
Primary Function(s): Pesticide
Found in or Used in the Manufacture of: Pesticides
Government Resource: Not available

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PYRENE *(CASRN: 129-00-0)*
Specific Hazards: PBT; high hazard for cancer; medium hazard for endocrine disruption activity
Primary Function(s): Combustion by-product
Found in or Used in the Manufacture of: Air; pesticides (manufacture); personal care products; cleaning products; building materials; manufacture/maintenance of vehicles; ink, pigments, and dyes
Government Resource: http://www.epa.gov/osw/hazard/wastemin/minimize/factshts/pyrene.pdf

PYRIPROXYFEN (CASRN: 95737-68-1)
Specific Hazards: Medium hazard for endocrine disruption activity
Primary Function(s): Pesticide
Found in or Used in the Manufacture of: Pesticides
Government Resource: http://hpd.nlm.nih.gov/cgi-bin/household/search?queryx=95737-68-1&tbl=TblChemicals&prodcat=all

THYMOL *(CASRN: 89-83-8)*
Specific Hazards: Very high hazard for skin irritation; medium hazard for respiratory effects
Primary Function(s): Preservative (antimicrobial) in personal care products, food additive, fragrance, pesticide ("Other")
Found in or Used in the Manufacture of: Personal care products; pesticides; food packaging and additives; cleaning products; building materials; cigarette chemicals; pharmacological products
Government Resource: http://hpd.nlm.nih.gov/cgi-bin/household/brands?tbl=chem&id=437&query=thymol&searchas=TblChemicals

TONALIDE *(CASRN: 1506-02-1)*
Specific Hazards: Medium hazard for endocrine disruption activity
Primary Function(s): Fragrance
Found in or Used in the Manufacture of: Personal care products; pesticides (inert ingredient); cleaning products; building materials
Government Resource: http://toxnet.nlm.nih.gov/ (search term: tonalide)

TRIBUTYL PHOSPHATE (TBP) *(CASRN: 126-73-8)*
Specific Hazards: High hazard for skin irritation; medium hazard for cancer, developmental effects; potential concern for neurotoxicity
Primary Function(s): Flame retardant, plasticizer, solvent
Found in or Used in the Manufacture of: Pesticides (inert ingredient); food packaging and additives; cleaning products; building materials; fabric, furniture, and upholstery; manufacture/maintenance of vehicles; ink, pigments, and dyes; electronics; toys and children's products; petroleum products/fuels
Government Resource: http://www.atsdr.cdc.gov/phs/phs.asp?id=1118&tid=239

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TRICLOSAN *(CASRN: 3380-34-5)*
Specific Hazards: PBT; high hazard for skin irritation; medium hazard for endocrine disruption activity
Primary Function(s): Preservative (antimicrobial) in personal care products and other consumer products, pesticide
Found in or Used in the Manufacture of: Personal care products; pesticides; cleaning products; building materials; fabric, furniture, and upholstery; pharmacological products
Government Resource: http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm205999.htm

TRIETHYLPHOSPHATE *(CASRN: 78-40-0)*
Specific Hazards: Little human data available; harmful if swallowed
Primary Function(s): Flame retardant, plasticizer, chemical intermediate, solvent
Found in or Used in the Manufacture of: Pesticides (inert ingredient); food packaging and additives; building materials; electronics
Government Resource: http://toxnet.nlm.nih.gov/ (search term: triethylphosphate)

TRIPHENYL PHOSPHATE (TPP) *(CASRN: 115-86-6)*
Specific Hazards: Medium hazard for endocrine disruption activity; potential concern for neurotoxicity
Primary Function(s): Flame retardant
Found in or Used in the Manufacture of: Pesticides (inert ingredient); food packaging and additives; building materials; fabric, furniture, and upholstery; manufacture/maintenance of vehicles; paper products; ink, pigments, and dyes; arts, crafts, hobby materials; toys and children's products; electronics
Government Resource: http://www.atsdr.cdc.gov/phs/phs.asp?id=1118&tid=239

TRIS(2-CHLOROETHYL) PHOSPHATE (TCEP) *(CASRN: 115-96-8)*
Specific Hazards: PBT; high hazard for cancer, reproductive effects; medium hazard for skin irritation
Primary Function(s): Flame retardant
Found in or Used in the Manufacture of: Personal care products; building materials; manufacture/maintenance of vehicles; toys and children's products
Government Resource: http://www.atsdr.cdc.gov/phs/phs.asp?id=1118&tid=239

TRIS(2-CHLORO-1-METHYLETHYL) PHOSPHATE (TCPP) *(CASRN: 13674-84-5)*
Specific Hazards: PBT
Primary Function(s): Flame retardant
Found in or Used in the Manufacture of: Pesticides (inert ingredient); building materials; fabric, furniture, and upholstery; electronics
Government Resource: http://www.atsdr.cdc.gov/phs/phs.asp?id=1118&tid=239

TRIS(2-ETHYLHEXYL) PHOSPHATE (TEHP) *(CASRN: 78-42-2)*
Specific Hazards: Medium hazard for skin irritation
Primary Function(s): Flame retardant, plasticizer, solvent
Found in or Used in the Manufacture of: Pesticides (inert ingredient); food packaging and additives; building materials; fabric, furniture, and upholstery
Government Resource:
http://oehha.ca.gov/prop65/public_meetings/ClC101211/101211Tris2ethylhexylphosphate.pdf

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III. Additional Information on the Wristband Technology

EDF partnered with MyExposome, Inc. on this project using the wristband technology and analytic methods from MyExposome. You can find more information here: www.MyExposome.com.

The personal environmental monitors used in this project are designed to detect organic chemical compounds in the environment. The monitors cannot detect metals (e.g., lead and mercury) or inorganic air pollutants (e.g., ozone and sulfur dioxide).

See here for the full list of chemicals the wristbands are able to detect:
http://www.myexposome.com/testedchems

International Agency for Research on Cancer
World Health Organization

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

IARC MONOGRAPHS - MEETINGS

Upcoming Meetings

Meeting 111: Some Nanomaterials and Some Fibres (30 September - 7 October 2014)

Preliminary List of Agents
Call for Data (closing date 3 September 2014)
Call for Experts (closing date 30 January 2014)
Request for Observer Status (closing date 3 June 2014)
WHO Declaration of Interests for this volume

Meeting 112: Some Organophosphate Insecticides (3-10 March 2015)

Call for Data (closing date 3 February 2015)
Call for Experts (closing date 30 July 2014)
Request for Observer Status (closing date 3 November 2014)
WHO Declaration of Interests for this volume

Future priorities for *IARC Monographs*
In addition, IARC may schedule other agents for review in response to new scientific information or an urgent public health need.

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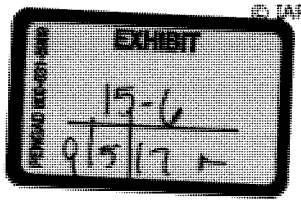
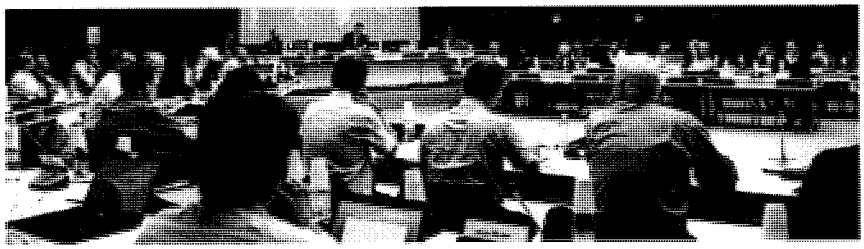


International Agency for Research on Cancer
World Health Organization

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans



IARC MONOGRAPHS - MEETINGS

Upcoming Meetings

Meeting 111: Some Nanomaterials and Some Fibres
(30 September - 7 October 2014)

Preliminary List of Agents
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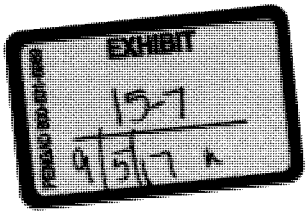

Meeting 112: Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos
(3-10 March 2015)

Call for Data (closing date 3 February 2015)
Call for Experts (closing date 30 July 2014)
Request for Observer Status (closing date 3 November 2014)
WHO Declaration of Interests for this volume

Meeting 113: Some Organochlorine Insecticides and Some Chlorphenoxy Herbicides
(2-9 June 2015)

Call for Data (closing date 2 May 2015)
Call for Experts (closing date 10 October 2014)
Request for Observer Status (closing date 2 February 2015)
WHO Declaration of Interests for this volume

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

PREAMBLE

LYON, FRANCE
2006

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Amended January 2006

Last update September 2015

PREAMBLE

The Preamble to the *IARC Monographs* describes the objective and scope of the programme, the scientific principles and procedures used in developing a *Monograph*, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a *Monograph* or list of evaluations.

A. GENERAL PRINCIPLES AND PROCEDURES

1. Background

Soon after IARC was established in 1965, it received frequent requests for advice on the carcinogenic risk of chemicals, including requests for lists of known and suspected human carcinogens. It was clear that it would not be a simple task to summarize adequately the complexity of the information that was available, and IARC began to consider means of obtaining international expert opinion on this topic. In 1970, the IARC Advisory Committee on Environmental Carcinogenesis recommended ' . . . that a compendium on carcinogenic chemicals be prepared by experts. The biological activity and evaluation of practical importance to public health should be referenced and documented.' The IARC Governing Council adopted a resolution concerning the role of IARC in providing government authorities with expert, independent, scientific opinion on environmental carcinogenesis. As one means to that end, the Governing Council recommended that IARC should prepare monographs on the evaluation of carcinogenic risk of chemicals to man, which became the initial title of the series.

In the succeeding years, the scope of the programme broadened as *Monographs* were developed for groups of related chemicals, complex mixtures, occupational exposures, physical and biological agents and lifestyle factors. In 1988, the phrase 'of chemicals' was dropped from the title, which assumed its present form, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*.

Through the *Monographs* programme, IARC seeks to identify the causes of human cancer. This is the first step in cancer prevention, which is needed as much today as when IARC was established. The global burden of cancer is high and continues to increase: the annual number of new cases was estimated at 10.1 million in 2000 and is expected to reach 15 million by 2020 (Stewart & Kleihues, 2003). With current trends in demographics and exposure, the cancer burden has been shifting from high-resource countries to low- and medium-resource countries. As a result of *Monographs* evaluations, national health agencies have been able, on scientific grounds, to take measures to reduce human exposure to carcinogens in the workplace and in the environment.

The criteria established in 1971 to evaluate carcinogenic risks to humans were adopted by the Working Groups whose deliberations resulted in the first 16 volumes of the *Monographs* series. Those criteria were subsequently updated by further ad-hoc Advisory Groups (IARC, 1977, 1978, 1979, 1982, 1983, 1987, 1988, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006).

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been

established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.

2. Objective and scope

The objective of the programme is to prepare, with the help of international Working Groups of experts, and to publish in the form of *Monographs*, critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures. The *Monographs* represent the first step in carcinogen risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that an agent could alter the age-specific incidence of cancer in humans. The *Monographs* may also indicate where additional research efforts are needed, specifically when data immediately relevant to an evaluation are not available.

In this Preamble, the term 'agent' refers to any entity or circumstance that is subject to evaluation in a *Monograph*. As the scope of the programme has broadened, categories of agents now include specific chemicals, groups of related chemicals, complex mixtures, occupational or environmental exposures, cultural or behavioural practices, biological organisms and physical agents. This list of categories may expand as causation of, and susceptibility to, malignant disease become more fully understood.

A cancer 'hazard' is an agent that is capable of causing cancer under some circumstances, while a cancer 'risk' is an estimate of the carcinogenic effects expected from exposure to a cancer hazard. The *Monographs* are an exercise in evaluating cancer hazards, despite the historical presence of the word 'risks' in the title. The distinction between hazard and risk is important, and the *Monographs* identify cancer hazards even when risks are very low at current exposure levels, because new uses or unforeseen exposures could engender risks that are significantly higher.

In the *Monographs*, an agent is termed 'carcinogenic' if it is capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity. The induction of benign neoplasms may in some circumstances (see Part B, Section 3a) contribute to the judgement that the agent is carcinogenic. The terms 'neoplasm' and 'tumour' are used interchangeably.

The Preamble continues the previous usage of the phrase 'strength of evidence' as a matter of historical continuity, although it should be understood that *Monographs* evaluations consider studies that support a finding of a cancer hazard as well as studies that do not.

Some epidemiological and experimental studies indicate that different agents may act at different stages in the carcinogenic process, and several different mechanisms may be involved. The aim of the *Monographs* has been, from their inception, to evaluate evidence of carcinogenicity at any stage in the carcinogenesis process, independently of the underlying mechanisms. Information on mechanisms may, however, be used in making the overall evaluation (IARC, 1991; Vainio *et al.*, 1992; IARC, 2005, 2006; see also Part B, Sections 4 and 6). As mechanisms of carcinogenesis are elucidated, IARC convenes international scientific conferences to determine whether a broad-based consensus has emerged on how specific mechanistic data can be used in an evaluation of human carcinogenicity. The results of such conferences are reported in IARC Scientific Publications, which, as long as they still reflect the current state of scientific knowledge, may guide subsequent Working Groups.

Although the *Monographs* have emphasized hazard identification, important issues may also involve dose–response assessment. In many cases, the same epidemiological and experimental studies used to evaluate a cancer hazard can also be used to estimate a dose–

response relationship. A *Monograph* may undertake to estimate dose–response relationships within the range of the available epidemiological data, or it may compare the dose–response information from experimental and epidemiological studies. In some cases, a subsequent publication may be prepared by a separate Working Group with expertise in quantitative dose–response assessment.

The *Monographs* are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.

3. Selection of agents for review

Agents are selected for review on the basis of two main criteria: (a) there is evidence of human exposure and (b) there is some evidence or suspicion of carcinogenicity. Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices). Chemical analogues and compounds with biological or physical characteristics similar to those of suspected carcinogens may also be considered, even in the absence of data on a possible carcinogenic effect in humans or experimental animals.

The scientific literature is surveyed for published data relevant to an assessment of carcinogenicity. Ad-hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998 and 2003 made recommendations as to which agents should be evaluated in the *Monographs* series. Recent recommendations are available on the *Monographs* programme website (http://monographs.iarc.fr). IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.

As significant new data become available on an agent for which a *Monograph* exists, a re-evaluation may be made at a subsequent meeting, and a new *Monograph* published. In some cases it may be appropriate to review only the data published since a prior evaluation. This can be useful for updating a database, reviewing new data to resolve a previously open question or identifying new tumour sites associated with a carcinogenic agent. Major changes in an evaluation (e.g. a new classification in Group 1 or a determination that a mechanism does not operate in humans, see Part B, Section 6) are more appropriately addressed by a full review.

4. Data for the *Monographs*

Each *Monograph* reviews all pertinent epidemiological studies and cancer bioassays in experimental animals. Those judged inadequate or irrelevant to the evaluation may be cited but not summarized. If a group of similar studies is not reviewed, the reasons are indicated.

Mechanistic and other relevant data are also reviewed. A *Monograph* does not necessarily cite all the mechanistic literature concerning the agent being evaluated (see Part B, Section

4). Only those data considered by the Working Group to be relevant to making the evaluation are included.

With regard to epidemiological studies, cancer bioassays, and mechanistic and other relevant data, only reports that have been published or accepted for publication in the openly available scientific literature are reviewed. The same publication requirement applies to studies originating from IARC, including meta-analyses or pooled analyses commissioned by IARC in advance of a meeting (see Part B, Section 2c). Data from government agency reports that are publicly available are also considered. Exceptionally, doctoral theses and other material that are in their final form and publicly available may be reviewed.

Exposure data and other information on an agent under consideration are also reviewed. In the sections on chemical and physical properties, on analysis, on production and use and on occurrence, published and unpublished sources of information may be considered.

Inclusion of a study does not imply acceptance of the adequacy of the study design or of the analysis and interpretation of the results, and limitations are clearly outlined in square brackets at the end of each study description (see Part B). The reasons for not giving further consideration to an individual study also are indicated in the square brackets.

5. Meeting participants

Five categories of participant can be present at *Monograph* meetings.

(a) The Working Group is responsible for the critical reviews and evaluations that are developed during the meeting. The tasks of Working Group Members are: (i) to ascertain that all appropriate data have been collected; (ii) to select the data relevant for the evaluation on the basis of scientific merit; (iii) to prepare accurate summaries of the data to enable the reader to follow the reasoning of the Working Group; (iv) to evaluate the results of epidemiological and experimental studies on cancer; (v) to evaluate data relevant to the understanding of mechanisms of carcinogenesis; and (vi) to make an overall evaluation of the carcinogenicity of the exposure to humans. Working Group Members generally have published significant research related to the carcinogenicity of the agents being reviewed, and IARC uses literature searches to identify most experts. Working Group Members are selected on the basis of (a) knowledge and experience and (b) absence of real or apparent conflicts of interests. Consideration is also given to demographic diversity and balance of scientific findings and views.

(b) Invited Specialists are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. They may also contribute text on non-influential issues in the section on exposure, such as a general description of data on production and use (see Part B, Section 1). Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.

(c) Representatives of national and international health agencies often attend meetings because their agencies sponsor the programme or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph,* or participate in the evaluations.

(d) Observers with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Attention will be given to achieving a balance of Observers from constituencies with differing perspectives. They are invited to observe the meeting and

should not attempt to influence it. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion. Observers agree to respect the Guidelines for Observers at *IARC Monographs* meetings (available at http://monographs.iarc.fr).

(e) The IARC Secretariat consists of scientists who are designated by IARC and who have relevant expertise. They serve as rapporteurs and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the *Monographs* programme website (http://monographs.iarc.fr) approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC (Cogliano *et al.*, 2005).

All participants are listed, with their principal affiliations, at the beginning of each volume. Each participant who is a Member of a Working Group serves as an individual scientist and not as a representative of any organization, government or industry.

6. Working procedures

A separate Working Group is responsible for developing each volume of *Monographs*. A volume contains one or more *Monographs*, which can cover either a single agent or several related agents. Approximately one year in advance of the meeting of a Working Group, the agents to be reviewed are announced on the *Monographs* programme website (http://monographs.iarc.fr) and participants are selected by IARC staff in consultation with other experts. Subsequently, relevant biological and epidemiological data are collected by IARC from recognized sources of information on carcinogenesis, including data storage and retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Industrial associations, labour unions and other knowledgeable organizations may be asked to provide input to the sections on production and use, although this involvement is not required as a general rule. Information on production and trade is obtained from governmental, trade and market research publications and, in some cases, by direct contact with industries. Separate production data on some agents may not be available for a variety of reasons (e.g. not collected or made public in all producing countries, production is small). Information on uses may be obtained from published sources but is often complemented by direct contact with manufacturers. Efforts are made to supplement this information with data from other national and international sources.

Six months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The working papers are compiled by IARC staff and sent, prior to the meeting, to Working Group Members and Invited Specialists for review.

The Working Group meets at IARC for seven to eight days to discuss and finalize the texts and to formulate the evaluations. The objectives of the meeting are peer review and consensus. During the first few days, four subgroups (covering exposure data, cancer in humans, cancer in experimental animals, and mechanistic and other relevant data) review the working papers, develop a joint subgroup draft and write summaries. Care is taken to ensure that each study summary is written or reviewed by someone not associated with the study being considered. During the last few days, the Working Group meets in plenary session to review the subgroup drafts and develop the evaluations. As a result, the entire volume is the joint product of the Working Group, and there are no individually authored sections.

IARC Working Groups strive to achieve a consensus evaluation. Consensus reflects broad agreement among Working Group Members, but not necessarily unanimity. The chair may elect to poll Working Group Members to determine the diversity of scientific opinion on issues where consensus is not readily apparent.

After the meeting, the master copy is verified by consulting the original literature, edited and prepared for publication. The aim is to publish the volume within six months of the Working Group meeting. A summary of the outcome is available on the *Monographs* programme website soon after the meeting.

B. SCIENTIFIC REVIEW AND EVALUATION

The available studies are summarized by the Working Group, with particular regard to the qualitative aspects discussed below. In general, numerical findings are indicated as they appear in the original report; units are converted when necessary for easier comparison. The Working Group may conduct additional analyses of the published data and use them in their assessment of the evidence; the results of such supplementary analyses are given in square brackets. When an important aspect of a study that directly impinges on its interpretation should be brought to the attention of the reader, a Working Group comment is given in square brackets.

The scope of the *IARC Monographs* programme has expanded beyond chemicals to include complex mixtures, occupational exposures, physical and biological agents, lifestyle factors and other potentially carcinogenic exposures. Over time, the structure of a *Monograph* has evolved to include the following sections:

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

In addition, a section of General Remarks at the front of the volume discusses the reasons the agents were scheduled for evaluation and some key issues the Working Group encountered during the meeting.

This part of the Preamble discusses the types of evidence considered and summarized in each section of a *Monograph*, followed by the scientific criteria that guide the evaluations.

1. Exposure data

Each *Monograph* includes general information on the agent: this information may vary substantially between agents and must be adapted accordingly. Also included is information on production and use (when appropriate), methods of analysis and detection, occurrence, and sources and routes of human occupational and environmental exposures. Depending on the agent, regulations and guidelines for use may be presented.

(a) General information on the agent

For chemical agents, sections on chemical and physical data are included: the Chemical Abstracts Service Registry Number, the latest primary name and the IUPAC systematic name are recorded; other synonyms are given, but the list is not necessarily comprehensive. Information on chemical and physical properties that are relevant to identification, occurrence and biological activity is included. A description of technical products of chemicals includes trade names, relevant specifications and available information on composition and impurities. Some of the trade names given may be those of mixtures in which the agent being evaluated is only one of the ingredients.

For biological agents, taxonomy, structure and biology are described, and the degree of variability is indicated. Mode of replication, life cycle, target cells, persistence, latency, host response and clinical disease other than cancer are also presented.

For physical agents that are forms of radiation, energy and range of the radiation are included. For foreign bodies, fibres and respirable particles, size range and relative dimensions are indicated.

For agents such as mixtures, drugs or lifestyle factors, a description of the agent, including its composition, is given.

Whenever appropriate, other information, such as historical perspectives or the description of an industry or habit, may be included.

(b) Analysis and detection

An overview of methods of analysis and detection of the agent is presented, including their sensitivity, specificity and reproducibility. Methods widely used for regulatory purposes are emphasized. Methods for monitoring human exposure are also given. No critical evaluation or recommendation of any method is meant or implied.

(c) Production and use

The dates of first synthesis and of first commercial production of a chemical, mixture or other agent are provided when available; for agents that do not occur naturally, this information may allow a reasonable estimate to be made of the date before which no human exposure to the agent could have occurred. The dates of first reported occurrence of an exposure are also provided when available. In addition, methods of synthesis used in past and present commercial production and different methods of production, which may give rise to different impurities, are described.

The countries where companies report production of the agent, and the number of companies in each country, are identified. Available data on production, international trade and uses are obtained for representative regions. It should not, however, be inferred that those areas or nations are necessarily the sole or major sources or users of the agent. Some identified uses may not be current or major applications, and the coverage is not necessarily

comprehensive. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their therapeutic efficacy.

(d) Occurrence and exposure

Information on the occurrence of an agent in the environment is obtained from data derived from the monitoring and surveillance of levels in occupational environments, air, water, soil, plants, foods and animal and human tissues. When available, data on the generation, persistence and bioaccumulation of the agent are also included. Such data may be available from national databases.

Data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed and the factors that contribute to the exposure are reported. Information is presented on the range of human exposure, including occupational and environmental exposures. This includes relevant findings from both developed and developing countries. Some of these data are not distributed widely and may be available from government reports and other sources. In the case of mixtures, industries, occupations or processes, information is given about all agents known to be present. For processes, industries and occupations, a historical description is also given, noting variations in chemical composition, physical properties and levels of occupational exposure with date and place. For biological agents, the epidemiology of infection is described.

(e) Regulations and guidelines

Statements concerning regulations and guidelines (e.g. occupational exposure limits, maximal levels permitted in foods and water, pesticide registrations) are included, but they may not reflect the most recent situation, since such limits are continuously reviewed and modified. The absence of information on regulatory status for a country should not be taken to imply that that country does not have regulations with regard to the exposure. For biological agents, legislation and control, including vaccination and therapy, are described.

2. Studies of cancer in humans

This section includes all pertinent epidemiological studies (see Part A, Section 4). Studies of biomarkers are included when they are relevant to an evaluation of carcinogenicity to humans.

(a) Types of study considered

Several types of epidemiological study contribute to the assessment of carcinogenicity in humans — cohort studies, case–control studies, correlation (or ecological) studies and intervention studies. Rarely, results from randomized trials may be available. Case reports and case series of cancer in humans may also be reviewed.

Cohort and case–control studies relate individual exposures under study to the occurrence of cancer in individuals and provide an estimate of effect (such as relative risk) as the main measure of association. Intervention studies may provide strong evidence for making causal inferences, as exemplified by cessation of smoking and the subsequent decrease in risk for lung cancer.

In correlation studies, the units of investigation are usually whole populations (e.g. in particular geographical areas or at particular times), and cancer frequency is related to a summary measure of the exposure of the population to the agent under study. In correlation studies, individual exposure is not documented, which renders this kind of study more prone

to confounding. In some circumstances, however, correlation studies may be more informative than analytical study designs (see, for example, the *Monograph* on arsenic in drinking-water; IARC, 2004).

In some instances, case reports and case series have provided important information about the carcinogenicity of an agent. These types of study generally arise from a suspicion, based on clinical experience, that the concurrence of two events — that is, a particular exposure and occurrence of a cancer — has happened rather more frequently than would be expected by chance. Case reports and case series usually lack complete ascertainment of cases in any population, definition or enumeration of the population at risk and estimation of the expected number of cases in the absence of exposure.

The uncertainties that surround the interpretation of case reports, case series and correlation studies make them inadequate, except in rare instances, to form the sole basis for inferring a causal relationship. When taken together with case–control and cohort studies, however, these types of study may add materially to the judgement that a causal relationship exists.

Epidemiological studies of benign neoplasms, presumed preneoplastic lesions and other end-points thought to be relevant to cancer are also reviewed. They may, in some instances, strengthen inferences drawn from studies of cancer itself.

(b) Quality of studies considered

It is necessary to take into account the possible roles of bias, confounding and chance in the interpretation of epidemiological studies. Bias is the effect of factors in study design or execution that lead erroneously to a stronger or weaker association than in fact exists between an agent and disease. Confounding is a form of bias that occurs when the relationship with disease is made to appear stronger or weaker than it truly is as a result of an association between the apparent causal factor and another factor that is associated with either an increase or decrease in the incidence of the disease. The role of chance is related to biological variability and the influence of sample size on the precision of estimates of effect.

In evaluating the extent to which these factors have been minimized in an individual study, consideration is given to a number of aspects of design and analysis as described in the report of the study. For example, when suspicion of carcinogenicity arises largely from a single small study, careful consideration is given when interpreting subsequent studies that included these data in an enlarged population. Most of these considerations apply equally to case–control, cohort and correlation studies. Lack of clarity of any of these aspects in the reporting of a study can decrease its credibility and the weight given to it in the final evaluation of the exposure.

Firstly, the study population, disease (or diseases) and exposure should have been well defined by the authors. Cases of disease in the study population should have been identified in a way that was independent of the exposure of interest, and exposure should have been assessed in a way that was not related to disease status.

Secondly, the authors should have taken into account — in the study design and analysis — other variables that can influence the risk of disease and may have been related to the exposure of interest. Potential confounding by such variables should have been dealt with either in the design of the study, such as by matching, or in the analysis, by statistical adjustment. In cohort studies, comparisons with local rates of disease may or may not be more appropriate than those with national rates. Internal comparisons of frequency of disease among individuals at different levels of exposure are also desirable in cohort studies, since

they minimize the potential for confounding related to the difference in risk factors between an external reference group and the study population.

Thirdly, the authors should have reported the basic data on which the conclusions are founded, even if sophisticated statistical analyses were employed. At the very least, they should have given the numbers of exposed and unexposed cases and controls in a case–control study and the numbers of cases observed and expected in a cohort study. Further tabulations by time since exposure began and other temporal factors are also important. In a cohort study, data on all cancer sites and all causes of death should have been given, to reveal the possibility of reporting bias. In a case–control study, the effects of investigated factors other than the exposure of interest should have been reported.

Finally, the statistical methods used to obtain estimates of relative risk, absolute rates of cancer, confidence intervals and significance tests, and to adjust for confounding should have been clearly stated by the authors. These methods have been reviewed for case–control studies (Breslow & Day, 1980) and for cohort studies (Breslow & Day, 1987).

(c) Meta-analyses and pooled analyses

Independent epidemiological studies of the same agent may lead to results that are difficult to interpret. Combined analyses of data from multiple studies are a means of resolving this ambiguity, and well-conducted analyses can be considered. There are two types of combined analysis. The first involves combining summary statistics such as relative risks from individual studies (meta-analysis) and the second involves a pooled analysis of the raw data from the individual studies (pooled analysis) (Greenland, 1998).

The advantages of combined analyses are increased precision due to increased sample size and the opportunity to explore potential confounders, interactions and modifying effects that may explain heterogeneity among studies in more detail. A disadvantage of combined analyses is the possible lack of compatibility of data from various studies due to differences in subject recruitment, procedures of data collection, methods of measurement and effects of unmeasured co-variates that may differ among studies. Despite these limitations, well-conducted combined analyses may provide a firmer basis than individual studies for drawing conclusions about the potential carcinogenicity of agents.

IARC may commission a meta-analysis or pooled analysis that is pertinent to a particular *Monograph* (see Part A, Section 4). Additionally, as a means of gaining insight from the results of multiple individual studies, ad-hoc calculations that combine data from different studies may be conducted by the Working Group during the course of a *Monograph* meeting. The results of such original calculations, which would be specified in the text by presentation in square brackets, might involve updates of previously conducted analyses that incorporate the results of more recent studies or de-novo analyses. Irrespective of the source of data for the meta-analyses and pooled analyses, it is important that the same criteria for data quality be applied as those that would be applied to individual studies and to ensure also that sources of heterogeneity between studies be taken into account.

(d) Temporal effects

Detailed analyses of both relative and absolute risks in relation to temporal variables, such as age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure (when appropriate) and time since cessation of exposure, are reviewed and summarized when available. Analyses of temporal relationships may be useful in making causal inferences. In addition, such analyses may suggest whether a carcinogen

acts early or late in the process of carcinogenesis, although, at best, they allow only indirect inferences about mechanisms of carcinogenesis.

(e) Use of biomarkers in epidemiological studies

Biomarkers indicate molecular, cellular or other biological changes and are increasingly used in epidemiological studies for various purposes (IARC, 1991; Vainio *et al.*, 1992; Toniolo *et al.*, 1997; Vineis *et al.*, 1999; Buffler *et al.*, 2004). These may include evidence of exposure, of early effects, of cellular, tissue or organism responses, of individual susceptibility or host responses, and inference of a mechanism (see Part B, Section 4b). This is a rapidly evolving field that encompasses developments in genomics, epigenomics and other emerging technologies.

Molecular epidemiological data that identify associations between genetic polymorphisms and interindividual differences in susceptibility to the agent(s) being evaluated may contribute to the identification of carcinogenic hazards to humans. If the polymorphism has been demonstrated experimentally to modify the functional activity of the gene product in a manner that is consistent with increased susceptibility, these data may be useful in making causal inferences. Similarly, molecular epidemiological studies that measure cell functions, enzymes or metabolites that are thought to be the basis of susceptibility may provide evidence that reinforces biological plausibility. It should be noted, however, that when data on genetic susceptibility originate from multiple comparisons that arise from subgroup analyses, this can generate false-positive results and inconsistencies across studies, and such data therefore require careful evaluation. If the known phenotype of a genetic polymorphism can explain the carcinogenic mechanism of the agent being evaluated, data on this phenotype may be useful in making causal inferences.

(f) Criteria for causality

After the quality of individual epidemiological studies of cancer has been summarized and assessed, a judgement is made concerning the strength of evidence that the agent in question is carcinogenic to humans. In making its judgement, the Working Group considers several criteria for causality (Hill, 1965). A strong association (e.g. a large relative risk) is more likely to indicate causality than a weak association, although it is recognized that estimates of effect of small magnitude do not imply lack of causality and may be important if the disease or exposure is common. Associations that are replicated in several studies of the same design or that use different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies. If there are inconsistent results among investigations, possible reasons are sought (such as differences in exposure), and results of studies that are judged to be of high quality are given more weight than those of studies that are judged to be methodologically less sound.

If the risk increases with the exposure, this is considered to be a strong indication of causality, although the absence of a graded response is not necessarily evidence against a causal relationship. The demonstration of a decline in risk after cessation of or reduction in exposure in individuals or in whole populations also supports a causal interpretation of the findings.

A number of scenarios may increase confidence in a causal relationship. On the one hand, an agent may be specific in causing tumours at one site or of one morphological type. On the other, carcinogenicity may be evident through the causation of multiple tumour types. Temporality, precision of estimates of effect, biological plausibility and coherence of the

overall database are considered. Data on biomarkers may be employed in an assessment of the biological plausibility of epidemiological observations.

Although rarely available, results from randomized trials that show different rates of cancer among exposed and unexposed individuals provide particularly strong evidence for causality.

When several epidemiological studies show little or no indication of an association between an exposure and cancer, a judgement may be made that, in the aggregate, they show evidence of lack of carcinogenicity. Such a judgement requires firstly that the studies meet, to a sufficient degree, the standards of design and analysis described above. Specifically, the possibility that bias, confounding or misclassification of exposure or outcome could explain the observed results should be considered and excluded with reasonable certainty. In addition, all studies that are judged to be methodologically sound should (a) be consistent with an estimate of effect of unity for any observed level of exposure, (b) when considered together, provide a pooled estimate of relative risk that is at or near to unity, and (c) have a narrow confidence interval, due to sufficient population size. Moreover, no individual study nor the pooled results of all the studies should show any consistent tendency that the relative risk of cancer increases with increasing level of exposure. It is important to note that evidence of lack of carcinogenicity obtained from several epidemiological studies can apply only to the type(s) of cancer studied, to the dose levels reported, and to the intervals between first exposure and disease onset observed in these studies. Experience with human cancer indicates that the period from first exposure to the development of clinical cancer is sometimes longer than 20 years; latent periods substantially shorter than 30 years cannot provide evidence for lack of carcinogenicity.

3. Studies of cancer in experimental animals

All known human carcinogens that have been studied adequately for carcinogenicity in experimental animals have produced positive results in one or more animal species (Wilbourn *et al.*, 1986; Tomatis *et al.*, 1989). For several agents (e.g. aflatoxins, diethylstilbestrol, solar radiation, vinyl chloride), carcinogenicity in experimental animals was established or highly suspected before epidemiological studies confirmed their carcinogenicity in humans (Vainio *et al.*, 1995). Although this association cannot establish that all agents that cause cancer in experimental animals also cause cancer in humans, it is biologically plausible that agents for which there is *sufficient evidence of carcinogenicity* in experimental animals (see Part B, Section 6b) also present a carcinogenic hazard to humans. Accordingly, in the absence of additional scientific information, these agents are considered to pose a carcinogenic hazard to humans. Examples of additional scientific information are data that demonstrate that a given agent causes cancer in animals through a species-specific mechanism that does not operate in humans or data that demonstrate that the mechanism in experimental animals also operates in humans (see Part B, Section 6).

Consideration is given to all available long-term studies of cancer in experimental animals with the agent under review (see Part A, Section 4). In all experimental settings, the nature and extent of impurities or contaminants present in the agent being evaluated are given when available. Animal species, strain (including genetic background where applicable), sex, numbers per group, age at start of treatment, route of exposure, dose levels, duration of exposure, survival and information on tumours (incidence, latency, severity or multiplicity of neoplasms or preneoplastic lesions) are reported. Those studies in experimental animals that are judged to be irrelevant to the evaluation or judged to be inadequate (e.g. too short a

duration, too few animals, poor survival; see below) may be omitted. Guidelines for conducting long-term carcinogenicity experiments have been published (e.g. OECD, 2002).

Other studies considered may include: experiments in which the agent was administered in the presence of factors that modify carcinogenic effects (e.g. initiation–promotion studies, co-carcinogenicity studies and studies in genetically modified animals); studies in which the end-point was not cancer but a defined precancerous lesion; experiments on the carcinogenicity of known metabolites and derivatives; and studies of cancer in non-laboratory animals (e.g. livestock and companion animals) exposed to the agent.

For studies of mixtures, consideration is given to the possibility that changes in the physicochemical properties of the individual substances may occur during collection, storage, extraction, concentration and delivery. Another consideration is that chemical and toxicological interactions of components in a mixture may alter dose–response relationships. The relevance to human exposure of the test mixture administered in the animal experiment is also assessed. This may involve consideration of the following aspects of the mixture tested: (i) physical and chemical characteristics, (ii) identified constituents that may indicate the presence of a class of substances and (iii) the results of genetic toxicity and related tests.

The relevance of results obtained with an agent that is analogous (e.g. similar in structure or of a similar virus genus) to that being evaluated is also considered. Such results may provide biological and mechanistic information that is relevant to the understanding of the process of carcinogenesis in humans and may strengthen the biological plausibility that the agent being evaluated is carcinogenic to humans (see Part B, Section 2f).

(a) Qualitative aspects

An assessment of carcinogenicity involves several considerations of qualitative importance, including (i) the experimental conditions under which the test was performed, including route, schedule and duration of exposure, species, strain (including genetic background where applicable), sex, age and duration of follow-up; (ii) the consistency of the results, for example, across species and target organ(s); (iii) the spectrum of neoplastic response, from preneoplastic lesions and benign tumours to malignant neoplasms; and (iv) the possible role of modifying factors.

Considerations of importance in the interpretation and evaluation of a particular study include: (i) how clearly the agent was defined and, in the case of mixtures, how adequately the sample characterization was reported; (ii) whether the dose was monitored adequately, particularly in inhalation experiments; (iii) whether the doses, duration of treatment and route of exposure were appropriate; (iv) whether the survival of treated animals was similar to that of controls; (v) whether there were adequate numbers of animals per group; (vi) whether both male and female animals were used; (vii) whether animals were allocated randomly to groups; (viii) whether the duration of observation was adequate; and (ix) whether the data were reported and analysed adequately.

When benign tumours (a) occur together with and originate from the same cell type as malignant tumours in an organ or tissue in a particular study and (b) appear to represent a stage in the progression to malignancy, they are usually combined in the assessment of tumour incidence (Huff *et al.*, 1989). The occurrence of lesions presumed to be preneoplastic may in certain instances aid in assessing the biological plausibility of any neoplastic response observed. If an agent induces only benign neoplasms that appear to be end-points that do not readily undergo transition to malignancy, the agent should nevertheless be suspected of being carcinogenic and requires further investigation.

(b) Quantitative aspects

The probability that tumours will occur may depend on the species, sex, strain, genetic background and age of the animal, and on the dose, route, timing and duration of the exposure. Evidence of an increased incidence of neoplasms with increasing levels of exposure strengthens the inference of a causal association between the exposure and the development of neoplasms.

The form of the dose–response relationship can vary widely, depending on the particular agent under study and the target organ. Mechanisms such as induction of DNA damage or inhibition of repair, altered cell division and cell death rates and changes in intercellular communication are important determinants of dose–response relationships for some carcinogens. Since many chemicals require metabolic activation before being converted to their reactive intermediates, both metabolic and toxicokinetic aspects are important in determining the dose–response pattern. Saturation of steps such as absorption, activation, inactivation and elimination may produce non-linearity in the dose–response relationship (Hoel *et al.*, 1983; Gart *et al.*, 1986), as could saturation of processes such as DNA repair. The dose–response relationship can also be affected by differences in survival among the treatment groups.

(c) Statistical analyses

Factors considered include the adequacy of the information given for each treatment group: (i) number of animals studied and number examined histologically, (ii) number of animals with a given tumour type and (iii) length of survival. The statistical methods used should be clearly stated and should be the generally accepted techniques refined for this purpose (Peto *et al.*, 1980; Gart *et al.*, 1986; Portier & Bailer, 1989; Bieler & Williams, 1993). The choice of the most appropriate statistical method requires consideration of whether or not there are differences in survival among the treatment groups; for example, reduced survival because of non-tumour-related mortality can preclude the occurrence of tumours later in life. When detailed information on survival is not available, comparisons of the proportions of tumour-bearing animals among the effective number of animals (alive at the time the first tumour was discovered) can be useful when significant differences in survival occur before tumours appear. The lethality of the tumour also requires consideration: for rapidly fatal tumours, the time of death provides an indication of the time of tumour onset and can be assessed using life-table methods; non-fatal or incidental tumours that do not affect survival can be assessed using methods such as the Mantel-Haenzel test for changes in tumour prevalence. Because tumour lethality is often difficult to determine, methods such as the Poly-K test that do not require such information can also be used. When results are available on the number and size of tumours seen in experimental animals (e.g. papillomas on mouse skin, liver tumours observed through nuclear magnetic resonance tomography), other more complicated statistical procedures may be needed (Sherman *et al.*, 1994; Dunson *et al.*, 2003).

Formal statistical methods have been developed to incorporate historical control data into the analysis of data from a given experiment. These methods assign an appropriate weight to historical and concurrent controls on the basis of the extent of between-study and within-study variability: less weight is given to historical controls when they show a high degree of variability, and greater weight when they show little variability. It is generally not appropriate to discount a tumour response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls, particularly when historical controls show high between-study variability and are, thus, of little relevance to the

current experiment. In analysing results for uncommon tumours, however, the analysis may be improved by considering historical control data, particularly when between-study variability is low. Historical controls should be selected to resemble the concurrent controls as closely as possible with respect to species, gender and strain, as well as other factors such as basal diet and general laboratory environment, which may affect tumour-response rates in control animals (Haseman *et al.*, 1984; Fung *et al.*, 1996; Greim *et al.*, 2003).

Although meta-analyses and combined analyses are conducted less frequently for animal experiments than for epidemiological studies due to differences in animal strains, they can be useful aids in interpreting animal data when the experimental protocols are sufficiently similar.

4. Mechanistic and other relevant data

Mechanistic and other relevant data may provide evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. The nature of the mechanistic and other relevant data depends on the biological activity of the agent being considered. The Working Group considers representative studies to give a concise description of the relevant data and issues that they consider to be important; thus, not every available study is cited. Relevant topics may include toxicokinetics, mechanisms of carcinogenesis, susceptible individuals, populations and life-stages, other relevant data and other adverse effects. When data on biomarkers are informative about the mechanisms of carcinogenesis, they are included in this section.

These topics are not mutually exclusive; thus, the same studies may be discussed in more than one subsection. For example, a mutation in a gene that codes for an enzyme that metabolizes the agent under study could be discussed in the subsections on toxicokinetics, mechanisms and individual susceptibility if it also exists as an inherited polymorphism.

(a) Toxicokinetic data

Toxicokinetics refers to the absorption, distribution, metabolism and elimination of agents in humans, experimental animals and, where relevant, cellular systems. Examples of kinetic factors that may affect dose–response relationships include uptake, deposition, biopersistence and half-life in tissues, protein binding, metabolic activation and detoxification. Studies that indicate the metabolic fate of the agent in humans and in experimental animals are summarized briefly, and comparisons of data from humans and animals are made when possible. Comparative information on the relationship between exposure and the dose that reaches the target site may be important for the extrapolation of hazards between species and in clarifying the role of in-vitro findings.

(b) Data on mechanisms of carcinogenesis

To provide focus, the Working Group attempts to identify the possible mechanisms by which the agent may increase the risk of cancer. For each possible mechanism, a representative selection of key data from humans and experimental systems is summarized. Attention is given to gaps in the data and to data that suggests that more than one mechanism may be operating. The relevance of the mechanism to humans is discussed, in particular, when mechanistic data are derived from experimental model systems. Changes in the affected organs, tissues or cells can be divided into three non-exclusive levels as described below.

(i) Changes in physiology

Physiological changes refer to exposure-related modifications to the physiology and/or response of cells, tissues and organs. Examples of potentially adverse physiological changes include mitogenesis, compensatory cell division, escape from apoptosis and/or senescence, presence of inflammation, hyperplasia, metaplasia and/or preneoplasia, angiogenesis, alterations in cellular adhesion, changes in steroidal hormones and changes in immune surveillance.

(ii) Functional changes at the cellular level

Functional changes refer to exposure-related alterations in the signalling pathways used by cells to manage critical processes that are related to increased risk for cancer. Examples of functional changes include modified activities of enzymes involved in the metabolism of xenobiotics, alterations in the expression of key genes that regulate DNA repair, alterations in cyclin-dependent kinases that govern cell cycle progression, changes in the patterns of post-translational modifications of proteins, changes in regulatory factors that alter apoptotic rates, changes in the secretion of factors related to the stimulation of DNA replication and transcription and changes in gap–junction-mediated intercellular communication.

(iii) Changes at the molecular level

Molecular changes refer to exposure-related changes in key cellular structures at the molecular level, including, in particular, genotoxicity. Examples of molecular changes include formation of DNA adducts and DNA strand breaks, mutations in genes, chromosomal aberrations, aneuploidy and changes in DNA methylation patterns. Greater emphasis is given to irreversible effects.

The use of mechanistic data in the identification of a carcinogenic hazard is specific to the mechanism being addressed and is not readily described for every possible level and mechanism discussed above.

Genotoxicity data are discussed here to illustrate the key issues involved in the evaluation of mechanistic data.

Tests for genetic and related effects are described in view of the relevance of gene mutation and chromosomal aberration/aneuploidy to carcinogenesis (Vainio *et al.*, 1992; McGregor *et al.*, 1999). The adequacy of the reporting of sample characterization is considered and, when necessary, commented upon; with regard to complex mixtures, such comments are similar to those described for animal carcinogenicity tests. The available data are interpreted critically according to the end-points detected, which may include DNA damage, gene mutation, sister chromatid exchange, micronucleus formation, chromosomal aberrations and aneuploidy. The concentrations employed are given, and mention is made of whether the use of an exogenous metabolic system *in vitro* affected the test result. These data are listed in tabular form by phylogenetic classification.

Positive results in tests using prokaryotes, lower eukaryotes, insects, plants and cultured mammalian cells suggest that genetic and related effects could occur in mammals. Results from such tests may also give information on the types of genetic effect produced and on the involvement of metabolic activation. Some end-points described are clearly genetic in nature (e.g. gene mutations), while others are associated with genetic effects (e.g. unscheduled DNA synthesis). In-vitro tests for

tumour promotion, cell transformation and gap–junction intercellular communication may be sensitive to changes that are not necessarily the result of genetic alterations but that may have specific relevance to the process of carcinogenesis. Critical appraisals of these tests have been published (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

Genetic or other activity manifest in humans and experimental mammals is regarded to be of greater relevance than that in other organisms. The demonstration that an agent can induce gene and chromosomal mutations in mammals *in vivo* indicates that it may have carcinogenic activity. Negative results in tests for mutagenicity in selected tissues from animals treated *in vivo* provide less weight, partly because they do not exclude the possibility of an effect in tissues other than those examined. Moreover, negative results in short-term tests with genetic end-points cannot be considered to provide evidence that rules out the carcinogenicity of agents that act through other mechanisms (e.g. receptor-mediated effects, cellular toxicity with regenerative cell division, peroxisome proliferation) (Vainio *et al.*, 1992). Factors that may give misleading results in short-term tests have been discussed in detail elsewhere (Montesano *et al.*, 1986; McGregor *et al.*, 1999).

When there is evidence that an agent acts by a specific mechanism that does not involve genotoxicity (e.g. hormonal dysregulation, immune suppression, and formation of calculi and other deposits that cause chronic irritation), that evidence is presented and reviewed critically in the context of rigorous criteria for the operation of that mechanism in carcinogenesis (e.g. Capen *et al.*, 1999).

For biological agents such as viruses, bacteria and parasites, other data relevant to carcinogenicity may include descriptions of the pathology of infection, integration and expression of viruses, and genetic alterations seen in human tumours. Other observations that might comprise cellular and tissue responses to infection, immune response and the presence of tumour markers are also considered.

For physical agents that are forms of radiation, other data relevant to carcinogenicity may include descriptions of damaging effects at the physiological, cellular and molecular level, as for chemical agents, and descriptions of how these effects occur. 'Physical agents' may also be considered to comprise foreign bodies, such as surgical implants of various kinds, and poorly soluble fibres, dusts and particles of various sizes, the pathogenic effects of which are a result of their physical presence in tissues or body cavities. Other relevant data for such materials may include characterization of cellular, tissue and physiological reactions to these materials and descriptions of pathological conditions other than neoplasia with which they may be associated.

(c) Other data relevant to mechanisms

A description is provided of any structure–activity relationships that may be relevant to an evaluation of the carcinogenicity of an agent, the toxicological implications of the physical and chemical properties, and any other data relevant to the evaluation that are not included elsewhere.

High-output data, such as those derived from gene expression microarrays, and high-throughput data, such as those that result from testing hundreds of agents for a single end-point, pose a unique problem for the use of mechanistic data in the evaluation of a carcinogenic hazard. In the case of high-output data, there is the possibility to overinterpret changes in individual end-points (e.g. changes in expression in one gene) without considering the consistency of that finding in the broader context of the other end-points (e.g. other genes

with linked transcriptional control). High-output data can be used in assessing mechanisms, but all end-points measured in a single experiment need to be considered in the proper context. For high-throughput data, where the number of observations far exceeds the number of end-points measured, their utility for identifying common mechanisms across multiple agents is enhanced. These data can be used to identify mechanisms that not only seem plausible, but also have a consistent pattern of carcinogenic response across entire classes of related compounds.

(d) Susceptibility data

Individuals, populations and life-stages may have greater or lesser susceptibility to an agent, based on toxicokinetics, mechanisms of carcinogenesis and other factors. Examples of host and genetic factors that affect individual susceptibility include sex, genetic polymorphisms of genes involved in the metabolism of the agent under evaluation, differences in metabolic capacity due to life-stage or the presence of disease, differences in DNA repair capacity, competition for or alteration of metabolic capacity by medications or other chemical exposures, pre-existing hormonal imbalance that is exacerbated by a chemical exposure, a suppressed immune system, periods of higher-than-usual tissue growth or regeneration and genetic polymorphisms that lead to differences in behaviour (e.g. addiction). Such data can substantially increase the strength of the evidence from epidemiological data and enhance the linkage of in-vivo and in-vitro laboratory studies to humans.

(e) Data on other adverse effects

Data on acute, subchronic and chronic adverse effects relevant to the cancer evaluation are summarized. Adverse effects that confirm distribution and biological effects at the sites of tumour development, or alterations in physiology that could lead to tumour development, are emphasized. Effects on reproduction, embryonic and fetal survival and development are summarized briefly. The adequacy of epidemiological studies of reproductive outcome and genetic and related effects in humans is judged by the same criteria as those applied to epidemiological studies of cancer, but fewer details are given.

5. Summary

This section is a summary of data presented in the preceding sections. Summaries can be found on the *Monographs* programme website (http://monographs.iarc.fr).

(a) Exposure data

Data are summarized, as appropriate, on the basis of elements such as production, use, occurrence and exposure levels in the workplace and environment and measurements in human tissues and body fluids. Quantitative data and time trends are given to compare exposures in different occupations and environmental settings. Exposure to biological agents is described in terms of transmission, prevalence and persistence of infection.

(b) Cancer in humans

Results of epidemiological studies pertinent to an assessment of human carcinogenicity are summarized. When relevant, case reports and correlation studies are also summarized. The target organ(s) or tissue(s) in which an increase in cancer was observed is identified. Dose–response and other quantitative data may be summarized when available.

(c) Cancer in experimental animals

Data relevant to an evaluation of carcinogenicity in animals are summarized. For each animal species, study design and route of administration, it is stated whether an increased incidence, reduced latency, or increased severity or multiplicity of neoplasms or preneoplastic lesions were observed, and the tumour sites are indicated. If the agent produced tumours after prenatal exposure or in single-dose experiments, this is also mentioned. Negative findings, inverse relationships, dose–response and other quantitative data are also summarized.

(d) Mechanistic and other relevant data

Data relevant to the toxicokinetics (absorption, distribution, metabolism, elimination) and the possible mechanism(s) of carcinogenesis (e.g. genetic toxicity, epigenetic effects) are summarized. In addition, information on susceptible individuals, populations and life-stages is summarized. This section also reports on other toxic effects, including reproductive and developmental effects, as well as additional relevant data that are considered to be important.

6. Evaluation and rationale

Evaluations of the strength of the evidence for carcinogenicity arising from human and experimental animal data are made, using standard terms. The strength of the mechanistic evidence is also characterized.

It is recognized that the criteria for these evaluations, described below, cannot encompass all of the factors that may be relevant to an evaluation of carcinogenicity. In considering all of the relevant scientific data, the Working Group may assign the agent to a higher or lower category than a strict interpretation of these criteria would indicate.

These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency). A classification may change as new information becomes available.

An evaluation of the degree of evidence is limited to the materials tested, as defined physically, chemically or biologically. When the agents evaluated are considered by the Working Group to be sufficiently closely related, they may be grouped together for the purpose of a single evaluation of the degree of evidence.

(a) Carcinogenicity in humans

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the

Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.

When the available epidemiological studies pertain to a mixture, process, occupation or industry, the Working Group seeks to identify the specific agent considered most likely to be responsible for any excess risk. The evaluation is focused as narrowly as the available data on exposure and other aspects permit.

(b) Carcinogenicity in experimental animals

Carcinogenicity in experimental animals can be evaluated using conventional bioassays, bioassays that employ genetically modified animals, and other in-vivo bioassays that focus on one or more of the critical stages of carcinogenesis. In the absence of data from conventional long-term bioassays or from assays with neoplasia as the end-point, consistently positive results in several models that address several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide *sufficient evidence*.

A single study in one species and sex might be considered to provide *sufficient evidence of carcinogenicity* when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations, or no data on cancer in experimental animals are available.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied.

(c) Mechanistic and other relevant data

Mechanistic and other evidence judged to be relevant to an evaluation of carcinogenicity and of sufficient importance to affect the overall evaluation is highlighted. This may include data on preneoplastic lesions, tumour pathology, genetic and related effects, structure–activity relationships, metabolism and toxicokinetics, physicochemical parameters and analogous biological agents.

The strength of the evidence that any carcinogenic effect observed is due to a particular mechanism is evaluated, using terms such as 'weak', 'moderate' or 'strong'. The Working Group then assesses whether that particular mechanism is likely to be operative in humans. The strongest indications that a particular mechanism operates in humans derive from data on humans or biological specimens obtained from exposed humans. The data may be considered to be especially relevant if they show that the agent in question has caused changes in exposed humans that are on the causal pathway to carcinogenesis. Such data may, however, never become available, because it is at least conceivable that certain compounds may be kept from human use solely on the basis of evidence of their toxicity and/or carcinogenicity in experimental systems.

The conclusion that a mechanism operates in experimental animals is strengthened by findings of consistent results in different experimental systems, by the demonstration of biological plausibility and by coherence of the overall database. Strong support can be obtained from studies that challenge the hypothesized mechanism experimentally, by demonstrating that the suppression of key mechanistic processes leads to the suppression of tumour development. The Working Group considers whether multiple mechanisms might contribute to tumour development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumours observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favoured mechanism.

For complex exposures, including occupational and industrial exposures, the chemical composition and the potential contribution of carcinogens known to be present are considered by the Working Group in its overall evaluation of human carcinogenicity. The Working

Group also determines the extent to which the materials tested in experimental systems are related to those to which humans are exposed.

(d) Overall evaluation

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

An evaluation may be made for a group of agents that have been evaluated by the Working Group. In addition, when supporting data indicate that other related agents, for which there is no direct evidence of their capacity to induce cancer in humans or in animals, may also be carcinogenic, a statement describing the rationale for this conclusion is added to the evaluation narrative; an additional evaluation may be made for this broader group of agents if the strength of the evidence warrants it.

The agent is described according to the wording of one of the following categories, and the designated group is given. The categorization of an agent is a matter of scientific judgement that reflects the strength of the evidence derived from studies in humans and in experimental animals and from mechanistic and other relevant data.

Group 1: The agent is *carcinogenic to humans.*

This category is used when there is *sufficient evidence of carcinogenicity* in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Group 2.

This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

Group 2A: The agent is *probably carcinogenic to humans.*

This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

Group 2B: The agent is *possibly carcinogenic to humans.*

This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans.*

This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.

Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.

An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans.*

This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

(e) Rationale

The reasoning that the Working Group used to reach its evaluation is presented and discussed. This section integrates the major findings from studies of cancer in humans, studies of cancer in experimental animals, and mechanistic and other relevant data. It includes concise statements of the principal line(s) of argument that emerged, the conclusions of the Working Group on the strength of the evidence for each group of studies, citations to indicate which studies were pivotal to these conclusions, and an explanation of the reasoning of the Working Group in weighing data and making evaluations. When there are significant differences of scientific interpretation among Working Group Members, a brief summary of the alternative interpretations is provided, together with their scientific rationale and an indication of the relative degree of support for each alternative.

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002787

From: Helene Lorenzen
To: [redacted] Ross, Matthew; [redacted] Lamia Tallaa; Fatiha El Ghissassi; Kathryn Guyton; Jiri Zavadil
Cc: [redacted]
Subject: e-mails Subgroup 4
Date: Tuesday, March 3, 2015 4:16:27 AM

[redacted]

000125

From: [redacted] on behalf of Matt Martin
To: Kathryn Guyton [redacted]
Cc: [redacted] Ross, Matthew; [redacted] Lamia Tallaa; Fatiha El Ghissassi; Jiri Zavadil; [redacted]
Subject: 4.5 Summary for 4.6 Sections
Date: Wednesday, March 4, 2015 5:12:53 PM
Attachments: IARC MONOGRAPH 112 Section 4.6 - 4.5 Summary 20150304.doc

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Section 4.6: summary of 4.5 (2 or 3 sentence summary)

Attached is a combined set of the 4 chemicals we have looked over so far.
I do not have a full list of target organ tumor sites, especially for human so this is very preliminary but I wanted to get caught up and provide folks with something to include in their respective 4.6 sections.

Good night and see you tomorrow,
Matt

~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~

Matt Martin, Ph.D.

Research Biologist

USEPA Office of Research & Development

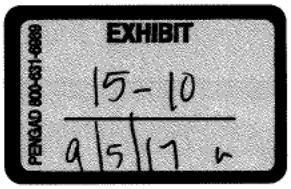
National Center for Computational Toxicology

919.541.4104

"It's tough to make predictions,

especially about the future." - Yogi Berra

~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~~*-*~



004265

From: Kathryn Guyton
To: Ross, Matthew; Lauren Zeise; frank lecurieux; Chris Portier
Cc: Matt Martin; Lamia Tallaa; Fatiha El Ghissassi
Subject: New files for review
Date: Friday, March 6, 2015 4:40:00 PM

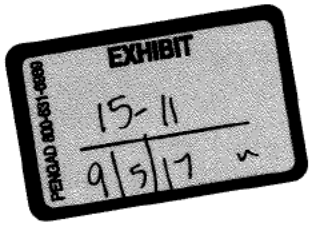
Dear all,

Many thanks to Lauren, Frank and also Matt(s) Ross for posting new versions at the links below! All will be printed for review tomorrow morning.

Also I have posted some comments on the 4.3s of TCVP and PAR on IOPS and sent them to Matt(s) and Ivan via email.

PS Matt(s) Ross— your figure file is as same as the text file, do repost if you have an updated figure.

Good night,
Kate



MAL-Section_4-2-4-2ndDraftRev 1.doc
PAR-Section_4-2-4-2ndDraftRev2.doc

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P118S2886_20150302114625_112-04-GLYP-Section_4-2-1-1stDraft_updatedFLC3.doc

P118S2750_20150305101353_112-04-GLYP-Section_4-1-2ndDraft.doc

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From: Kate Guyton <[redacted]
Date: Friday 6 March 2015 20:00
To: Matthew Ross <[redacted]>, Lauren Zeise <[redacted]>, frank lecurieux <[redacted]>, Chris Portier <[redacted]>
Cc: Matt Martin <[redacted], Lamia Tallaa [redacted]>, Fatiha El Ghissassi <[redacted]>
Subject: Updated meeting time: 8:30 am

Dear all,

We will convene in Subgroup at 8:30 am tomorrow and begin with discussion of the 4.3s. We will then finish all sections of GLY, plus the outstanding 4.2.4s of PAR and MAL.

Frank has special permission to arrive at 9 am. If you also need such special permission, don't hesitate to offer a suitable bribe. Note: limited offer.

See you tomorrow!!
Kate

From: Kate Guyton <[redacted]
Date: Friday 6 March 2015 17:50
To: Matthew Ross <[redacted]>, Lauren Zeise [redacted], frank lecurieux <[redacted]>, Chris Portier [redacted]
Cc: Matt Martin [redacted] Lamia Tallaa [redacted], Fatiha El Ghissassi <[redacted]
Subject: Sections 4.3- supplemental file; General remarks from Ivan

Dear all,

Many thanks to Ivan and Matt for their efforts on the Sections 4.3! Matt has posted this supplemental file. We will review this tomorrow. Unless you let me know that you'd like one, we will NOT provide print copies.

IARC Monograph 112 Section 4-3 Supplemental File 20150305.xlsx

Additionally, Ivan has posted draft General Remarks here: General remarks Rusyn.docx .

As a reminder we will regroup in SubGroup at 8 am on Saturday.

Thanks,
Kate

---

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004380

3/6/15 Plenary General Remarks:

EXHIBIT 15-12

Group I. Exposure Assesment.

Exposure assessment yes/no.
Few to individual pesticides
Questionaires
Except for the Ag. Health Study.

Used most: glyphosate low production for many
banned: malathion

Group II. Epidemiology

Ag. Heath Study. 2 case-controls
Midwest Canadian

Exposure Assessments

TCVP - Inadequate for carcinogenity

Parathion - excess risk for melanoma - limited
~~[illegible]~~ others inadequate

Malathion - limited

Diazinon - More evidence for cancers
limited NHL, leukemia, lung

Glyphosate - limited NHL
inadequate MM

Group III - Animal studies

Early-mid 70s Animal bioassay

Limited # of animals
Number of limited ~~factor~~

All studies were considered adequate

FOAs - EPA documents - studies submitted for Registration purposes to EPA from Ag. comp.

TCVP - ↑ liver tumors mice } sufficient
↑ Renal carcinomas

A switch from limited → Sufficient

Group IV.

10 key charac. of agents that cause cancer

TCVP genotox - moderate

004382

Group I

Parathion

Group II

Parathion – Epi. not a Lat in humans

Orginally: Group III

→ Lung cancer Prostate ← some signals OR 1.5

Group III

Parathion

Sufficient evidence for animal Carcinogenicity

nasal adenoma
lymphoma
Rats adrenal
Mamm.
Pancreatic

Group IV

Parathion,

Group I
Malathion – exposure

Group II
Malathion – prostate, NHL

Group III
malathion – mouse liver (M, F) ↑
rat liver
rat mammary

} Sufficient in animals

004383

FOIA - Malathion | MAL/DZN/GLY

→ mechanisms operable in humans ←

Group IV
Malathion Mechanism Upgrade.

Group I
Diazinon

Group II
Diazinon - NHL | Lung cancer | Limited.

Group III
Diazinon 1 study NTP Mouse - Hcc
Rat - leukemias
Inadequate evidence in animals

Group IV

Group I
Glyphosate — detectable in water & food.

Group II
Glyphosate negative NHL
Case-control Glyph. → NHL
AHS negative data.

Group III
Glyphosate - limited to inadequate.

Group V
Glyphosa

4.3
Full data sets

003606

From: Ross, Matthew
To: Rusyn, Ivan
Subject: Made it
Date: Wednesday, March 11, 2015 3:40:41 PM
Attachments: image001.png

Thanks, Ivan! I made my connecting flight with a few minutes to spare. Hope you made yours, too.

Let's keep in touch. You did a fantastic job as chair.

Best regards
Matt

On Mar 9, 2015, at 04:42, Rusyn, Ivan <[redacted]> wrote:

> **I would like to convene Group 4 downstairs in the first coffee break to discuss the information below.**
>
> Just to make sure we are all on the same page. Below are the evaluations from Groups 2 and 3 and the IARC matrix to get us to understand where our conclusions fit.
>
> MAL: Human – Limited; Animal – sufficient → 2A; Group 4 evidence is strong to support carcinogenesis and we have data to show that the mechanisms can operate in humans, so we support the classification in 2A
>
> DZN: Human – Limited; Animal – Inadequate (only one study) → 2B. Group 4 concludes that there is strong evidence for genotoxicity and oxidative stress and that these mechanisms can operate in humans. So we may consider upgrade to 2A.
>
> GLY: Human – Limited; Animal – Limited → 2B. I have questions on the "limited" in animals as there are 2 studies showing significant effect… Nonetheless, Group 4 concludes that there is strong evidence for genotoxicity and oxidative stress and that these mechanisms can operate in humans. So we may consider upgrade to 2A.
>
> <image001.png>

003397

From: Kathryn Guyton
To: Isabelle Baldi; Blair, Aaron (NIH/NCI) [V]; [redacted] Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; Kromhout, J. (Hans); frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Ross, Matthew; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise; Christopher Portier
Cc: [redacted]
Subject: IARC Monograph vol 112- Lancet oncology article draft
Date: Friday, March 13, 2015 9:36:10 AM
Attachments: TLO_vol 112_13 March 2015.docx

Dear all,

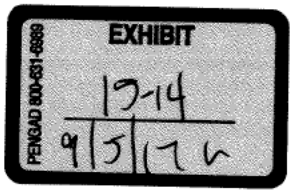
We thank you again for your outstanding contributions to the IARC Monograph volume 112 meeting!

We provide for your review and comment **no later than Monday COB in your time zone** a draft of the Lancet Oncology article. We ask for your feedback using track changes, *preferably using the google doc sent separately* or in the appended Word file. Please turn on track changes before entering any suggested edits. We strongly prefer direct edits to the text but will attempt to address any comments as well.

Please be reminded that the information summarised herein is **strictly embargoed** until the Lancet Oncology article is published online. We will be pleased to inform you when this has occurred.

My very best regards,
With thanks to you all,
Kate

Kate Z. Guyton PhD DABT
Responsible Officer, Volume 112
Monographs Section
International Agency for Research on Cancer
150, cours Albert Thomas
69372 Lyon Cedex 08
France
Tel: [+33] (0)4 72 73 86 54
[redacted]



C. Portier Consultations

< 2015 >

Organisation not currently on the register; registration as it was on 21 Dec 2015

How to read and use (/how-to#data-cards) this data card.

This representative is currently not registered.

LOBBYING COSTS:

NO FIGURE AVAILABLE

Financial year: -

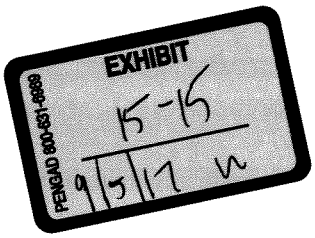
LOBBYISTS DECLARED: **0.25 FTE (1)**

0.25

LOBBYISTS WITH EP ACCREDITATION: **0**

MEETINGS WITH EUROPEAN COMMISSION: **0**

LOBBYING COSTS OVER THE YEARS:



C. Portier Consultations

Registration on EU Transparency Register

346450820048-50 (http://ec.europa.eu/transparencyregister/public/consultation/displaylobbyist.do?id=346450820048-50) (First registered: 21 Dec 2015)

Goals / Remit

This is a private consultancy on issues related to research, interpretation and regulation of environmental agents that are potentially harmful to...

Read more

Issues

Reregistration of the pesticide glyphosat

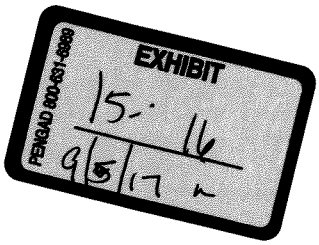
Address

Head office:
Scheibenstrasse 15
Thun CH-3600
Switzerland

Report Data Inaccuracies

To: Kromhout, J. (Hans) [redacted]
Cc: Chris Portier [redacted] Isabelle Baldi [redacted]; Aaron Blair [redacted]; [redacted]; Egeghy, Peter [redacted]; Forastiere, Francesco [redacted]; Lin Fritschi [redacted] Jahnke, Gloria (NIH/NIEHS) [E] [redacted]; Bill Jameson [redacted]; frank lecurieux [redacted]; Martin, Matt [redacted] John McLaughlin [redacted]; Teresa Rodriguez [redacted]; Matthew Ross [redacted]; Rusyn, Ivan [redacted]; Mannetje, Andrea [redacted]; Lauren Zeise [redacted] Kate Guyton [redacted]
From: Consolato Sergi
Sent: Mon 11/9/2015 6:34:12 PM
Subject: Re: IARC Monograph vol 112- EFSA Review of Glyphosate
IARCWG112ResponseV2_Sergi.docx

Hi Chris,
I agree with Hans. However, please read my changes (track changes).
I reviewed the style, because we need to show our academic superior peer-review process, not just arguing, in my opinion
and how the process is.
Please let me know, what you think.
I would suggest to target Lancet Oncology or Science first
Another option may be Scientific Reports.
Best,
Consolato



On Mon, Nov 9, 2015 at 8:35 AM, Kromhout, J. (Hans) <[redacted]> wrote:

> Hi Chris,
>
> You did a great job and I'm more than willing to be a co-author of the letter.
>
> Best, Hans
>
> ---
> From: Chris Portier [redacted]
> Sent: Monday, November 09, 2015 12:05 PM
> To: Isabelle Baldi; Aaron Blair; [redacted]; Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; Kromhout, J. (Hans); frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Matthew Ross; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise
> Cc: Kate Guyton
> Subject: IARC Monograph vol 112- EFSA Review of Glyphosate
>
> Dear all,
>
> This week, the European Food Safety Agency (EFSA) will release their reassessment of glyphosate. In this review, they will conclude that glyphosate has no carcinogenic potential. This creates two problems as I see it. The first is that this wekens the strength of

the IARC Monograph Program to stimulate change in how some of these agents are reviewed and addressed. The second is that it suggests we did not do our assessment adequately and that, had we seen all of the data they saw, we would have gotten a different answer. I do not intend to let this happen.

The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. This report was drafted prior to the IARC review. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. I have decided to draft a letter that I intend to try to get published in Carcinogenesis that addresses the points made by the BfR in their review. Failing my ability to get this into Carcinogenesis, EHP or some other Journal, I intend to send it as an open letter to the European Commission. I am enclosing both the BfR Addendum and my response for you to look over. I would like as many members of the Working Group to be co-authors on this as possible. If you wish to see changes made to the letter I can certainly work on that. If you are uncomfortable signing on to such a letter, I can appreciate that as in my previous job this would have been impossible. Please let me know by Friday November 13 if you can or cannot join me in this endeavor.

Sincerely,

Christopher Portier

--
Consolato Maria Sergi, MSc, MD, PhD, FRCPC
Professor of Pathology and Adj. Professor of Pediatrics
Dept. of Lab. Med. & Pathology (5B4.09), Univ. of Alberta, 8440 112 St, NW, Edmonton, AB, T6G 2B7, Canada
[redacted] (http://www.med.ualberta.ca/)
Tel. +1.780.407.7951 (Office - Direct Line) [redacted]
Fax. +1.780.407.3009 (U of A Departmental Fax) / Prof. Networks: LinkedIn, ResearchGate

003383

From: Chris Portier
To: Isabelle Baldi; Aaron Blair; GMC24@columbia.edu; Egeghy, Peter; Forastiere, Francesco; Lin Fritschi; Jahnke, Gloria (NIH/NIEHS) [E]; Bill Jameson; Kromhout, J. (Hans); frank lecurieux; Matt Martin; John McLaughlin; Teresa Rodriguez; Ross, Matthew; Rusyn, Ivan; Consolato Sergi; Mannetje, Andrea; Lauren Zeise; [redacted]
Elizabeth Ward; [redacted]
Subject: IARC Monograph on Glyphosate
Date: Wednesday, November 11, 2015 6:57:53 AM
Attachments: IARCWG112ResponseV3.docx
ATT00001.htm

Dear Colleagues,

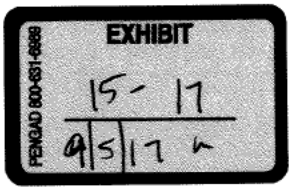
For IARC Monograph 112, 17 scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The Working Group concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they became available on July 29, 2015. During this period, the European Food Safety Agency (EFSA) was in the middle of a reassessment of the safety of glyphosate. The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. The draft, prior to the IARC Monograph, concluded there was no carcinogenic potential of glyphosate. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. This was presented to EFSA several weeks ago and leaked by the press.

This week, EFSA will release their reassessment of glyphosate. In this review, they will again conclude that glyphosate has no carcinogenic potential. This review is based on the BfR Addendum which has some severe scientific flaws. I am concerned that this evaluation, if it stands, could weaken the effectiveness of the IARC Monograph Programme. I am also concerned that the serious flaws in the BfR Addendum, if not challenged, could continue to be used by regulatory agencies to dismiss critical science pertinent to a regulatory decision, including broad exclusion of literature data and epidemiological data.

The European Commission ENVI Committee will meet on December 1, 2015 to receive the reassessment report from EFSA. I have drafted a letter of concern that I wish to present to the ENVI Committee as they consider whether to accept or reject the EFSA evaluation. I would like to invite you to join with me in signing this open letter. I have obtained your names from many different lists, mostly from previous IARC monographs but also from other sources. It is possible I have included your name more than once on this list and I apologize for sending you multiple copies.

I am open to changes to improve the letter, but because of the short time-frame, I hope you can agree to sign on with only modest modifications (I am sending this to several hundred colleagues). I have included the letter but have not included the BfR Addendum or the Reassessment Report because of size. These are available at:

Addendum: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html (NOTE: click on Herunterladen to download the report)



RAR: http://dar.efsa.europa.eu/dar-web/provision

The more important report is the Addendum.

If you agree to joining me in signing this letter, please respond by November 25 with the following that I can then add to my letter.

Title (Prof, Dr., …), Name
Position Title (e.g. Director, Named Chair, etc)
Affiliation
City, Country

I look forward to hearing from you.

Sincerely,

Christopher Portier

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Attorney Work Product

In re Glyphosate/Roundup Litigation

March 29, 2015

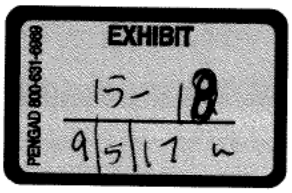
Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

Expert Name
Christopher J. Portier, Ph.D.
Email: [redacted]

Dear Dr. Portier:

This will confirm that Hunter W. Lundy, acting on behalf of the law firms of Lundy, Lundy, Soileau and South, LLP and Weitz & Luxenberg, PC ("Attorneys" or "Firms"), has retained you for the sole purpose of consulting with these Attorneys in connection with anticipated litigation involving claims arising from injury or damage caused, or potentially caused, by exposure to Roundup and/or other herbicides containing Glyphosate (the "Engagement"). The terms of the Engagement are as follows:

1. You are hereby engaged to provide expert consultation and analysis in connection with the cases to be filed (the "Roundup Cases"), relating to, without limitation, any area of expertise that you have or possess pertaining to the question of whether Roundup and/or Glyphosate-containing herbicides can cause adverse biological/physiological health effects in humans; relevant mechanisms of injury; any research or scientific studies that you have conducted or participated in conducting; and any other related issues.



Privileged and Confidential
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Attorney Work Product

2. All work conducted in connection with this Engagement as a consulting expert and/or a testifying expert witness pursuant to the direction, authority, and/or funding of the referenced Attorneys, including any reports, drafts, data, notes, work papers, correspondence, or other work documents you may generate or receive in connection with the Roundup Cases shall be considered and treated as confidential work product. All such documents and materials (and any information they contain that is not publicly available data or previously available to you) may be used only for purposes of this Engagement and may not be disclosed to anyone without our written consent in advance. This Engagement does not pertain to nor shall it affect your research and/or scientific studies, and it is expressly understood and acknowledged that we have not, nor will we fund, participate, sponsor or be involved in any of your past, present or future research or scientific studies.

3. In recognition of the confidential nature of this Engagement and subject to the terms of paragraph 2, you agree to not discuss or share any of this work, work product, analysis and/or opinions developed or prepared in connection with this Engagement with anyone else including, but not limited to, media organizations, trade journals, professional publications, members of the public, other purported experts, etc., and to notify us promptly if you receive:

   a. Any request to reveal information related to this Engagement or to examine, inspect or copy any documents you generate or receive; or

   b. Any actual or attempted service of a subpoena, summons or order purporting to require the disclosure of any such information or documents; and

   c. In consequence of such requests, subpoena(s), summons or order to require disclosure, the above-named law firm shall provide whatever legal services that are required to Christopher J. Portier without fee, any resultant out-of-pocket expenses, and payment of hourly rate.

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Attorney Client Privilege
Attorney Work Product

4. You have assured us that you do not have any conflict of interest which might interfere with your performance of services contemplated by this Engagement, and you agree to avoid any such conflict during the term of this Engagement. More specifically, it is understood that until this matter is resolved (including any appeals), you will not accept any Roundup and/or Glyphosate-related engagement with any law firm that is a party to Roundup and/or Glyphosate-related litigation without our written consent in advance. However, if written consent is requested by Christopher J. Portier regarding another matter outside the specifics of this litigation, such consent shall not be unreasonably withheld. The request shall list the reasons why consent is requested. Should requested consent be withheld by Firms, they shall supply specific written reasons referencing the specific reasons listed in the written consent request. If Expert and Firms cannot agree, a single arbiter agreed upon by both parties shall decide.

5. Your fee for specific consultation, analysis and any requested report(s) shall be $450.00 (US Dollars) per hour in addition to reimbursement for any out-of-pocket expenses. You shall receive a retainer of $5,000.00 from which charges shall be drawn. You will send a monthly invoice as necessitated by the requested work which identifies the time spent and services rendered. Upon the depletion of the $5,000.00 retainer, payment will be made within 30 days from receipt of your invoice. Bills should be issued to the attention of Hunter W. Lundy at Lundy, Lundy, Soileau & South, LLP, 501 Broad Street, Lake Charles, LA 70601.

6. You will be working under the exclusive direction of Hunter W. Lundy, Matthew E. Lundy and Kristie M. Hightower with the law firm of Lundy, Lundy, Soileau & South, LLP, and Robin L. Greenwald with the law firm of Weitz and Luxenberg, PC.

7. Any and all work product created by you or on your behalf in whole or in part during the course of this Engagement, authorized by the Committee, shall be considered a work for hire and the property of the Firms.

8. You or we may terminate this agreement in writing at any time, in which event

you must stop work and bill only for the work performed up until receipt of the written termination. However, in the event of such termination, the restrictions described in paragraphs 2, 3 and 4 (related to work product generated) above will remain in effect absent a mutual agreement to the contrary. Such mutual agreement shall not be unreasonably withheld.

9. Any controversy, dispute or claim arising out of or relating to this Engagement or breach of this Agreement, shall be decided by a single arbitrator to be mutually selected in a privately administered arbitration to be held in _____, using the rules of the American Arbitration Association. The Firms and you expressly consent to personal jurisdiction in the courts of _____, and waive any objection thereto.

Please acknowledge that you accept these terms by signing the enclosed copy of this letter and returning it to us.

Sincerely,

LUNDY, LUNDY, SOILEAU & SOUTH, LLP

By:_____
Hunter W. Lundy

Agreed to by:

_____
Christopher J. Portier, Ph.D.

Dated: _____

INVOICE

Christopher Portier

Regarding:

Bill to:
Glyphosate/Roundup Litigation
Attn: Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

Invoice Date: 10/19/2015
Invoice #: 15002

Quantity	Date	Unit	Description	Rate	Amount Due
0.5	6/17/15	hr	Meet with H. Lundy at BIOEM meeting, general issues regarding Glyphosate	$450.00	$225.00
1	6/19/15	hr	Meet with H. Lundy and Robin Greenwald in Davis, CA, general issues regarding Glyphosate	$450.00	$450.00
2	7/9/15	hr	Background research on glyphosate and AML, cancers in the Ag. Health Study and onset time for NHL	$450.00	$900.00
3.5	10/19/15	hr	Reduce value of retainer (balance $5000.00) by cost this invoice (new balance $3425.00)	-$450.00	-$1575.00
				Total	$0.00

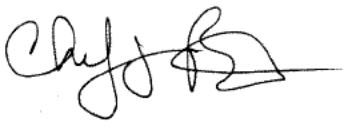
Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:



INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

Invoice Date: 3/29/2016
Invoice #: 15003

Quantity	Date	Unit	Description	Rate	Amount Due
2	12/4/15	hr	Phone call followed by research on glyphosate references	$450.00	$900.00
3	12/16/15	hr	Meet with Robin Greenwald and staff in NYC RE: Glyphosate	$450.00	$1350.00
3	3/11/16	hr	Meet with Hunter Lundy, Kristie Hightower and Rudie Soileau in Lake Charles	$450.00	$1350.00
3	3/11/16	hr	Travel to Lake Charles	$150.00	$450.00
3	3/11/16	hr	Travel from Lake Charles to New Orleans	$150.00	$450.00
			Credit from retainer	$3425.00	-$3425.00
				Total Invoice	$1085.00

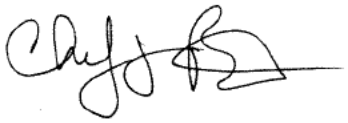
Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:



INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

Invoice Date: 6/30/2016
Invoice #: 15004

Quantity	Date	Unit	Description	Rate	Amount Due
8	5/12/16	hr	Read and evaluate EPA glyphosate document	$450.00	$3600.00
5	5/13/16	hr	Read and evaluate EPA glyphosate document	$450.00	$2250.00
4	5/14/16	hr	Read and evaluate EPA glyphosate document	$450.00	$1800.00
2	5/15/16	hr	Read and evaluate EPA glyphosate document	$450.00	$900.00
				Total Invoice	$8550.00

Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:

INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 2/6/2017
Invoice #: 17001

Quantity	Date	Unit	Description	Rate	Amount Due
10	10/1/2016 to 12/31/2016	hr	Multiple phone meetings, reviews and background development	$450.00	$4,500.00
12	1/1/17 to 2/6/17	hr	Multiple phone meetings and slide preparation	$450.00	$5,400.00
1	1/31/17	tckt	Airline ticket for flight to and from San Francisco/NYC (see attached)	$7,777.71	$7,777.71
				Total Invoice	$17,677.71

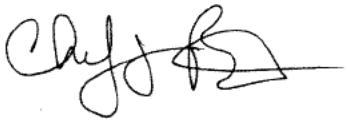
Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:



INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 3/7/2017
Invoice #: 17002

Quantity	Date	Unit	Description	Rate	Amount Due
17	2/8/17 to 2/26/17	hr	Slide preparation and discussion for "Science Day"	$450.00	$7,650.00
6	2/25/17	hr	Travel time to San Francisco	$100.00	$600.00
6.5	2/27/17	hr	"Science Day"	$450.00	$2,925.00
4	3/2/17	hr	Preparation of expert report	$450.00	$1,800.00
6	3/3/17	hr	Meet with legal team	$450.00	$2,700.00
5	3/5/17	hr	Travel time to home	$100.00	$500.00
1	2/25/17	cost	Taxi from airport to hotel in San Francisco	$50.00	$50.00
1	2/25/17	cost	Hotel in San Francisco	$560.50	$560.50
1	3/1/17	cost	Taxi to hotel in NYC	$62.84	$62.84
1	3/1/17	cost	Hotel in NYC	$601.40	$601.40
1	3/5/17	cost	Taxi to airport in NYC	$66.34	$66.34
				Total Invoice	$17,516.08

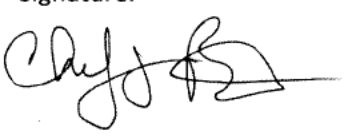
Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:



INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 4/4/2017
Invoice #: 17003

Quantity	Date	Unit	Description	Rate	Amount Due
163	Various dates	hr	Drafting of Expert Report (individual daily activities on Page 2)	$450.00	$73,350.00
			Total Invoice		$73,350.00

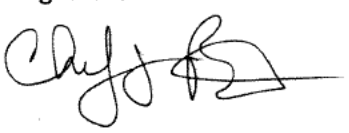
Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:



Quantity	Date	Units	Description	Rate	Charge
5.5	3/7/17	hr	Drafting of Expert Report	$450.00	$2,475.00
6.5	3/8/17	hr	Drafting of Expert Report	$450.00	$2,925.00
2	3/9/17	hr	Drafting of Expert Report	$450.00	$900.00
4	3/10/17	hr	Drafting of Expert Report	$450.00	$1,800.00
6	3/13/17	hr	Drafting of Expert Report	$450.00	$2,700.00
8	3/14/17	hr	Drafting of Expert Report	$450.00	$3,600.00
7	3/15/17	hr	Drafting of Expert Report	$450.00	$3,150.00
8	3/16/17	hr	Drafting of Expert Report	$450.00	$3,600.00
6	3/17/17	hr	Drafting of Expert Report	$450.00	$2,700.00
4	3/18/17	hr	Drafting of Expert Report	$450.00	$1,800.00
8	3/19/17	hr	Drafting of Expert Report	$450.00	$3,600.00
9	3/20/17	hr	Drafting of Expert Report	$450.00	$4,050.00
9	3/21/17	hr	Drafting of Expert Report	$450.00	$4,050.00
9	3/22/17	hr	Drafting of Expert Report	$450.00	$4,050.00
8	3/23/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/24/17	hr	Drafting of Expert Report	$450.00	$3,600.00
3	3/25/17	hr	Drafting of Expert Report	$450.00	$1,350.00
8	3/26/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/28/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/29/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/30/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/31/17	hr	Drafting of Expert Report	$450.00	$3,600.00
2	4/1/17	hr	Drafting of Expert Report	$450.00	$900.00
7	4/2/17	hr	Drafting of Expert Report	$450.00	$3,150.00
3	4/3/17	hr	Drafting of Expert Report	$450.00	$1,350.00
Totals					
163	25 days				$73,350.00

INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 6/18/2017
Invoice #: 17004

Quantity	Date	Unit	Description	Rate	Amount Due
72	Various dates	hr	Drafting of Expert Report (individual daily activities on Page 2)	$450.00	$32,400.00
			Total Invoice		$32,400.00

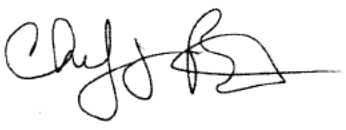
Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:



Quantity	Date	Units	Description	Rate	Charge
2	4/5/17	hr	Q&A	$450.00	$900.00
3	4/6/17	hr	Q&A, Work on expert report	$450.00	$1,350.00
4	4/7/16	hr	Read parts of various depositions	$450.00	$1,800.00
8	4/13/17	hr	Read FIFRA SAP Report, include in Expert Report	$450.00	$3,600.00
9	4/18/17	hr	Correct typos to Expert Report, explain certain parts, expand explanations of animal data	$450.00	$4,050.00
6	4/23/17	hr	Check all numbers and tables in expert report, clarify text	$450.00	$2,700.00
7	4/24/17	hr	Check all numbers and tables in expert report, clarify text	$450.00	$3,150.00
4	4/30/17	hr	Edit and refine Expert Report	$450.00	$1,800.00
9	5/1/17	hr	Edit and refine Expert Report	$450.00	$4,050.00
3	6/5/17	hr	Edit and refine Expert Report	$450.00	$1,350.00
4	6/6/17	hr	Edit and refine Expert Report	$450.00	$1,800.00
4	6/7/17	hr	Edit and refine Expert Report	$450.00	$1,800.00
5	6/8/17	hr	Edit and refine Expert Report	$450.00	$2,250.00
2	6/9/17	hr	Edit and refine Expert Report	$450.00	$900.00
2	6/13/17	hr	Edit and finalize final Expert Report	$450.00	$900.00
Totals					
72	15 days				$32,400.00

INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 7/13/2017
Invoice #: 17005

Quantity	Date	Unit	Description	Rate	Amount Due
1	20-June to 19 July, 2017	ea	Airplane ticket for deposition in NYC in July, 2017 (cancelled)	$4,046.56	$4,046.56
				Total Invoice	$4,046.56

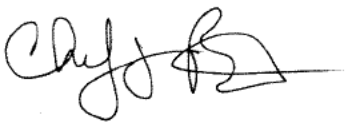
Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:



November 27, 2015

Mr. Vytenis Andriukaitis
Commissioner Health & Food Safety
European Commission
Rue de la Loi / Wetstraat 200
1049 Brussels
Belgium

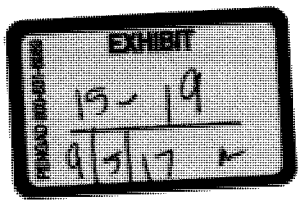
Cc: (email only)
Mr. Phil Hogan, European Commissioner for Agriculture and Human Development
Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety
Dr. Bernhard Url, Executive Director, EFSA
Dr. Giovanni La Via, Chair, ENVI Committee
EFSA Panel on Plant Protection Products and their Residues
Mr. Christian Schmidt, Minister of Food and Agriculture
Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)
Professor Dr. Dr. Andreas Hensel, President, BFR
Dr. Christopher Wild, Director, IARC
Mr. Jim Jones, Assistant Administrator, USEPA

Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR

Dear Commissioner Andriukaitis,

We are a group of independent academic and governmental scientists from around the world who have dedicated our professional lives to understanding the role of environmental hazards on cancer risks and human health. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety Agency (EFSA) decision[1] that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you forward the letter to the representatives of all EU member states before the next meeting of the Standing Committee on Plants, Animals, Food and Feed (December 10/11).

The EFSA decision, based upon the Renewal Assessment Report[2] provided by the German Federal Institute for Risk Assessment (BfR), runs counter to the finding earlier this year by the International Agency for Research on Cancer (IARC), the highly respected cancer arm of the World Health Organization that glyphosate is a *probable human carcinogen*. This IARC classification is based on a comprehensive assessment of the peer-reviewed toxicologic and epidemiologic literature undertaken over a 12-month period by a Working Group of 17 independent expert scientists. The IARC review linked glyphosate to dose-related increases in malignant tumors at multiple anatomical sites in experimental animals and to an increased incidence of non- Hodgkin lymphoma in exposed humans.



We reviewed these two differing decisions on the human carcinogenicity of glyphosate and conclude that the IARC WG decision is by far the more credible. The IARC WG decision was reached relying on open and transparent procedures by independent scientists who completed thorough conflict-of-interest statements and were not affiliated or financially supported in any way by the chemical manufacturing industry. It is fully referenced and depends entirely on reports published in the open, peer-reviewed biomedical literature. It is part of a long tradition of deeply researched and highly credible reports on the carcinogenicity of hundreds of chemicals issued over the past four decades by IARC and used today by international agencies and regulatory bodies around the world as a basis for risk assessment, regulation and public health policy.

In contrast, the BfR decision is not credible because it is not supported by the evidence and it was not reached in an open and transparent manner.

Accordingly, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature.

The IARC Working Group Decision

The International Agency for Research on Cancer (IARC) Monographs Programme identifies environmental causes of cancer in humans and has evaluated more than 950 agents since 1971. The Monographs Programme evaluates chemicals, drugs, mixtures, occupational exposures, lifestyles and personal habits, physical agents and biological agents. Monographs are written by an ad hoc Working Group (WG) of international scientific experts over a period of about 12 months ending in an eight-day meeting. The WG evaluates all of the publically-available scientific literature on a given substance and, through a transparent and rigorous process[3], reaches a decision on the degree to which the scientific evidence supports that substance's ability to cause or not cause cancer.

For Monograph 112[4], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate[5]. The WG concluded that the data for glyphosate meets the criteria to be identified as a *probable human carcinogen*. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation by numerous agencies of the IARC monograph results when they became available on July 29, 2015.

The BfR Addendum

In October, 2015, the EFSA reported[1] on their evaluation of the Renewal Assessment Report[2] (RAR) for glyphosate. EFSA concluded that "glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential". Addendum 1 (the BfR Addendum) of the RAR[2] discusses the scientific rationale for differing from the IARC WG conclusion.

We have serious concerns with regard to the scientific evaluation in the BfR Addendum and feel that it is misleading regarding the potential for a dose-dependent carcinogenic hazard from exposure to glyphosate. Since the BfR Addendum is the basis for the European Food Safety Agency (EFSA) conclusion[1], it is critical that we express these concerns. We are also concerned about some of the implications of the BfR Addendum regarding the use of human data in identifying carcinogenic hazards.

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

The BfR agrees with the IARC WG that there is "*limited evidence* in humans for the carcinogenicity of glyphosate". In the IARC review process, *limited evidence* is assigned if "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[3] The EFSA conclusion that "glyphosate is unlikely to pose a carcinogenic hazard to humans" is inappropriate when available data support the determination of *limited evidence* of carcinogenicity in humans. The BfR Addendum (p. ii) characterizes the IARC interpretation as "precautionary" and that the BfR takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two arguments here and discuss the third argument at the end of this letter.

The finding of *limited evidence* by the IARC WG was for non-Hodgkin lymphoma (NHL). High-quality cohort studies are particularly valuable for determining the carcinogenicity of an agent because their design can facilitate exposure assessment and reduce the potential for certain biases. The Agricultural Health Study[6] (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7-1.9) with no apparent exposure response in the results. The BfR refers to this study as "the most powerful study" and notes that it was "negative" for NHL.

Several potential limitations of case-control studies are laid out in epidemiology textbooks[7, 8]. The BfR uses these limitations to label all of the case-control studies as unreliable. This gives the impression that all of the studies are equal in quality and unusable for an overall evaluation. This is not the case: well-designed case-control studies are recognized as an efficient alternative to cohort studies[8]. An IARC WG carefully evaluates all of the available epidemiology data, looking at the study's strengths and weaknesses. This is key to determining whether the positive associations seen in case-control studies are a reliable indication of an association or simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to their quality rather than simply count the number of positives and negatives. The meta-analyses cited in the IARC Monograph[9] and done by the WG

are excellent examples of an objective evaluation of the existence of a consistent positive association; both meta-analyses showed a statistically significant association. The BfR provided no justification for their evaluation of "no consistent positive association". Finally, despite the potential advantages of prospective cohort studies versus case-control, there are fewer cases to include in analyses, depending on the follow-up time resulting in limited statistical power. There were only 92 NHL cases included in the AHS unadjusted analysis and fewer in adjusted analyses, compared to 650 in a pooled case-control analysis from the United States[10].

The final BfR conclusion (p. 21) that "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate" is misleading. IARC, like many other groups, uses three levels of evidence for human data[3]. *Sufficient evidence* means "that a causal relationship has been established" between glyphosate and NHL. IARC does not state that the evidence is *sufficient*. BfR concludes that the IARC designation of *limited evidence* was not applicable because there was not "an unequivocal and consistent excess". In fact, that is the equivalent to the criteria for *sufficient evidence*, not *limited evidence*. Thus BfR's conclusion is equivalent to concluding there is not *sufficient evidence*. Legitimate public health concerns arise when "causality is credible", i.e., when there is *limited evidence*. BfR's language is misleading and not internationally acceptable and thus fails to meet EC Guidelines.

Evidence from Animal Carcinogenicity Studies

We find the conclusions of the BfR regarding the animal carcinogenicity data to be scientifically unacceptable. The IARC WG review found a significant positive trend for renal tumors in CD-1 mice[11], a rare tumor although no comparisons of any individual exposure group to the control group were statistically significant. A significant positive trend means that the pattern seen in the data supports an increasing risk with increasing dose. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice[12], again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of pancreatic islet cell adenomas in two studies in Sprague-Dawley rats[13-15]. In one of these rat studies, thyroid gland adenomas in females and liver adenomas in males were also increased. Thus, glyphosate was positive for malignant tumors in both of the mouse studies examined and for benign tumors in two of the five rat studies examined. By the IARC review criteria[3], the evidence in the mouse constitutes *sufficient evidence* in animals and the increased incidences of benign tumors constitutes additional support.

The BfR agreed, stating (p. 43) "it is obvious that IARC concludes on "*sufficient evidence* of carcinogenicity" because the above criteria for this conclusion are fully met." The IARC WG reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[3]). Based on the BfR Addendum, it seems there were three additional mouse studies and two additional rat studies that were unpublished but available for review. BfR reported on two additional studies with a positive trend for renal tumors, one in CD-1 mice[16], and one in Swiss-Webster mice[17]. One of these studies[16] also reported a positive trend for hemangiosarcoma. Moreover, BfR reported two studies in CD-1 mice showing significant trends for malignant

lymphoma[16, 18]. For all of the mouse tumors described above, a positive trend was seen against the concurrent control.

However, in all studies in CD-1 mice, including those reviewed by the IARC, the BfR dismisses the observed trends in tumor incidence because there are no individual treatment groups that are significantly different from controls and because the maximum observed response is reportedly within the range of the historical control data (Table 5.3-1, p. 90). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[3, 19], scientific reports[20] and publications[21-23] on this issue, the recommended first choice is the use of the concurrent controls. For instance, the Preamble to the IARC Monographs states, "it is generally not appropriate to discount a tumor response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls...". When using historical control data, they should be from studies in the same timeframe, for the same exact animal strain, preferably from the same laboratory or the same supplier and preferably reviewed by the same pathologist[19]. This was not the case for the historical control database used by BfR. One of the mouse studies[11] was clearly done before this historical control database was developed, one study[16] used Crj:CD-1 mice rather than Crl:CD-1 mice, and one study[12] did not specify the substrain and was reported in 1993 (probably started prior to 1988); hence only a single study[18] used the same mouse strain as the historical controls, but was reported more than 10 years after the historical control dataset was developed. Interestingly, the historical control data used by the BfR[24] was from studies in seven laboratories using the Charles River Laboratory CD1 mice. It is important to note that there is a second report[25] by the same authors with a larger control database using the same mouse strain from 11 laboratories over the same time period (1987-2000) showing very different results. For example, the 2000 publication[24] shows five and four studies out of 46 with renal adenomas (no more than two in any one study) and renal adenocarcinomas (one in each study) respectively whereas the 2005 report[25] shows only one study each out of 54 studies with a single renal adenoma and a single renal adenocarcinoma; all other studies had no renal tumors.

Given this evidence, it is clear that BfR differed from standard scientific practices in order to reach their conclusions. BfR reported seven positive mouse studies with three studies showing increases in renal tumors, two with positive findings for hemangiosarcomas, and two with positive findings for malignant lymphomas. BfR additionally reported two positive findings for tumors in rats. Eliminating the inappropriate use of historical data, the unequivocal conclusion is that these are not negative studies, but in fact document the carcinogenicity of glyphosate in laboratory animals.

Mechanistic Information

The BfR Addendum dismisses the WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that unpublished evidence not seen by the IARC WG was overwhelmingly negative and that, since the studies that were reviewed were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews only publicly available data. Thus the use of confidential data submitted to the BfR makes it impossible for any scientist not associated with BfR to review this conclusion with scientific

confidence. Further skewing their interpretation, the BfR did not include evidence of chromosomal damage from exposed humans[24] that was highlighted in the IARC Monograph.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but does not agree that this is strong support for an oxidative stress mechanism. They minimize the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. The WG concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". From a scientific perspective, these types of mechanistic studies can play a key role in distinguishing between the effects of mixtures, pure substances and metabolites and we encourage the BfR to carefully review this science.

Finally, we strongly disagree that data from studies published in the peer-reviewed literature should automatically receive less weight than guideline studies. Once a chemical or its formulations are on the market, the majority of the research done on these chemicals will be done by research laboratories using various models to address specific issues related to toxicity that will often not have testing guidelines associated with them. These peer-reviewed and published findings have great value in understanding mechanisms of carcinogenicity and should be given appropriate weight in an evaluation based on study quality and not just guideline rules.

General Comments

Science moves forward based on data, careful evaluation of those data and a rigorous review of the findings and conclusions. One important aspect of this process is transparency and the ability to question or debate the findings of others. This ensures the validity of the results and provides a strong basis for decisions. Many of the aspects of transparency do not exist for the RAR[2] or the BfR Addendum. For example, citations for almost all of the references, even those from the open scientific literature, have been redacted from the document. The ability to objectively evaluate the findings of a scientific report requires a complete list of the cited supporting evidence. As another example, there are no authors or contributors listed for either document, a requirement for publication in virtually all scientific journals. This is in direct contrast to the IARC WG evaluation listing all authors, all publications and public disclosure of pertinent conflicts of interest prior to the WG meeting[26].

A second important aspect of the scientific process is a careful evaluation and analysis of the facts. Several guidelines have been devised for analyzing carcinogenicity data, most after consultation with scientists from around the world. One of the most widely used guidelines is the OECD guidance on the conduct and design of chronic toxicity and carcinogenicity studies[19] which is cited in the BfR Addendum. This OECD guidance is in contradiction to the methods used by the BfR for both historical controls and for trend analysis; the two reasons given by the BfR for dismissing these data. Thus, BfR uses the

concept of testing guidelines to exclude substantive scientific evidence from their risk assessment and ignore OECD guidelines in addressing the important issues of historical controls and trend analyses.

Due to the potential public health implications of this extensively used pesticide it is essential that all scientific evidence be freely available, reviewed openly in an objective manner, and that financial support, conflicts of interest and affiliations of authors be fully disclosed. Many aspects of the evaluation conducted by the BfR and EFSA do not meet this fundamental objective criteria and raise significant questions of validity.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A due to *sufficient evidence* of carcinogenicity in animals, *limited evidence* of carcinogenicity in humans and *strong* mechanistic data.

- The IARC WG found an association between non-Hodgkin lymphoma and glyphosate based on the available human evidence.
- The IARC WG found significant carcinogenic effects in laboratory animals for two tumor types in two mouse studies and benign tumors in two rat studies.
- Finally, the IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available research, including findings of DNA damage in the peripheral blood of exposed humans.

In their RAR, BfR concluded (Vol. 1, p. 160) "classification and labeling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential".

- BfR agreed with the IARC on *limited evidence* in humans but then dismissed the association as "insufficiently consistent" with no justification.
- Using an inappropriate historical control dataset in an incorrect manner and ignoring established OECD guidelines cited in their report, BfR dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies. Thus, BfR incorrectly discarded all of the glyphosate-induced carcinogenic findings in animals as chance occurrences.
- The BfR ignored important laboratory and human evidence of genotoxicity.
- The BfR confirmed that glyphosate induces oxidative stress and dismissed this finding for lack of any other finding because they had dismissed all of the other evidence.

The most parsimonious scientific explanation of the cancers seen in humans and laboratory animals supported by the mechanistic data is that glyphosate is a *probable* human carcinogen. On the basis of this conclusion and in the absence of

contrary evidence, it is reasonable to conclude that glyphosate formulations should also be considered probable human carcinogens.

We believe that the arguments promoted by the BfR to negate the human, animal and mechanistic evidence are fundamentally and scientifically flawed and should be rejected. We strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide. We believe that the IARC WG evaluation of *probably carcinogenic to humans* accurately reflects the results of the published scientific literature on glyphosate and, on the face of it, the unpublished studies to which the BfR refers. Conversely, the BfR evaluation, and consequently the EFSA evaluation, do not reflect the available science.

Thus, repeating our earlier request, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature.

The views expressed in this letter are the opinion of the scientists who are listed below and DO NOT imply an endorsement or support for these opinions by any organizations to which they are affiliated.

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EXHIBIT 95 Part 2

Comments of Christopher J. Portier, PhD.
USEPA (EPA-HQ-OPP-2016-0385-0094)
Glyphosate Issue Paper: Evaluation of Carcinogenic Potential
October 4, 2016

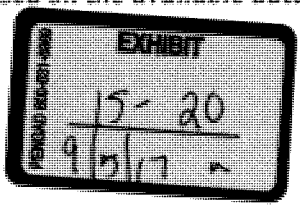
Disclaimer: This work was done with my own resources and on my own time. I have received no reimbursement for any of these comments and no other party has contributed to the drafting of these comments. These comments are solely my opinion and my responsibility.

General Comments and Overall Summary

My comments on the glyphosate review by the USEPA (EPA-HQ-OPP-2016-0385-0094) is rather long and detailed. Realizing that the time and energies of the Science Advisory Panel (SAP) are limited, I will summarize my findings here. Each summarized finding is linked to the line(s) in my more technical review for those who wish to see more details. Because of my own limited time, I have chosen to focus my comments on the human evidence and the animal carcinogenicity evidence, foregoing the review of the other evidence presented. However, I will note that after reading the review on the mechanistic evidence relating to genotoxicity and oxidative stress, I still agree with the findings from the IARC Working Group that there is *strong evidence* that these mechanisms are operable.

Human Evidence Findings

1. The meta-analyses are improperly characterized by the EPA (lines 21-33)
2. The exposure-response relationship in the Agricultural Health Study (AHS) has greater weight than in the other studies, but has problems of its own (lines 39-45)
3. It is not clear in which direction possible confounding would alter the relative risks (lines 61-66) although possible confounding is an issue (line 68).
4. Recall bias is a concern, especially with the case-control studies (lines 70-72)
5. The EPA speculates without data that the more positive studies should have had lower relative risks than other studies (lines 77-80)
6. The follow-up time in the AHS study is likely to be too short to have seen an impact of the magnitude seen in the case-control studies and EPA does a poor job of characterizing the data they used to reach an opposite conclusion (lines 85-109)
7. The EPA speculates that earlier years of exposure prior to the start of the AHS would have effectively expanded the time on study in the AHS without any solid basis (lines 111-114)
8. The Bradford-Hill criteria outlined in the 1997 Guidelines for Carcinogenic Risk Assessment (GCRA) support a conclusion that a causal association in the epidemiology data is credible, but that chance, bias and or confounding could possibly explain the results. (lines 116-127)
9. EPA's interpretation that "*the association between glyphosate exposure and risk of NHL cannot be determined based on the available data*" does not correctly



characterize the human data presented. A better interpretation is that "*a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence*". This is the interpretation given these data by the IARC Working Group (lines 129-139)

Animal Carcinogenicity Data Findings

1. EPA's QCAR sets clear guidelines on evaluating animal cancer data with regard to when a high dose is exceeded (lines 151-159), how to interpret trend tests and pairwise comparisons (lines 163-169), how to use historical control data (lines 173-176) and what constitutes a valid historical control data set (180-182)
2. EPA has misinterpreted the language in OCSPP 870.4200 and OCSPP 870.4300 by assuming that an optional highest dose in an animal carcinogenicty study is also a threshold for inclusion of doses in their evaluation. In other words, 1000 mg/kg/day is not an upper bound, 5% in diet is the upper bound (lines 184-210)
3. I have individual comments on every rat study evaluated by the EPA (lines 212-287).
4. EPA consistently dismisses significant findings in rat studies because of a lack of a preneoplastic finding (studies listed starting a lines 217, 229, 277). This presumes that all mechanisms by which chemicals induce tumors in animals will involve enough stages that there would be a histologically identifiable preneoplastic lesion from which final tumors are formed. This simply is not the case and this criteria is applied without any concern for its validity by the EPA.
5. EPA consistently dismisses significant findings in rat studies because of a lack of a significant pairwise comparison even though there is a significant trend in violation of the GCRA (studies listed starting a lines 229, 255, 277).
6. EPA gives less weight to responses seen at doses above 1000 mg/kg/day in all rat studies, even though no dose exceeds 5% of feed. Considering that these findings are in studies with only 50-60 animals per group, that no study appears to have exceeded a maximum tolerated dose (as defined by the EPA and others), it is not clear why EPA does not accept these findings and then do an appropriate margin-of-exposure evaluation or linear extrapolation from these data to show a lack of risk in humans.
7. EPA's summary, which states that *"In 5 of the 9 rat studies conducted with glyphosate, no tumors were identified for detailed evaluation."* is misleading and fails to properly characterize the broad array of findings in these data (lines 291-322). In short, three of these studies were inadequate leaving 2 studies in Sprague-Dawley rats (1 positive) and four studies in Wistar rats (2 positive).
8. With only two studies in Sprague-Dawley rats, the strong positive response seen for thyroid c-cell carcinomas in female rats in one of these studies should be considered positive and due to exposure to glyphosate (lines 324-330)

9. I have individual comments on every mouse study evaluated by the EPA (lines 337-460).
10. EPA consistently dismisses significant findings in mouse studies because of a lack of a preneoplastic finding (studies listed starting a lines 342, 380). This presumes that all mechanisms by which chemicals induce tumors in animals will involve enough stages that there would be a histologically identifiable preneoplastic leasion from which final tumors are formed. This simply is not the case and this criteria is applied without any concern for its validity by the EPA.
11. EPA dismisses significant findings in ALL mouse studies because of a lack of a significant pairwise comparison even though there is a significant trend in violation of the GCRA (lines 337-460).
12. EPA gives less weight to responses seen at doses above 1000 mg/kg/day in all mouse studies, even though no dose exceeds 5% of feed. Considering that these findings are in studies with only 50-60 animals per group, that no study appears to have exceeded a maximum tolerated dose (as defined by the EPA and others), it is not clear why EPA does not accept these findings and then do an appropriate margin-of-exposure evaluation or linear extrapolation from these data to show a lack of risk in humans.
13. EPA uses an outside historical control dataset in one study (start line 380) to dismiss findings and fails to use an equally valid historical control data set identified by the IARC to assess the importance of renal tumors in another study (start line 342). A full evaluation of this second study using the historical control data identified by the IARC supports a strong positive finding in this study (lines 350-365).
14. EPA relies on two-sided p-values for trend tests when one-sided p-values would be more appropriate for identifying adverse effects (lines 367-370; 410-413; Tables 2,4,6)
15. EPA has serious errors in the use of a historical control population that uses data from animals that lived 24 months to compare to response in a study that only went 18 months (lines 388-408). When properly applied, the finding is significant compared to the historical control rate.
16. EPA excludes three positive findings in one study, identified by the European Food Safety Agency for which I sent them data prior to this current EPA review being released (lines 425-434)
17. EPA excludes positive results in a study in Swiss Albino mice because there is an infection in the animals that are not seen in any of the data evaluated by others and for which no documentation is provided (lines 445-460)
18. EPA summarizes the mouse data incorrectly (as they did with rats) when they state that *"No tumors were identified for detailed evaluation in 2 of the 6 mouse carcinogenicity studies."* One study had inadequate dosing and should have been excluded, and one study used Glyphosate trimesium salt rather than pure glyphosate. The remaining four mouse studies all had at least one positive finding (lines 464-475)
19. EPA did not analyze the consistency across mouse studies on the findings relating to renal tumors. I did (Tables 1-3, lines 498-532). Note, all studies were adjusted to an estimated 24 month response using the poly-3 adjustment (lines 487-517)

20. EPA did not analyze the consistency across mouse studies on the findings relating to malignant lymphomas. I did (Tables 1, 4-5, lines 536-541). Note, all studies were adjusted to an estimated 24 month response using the poly-3 adjustment (lines 487-517)
21. EPA did not analyze the consistency across mouse studies on the findings relating to heamngiosarcomas. I did (Tables 1, 6-7, lines 566-599). Note, all studies were adjusted to an estimated 24 month response using the poly-3 adjustment (lines 487-517)
22. Trends in male mice for malignant lymphomas and hemangiosarcomas remained even after doses above 1000 mg/kg/day were excluded (Tables 4-7, lines 536-599).
23. My conclusion is that the mouse data clearly indicates that glyphosate can induce malignant lymphomas and hemangiosarcomas in male CD-1 mice, even when doses above 1000 mg/kg/day are eliminated. There is also a suggestion that glyphosate can induce hemangiomas in female CD-1 mice. The mouse data also demonstrate that glyphosate can induce malignant lymphomas in male CD-1 mice and male Swiss Albino mice. Finally, the renal tumors seen in the CD-1 mice also appear in the Swiss Albino mice, supporting the role glyphosate plays in inducing these tumors. This is clearly sufficient evidence of the carcinogenicity of glyphosate in mice. (lines 573-600)

In summary, these data demonstrate an association in humans to NHL, evidence in rats for thyroid tumors, and very strong evidence in mice for renal tumors, hemangiosarcomas and malignant lymphomas. EPA's exclusion of doses above 1000 mg/kg/day is unscientific and their argument of a lack of significance above this dose is unsupported.

In every case where EPA could choose between a public health protective choice where slight weaknesses in a study or a lack of a very strong finding could raise concerns versus a choice where every study must be perfect and definitive otherwise it is not used, EPA has chosen to discard positive findings leaving them to finally conclude there is no concern. These data simply do not support a finding that glyphosate is *"not likely to be carcinogenic to humans"*.

EPA should declare glyphosate a probable human carcinogen and go on to do a risk assessment to determine if human exposure is sufficient to warrant concern. That resulting risk assessment should be reviewed by the Science Advisory Panel.

DETAILED TECHNICAL REVIEW

Human Evidence

The EPA's final conclusion on the evidence from human exposures to glyphosate and the risk of NHL is as follows:

Page 68: *"Based on the weight-of-evidence, the agency cannot exclude chance and/or bias as an explanation for observed associations in the database. Due to study limitations and contradictory results across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data. The agency will continue to monitor the literature for studies and any updates to the AHS will be considered when available."*

The Agency provides many reasons for this finding. I would summarize them as follows:

1. *"All meta-analysis estimates reported were non-statistically significant except the meta-risk ratio reported by IARC (2015), which was borderline significant with the lower limit of the 95% CI at 1.03"*

Comment: In fact, there were three groups that did meta-analyses. Two were reported as significant (Schinasi and Leon, 2014 and IARC, 2015), although the IARC (2015) corrected an issue they saw with the Schinasi and Leon analysis. The IARC study showed a meta-RR of 1.3 with a confidence bound of (1.03-1.65). The other group (Chang and Delzel, 2016) provided four separate meta-analyses, all of which are reported as having a meta-RR of 1.3 with associated confidence bounds ranging from (1.0-1.6) to (1.0-1.8). Chang and Delzell presented only 1 significant digit for the lower confidence bounds and since their model 1 is exactly the same as the IARC model, they also had at least one significant finding. In fact they characterize their findings as *"we found marginally significant positive meta-RRs for the association between glyphosate use and risk of NHL"*. Thus, the data across all studies, when combined, point to a positive association between glyphosate and NHL in humans.

2. The exposure-response relationship seen in Eriksson et al. (2008) and McDuffie et al. (2001), even though significant, contradicted the exposure-response seen in the Agricultural Health Study (AHS).

Comment: There were 92 cases of NHL in the AHS, with 77.2% (71 cases) having some exposure, whereas the analysis of the tertiles to investigate exposure response relationships, used only 61 cases. Thus, 14% of the exposed cases were excluded. In comparison, both Eriksson et al. (a highly rated study by EPA) and McDuffie et al. were able to characterize all exposed individuals into their exposure groupings with zero loss. To characterize the exposure-response relationship in the AHS as superior to the other two studies is inappropriate.

3. Control for confounding varied across studies and there is a strong potential for

confounding by co-exposures to other pesticides.

Comment: This is correct with some studies doing better than others. However, the magnitude of the impact of this confounding differs by study as well. They cite the one case, Eriksson where the effect estimate went from 2.02 (1.10-3.71) unadjusted to 1.51 (0.77-2.94) adjusted. Others included in the meta-analysis are as follows: DeRoos et al. (2005), 1.2 (0.7-1.9) unadjusted, 1.1 (0.7-1.9) adjusted; DeRoos et al., 2003, 2.1 (1.1-4.0) unadjusted, 1.6 (0.9-2.8) adjusted; Hardell et al., 2002, 3.01 (1.08-8.52) unadjusted, 1.85 (0.55-6.20) adjusted). Orsi et al. (RR 1.0 (0.5-2.2)) and McDuffie et al. (RR 1.2 (0.83-1.74)) did not do analyses adjusting for other pesticides. EPA could remove these studies from the meta-analysis and redo it, but it is unlikely to dramatically change the overall results.

The EPA also expressed concern that what they see as a reduction when you correct for other pesticide exposures would carry over for other confounders. This is highly speculative since many of the NHL patients had no exposure to glyphosate and there are likely truck operators and mechanics (diesel exhaust fumes), factory workers (solvents) and other outdoor workers (UV radiation) in the cases and controls and the result of correcting for the confounders could go either way.

However, it is fair to say that confounding could not be ruled out in these studies.

4. Recall bias is a concern, especially in the case-control studies.

Comment: I agree.

5. The highest risk measures are coming from studies that would likely have lower exposures to glyphosate.

Comment: This is entirely speculative and is based upon an ecological assessment (glyphosate use has increased dramatically over time) and not upon actual data pertaining to the studies at hand. Nor does it fully account for the time since first exposure for the studies done with earlier cohorts.

6. The follow-up time in the DeRoos et al. (2005) study is sufficient that it should be given more weight than the other studies.

Comment: As noted by Portier et al., the median follow-up time in the AHS study was 6.7 years (not 7) and there is a question of whether this is long enough. EPA actually provides a solid argument for why there is concern. EPA gave three publications that they suggest puts the latency period for NHL between 1 and 25 years. Kato et al. (2005) in a high quality population-based, incidence case-control study looking at the relationships between organic solvent exposure and NHL in women found statistical significance only for women occupationally exposed prior to 1970 (cases and controls were recruited between 1995 and 1998) and cited two other studies with similar results (no reference given). They concluded this long latency was either due to higher exposures prior to 1970 or "*at least a 25 year*

latency period is required for NHL induction by these exposures". Weisenburger (1992), in discussing the problems with pathological identification of NHL and the known mechanisms in 1992 states that "The latency for NHL following an environmental exposure is largely unknown" then goes on to say that following chemotherapy for Hodgkin's disease, "the median latency is 5-6 years" based upon 44 case reports from two publications. I was unable to get a copy of one publication, but the publication by Jacquillat et al (1991) showed 24 patients, 17 of whom received radiation therapy along with chemotherapy, 5 radiation alone, three chemotherapy alone and one unknown. The latency ranged from 1 to 11 years in this paper (median 5.5 years) and up to 16 years in the other (abstract review only) These are rather extreme exposures relative to those from glyphosate and it would not be surprising for the glyphosate lag time to be longer than that from chemotherapy and radiation treatment, as suggested by Weisenberger et al. I was unable to obtain a copy of the third paper (Fontana et al., 1998) and the abstract provides no information on lag times.

The rest of the arguments are speculative dealing mostly with years of exposure prior to the beginning of the AHS. Without an analysis including this prior information on exposure with concurrent exposure, it is unclear that the resulting relative risks would go down or up.

Summary: The conclusion by the EPA that "*the association between glyphosate exposure and risk of NHL cannot be determined based on the available data*" fails to account for the overall strength of this evidence and the nature of that evidence. Using the Bradford-Hill criteria for causality described in the 2005 Guidelines for Carcinogenic Risk Assessment (GCRA), I would note that the observations are consistent (relative risks are positive, meta-analyses are positive), significant (in the meta-analysis), not specific (and as noted in the GCRA *"although the presence of specificity may support causality, its absence does not exclude it"*), temporally observed, shows a biological gradient, is coherent with the animal evidence (discussed later), has no experimental evidence from humans, and has no support from structure-activity relationships. So, is causality plausible here? Yes, absolutely. Is it demonstrated? No, clearly not. Are the findings possibly the result of chance, bias and or confounding? Yes, but more unlikely than likely.

The IARC Working Group concluded that there was "*limited evidence of carcinogenicity in humans*" from exposure to glyphosate where, as defined in the IARC Preamble, limited evidence means "*a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.*" This is a more accurate description of these data than that used by the EPA. If chance, bias and confounding could be ruled out, the IARC Working Group would have classified this as a *"known human carcinogen"*, a much stronger finding. By arguing that "*the association between glyphosate exposure and risk of NHL cannot be determined based on the available data*", the EPA has given no weight to the human evidence in their final evaluation.

Animal Carcinogenicity Studies

According to the EPA, of the 9 available rat studies, 4 showed treatment related effects in various organs and of the 6 mouse studies they evaluated, 4 showed treatment effects in three tumors. In all cases, the EPA considers these findings to be not treatment related. I will first address the interpretations of individual studies, then discuss the entire package of studies.

Let's begin by repeating guidance from the GCRA :

"Other signs of treatment-related toxicity associated with an excessive high dose may include (a) significant reduction of body weight gain (e.g., greater than 10%), (b) significant increases in abnormal behavioral and clinical signs, (c) significant changes in hematology or clinical chemistry, (d) saturation of absorption and detoxification mechanisms, or (e) marked changes in organ weight, morphology, and histopathology. It should be noted that practical upper limits have been established to avoid the use of excessively high doses in long-term carcinogenicity studies of environmental chemicals (e.g., 5% of the test substance in the feed for dietary studies or 1 g/kg body weight for oral gavage studies [OECD, 1981])."

and

"A trend test such as the Cochran-Armitage test (Snedecor and Cochran, 1967) asks whether the results in all dose groups together increase as dose increases. A pairwise comparison test such as the Fisher exact test (Fisher, 1950) asks whether an incidence in one dose group is increased over that of the control group. By convention, for both tests a statistically significant comparison is one for which p is less than 0.05 that the increased incidence is due to chance. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."

and

"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."

and

"The most relevant historical data come from the same laboratory and the same supplier and are gathered within 2 or 3 years one way or the other of the study under review; other data should be used only with extreme caution."

These guidelines are critical in the discussions that follow. I will note that the EPA assessment cites OCSPP 870.4200 and OCSPP 870.4300 several times referring to an upper limit for evaluating the high dose in a carcinogenicity study. Theses guidelines give multiple guidance for how to select the appropriate dose. Here are the first two:

(i) For risk assessment purposes, at least three dose levels should be used, in

addition to the concurrent control group. Dose levels should be spaced to produce a gradation of effects. A rationale for the doses selected must be provided.

(ii) The highest-dose level should elicit signs of toxicity without substantially altering the normal life span due to effects other than tumors. The highest dose should be determined based on the findings from a 90–day study to ensure that the dose used is adequate to assess the carcinogenic potential of the test substance. Thus, the selection of the highest dose to be tested is dependent upon changes observed in several toxicological parameters in subchronic studies. The highest dose tested need not exceed 1,000 mg/kg/day.

Nowhere in this guidance does it state that the high dose **cannot exceed** 1,000 mg/kg/day; just that it **does not need to exceed** that number. The EPA notes this fact on Page 69 of the Report, but then later interprets it as a hard limit for excluding doses. Because other data are used to justify the high dose that have not been presented here, we must assume that the highest doses used in the Guideline studies were at or near the maximum-tolerated dose (MTD) and wholly appropriate for the overall evaluation. Thus, 1,000 mg/kg/day is not a threshold for determining where to cut off the data. The only document discussing excessive doses is the QCRA which uses >5% in feed for feeding studies and all doses used here are below that threshold.

Rat Studies

Burnett et al., 1979 (MRID 00105164): As noted by EPA, this study is inadequate due to insufficiently high dose. This study should not be considered negative.

Lankas, 1981 (MRID 00093879): This study in Sprague-Dawley rats was considered inadequate due to the highest dose being far below the MTD. However, the study did see an increase in testicular tumors. These tumors were dismissed because of a non-monotonic dose-response (0%, 6%, 2%, 12% in increasing dose), a lack of pre-neoplastic findings and a range of historical controls (mean 4.5%, range 3.4% to 6.7%) that was higher than seen in the controls, inflating the p-value (as noted in the GCRA, this argument is not an acceptable argument). Nonetheless, the finding in the high exposure group is clearly significant against concurrent controls and, had they presented all of the historical control evidence, might have been significant there as well. Since no data for this tumor is presented for any other study, it is hard to determine if this finding is unique among the studies.

Stout and Ruecker, 1990 (MRID 41643801): The Sprague-Dawley rats in this study were given doses considerably higher (max 1183 mg/kg/day) than those in the Lankas study and was considered adequate by the EPA for evaluation, although they warn that tumor doses in the highest group will be given less weight because it is so high. They found a statistically significant increase in adenomas of the liver and the pancreatic islet cells in males. For pancreatic tumors, EPA points to a lack of clear dose-response (2%, 18%, 10% 15%) and unusually low background response (historical controls provided were 5% mean, 2.9%, 8.5%, 5.8%, 1.8%, 8.3%, 5.0% and 5.1%, all in control groups larger than the concurrent control in this study; since 2% is near 1.8% and only 7 controls are given, this is not an unusually low

response). For liver adenomas (5%, 4%, 6%, 15%), EPA cites a lack of pairwise significance, a plateau of dose-response in the middle dose groups and no preneoplastic lesions as reasons to reject these findings. No historical control data is presented.

In female rats, thyroid C-cell adenomas and combined adenomas and carcinomas were significantly elevated by trend test but not by pairwise comparison. Because of this, they concluded *"although there may be an indication of a dose-response in females, the increases observed in the glyphosate treated groups were not considered to be different than those observed in the concurrent controls"* ignoring their Guidelines regarding *"Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."* Here, preneoplastic lesions were observed, but no monotonic dose-response so they were ignored. Thyroid tumors in male rats were marginally significant (p~0.08).

Atkinson et al., 1993a (MRID 496317023): No adverse effects reported in Sprague-Dawley rats given doses in the same range as the Stout and Ruecker study. No data provided.

Brammer, 2001 (MRID 49704601): This is a two-year study in Wistar rats which showed a statistically significant trend in liver adenomas in male rats (0%, 4%, 0%, 10%) with a maximum dose of 1498 mg/kg/day. EPA provides three reasons for dismissing these findings: non-monotonic dose-response, higher survival in the controls, and multiple comparisons p-value adjustment.

Pavkov and Wyand 1987 (MRIDs 40214007, 41209905, 41209907): This is again a study in Sprague-Dawley rats (substrain given for this study). This study showed no significant findings. The EPA did not comment on the dosing used, however, the maximum dose used in this study was 55.7 mg/kg/day, not much difference from the doses used in Burnett (30 mg/kg/day) and Lankas (34 mg/kg/day) and far lower than doses showing no toxicity in Sprague-Dawley rats. This study should be considered inadequate by the EPA.

Suresh, 1996 (MRID 49987401): This two-year study in Wistar rats using a maximum dose of 886 mg/kg/day saw no significant increases in any tumors. Again, no details are given on tumors appearing in other studies.

Enemoto, 1997 (MRID 50017103-50017105): Also conducted in Wistar rats, but with a maximum dose of 1247 mg/kg/day, demonstrated no increases in tumors. Again, no details are given on tumors appearing in other studies.

Wood et al., 2009a (MRID 49957404): In a last study performed in Wistar rats with a maximum dose of 1229.7 mg/kg/day, a significant increase in female rat mammary tumors (adenomas and carcinomas combined) was observed (4%, 6%, 2%, 16%). EPA dismissed these findings based upon multiple comparisons and no pre-neoplastic lesions.

Excel, 1997: Excluded by the EPA because they had insufficient information on the study and an industry-sponsored review of the literature (Greim et al., 2015) stated it was *"unreliable"*. Greim et al. had multiple errors and considerable missing data (pointed out to EPA in a previous mailing) making it an unreliable source for this decision. No information

is given on this study in any available documents I was able to find including the review by EFSA.

Summary and Comments on the Rat Studies

All told, there are 9 rat studies presented, four in Wistar rats and 5 in Sprague-Dawley rats.

EPA states that *"In 5 of the 9 rat studies conducted with glyphosate, no tumors were identified for detailed evaluation."*, but two of these studies have inadequate dosing to identify.

They also state *"Some of the tumor incidences at the highest dose tested (approaching or exceeding 1,000 mg/kg/day for almost all studies) were statistically significant from concurrent controls using raw (unadjusted) p-values; however, none of the pairwise comparisons were found to be statistically significant following adjustment for multiple comparisons, except the testicular tumors seen in a single study. Furthermore, these high-dose tumors were given less weight."* However, as noted below in my calculation of the limit of 5% of compound in diet, the dose can easily go over 2000 mg/kg/day before reaching this value. They have confused the maximum gavage dose with the maximum dietary dose. These findings should carry equal weight as all other doses.

Three of the Sprague-Dawley rat studies used doses so low that the statistical power to detect an effect was compromised. Even still, one of these studies saw an increase in testicular tumors that was not noted in any other study and could be disregarded (provided there really is no response for this tumor in the other studies). In the remaining two studies (Stout/Ruecker and Atkinson), the EPA argues the highest dose *"exceeds the highest dose recommended in the test guidelines on how to conduct carcinogenicity studies"*. According to Laaksonen et al. (, Lab. Anim. 47(4) 245-56, 2013), Sprague-Dawley rats eat, on average, about 600g/kg/week at study start and about half that at 2 years. Based on the guidelines, 5% in diet is acceptable and on a daily basis would be between 2.1 g/kg/day to 4.3 g/kg/day; thus the <2 g/kg/day used in these two studies should be acceptable. This argument is not supported for these studies. These two studies differed on their findings of cancer with Atkinson negative for all cancers and Stout/Ruecker positive for two cancers, one in females and one in males. The remaining reasons for dismissing these findings include a lack of preneoplastic findings and a non-monotonic dose-response.

The thyroid tumors in female rats Stout/Ruecker) should be considered a positive finding. The dose-response is clear and the marginal findings in males should increase the concern for this tumor. There is no reason to believe that adenomas and carcinomas MUST arise from preneoplastic lesions in thyroid C-cell tumors. The rates from the other study for these tumors are no presented, but even if they had been, how do you judge one positive study against one negative study? The public protective decision in this case should be to conclude these tumors arose as a function of exposure to glyphosate.

The remaining tumors can be debated; in all cases where a decision could go either way, EPA dismisses findings rather than accepts them.

Mouse Studies

Reyna and Gordon, 1973 (MRID 00061113): This study is new to the EPA assessment. This study used doses as high as 50 mg/kg/day, far below the maximum doses used in the other studies that were below the maximum tolerated dose. In essence, this study is inadequate and should not be used for making a decision.

Knezevich and Hogan, 1983 (MRID 00130406): This is the first 24 month study in CD-1 mice at dietary doses of up to 6069 mg/kg/day according to EPA. EPA does not show their conversion from ppm in feed to mg/kg/day so it is unknown why this number is different from the European Food Safety Authority (EFSA) which lists the highest dose as 5874 mg/kg/day. The actual high dose used, according to EFSA, was 30,000 ppm or 3% in feed, below the EPA threshold given in the GCRA. According to EPA, *"No effect on survival was observed"* suggesting this high dose did not exceed the MTD.

This study saw an increase in kidney tubular cell adenomas and carcinomas (2%, 0%, 0%, 6%), a very rare tumor in these mice. Four reasons were given for discounting this finding: *"1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the concurrent controls and there was no evidence of a statistically significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound-related nephrotoxic lesions, including pre-neoplastic changes, were not present in male mice in this study"*. In fact, the one-sided p-value (alternative is an increased risk) for this study was 0.03. In 1986, the EPA did have an adequate historical control population for these tumors and found they were highly statistically significant. The IARC also identified an adequate historical control population (Chandra and Frith, 1994) who reported only 1 tumor in 725 CD-1 mice also supporting a highly significant finding. As noted earlier, the second reason violates the QCRA if the one-sided test is applied. The third argument is not supported with such a small number of affected animals and a very rare tumor and the fourth reason, while arguable, presumes there would be a preneoplastic lesion rather than a unique mutational event to begin the cancer process.

Note: The raw p-value presented in Table 4.12 is for a two-sided test, a one-sided test is more appropriate here and has a raw p-value of 0.034. If the true control rate is 0.0014 as noted by Chandra and Frith (1994), the probability of seeing a finding more extreme than the one noted here is 0.0017. Even if the background is as high as 1%, the p-value would be 0.026.

Atkinson, 1993b (MRID 49631702): This 24 month study in CD-1 mice showed an increase in hemangiosarcomas (0%, 0%, 0%, 9%) which was statistically significant (p=0.003) with a marginally significant comparison between control and high dose of 0.053. The only negative comment given by the EPA on this study was *"however, the incidence of hemangiosarcomas at the high-dose was not statistically significant when compared to the concurrent controls"*, thus excluding the finding from the trend test because of a non-significant pairwise test, in violation of the QCRA.

Wood et al., 2009b (MRID 49957402): This study, also in CD-1 mice, was for 80 weeks (approximately 18 months) with a high dose in males of 810 mg/kg/day (again, not exceeding the 5% dose in feed). There was no effect on survival suggesting the study did not exceed the MTD. There was a monotonic increase in lung adenocarcinomas (10%, 10%, 14%, 22%) and a monotonic increase in malignant lymphomas (0%, 2%, 4%, 10%). For the lung cancers, the EPA again argued a lack of significance for pairwise comparisons (in violation

of their QCRA) and there was no evidence of progression from adenomas to carcinomas.

For the malignant lymphomas, the EPA 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) and Huntingdon Laboratories (20 studies from 1990-2002; Son and Gopinath, 2004)."* These controls are not from the same laboratory at the same time, but EPA did paraphrase the QCRA noting that these data *"should be used with caution"* whereas the GCRA states *"other data should be used only with extreme caution"*. In this case they did neither. The paper by Son and Gopinath documents the numbers of tumors seen in animals that die prior to 80 weeks out of 1453 males in 20 control groups. They saw a total of 36 animals with lymphomas, for a raw rate of 2.4%; however this is a lower bound on the rate since they did not look at all animals at 80 weeks to get obtain the number that are alive and having a tumor. It is not clear how EPA interpreted these numbers in their presentation. The study by Giknis and Clifford (2005) had 52 studies (not 59) and only 26 of them were for 18 months; the rest were for 2 years and these last 26 would be inappropriate as a historical control. The numbers cited by the EPA *("4.5% (range: 1.5%-21.7%)"*) are directly out of Giknis and Clifford for all 52 studies and the range fails to include the 11 studies with no tumors (lower end of range is 0). In the 26 studies ending at 18 months, Giknis and Clifford saw tumor incidence as follows (0/60, 0/50, 0/50, 0/50, 0/50, 0/50, 0/50, 0/50, 1/69, 1/50, 1/50, 1/50, 1/50, 1/50, 1/50, 1/50, 2/60, 2/59, 2/53, 2/50, 2/47, 2/46, 3/60, 3/59, 4/49, 7/50) thus ranging from 0% to 14% with a weighted mean of 2.5%.

NOTE: The p-value sited by EPA for the trend test is the two-sided p-value; a one sided p-value is more appropriate and the correct value is 0.0043. If you assume that 2.5% is the historical control rate, the probability of seeing a more significant finding that the one seen in this study is 0.0079.

Sugimoto, 1997 (MRID 50017108 - 50017109): In another study in CD-1 mice (with sub strain noted), mice were given, for 18 months, a maximum dose of 40,000 ppm of glyphosate which is 4% in the diet, again below the 5% in feed set by the QCRA. The second highest dose was 0.8% in diet. This study demonstrated a clear dose-response for hemangioma in female mice (0%, 0%, 4%, 10%) with a p-value for trend of p=0.002 by EPA's calculation. There were no treatment effects on survival suggesting this dose did not exceed the MTD. This tumor was not considered treatment related by the EPA because of no pairwise significance with the high dose versus control using a multiple comparisons analysis (the uncorrected p-value is 0.028 and the corrected p-value is 0.055).

What is not mentioned by the EPA but was evaluated by the EFSA, was the dose-response trend for hemangiosarcoma in male mice for which the one-sided p-value for trend is 0.008. Here the responses are 0%, 0%, 0% and 4%, a very low response rate. However, this is only an 18 month study, so low rates of tumors are to be expected.

What is also not mentioned are the malignant lymphomas and kidney tumors also found in males in this study (EFSA, 2015). The renal tumors had rates of 0%, 0%, 0%, 4% (the same as the hemangiosarcomas in males) with a p-value for trend of 0.008. The malignant lymphomas had rates of 4%, 4%, 0%, 12% with a p-value for trend of 0.008. I will compare these rates to those seen in the other studies later.

Pavkov and Turnier, 1987 (MRIDs 40214006, 41209907): This is a two-year chronic toxicity study in CD-1 mice with a maximum dose of 991 mg/kg/day. They list this study as completely negative for any cancer findings. However, this study evaluated Glyphosate trimesium salt (52.6% pure). No details on this study are provided by the EPA and I could find no other regulatory body that has reviewed this study nor is it listed in the Greim et al. (2015) manuscript. It is also the only carcinogenicity study with such a low percentage of pure glyphosate.

Kumar, 2001: This 18-month chronic carcinogenicity study in Swiss Albino mice with high-dose exposures of 10,000 ppm (1% diet) was excluded by the EPA *"due to the presence of a viral infection within the colony, which confounded the interpretation of the study findings"*. No information on this viral infection is given in the EPA Assessment. It is not possible to determine where this information on a viral infection came from. In the most recent draft classification document on glyphosate by the European Chemical Agency, they state that *"in the study report itself, there was no evidence of health deterioration due to suspected viral infection and, thus, the actual basis of EPA's decision is not known"* when referring to this study. The only reference I can find is from the paper by Greim et al. who down-rated the study *"based on speculation of a viral infection within the colony"*.

This study is important as they saw increases in kidney tumors (0%, 0%, 2%, 4%) and malignant lymphomas (20%, 30%, 32%, 38%) with one-sided p-values for trend of 0.04 and 0.05 respectively. While these are not strikingly strong p-values, they show a consistency in the male mouse data for these tumors.

Summary and Comments on the Mouse Studies

EPA concluded that *"No tumors were identified for detailed evaluation in 2 of the 6 mouse carcinogenicity studies."* One of these mouse studies should have been excluded because of the low doses used in the study. The other study has no details provided by the EPA or any other regulatory body and uses Glyphosate trimesium salt (52.6% pure).

EPA then concluded *"In the remaining 4 mouse studies, 3 observed a statistically significant trend in tumor incidences in the hemangiosarcomas, lung adenomas, malignant lymphomas or hemangiomas; however, the agency determined that none of the tumors observed in the mouse are treatment related."* In fact, there were 5 additional studies since they excluded the one study in Swiss Albino mice because of an infection in the study animals that appears to be speculative. Let's consider these 5 remaining studies. Since the hemangiomas only occurred in one study in female mice, I will not discuss it further.

Table 1 provides a summary of the findings in the 5 studies for which I could find sufficient data to make a comparison across the three main tumor findings in male mice: renal tumors, hemangiosarcoms and malignant lymphomas. A review of all of the studies in one simple picture illustrates the consistency of the findings across the various studies. Now, let's compare the actual tumor rates to see how they compare.

Table 1: Cancer findings in studies of glyphosate in male mice

1983[5]	Crl:CD-1	24	4,841	+[3]		
1993[5]	?:CD-1	24	1,000		+	+/-[4]
1997	CrJ:CD-1	18	4,843	+[5]	+[5]	+[5]
2001	Swiss	18	1,460	+[5]	**No Data**	+[5]
2009	Crl:CD-1	18	810			+

Cancer increases in risk generally as a power of length of exposure (1). This relationship was used to develop a means to adjust the length of time an animal is on a study, enabling a scientist to determine risk at the end of two-years, the typical time used for animal bioassays (2, 3). This is called the Poly-3 adjustment. The US National Toxicology Program uses the Poly-3 test to evaluate significance in their animal bioassays. Now you will note that three of the mouse studies were only conducted for 18 months. (Comparing 18 month studies with 24 month studies without making an adjustment for the differences in length of exposure is like comparing cancer rates in 40 year-olds exposed for 20 years to cancer rates in 65 year-olds exposed for 45 years and concluding they are not consistent with each other; the conclusion is meaningless because the correct evaluation was not done.) Thus, in order to compare all 5 studies, we must use the Poly-3 adjustment to extrapolate the 18 month studies to estimate what we think the cancer risk would have looked like at 24 months. The adjustment decreases the number of animals without tumors in all groups in the 18 month studies by $(18/24)^{3}$. The one-sided p-values for both the unadjusted trend test and the poly-3 adjusted trend test are given in Table 2 for male mouse renal tumors.

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[1] months
[2] mg/kg/day
[3] indicates p-value for trend <0.05
[4] p=0.08
[5] not evaluated by the EPA

Table 2: Analysis of Male Mouse Renal Tumors From the Individual Studies

83	Crl:CD-1	24	157, 814, 4841	1/50, 0/49, 1/50, 3/50	0.03 (0.03)
93	?:CD-1	24	100, 300, 1000	2/50, 2/50, 0/50, 0/50	0.94 (0.94)
97	CrJ:CD-1	18	165, 838, 4348	0/50, 0/50, 0/50, 2/50	0.008 (0.009)
01	SW	18	15, 151, 1460	0/49, 0/49, 1/50, 2/50	0.04 (0.04)
09	Crl:CD-1	18	71, 234, 810	0/51, 0/51, 0/51, 0/51	-

As an example of how the Poly-3 adjustments work, consider a comparison of the high-dose renal tumor response in the 1983 study (3/50=6%) to the high-dose response in the 1997 study (2/50=4%). In the 1997 study, 48 animals had no tumors at 18 months; the poly-3 adjustment reduces this to 20.25 leading to an incidence estimate of 2/22.25=9%. Because the Poly3 test effectively reduces the number of animals on study, even though the incidence estimate goes up, the p-value for the trend test goes down. Numerous evaluations of the validity of the poly-3 adjustment have been published in the peer-reviewed literature and it seems to work very well.

Now that the lengths of the studies have been adjusted, the next question to ask is whether this dose-response is consistent across all of the studies or whether there are anomalies. Combining all of the studies into one analysis can help us to evaluate this question; if the pooled data are no longer significant or less significant, the studies are not consistent and do not complement each other. Combining all of the studies into one pooled analysis and performing a trend analysis on the pooled data yields highly significant findings (Table 3, Line 1). Excluding the Swiss Albino mouse study and only using the CD-1 mice also yields a significant trend (Table 3, Line 2). Repeating these analyses with the Poly-3 adjusted data does not alter the significant findings. Since EPA is concerned about doses above 1000 mg/kg/day, I excluded doses above this dose and re-analyzed the data. The results of the restricted analysis are shown in Table 3, Lines 3-4. Without the doses above 1000 mg/kg/day, the effect disappears.

Table 3: Pooled Analysis of Male Mouse Renal Tumors

All Combined	CD-1 and Swiss	0.0004 (0.001)
CD-1 Combined	CD-1	0.001 (0.001)
All Combined, doses>1000 dropped	CD-1 and Swiss	0.80 (0.84)
CD-1 Combined, doses>1000 dropped	CD-1	0.85 (0.86)

Tables 4 and 5 repeat these analyses for malignant lymphomas. Because of the different backgrounds between the Swiss mice and the CD-1 mice, when they are all combined, the joint analysis is not significant (Table 5, line 1). Removing the Swiss mouse study and only evaluating the CD-1 mice leads to highly significant trends in all analyses (Table 5, lines 2). A significant trend remains in CD-1 mice even after removing the doses>1000 mg/kg/day (Table 5, line 4) suggesting this is not a high-dose only effect.

Table 4: Analysis of Male Mouse Malignant Lymphoma From the Individual Studies

1983	Crl:CD-1	24	157, 814, 4841	2/50, 5/49, 4/50, 2/50	0.51 (0.51)
1993	?:CD-1	24	100, 300, 1000	4/50, 2/50, 1/50, 6/50	0.08 (0.08)
1997	CrJ:CD-1	18	165, 838, 4348	2/50, 2/50, 0/50, 6/50	0.008 (0.012)
2001	SW	18	15, 151, 1460	10/49, 15/49, 16/49, 19/49	0.05 (0.09)
2009	Crl:CD-1	18	71, 234, 810	0/51, 1/51, 2/51, 5/51	0.004 (0.005)

Table 5: Pooled Analysis of Male Mouse Malignant Lymphoma

All Combined	CD-1 and Swiss	0.17 (0.19)
CD-1 Combined	CD-1	0.02 (0.01)
All Combined, doses>1000 dropped	CD-1 and Swiss	0.86 (0.93)
CD-1 Combined, doses>1000 dropped	CD-1	0.03 (0.05)

Tables 6 and 7 repeat these analyses for hemangiosarcomas. The findings in the Swiss mouse were unavailable so Tables 6 and 7 only contain analyses of the CD-1 mouse data. All pooled analyses are highly significant (Table 7) and they remain significant if doses>1000 are excluded (Table 7, line 2). So again, this is not a high dose-only effect.

Table 6: Analysis of Male Mouse Hemangiosarcomas From the Individual Studies

1983	Crl:CD-1	24	157, 814, 4841	0/50, 0/49, 1/50, 0/50	0.63 (0.63)
1993	?:CD-1	24	100, 300, 1000	0/50, 0/50, 0/50, 4/50	0.0004 (0.0004)
1997	CrJ:CD-1	18	165, 838, 4348	0/50, 0/50, 0/50, 2/50	0.008 (0.009)
2001	SW	18	15, 151, 1460	No Data	-
2009	Crl:CD-1	18	71, 234, 810	0/51, 0/51, 0/51, 0/51	-

Table 7: Pooled Analysis of Male Mouse Hemangiosarcomas

CD-1 Combined	CD-1	0.02 (0.03)
CD-1 Combined and Doses Pooled[1]	CD-1	0.02 (0.02)
CD-1 Combined, doses>1000 dropped	CD-1	<0.0001 (<0.0001)
CD-1 Combined, doses>1000 dropped and Doses Pooled[2]	CD-1	0.0003 (0.0003)

In summary, the results seen for renal tumors, malignant lymphomas and hemangiosarcomas in male mice in the 4 CD-1 studies for which the data were available are consistent and have a much stronger trend when all of the data are combined. The trend tests for malignant lymphomas and hemangiosarcomas in these studies remain significant when doses above 1000 mg/kg/day are eliminated.

EPA's approach has been to eliminate each study separately, generally by arguing the dose is too high (even though no signs of exceeding the MTD are apparent and their guidelines do not support the cut-off they are using), that there are no precursor lesions (suggesting cancer cannot arise without precursor lesions which is not a scientific necessity), and that the pairwise comparisons are not significant so the trend test should be ignored (in violation of their own guidelines). In addition, EPA has failed to present all of the positive tumor sites seen in these mouse studies, they have incorrectly used (probably inappropriate) historical controls and when these are used correctly a significant finding remains, they have included studies that should have been dismissed due to power issues, have included a study for which there is almost no available information other than the one paragraph they have presented, and have not evaluated the data across the studies to look for consistency in the response for tumors that appear in multiple studies. In essence, this is a very weak scientific evaluation of the available mouse carcinogenicity data.

My conclusion is that the mouse data clearly indicates that glyphosate can induce malignant lymphomas and hemangiosarcomas in male CD-1 mice, even when doses above 1000 mg/kg/day are eliminated. There is also a suggestion that glyphosate can induce hemangiomas in female CD-1 mice. The mouse data also demonstrate that glyphosate can induce malignant lymphomas in male CD-1 mice and male Swiss Albino mice. Finally, the renal tumors seen in the CD-1 mice also appear in the Swiss Albino mice supporting the role glyphosate plays in inducing these tumors. This is clearly sufficient evidence of the carcinogenicity of glyphosate in mice.

1. Portier CJ, Hedges JC, Hoel DG. Age-specific models of mortality and tumor onset for historical control animals in the National Toxicology Program's carcinogenicity experiments. *Cancer Res* (1986) **46**(9):4372-8. PubMed PMID: 3731095.
2. Bailer AJ, Portier CJ. Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples. *Biometrics* (1988) **44**(2):417-31. PubMed PMID: 3390507.
3. Portier CJ, Bailer AJ. Testing for increased carcinogenicity using a survival-adjusted quantal response test. *Fundam Appl Toxicol* (1989) **12**(4):731-7. PubMed PMID: 2744275.

www.agri-pulse.com/articles/7584-oh-brother-croplife-questions-makeup-of-glyphosate-panel

Oh, brother: CropLife questions makeup of glyphosate panel

Steve Davies (/authors/2-steve-davies)
October 12, 2016

WASHINGTON, Oct. 12, 2016 - When the Scientific Advisory Panel begins four days of meetings next week to examine the carcinogenic potential of glyphosate, Christopher Portier won't be there.

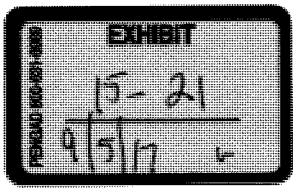
But his brother Kenneth, whom EPA picked to serve as one of the scientists reviewing the world's most widely used herbicide, will be in attendance.

And that has the crop-protection industry concerned.

Christopher Portier, former director of the U.S. National Center for Environmental Health at the Centers for Disease Control and Prevention, served as an "invited specialist" on the International Agency for Research on Cancer panel that determined glyphosate is "probably carcinogenic to humans."

He has been a lightning rod for criticism since the IARC assessment came out in March 2015 and sparked a worldwide pushback from principal manufacturer Monsanto and the ag chemical industry in general to prove that it is not.

The European Food Safety Authority
released
(https://www.efsa.europa.eu/en/efsajournal/pub/4302)
its own analysis, which concluded glyphosate is not likely to be carcinogenic, after which Portier led a group of 95 scientists who
wrote a letter to EFSA
(https://www.efsa.europa.eu/en/press/news/160113)
and
published a study
(http://jech.bmj.com/content/early/2016/03/03/jech-2015-207005.full)
disputing that characterization and taking issue with EFSA's methodology.



Christopher's brother, Kenneth Portier, is also a scientist: He's vice president of the Statistics & Evaluation Center at the American Cancer Society, and has served on more than 60 Scientific Advisory Panels for EPA.

Despite those qualifications, his family ties have CropLife America raising questions about the SAP.

"It's hard to know if it's a fair panel," said Janet Collins, CLA's senior vice president of science and regulatory affairs, when asked about the SAP members last week. (Technically, the appointed scientists are members of the Science Review Board. The SAP is a permanent body that contributes a few of its members to panels that examine issues arising under the Federal Insecticide, Fungicide, and Rodenticide Act.)

When questioned specifically about Kenneth Portier, Collins noted that Christopher Portier has been "leading the charge" in defending IARC's monograph and speculated that the brothers have "probably talked about" this area of common interest.

"I'm not intending to call this particular gentleman out," she said, referring to Kenneth Portier. "I'm not in any way disparaging him or his credentials." But she added, "There appears to be a conflict of interest."

"Somebody who wanted to could argue that he shouldn't be on the panel," she said.

Agri-Pulse
could not reach Kenneth Portier for comment, but Christopher defended his brother's credentials. In a phone interview, he said that Kenneth is "perfectly well qualified" to be on the glyphosate SAP.

"I don't believe anybody in their right mind would say he's not perfectly qualified. If they're trying to say he's biased, good luck, how are you going to prove it?"

"My brother chaired EPA's SAP for seven years," he continued. "Nobody has ever questioned his integrity or his scientific acumen – in fact, his statistical acumen. They're welcome to question it now, but they're just going to get a lot of negative feedback on it because he's done an excellent job for EPA over the years."

Portier also said that he and his brother don't always see eye to eye. "He doesn't agree with everything I believe," Christopher said.

Asked whether he had spoken with his brother about glyphosate, Christopher Portier said, "In broad terms. I told him it's a battle between hazard and risk, and that he does understand."

"It's always an interesting tactic, I find, to change the message," Christopher said. "The message is not what I'm saying is wrong, the message becomes, 'But his brother's on the panel.' I'd prefer if they'd come straight at me and come after my message."

Portier also addressed the criticism that because he works part time for the Environmental Defense Fund – and did at the time of the IARC review – that his involvement with the IARC monograph is somehow tainted.

"I work for them two days a week, mostly on air pollution and air pollution modeling, and on climate change and climate change modeling." The work, he said, has "nothing to do with pesticides."

"Nobody has paid me a cent to do what I'm doing with glyphosate," he said. "I have no conflict of interest whatsoever."

Christopher Portier has submitted
comments
(http://www.agri-pulse.com/uploaded/glyphosate-portier-sap-comments.pdf)
to EPA in advance of the SAP meeting, at which the scientists will consider the studies and methods used by EPA
to conclude in a recent paper
(http://www.agri-pulse.com/uploaded/glyphosate-issue-paper-epa.pdf)
that glyphosate is not likely carcinogenic.

In his comments, Portier said EPA incorrectly downplayed the significance of rat and mouse studies because of the size of the doses, even though the doses did not exceed 5 percent of the animals' body weight.

The data he examined, he said, "demonstrate an association in humans to (non-Hodgkin lymphoma), evidence in rats for thyroid tumors, and very strong evidence in mice for renal tumors, hemangiosarcomas and malignant lymphomas. EPA's exclusion of doses above 1,000 mg/kg/day is unscientific and their argument of a lack of significance above this dose is unsupported."

"In every case where EPA could choose between a public health protective choice where slight weaknesses in a study or a lack of a very strong finding could raise concerns, versus a choice where every study must be perfect and definitive, otherwise it is not used, EPA has chosen to discard positive findings, leaving them to finally conclude there is no concern. These data simply do not support a finding that glyphosate is 'not likely to be carcinogenic to humans.'"
Also commenting
(https://www.regulations.gov/document?D=EPA-HQ-OPP-2016-0385-0221)
were some of the scientists who recently prepared a paper that found glyphosate is not likely be carcinogenic. Intertek Scientific and Regulatory Consultancy Services put together the panel for that paper on commission from Monsanto.

That paper said that "even without data IARC did not include, there is no support for IARC's conclusion that glyphosate is 'probably carcinogenic to humans.'"

In their comments, five of the 15 scientists on the Intertek panel praised EPA for "an excellent and thorough review of glyphosate."

"We agree with the agency that it is important to give more weight to studies evaluating endpoints that measured gene mutations and chromosomal aberrations (i.e. permanent DNA damage) than to endpoints reflecting DNA events that may be transient or reversible such as primary DNA damage (e.g., comet assays)," they said.

The SAP meeting will be held Oct. 18-21 in Arlington, Virginia. The online docket for the meeting is here
(https://www.regulations.gov/docket?D=EPA-HQ-OPP-2016-0385)
.

To: Jones, Jim[redacted]
From: Chris Portier
Sent: Wed 5/4/2016 11:38:18 AM
Subject: Fwd: glyphosate: POLITICO on EPA report

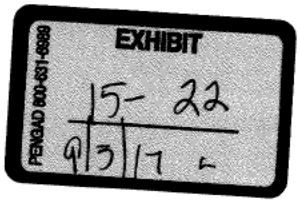
;;;;Jim,
FYI.

C.

Subject: glyphosate: POLITICO on EPA report

GLYPHOSATE STORM'S A-BREWIN': The U.S. Environmental Protection Agency has made a preliminary finding that glyphosate is unlikely to cause cancer in humans — but the agency isn't ready to go public yet. The EPA briefly posted online an October 2015 final report from its Cancer Assessment Review Committee, which concluded glyphosate is "not likely to be carcinogenic to humans." It then pulled it from its website. The committee said evidence from existing epidemiological studies and tests of lab animals doesn't meet the bar for classifying the herbicide as a carcinogen. An agency spokesperson told POLITICO the report was removed because assessment was ongoing. "Our assessment will be peer reviewed and completed by end of 2016," said the spokesperson.

— Why this matters for the EU: A political scrum over what to do about glyphosate is underway in the EU. Parliament voted to extend the chemical's authorization for seven years, the Commission is pushing for 10, but the real decision comes in a Plant, Animal, Food and Feed Committee meeting on May 18-19. Advocates for banning glyphosate altogether cite a March 2015 study by International Agency for Research on Cancer, which said it caused cancer. Glyphosate's political supporters cite a November study with the opposite conclusions. This latter group might now have another study in their arsenal — and from a reputable U.S. government agency. "In line with the 90,000 pages, and 3,300 studies already published in support of the reapproval of glyphosate, the EPA report casts yet more doubt on the conclusions of IARC," a spokesperson for the European Crop Protection Association told Morning Agri. Greenpeace EU, which opposes using glyphosate as long as there is no scientific consensus, told Morning Agri it had not yet read the study and so couldn't comment. More: http://reut.rs/23mbxYf.



From: "Lowit, Anna" <[redacted]>
Subject: FW: Sorry
Date: June 24, 2016 at 8:18:40 PM GMT+2
To: "[redacted]" <[redacted]>

Hi Chris

Jim Jones forwarded me some files from you. thanks for sending them. I have a quick Q for you.

in this PPT file, what is the citation(s) for the metaanalysis of the animal tumor data?

Thanks
Anna

Sent from my Windows Phone

From: Jones, Jim
Sent: 6/24/2016 7:43 AM
To: Housenger, Jack; Lowit, Anna
Subject: FW: Sorry

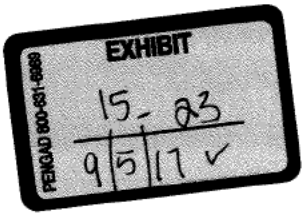
As per my conversation with Jack. Jim

-----Original Message-----
From: Chris Portier [redacted]
Sent: Thursday, June 23, 2016 2:17 PM
To: Jones, Jim <[redacted]>
Subject: Sorry

Jim,

I had an error in one Table that I had to correct. New version attached.

C,



From: "Lowit, Anna" <[redacted]>
Subject: RE: Sorry
Date: June 24, 2016 at 9:11:58 PM GMT+2
To: Chris Portier <[redacted]>

Ditto on the terse emails, it's too easy on the phone to be quick and even rude! I do it too.

Thanks for the quick response.

Would you mind sharing the code? I'm interested in the analysis, it's a different approach to the data compared to all the others "floating around".

Sent from my Windows Phone

From: Chris Portier
Sent: 6/24/2016 2:22 PM
To: Lowit, Anna
Subject: Re: Sorry

Anna,

Oh, and I wanted to say Hi Anna. Sometimes my emails are a bit short.

If you need any background from me, I'll be happy to help you out. I am also in DC if you want to meet and discuss this.

C.

On Jun 24, 2016, at 2:18 PM, Lowit, Anna <[redacted]> wrote:
Hi Chris

Jim Jones forwarded me some files from you. thanks for sending them. I have a quick Q for you.

in this PPT file, what is the citation(s) for the metaanalysis of the animal tumor data?

Thanks
Anna

Sent from my Windows Phone

From: Jones, Jim
Sent: 6/24/2016 7:43 AM
To: Housenger, Jack; Lowit, Anna
Subject: FW: Sorry

As per my conversation with Jack. Jim

-----Original Message-----
From: Chris Portier [redacted]
Sent: Thursday, June 23, 2016 2:17 PM
To: Jones, Jim <[redacted]
Subject: Sorry

Jim,

I had an error in one Table that I had to correct. New version attached.

C,

<FiguresandTablesEPA.pptx>

From: "Lowit, Anna" <[redacted]>
Subject: RE: Sorry
Date: June 27, 2016 at 2:17:34 AM GMT+2
To: Chris Portier <[redacted]>

Thanks!

Sent from my Windows Phone

From: Chris Portier
Sent: 6/26/2016 6:42 PM
To: Lowit, Anna
Subject: Re: Sorry

Anna,

Per your request. I believe these are all of the files you will need. Let me know if these do not work for you. I had some minor errors in the tables again because I was not taking direction into account for the trend test (up or down). That is now fixed.

C.

From: "Lowit, Anna" <[redacted]>
Subject: RE: Sorry
Date: June 24, 2016 at 9:23:09 PM GMT+2
To: Chris Portier <[redacted]>

That would be great ☺

Sent from my Windows Phone

From: Chris Portier
Sent: 6/24/2016 3:14 PM
To: Lowit, Anna
Subject: Re: Sorry

No problem. Shall I clean it up a bit first. I can get it to you by monday.

On Jun 24, 2016, at 3:11 PM, Lowit, Anna <[redacted]> wrote:
Ditto on the terse emails, it's too easy on the phone to be quick and even rude! I do it too.

Thanks for the quick response.

Would you mind sharing the code? I'm interested in the analysis, it's a different approach to the data compared to all the others "floating around".

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Anna

Sent from my Windows Phone

From: Jones, Jim
Sent: 6/24/2016 7:43 AM
To: Housenger, Jack; Lowit, Anna
Subject: FW: Sorry

As per my conversation with Jack. Jim

-----Original Message-----
From: Chris Portier [redacted]
Sent: Thursday, June 23, 2016 2:17 PM
To: Jones, Jim <[redacted]
Subject: Sorry

Jim,

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C,

<FiguresandTablesEPA.pptx>

White, Dylan

From: Chris Portier [redacted] on behalf of Chris Portier
Sent: Monday, March 07, 2016 6:17 AM
To: Dr. Christopher Portier
Subject: Keeping you all informed...
Attachments: Horizons_Glyphosate.pdf; ATT00001.htm; voting-calculator-results.pdf; ATT00002.htm

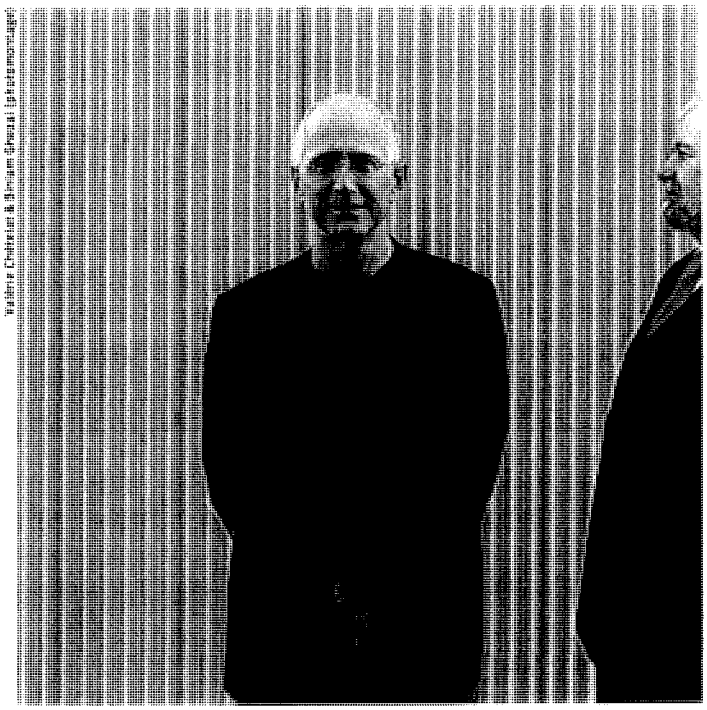
Follow Up Flag: Follow up
Flag Status: Flagged

I did a Pro-Con piece for the Swiss science magazine Horizons a month or so ago on glyphosate and cancer and it just came out. The head of the EFSA pesticides program did the Con. The words he chose were very carefully nuanced so the reader does not see the debate about trend analysis but it is written in the piece. Very interesting. (Attached)

DEBATE

Is glyphosate carcinogenic?

Glyphosate is the world's most widely used herbicide. While it's important in controlling weeds, its possible effects on humans are hotly debated among scientists.



Yes

says the environmental health researcher Christopher Portier

How strong is the evidence that humans are more likely to get cancer when widely exposed to glyphosate? This question centres on three issues: finding evidence in humans, finding evidence in laboratory animals and finding evidence of a molecular mechanism by which glyphosate might cause cancer.

Some 26 cancer studies have been carried out on humans who have been exposed to glyphosate formulations. Most of them found no connection. Nine of these studies examined non-Hodgkin lymphoma. Four case-control studies, when pooled, showed there to be an association between this cancer and glyphosate, as did two other case-control studies. The studies of higher quality adjusted for multiple exposures to other pesticides but still demonstrated an association, with the length of exposure increasing the strength of the association. However, these studies had certain limitations that made it impossible to rule out bias or other confounding factors. The conclusion we must draw is that glyphosate formulations are associated with non-Hodgkin lymphoma in humans, but there is only limited evidence of causality.

Five laboratory studies were carried out on mice, and nine on rats. All five of the mouse studies displayed increased tumour growth in at least one site. Three studies showed growth in kidney tumours, which rarely occur in mice; two studies showed an increase in hemangiosarcomas (a cancer arising in the blood vessels); and two studies also showed growth in malignant lymphomas. With the exception of growth in a few non-malignant tumours, none of the rat studies showed any effect. The conclusion is that glyphosate causes various tumours in laboratory mice.

> "There is evidence of a mechanism by which glyphosate causes cancer".

As to the molecular mechanism, publicly available data demonstrates that glyphosate and glyphosate formulations cause DNA damage in human and animal cells as well as in laboratory animals, but so far not in bacterial cells. In two studies, glyphosate formulations also induced DNA damage in the blood cells of exposed humans. In human and other cells, glyphosate and glyphosate formulations have been shown to induce free oxygen radicals that are capable of damaging DNA. The conclusion is that there is indeed evidence of a mechanism by which glyphosate causes cancer.

From all this information, it is reasonable to conclude that, at sufficient levels of exposure, glyphosate and glyphosate formulations are probably carcinogenic to humans.

Christopher Portier is the former Director of the US National Institute of Environmental Health. He lives in Switzerland and wrote the 'Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR' to the European Commission that was signed by 95 scientists from around the world.

No

says Jose Tarazona from the European Food Safety Authority

The European Food Safety Authority (EFSA) has recently reviewed the toxicological profile of glyphosate and proposed new toxicological reference values for risk assessment. The EFSA did not confirm the recent classification of glyphosate as probably carcinogenic by the International Agency for Research on Cancer (IARC).

The IARC considered there to be "limited evidence in humans" for an association between glyphosate and non-Hodgkin lymphoma, while for the EFSA the evidence was insufficient to support such a classification. As the evidence from studies in humans alone had been insufficient for concluding that glyphosate is carcinogenic, the assessment of evidence in laboratory animals was key, and led to the different conclusions of the two bodies.

Significant trends in reports on industry-sponsored studies have been observed by the IARC. The EFSA searched the recent, large database of animal carcinogenicity studies in its entirety, but found no significant differences between control and treatment groups in the studies that were valid. Reviewing the biological relevance of the incidences observed, the EFSA noted that the statistical trends were the result of bias, driven by secondary toxicity at excessively high doses, or chance results not related to glyphosate treatment.

"The lab results don't show a dose-response".

It is well known that excessive toxicity can affect the carcinogenic responses in bioassays. Such toxicity can cause effects such as cell death with associated regenerative cell proliferation. This can lead to tumour development as a secondary consequence, and is unrelated to the intrinsic potential of the substance to cause tumours at lower, less toxic doses.

The observed incidences were within the historical range observed in untreated animals. The laboratory results did not show a dose-response, and remain unconfirmed by equivalent studies at similar or higher doses. Therefore, besides the absence of statistically significant differences with the concurrent controls, the observed tumour incidences also lacked biological relevance.

The EFSA also concluded that glyphosate is unlikely to cause DNA damage, as has been confirmed by a large number of studies showing no effect. However, effects were reported for glyphosate formulations containing other ingredients, and the EFSA's assessment of a surfactant frequently used in these formulations revealed some concerns. This led the EFSA to recommend carrying out further assessments regarding the possibility of DNA damage being caused by formulated products.

Jose Tarazona is the Head of the Pesticides Unit at the European Food Safety Authority (EFSA) and vice-chairman of the EU Scientific Committee on Health and Environmental Risks.

Arch Toxicol
DOI 10.1007/s00204-017-2009-7

REPLY

Re: Tarazona et al. (2017): Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. doi: 10.1007/s00204-017-1962-5

Christopher J. Portier[1] · **Peter Clausing**[2]

Received: 18 May 2017 / Accepted: 1 June 2017

Recently Tarazona et al. (2017) explained the methodology used by the European Food Safety Authority (EFSA 2015) for the scientific assessment of carcinogenicity as applied to glyphosate. We noted a number of inaccuracies in this paper which may have affected the outcome of the assessment, i.e., glyphosate is considered as non-carcinogenic. These problems relate to the evaluation of individual studies, the objective evaluation of the combined evidence and the weight of evidence approach.

The authors point out that one mouse carcinogenicity study (study N) was "found unreliable after *detailed assessment* due to the occurrence of a viral infection *in all groups including controls*" (EFSA 2015, Table 4, footnote). This decisive statement is in contradiction to the contents of the draft report by the European Chemical Agency (BAuA 2016) concerning the same study. There it is stated that "No information is available on possible abundance of oncogenic viruses in the mouse colonies from which the animals used in the glyphosate studies were obtained" (BAuA 2016, p. 72). According to the draft BAuA report, the "detailed assessment" seems to be based on a remark from the U.S. EPA observer during a teleconference, but as stated in the draft BAuA report "in the study report itself, there was no evidence of health deterioration due to suspected viral infection, and thus, the actual basis of EPA's decision is not known" (BAuA 2016, p. 72). In addition, the incidence of malignant lymphomas in the control group of this study was 20% as compared to an average incidence of 18.4% in the historical control database from five earlier studies (BAuA 2016, p. 67). This negligible difference does not suggest that oncogenic viruses increased the incidence of malignant lymphoma in this particular study.

In comparison, mouse study B, was used in the EFSA evaluation (Tarazona et al. 2017) despite serious concerns regarding the quality of the data with regard to malignant lymphomas. According to regulatory documents (Germany 2015; BAuA 2016), the assessment of malignant lymphomas in this study was "based on histological examination of lymph nodes with macroscopic changes", a wholly unacceptable pathological assessment by OECD guidelines (OECD 2009). However, even this description is wrong since the individual animal data from the study show animals with lymphoreticular neoplasia in the thymus without any lymph node macroscopic changes and animals with lymph node macroscopic changes not examined histopathologically. Finally, it was only "assumed" (BAuA 2016, p. 71) that the "lymphoreticular neoplasia" identified in study A were equivalent to malignant lymphomas without histopathological confirmation. Including study B but excluding study N shows a clear bias by Tarazona et al. against positive findings.

EFSA (2015) also approached the statistical analysis of the data from these studies using a "balancing" between the statistical significance found in trend tests versus the lack of statistical significance in pair-wise comparisons. EFSA (2015) used two-sided tests in the statistical analysis of the tumor incidences while conformity with good scientific practice and OECD guidance 116 (OECD 2012) would have required one-sided tests. If the authorities had followed these recommendations, the significance of the findings would have tilted to "significance" for both pair-wise testing and trend tests. For the only two studies in CD-1 mice exposed for 18 months, the one-sided p values for incidence of malignant lymphomas in control animals

✉ Peter Clausing
pcl@jpberlin.de

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[2] PAN Germany, Nernstweg 32, 22765 Hamburg, Germany

Published online: 15 June 2017

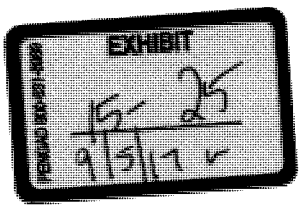

Table 1 Additional tumors with significant ($p < 0.05$) trends (exact Cochran-Armitage linear trend test in proportions) in the carcinogenicity studies not cited by Tarazona et al. (2017)

Study species	Tumor type Sex; incidences	p value (one-sided)
C Mouse	Hemangioma Females; 0/50, 0/50, 2/50, 5/50*	0.002
D Mouse	Lung adenocarcinomas Males; 5/51, 5/51, 7/51, 11/51	0.028
G Rat	Thyroid follicular cell adenomas and carcinomas Males; 0/50, 0/50, 0/50, 2/50, 2/49	0.034
E Rat	Thyroid c-cell carcinomas Females; 1/47, 0/49, 2/50, 6/47	0.003
J Rat	Kidney adenoma Male; 0/50, 0/50, 0/50, 4/50	0.004
K Rat	Hepatocellular adenoma Males; 0/52, 2/52, 0/52, 5/52*	0.008
L Rat	Skin keratoacanthoma Males; 2/51, 3/51, 0/51, 6/51	0.030
L Rat	Mammary gland adenomas and adenocarcinomas Males; 2/51, 3/51, 1/51, 8/51*	0.007

* These groups have a significantly increased ($p<0.05$) incidence of tumors relative to the controls by the Fisher Exact Test in addition to a significantly positive trend test finding

versus high dose animals are 0.134 and 0.028 for studies C and D (Fisher's exact test), respectively, while one-sided exact p values for the Cochran–Armitage trend tests are 0.02 and 0.008 for studies C and D, respectively.

As can be derived from Table 31 of the draft CLH report, studies C, D and N show dose–response relationships for malignant lymphomas (BAuA 2016).

Tarazona et al. (2017) give five reasons for dismissing all of the positive findings in all of the studies. First, they claim to have "balanced" the positive trend test findings against lack of significance in pairwise tests. The guidelines they cite clearly state that "Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result" (OECD 2012). While appropriate to require the determination of the statistical methods in the study plan (OECD 2009), this should not prevent regulatory authorities from applying a more comprehensive statistical analysis. Thus, this "balancing" appears to violate their guidance. Second, they cite a lack of consistency in multiple animal studies. However, to arrive at this conclusion, they group together studies with different strains, different durations, different pathology (see comment about Study B above) done at different times in different labs. Table 5 is an excellent example of an incorrect assessment comparing across mouse studies with different durations, with different substrains and markedly different pathology. Third, they argue that they are seeing effects only at or above the MTD. No "excessive toxicity" was found in any of the mouse or rat carcinogenicity studies (Germany 2015). The reduced body weight in high dose animals seen in some of these studies was associated with an even higher reduction in food consumption—not surprising at dietary concentrations of 30,000 ppm of glyphosate or higher. No evidence for excessive toxicity in any of the studies was provided by Tarazona et al. (2017). In addition, this "limit dose" of 1000 mg/kg does not apply to some studies with positive findings. For example, the high dose in study D was 810 mg/kg. Study D had significant increases in malignant lymphomas and lung adenocarcinomas in males. Fourth, they claim there is a lack of preneoplastic lesions, yet, for example, there was a significant increase in bilateral chronic interstitial nephritis ($p = 0.008$, exact trend test) in Study A which also showed kidney tumors. In addition, it is not clear what preneoplastic lesions they would be looking for when dealing with malignant lymphomas or hemangiosarcomas. Finally, they exclude positive findings falling within the range of the historical controls. Despite formal statistical methods for using historical control data appropriately in an evaluation (Fung et al. 1996; Greim et al. 2003; Haseman 1984; Peddada et al. 2007), EFSA (Germany 2015), EChA (BUaU 2016) and many other regulatory agencies (e.g., EPA, 2016) continue to use this inappropriate rule when evaluating these types of data. Formal statistical analysis of the mouse kidney, malignant lymphoma and hemangiosarcoma findings using historical controls results in two marginal findings becoming significant and did not reverse any of the positive findings relative to the concurrent controls.

Finally, a considerable number of tumors were missed in the evaluation by both EFSA and EChA (Table 1). Our calculations were based on data in the supplemental information provided by Greim et al. (2015). These significant increases were not mentioned by either EFSA (Germany

2015) or ECHA (BAuA 2016). In addition, Table 6 of Tarazona et al. (2017) failed to mention thyroid c-cell carcinoma in female rats (Study F), also seen in Study E, and their Table 4 included a non-chronic study (I).

In conclusion, the weight of evidence discussed by Tarazona et al. (2017) needs to be re-assessed taking into account the five key issues raised above. They clearly need to be more precise in their evaluation of the evidence and more cautious in their indiscriminate exclusion of positive findings.

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Haseman JK (1984) Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies. Environ Health Perspect 58:385–392

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OECD (2012) Guidance document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453, 2nd edn. Series on testing and assessment No 116. Env/jm/mono(2011)47

Peddada SD, Dinse GE, Kissling GE (2007) Incorporating historical control data when comparing tumor incidence rates. J Am Stat Assoc 102:1212–1220

Tarazona JV, Court-Marques D, Tiramani M, Reich H, Pfeil R, Istace F, Crivellente F (2017) Glyphosate toxicity and carcinogenicity: a review of the scientific basis of the European Union assessment and its differences with IARC. Toxicol, Arch. doi:10.1007/s00204-017-1962-5

The glyphosate saga: an example of influence of unsound science and interest groups in public health decision making

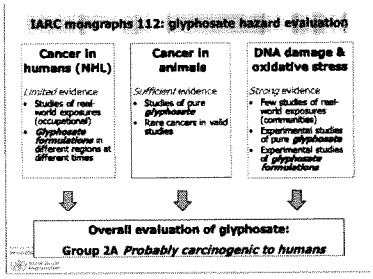
Xaver Baur, Daniele Mandrioli, Lygia Therese Budnik, Ellen Silbergeld, Philip J. Landrigan, Christopher J. Portier

Xaver Baur, Charité University Medicine, Berlin, Germany; EOM Society, Berlin, Germany, ***Ramazzini Fellow***
Daniele Mandrioli, Cesare Maltoni Cancer Research Center of the Ramazzini Institute, Bologna, Italy, ***Ramazzini Fellow***
Lygia Therese Budnik, University of Hamburg, Hamburg, Germany, EOM Society, Berlin, Germany, ***Ramazzini Fellow***
Ellen Silbergeld, Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, USA, ***Ramazzini Fellow***
Philip J. Landrigan, Mount Sinai School of Medicine, New York City, USA, ***Ramazzini Fellow***
Christopher J. Portier, Maastricht University, the Netherlands & Environmental Health Consultant, Switzerland

Background

The International Agency for Research on Cancer (IARC) evaluated the carcinogenic hazard of the herbicide glyphosate. It concluded that the data for glyphosate meet the criteria for classification as a probable human carcinogen (group 2A). On the other hand, the European Food Safety Authority (EFSA) and German Federal Institute for Risk Assessment (BfR) came to the conclusion that glyphosate carcinogenicity is unlikely(1). FAO/WHO did not challenge the IARC findings, but concluded that cancer risk was unlikely at typical human ingestion levels. Ongoing evaluations of glyphosate carcinogenicity by the US Environmental Protection Agency (US EPA) and the European Chemical Agency (ECHA) have both been published as drafts still under review. We summarized the methods used by different public health decision makers and their limits in terms of science, transparency and conflicts of interests.

Figure 1: Evaluation of glyphosate by IARC: evidence of its carcinogenicity in humans, animals and mechanistic *models (Fig: courtesy: Kate Z. Guyton).*



Public Health Decision Making Processes

IARC: IARC applied a transparent and rigorous scientific process by 17 publicly identified independent experts, and a highly professional standardized evaluation of all publically available studies(2). The IARC Working Group found an association between NHL and glyphosate based on the available human evidence and significant carcinogenic effects in laboratory animals for rare kidney tumours and hemangiosarcoma in two mouse studies and benign tumours in two rat studies. The IARC WG summarized that there was strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available research, including findings of DNA damage in the peripheral blood of exposed humans. The IARC WG concluded that there is sufficient evidence of carcinogenicity in animals, limited evidence of carcinogenicity in humans and strong evidence for two carcinogenic mechanisms.

EFSA/BfR: The EFSA/BfR evaluation of glyphosate carcinogenicity, based on the Renewal Assessment Report (RAR) for glyphosate prepared by the Rapporteur Member State (BfR), concludes that: "glyphosate is unlikely to pose a carcinogenic hazard to humans"(3). No authors or contributors are listed for either document by BfR and EFSA(4). The use of confidential data submitted to the BfR makes it impossible for any scientist not associated with BfR or EFSA to review this conclusion. Three known experts from the chemical industry are members of the Pesticide Committee of the BfR(5).

EFSA classified the human evidence as 'very limited' and then dismissed any association of glyphosate with cancer without clear explanation or justification. Ignoring established guidelines by OECD and ECHA, cited in their report, EFSA dismissed evidence of renal tumours in three mouse studies, hemangiosarcoma in two mouse studies and malignant lymphoma in two mouse studies. Thus, EFSA incorrectly discarded all findings of glyphosate-induced cancer in animals as chance occurrences. EFSA ignored important laboratory and human mechanistic evidence.

FAO/WHO: The joint FAO/WHO meeting of pesticide residues concluded that "glyphosate is unlikely to pose a carcinogenic risk to humans from exposure through the diet". This is both a risk and a hazard statement; no independent hazard statement was prepared. A transparent disclosure of the criteria used for assessing carcinogenic risk is missing. No reference was provided in the document. No list of authors and disclosure of conflicts of interests was provided in the document. Nevertheless, different members, including the chairman, of the joint FAO/WHO meeting of pesticide residues had been reported to have financial conflicts of interests with industry(6).

ECHA: Glyphosate classification is also currently under review by ECHA. A draft of the report by ECHA has been published for public comments(7). It concludes that no hazard classification for its carcinogenicity is warranted. But males in all five mouse carcinogenicity studies considered by ECHA to be of acceptable quality show a statistically significant increase in the incidence of one or several tumor types. Importantly, the finding of an increased incidence of malignant lymphoma in animals is further supported by the results of epidemiological studies indicating an association between glyphosate exposure and Non-Hodgkin lymphoma. This clearly exceeds the criteria for classification as a carcinogen as given in CLP Regulation, documented on page 95 of the Dossier(8).

US EPA: Glyphosate is currently undergoing a registration review by US EPA. The recently proposed classification by US EPA is that glyphosate is not likely to be carcinogenic at doses relevant for human health risk assessment(9). This is again a risk and hazard statement with no independent hazard statement provided. However, this is based on some speculation, i.e. that the more positive epidemiological studies should have had lower relative risks than other studies; further, it is assumed that there were previous exposures in the greatly weighted Agricultural Health Study which has a rather short follow-up time. US EPA's interpretation that "the association between glyphosate exposure and the risk of NHL cannot be determined based on the available data" does not correctly characterize the human data presented. Findings on multiple myeloma that were included in the IARC evaluation were not considered adequately.

The evaluation of the animal carcinogenicity data and mechanistic data for glyphosate missed important findings, but basically follows along the same lines as the EFSA/BFR review, suggesting a lack of independent review.

Conclusion

The glyphosate issue is just one example of inappropriate corporate influences on public health regulations by use of unsound scientific reviews. These economically motivated activities leave a resulting health burden on society. We call for increased sensitivity, full transparency and the implementation of effective rules governing decision making bodies(10).
We urge the Collegium Ramazzini to again support an IARC evaluation of carcinogenicity(11), since the most appropriate and scientifically based evaluation of the cancers reported in humans and laboratory animals as well as supportive mechanistic data is that glyphosate is a probable human carcinogen(1). We suggest that common commercial formulations of GBHs should be prioritized for inclusion in government-led toxicology testing programs such as the U.S. National Toxicology Program, as well as for biomonitoring as conducted by the U.S. Centers for Disease Control and Prevention(12).

1 - http://jech.bmj.com/content/early/2016/03/03/jech-2015-207005.full
2 - http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf
3 - European Food Safety Authority. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA J 2015;13:4302)
4 - http://registerofquestions.efsa.europa.eu/roqFrontend/outputLoader?output=ON-4302
5 - http://corporateeurope.org/food-and-agriculture/2015/04/glyphosate-saga-independent-scientific-advice-according-germany-uk
6 - https://www.theguardian.com/environment/2016/may/17/ unwho-panel-in-conflict-of-interest-row-over-glyphosates-cancer-risk
7 - https://echa.europa.eu/documents/10162/13626/clh_report_glyphosate_en.pdf
8 - http://www.pan-germany.org/download/ PAN_Germany_Comment_on_CLH-Report_regarding_Carcinogenicity_1607.pdf
9 - https://www.epa.gov/pesticides/scientific-advisory-panel-meet-cancer-potential-glyphosate
10 - http://ehp.niehs.nih.gov/1509880/
11 - http://www.collegiumramazzini.org/download/12-SeventeenthCRStatement(2015).pdf

CURRICULUM VITAE
Christopher J. Portier, Ph.D.

Personal Data: Birth Date [redacted]
Birthplace [redacted]

Address: [redacted]

Education:

1981	Ph.D.	(Biostatistics), University of North Carolina, Chapel Hill
1979	M.S.	(Biostatistics), University of North Carolina, Chapel Hill
1977	B.S.	(Mathematics), summa cum laude, Nicholls State University

Employment:

2013-present	**Consultant** to various governmental agencies (multiple countries)
2013-2014	**Senior Visiting Scientist**, International Agency for Research on Cancer, Lyon, France
2013-present	**Senior Contributing Scientist**, Environmental Defense Fund, New York City, NY
2010-2013	**Director**, National Center for Environment Health, Centers for Disease Control and Prevention, Atlanta, GA
2010-2013	**Director**, Agency for Toxic Substances and Disease Registry, Atlanta, GA
2009 – 2010	**Senior Advisor to the Director**, National Institute of Environmental Health Sciences and National Toxicology Program, Research Triangle Park, North Carolina.
2009 – 2010	**Visiting Scientist**, National Research Centre for Environmental Toxicology (EnTox), Queensland, Australia
2006 - 2009	**Associate Director**, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
2006 - 2009	**Director, Office of Risk Assessment Research**, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
1993 – 2010	**Head, Environmental Systems Biology** (originally Stochastic Modeling), Laboratory of Molecular Toxicology, National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina.
2000 - 2006	**Associate Director, National Toxicology Program**, National Institute of Environmental Health Sciences, Division of Intramural Research, Research Triangle Park, North Carolina.
2000 - 2006	**Director, Environmental Toxicology Program**, National Institute of Environmental Health Sciences, Division of Intramural Research, Research Triangle Park, North Carolina.
2006-2007	**Scientific Advisor to the Director**, Public Health and the Environment Department, World Health Organization, Geneva, Switzerland (detail from NIEHS – four months)
1993 - 2005	**Chief, Laboratory of Computational Biology and Risk Analysis** (originally the Laboratory of Quantitative and Computational Biology), National Institute of Environmental Health Sciences, Division of Intramural Research, Research Triangle Park, North Carolina.

1996 - 2000	**Associate Director for Risk Assessment**, Environmental Toxicology Program National Institute of Environmental Health Sciences, Division of Intramural Research, Research Triangle Park, North Carolina.
1990 - 1993	**Head, Risk Methodology Section**, National Institute of Environmental Health Sciences, Division of Biometry and Risk Assessment, Research Triangle Park, North Carolina.
1987, 1992, 1990	**Guest Scientist**, German Cancer Research Center, Heidelberg, Germany.
1978 - 1990	**Mathematical Statistician**, National Institute of Environmental Health Sciences, Division of Biometry and Risk Assessment, Research Triangle Park, North Carolina.
1977	**Mathematician**, Computer Sciences Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee.
1976	**Undergraduate Research Trainee**, Neutron Physics Division, Oak Ridge National Laboratory, Oak Ridge, Tennessee.

University Affiliations:

2014 – present	Visiting Professor, Department of Toxicogenomics, Maastricht University, The Netherlands
2013 – present	Honorary Professor, National Research Centre for Environmental Toxicology, University of Queensland, Brisbane, Australia
2011 – present	Adjunct Professor, Department of Environmental Health, Emory University, Atlanta, GA, USA
2009 – 2010	Visiting Professor, University of Queensland, Brisbane, Australia
1986 - 2007	Adjunct Professor of Biostatistics, University of North Carolina, School of Public Health, Chapel Hill, North Carolina.
1990-1992	Adjunct Professor of Statistics, University of Waterloo, Waterloo, Ontario, Canada

Honors & Awards:

- 2013 President's Dream Green Team Award for "A Human Health Perspective on Climate Change"
- Fellow, World Innovation Foundation, 2006
- Society of Toxicology, Risk Assessment Specialty Section, Paper of the Year, 2006
- Society of Toxicology, Risk Assessment Specialty Section, Paper of the Year, 2005
- Outstanding Risk Practitioner Award, International Society for Risk Analysis, 2000.
- Elected Fellow, International Statistical Institute, 2000.
- Outstanding Performance Award, National Institute of Environmental Health Sciences, numerous dates.
- Commendation for Sustained High Quality Work Performance, National Institute of Environmental Health Sciences, numerous dates.
- Merit Award, National Institute of Health, 1998.
- Board of Publications, Best Paper Award, Society of Toxicology, 1995.
- Distinguished Achievement Award, Section on Statistics and the Environment, American Statistical Association, 1995.
- Spiegelman Award presented by the American Public Health Association to the most outstanding public health statistician under the age of 40, 1995.
- Best-applied statistics paper, Centers for Disease Control, 1993.
- Elected Fellow, American Statistical Association, 1992.

- Elected Foreign Correspondent, Russian National Academy of Natural Sciences, 1992.
- First recipient of the James E. Grizzle Distinguished Alumnus Award, The Department of Biostatistics, The University of North Carolina, 1991.

Professional Societies Membership:

Society of Toxicology, American Public Health Association, International Statistics Institute, Society for Risk Analysis, EcoHealth Society, American Association for Cancer Research, American Association for the Advancement of Science

Editorial Activities:

- Editor in Chief - The Open Environmental Journal (2008 to 2010)
- Associate Editor – Frontiers in Predictive Toxicity (2010 to present)
- Associate Editor - Environmental Health Perspectives (1987-2006)
- Associate Editor - Risk Analysis: An International Journal (1989-2003)
- Editorial Board – Environmental and Ecological Statistics (2004-2007)
- Associate Editor – Statistics in Medicine (1998-2002)
- Associate Editor - Biometrics (1997-99)
- Editorial Board Member/Reviewer (different dates): Biometrika, Cancer Research, Communications in Statistics, Fundamental and Applied Toxicology, Journal of Applied Toxicology, Journal of the American Statistical Association, Journal of Toxicology and Environmental Health, Science, Mathematical Biosciences, Journal of Mathematical Biology, Carcinogenesis, Science, PNAS, Toxicological Sciences

Advisory & Review Committees:

2015 – 2016	Member, Committee to Review the Draft Interagency Report on the Impacts of Climate Change on Human Health in the United States, National Research Council, National Academy of Sciences, USA
2010 – present	Member, Science Advisory Group on Electromagnetic Fields and Health, Netherlands Organisation for Health Research and Development
2009 – 2010	Coordinating Lead Author, Interagency Working Group on Climate Change and Health
2009 – present	Member, Institute of Medicine Roundtable on Environmental Health Sciences Research and Medicine
2009 – 2012	Member, National Academies of Science Roundtable on Science and Technology for Sustainability
2009	Member, WHO Advisory group on the health implications of the use of DDT to reduce risks of malaria.
2005 – 2010	Chair, Subcommittee on Toxics and Risk, President's National Council on Science and Technology
1997 - 2012	Advisor, *World Health Organization*, International Program on Chemical Safety, EMF Project.
2008 – 2010	Member, Environmental Protection Agency, Science Advisory Board
2007 – 2010	Member, International Life Sciences Institute, Health and Environmental Sciences Institute, Subcommittee on Susceptible Populations
2008	Center Review Committee, Canadian National Science and Engineering Research Council Chair in Risk Assessment

2008	Chair, International Agency for Research on Cancer Monographs Advisory Group, Lyon, France
2008	Advisory Group, Center for Environmental Oncology, University of Pittsburgh Cancer Institute
2007.	Chair, WHO Workshop on Low Cost Options for Reducing Exposures to ELF-EMF, Geneva
2007.	Invited Participant, International Program on Chemical Safety Workshop on Aggregate and Cumulative Risk Assessment, Washington, DC.
2006	Rapporteur, International Agency for Research on Cancer, Scientific Advisory Group to Plan Volume 100 of the IARC Monograph Series
2005	Chair, International Agency for Research on Cancer, Scientific Advisory Board on the Preamble to the Cancer Monograph Series
2005	Chair, World Health Organization Expert Panel on Health Criteria Document for Extremely Low Frequency Electric and Magnetic Fields
2003 – 2005	Co-Chair, Subcommittee on Health and Environment, President's National Council on Science and Technology
2003	Ad-Hoc member, EPA Science Advisory Board, Review of Children's Cancer Risk Assessment Supplement to Cancer Guidelines
2002 – 2006	Co-Chair, Subcommittee on Mercury, President's National Council on Science and Technology
2000 – 2007	Member, Finish Academy of Sciences Centers of Excellence Program Science Advisory Committee
2000	Reviewer, *Congressional Research Service, Library of Congress*; Research needs relevant to children's environmental health risks.
1998 - 2004	Member and Chair, *Environmental Protection Agency*, FIFRA Science Advisory Panel.
1997 - 2006	Member, National Occupational Research Agenda Team, *National Institute of Occupational Safety and Health.*
1995 - 2000	Advisor, *Australian Health Council,* Risk Assessment Methodology, Member *NHMRC* Steering Committee on Cancer Risk Assessment Guidelines.
1992 - 2000	Member, *EPA* Dioxin Reassessment Working Group.
1985 - 2007	Thesis director for graduate students, Department of Biostatistics, *University of North Carolina - Chapel Hill, North Carolina.*
1997	Advisor, *Netherlands National Health Council,* Risk Assessment Methodology.
1997	Reviewer, *Air Force Office of Scientific Research.*
1996 - 1997	Temporary Advisor, *World Health Organization,* Expert Committee on Food Additives.
1996	Advisor, *Environmental Protection Agency;* Evaluation of the benchmark dose methodology.
1996	Advisor, *Environmental Protection Agency;* Evaluation of risks from exposure to PCBs.
1996	Expert Review Committee, *Environmental Protection Agency;* Cancer dose-response for PCB's.
1995 - 1996	Member, *California Environmental Protection Agency,* Risk Assessment Advisory Committee.

1994 - 1997	Science Advisory Panel, *Public Broadcasting System Production* "Poisons in the Womb".
1991 - 1995	Ad-Hoc Member, *Environmental Protection Agency*, Science Advisory Panel.

Legislative Hearings:

- Glyphosate Carcinogenicity, European Parliament, Brussels, December 2015
- Glyphosate Carcinogenicity, German Parliament, Berlin, July 2015
- Lead and Children's Health, Senate Committee on Environment and Public Works, July, 2012
- Asthma and Children's Health, Senate Committee on Environment and Public Works, May, 2012
- Contaminated Drywall, Senate Committee on Commerce, Science and Transportation, December, 2012.
- Camp Lejeune Contaminated Drinking Water, House Committee on Science and Technology, September, 2010.
- Autism and Vaccines, House Committee on Government Reform, December, 2002.

US Government Service Activities:

- Member, President's Task Force on Environmental Justice 2010-2013
- Member, President's Task Force on Children's Environmental Health 2009-2013
- Member, National Toxicology Program Executive Committee 2010-2013
- Financial Support and International Press Conference for research on "The Health Benefits of Tackling Climate Change" appearing as a series in Lancet, November 25, 2009
- Organizing Committee, White House Stakeholder briefing on Climate Change and Human Health, Old Executive Office Building, November 2009.
- Member, US Delegation, World Climate Congress, Geneva (September 2009)
- Member, US Delegation, Global Risk Communication Dialogue (2008-2009)
- Member, NIEHS Corrective Action Plan Management Committee (2008-2009)
- Primary focus, all interagency activities on hazards and risk (2006 to present)
- Co-Organizer, NIEHS/EPA Workshop on Children's Environmental Health, RTP, NC, January, (2007)
- Co-Organizer, NIEHS/NTP Workshop on the Identification of Targets for the HTS Roadmap Project (2007)
- Coordinator, NIEHS/EPA Review of the Children's Environmental Health Centers Program (2006-2007)
- Organizing Committee, Global Environmental Health Initiative, NIEHS (2006 to 2009)
- NIEHS Leadership Council (2005 to 2009)
- Organizer, formal collaborative agreements between NTP and Ramazzini Foundation (2001 to 2006)
- Organizer, formal collaborative agreements between NTP and Korean NTP (2002 to 2006)
- NIEHS Title 42 Review Committee (2003 to 2004)
- NIEHS Executive Committee and Operations Update Committee (2000 to 2005)
- NIEHS Leadership Retreats, DERT Retreats, DIR Retreats (all years since 1997)
- Presenter, NIEHS-sponsored National Academy of Sciences Committee on Emerging Issues in Environmental Health, November, 2001
- Organizer and presenter, National Toxicology Program Executive Committee Meetings (multiple dates since 2000)
- Organizer and presenter, National Toxicology Program Board of Scientific Counselors (multiple dates since 1998)

- Organizer, Joint NIEHS/US Geological Survey Interagency Program on Exposure Assessment, April 2001 to present)
- Organizer, US-Vietnam Scientific Conference on the Health and Environmental Effects of Agent Orange/Dioxin in Vietnam, March, 2002
- Organizing Committee, National Toxicology Program/EPA/FDA Scientific Conference on the Allergenicity of Genetically Modified Food, November, 2001
- NIEHS Town Hall Meeting, Los Angeles California, November, 2001
- NTP Research Directions, NAEHSC, Research Triangle Park, NC. May, 2001.
- NCI Study Section Center Presite Meeting, Seattle, Washington, January, 2001.
- Program committee member, *NIEHS/Colorado State University* conference on the Application of Technology to Chemical Mixture Research, 2001.
- Coordinating Core Committee, National Center for Toxicogenomics, NIEHS, 2000 to present
- Organizer, Joint US-Vietnam Consultation on Research on Agent Orange Health Effects in Vietnam. Singapore, 2000
- *ICCVAM/NICEATM*, Up-and-Down Procedure Peer Review Meeting, 2000.
- Chairman, *NIEHS* Risk Assessment Research Committee, 1995-present.
- Discussant, *NIEHS/PNNL* Workshop on Human Biology Models for Environmental Health Effects, 2000.
- Risk Assessment Coordinator, *NIEHS* US *RAPID* Program for the Evaluation of Health Risks from Exposure to Electric and Magnetic Fields, 1996-99.
- Organizer and Chair, Four Public Comment Sessions on the report of the *NIEHS/DOE* Working Group on the Health Effects of Exposure to Electric and Magnetic Fields, 1998.
- Organizer and Co-Chair, *NIEHS/DOE* Working Group on the Health Effects of Exposure to Electric and Magnetic Fields, 1998.
- Scientific Organizing Committee, *NIEHS* Workshop on Risk Assessment Issues Associated with Endocrine Disrupting Chemicals, 1998.
- Organizer, *NIEHS/DOE* Science Research Symposium on the Health Effects of Exposure to Electric and Magnetic Fields I: Biophysical Mechanisms and *In Vitro* Experimentation, 1998.
- Organizer, *NIEHS/DOE* Science Research Symposium on the Health Effects of Exposure to Electric and Magnetic Fields II: Epidemiological Findings, 1998.
- Organizer, *NIEHS/DOE* Science Research Symposium on the Health Effects of Exposure to Electric and Magnetic Fields III: *In Vitro* and Clinical Research Findings, 1998.
- Head, Toxicokinetics Faculty, *NIEHS*, 1994-97.
- Coordinator/Director, *NIEHS/ATSDR* Interagency Course on Mechanistic Modeling in Environmental Risk Assessment, 1996.
- Organizer, *NIEHS/EPA* Workshop on Research Priorities for New Risk Assessment Guidelines, 1996.
- Co-Organizer, *National Institute of Statistical Sciences*, *NIEHS/EPA* Workshop on Mechanistic Modeling in Risk Assessment, 1995.
- Scientific Coordinator and Mission Director, *NIEHS* "Mission to Vietnam" to assess the potential for scientific collaboration on the impact of Agent Orange on the Vietnamese Population, 1995.
- Chairman, *NIEHS* Computer Science Focus Group, 1995.
- Discussant, National Toxicology Program Workshop on Mechanistic Modeling in Toxicology, *NIEHS*, 1995.
- Discussant, National Toxicology Program Workshop on Mechanisms of Carcinogenesis, *NIEHS*, 1995.
- Co-Organizer, International Conference on The Role of Cell Proliferation in Carcinogenesis, co-

sponsored by *NIEHS*, *The Chemical Industry Institute of Toxicology*, *The International Life Sciences Institute* and *The American Industrial Health Council*, 1992.

- Organizer and Director, Scientific Basis of Animal Carcinogenicity Testing, Moscow, Russia, co-sponsored by the *International Agency for Research on Cancer*, *NIEHS*, *Health and Welfare Canada* and *The All-Union Cancer Research Center*, 1991.
- Chairman, Computer Technology Advisory Forum, *NIEHS*, 1989.
- Organizer and Director, Design and Analysis of Long-Term Animal Carcinogenicity Experiments, Lyon, France, co-sponsored by the *International Agency for Research on Cancer* and the *NIEHS*, 1988.

Extramural Activities:

- Member, NRC Committee to review the Draft Interagency Report on the Impacts of Climate Change on Human Health in the United States, Washington, DC, 2015
- Expert Scientist, International Agency for Research on Cancer Monograph Meeting on Some Organophosphate Pesticides and Herbicides, Lyon, France, March, 2015
- Overall Chair, International Agency for Research on Cancer Monograph Meeting on Diesel and Gasoline Engine Exhausts and related compounds, Lyon, France, June, 2012
- Advisor to Wellcome Trust at "International Research Futures Symposium on Global Change, Economic Sustainability, and Human Health", London, England, March, 2012.
- Expert Panel Member for review of Hollings Marine Laboratory, National Oceanographic and Atmospheric Agency, Charleston, USA, February, 2012.
- Chair, Mechanism Subgroup, International Agency for Research on Cancer Monograph Meeting on Radiofrequency Electric and Magnetic Fields, Lyon, France, May, 2011
- Advisor, Greek Ministry Health, Working group on hexavalent chromium in the environment, January, 2011
- Member, WHO Consultation on Human Health Risks from DDT, Geneva, Switzerland, November, 2010
- Associate Editor, Frontiers in Predictive Toxicity, 2010 – 2011
- Scientific Advisor, Health Investigation Levels Workshop, Canberra, Australia, January, 2010
- Chair, IARC Working Group, IARC Monograph 100-G, Lyon, France, October, 2009
- Scientific Organizing Committee, VII World Congress on Alternatives and Animal Use in Life Sciences, Rome, Italy, September, 2009
- Chair, Research Directions Working Group, World Health Organization Consultation on Global Research on Climate Change and Health, October, 2008.
- Editor-in-Chief, The Open Environment Journal, May 2008-August, 2010
- Member, EPA Science Advisory Board, July, 2008-present
- Working Group Member, IARC Monograph 98 - Fire-fighting, Painting and Shift-work, Lyon, France, November, 2007
- Chair, WHO Extremely Low Frequency Magnetic and Electric Fields Workshop on Intervention Strategies, June, 2007
- Special Advisor to the Director, Program on Public Health and the Environment, WHO, Geneva, May-July, 2007
- Member, International Life Sciences Institute Working Group on Susceptible Populations, March, 2007 – present
- Special Advisor to the Director, Program on Public Health and the Environment, WHO, Geneva, November, 2006-January, 2007

- Breakout Group Chair, International Workshop on Uncertainty and Variability in PBPK Modeling, RTP, NC USA, October, 2006
- Member, Health Effects Sciences Institute Committee on Sensitive Subpopulations and Groups, Washington, DC, 2006 to present
- Rapporteur, Steering Committee for developing the 100th Monograph of the International Agency for Research on Cancer, Lyon, France, September, 2006
- Co-Organizer, parallel workshops on the advancement of PBPK modeling in risk assessment, Research Triangle Park, November, 2006, Corfu, Greece, April, 2007.
- Organizer, Alternative Models in Developmental Neurotoxicity, Alexandria, Virginia, March, 2006.
- Organizer, NTP High Throughput Screening Workshop, Washington, DC, December, 2005
- Organizer, ISRTP Meeting on Alternative Methods in Toxicology, Baltimore, Maryland, November, 2005
- Organizer, NTP 25th Anniversary Meeting, Washington, DC, May, 2005
- Organizer, IPCS/WHO Workgroup on Dose-Response Modeling, Geneva, Switzerland, September, 2004
- Organizer, Consultation on harmonization of toxicological research between the NTP, Ramazzini Foundation and the European Union, European Congress of Toxicology, Florence, Italy, September, 2003.
- Member, WHO Workgroup on the epidemiology of cellular phone toxicity, Tskuuba, Japan, September, 2003.
- Program Committee, 12th International Conference on Global Warming, Boston, Massachusetts, May 2003
- Program Committee, International Conference on Cancer Risk Assessment, Athens, Greece, August, 2003
- Chair, WHO Public Consultation on Risk Communication, Luxembourg, February, 2003.
- Chair, WHO Committee on Establishing a Plan for Implementation of the Precautionary Principle in Risk Management. Luxembourg, February, 2003.
- Presenter (on behalf of US Government), National Academy of Sciences Panel on the Use of Third Party Toxicity Research with Human Research Participants, December, 2002
- Member, US Science Delegation, United Nations Environmental Program Consultation on Organic Mercury, September, 2002
- Science Panel Member, IARC Carcinogenicity Review of ELF-EMF, Lyon, France, June, 2001.
- Reviewer, Finish Ministry of Health Centers of Excellence Program, Helsinki, April, 2001.
- *EPA* dioxin reassessment peer review workshop and public comment session, Washington, DC, 2000.
- Organizer: Dioxin Dose-Response Working Group Meeting, Fort Collins, Colorado, February, 2000.
- Chair, Spiegelman Award Committee, *American Public Health Association*, 1998.
- Chair, *Bioelectromagnetics Society* Symposium on the use of Transgenic Animals in Evaluating Health Risks from Exposure to Cellular Phones, St. Petersburg, Florida, 1998.
- Member, *World Health Organization* International Program on Chemical Safety, Workshop on Issues in Cancer Risk Assessment, 1998.
- Advisor, *Joint Committee on Food Additives, World Health Organization/Food and Agriculture Organization*. Evaluation of certain food additives and contaminants
- Member, US Government Methylene Chloride Risk Characterization Science Committee, 1996-1998.
- Scientific Organizing Committee, *Colorado State University* Workshop on Biomedical Advances on Chemical Mixtures, 1997.
- *National Academy of Sciences*, Institute of Medicine, Committee on Funding Future Agent Orange

Research in Vietnam, 1996.
- Discussant, Workshop on the role of Endocrine Disruptors in Human Health, 1995.
- Advisor to *Australian Health Council* on Risk Assessment Methodology, Member *NHMRC* Steering Committee on Cancer Risk Assessment Guidelines
- Participant, International Program on Chemical Safety of the *World Health Organization* Workshop on Chemical Risk Assessment, London, England, 1995.
- Participant, *IARC* Workshop on Receptor-Mediated Carcinogenesis, Lyon, France, 1994.
- Co-Organizer, Symposium on Quantitative Risk Assessment, *German Cancer Research Center*, Heidelberg, Germany, 1993.
- Participant, *IARC* Monograph on Risk Assessment Methodology, *International Agency for Research on Cancer*, Lyon, France, 1993.
- Thesis advisor for graduate student, *University of Waterloo*, Waterloo, Ontario, Canada. 1991-93.
- Co-Organizer, *Russian Academy of Sciences* Informatics and Cybernetics Research Award, 1992.
- Official Observer, IARC Monograph on the Biological Effects of Ultraviolet Radiation, *International Agency for Research on Cancer*, Lyon, France, 1992.
- Member, *International Life Sciences Institute*, Dose-Response Working Group, 1991.
- Participant in Banbury Conference on Human Health Risks from Exposures to Dioxins, Banbury Conference Center, Cold Spring Harbor, New York, 1990.
- Co-Chairman, Session on Biostatistical Developments in Cancer Research, *15th International Cancer Congress*, Hamburg, Germany, 1990.
- Participant in *Environmental Protection Agency* Workshop on Risk Assessment Guidelines, Virginia Beach, Virginia, 1989.

Invited Presentations (present-1999)

"Glyphosate Carcinogenicity", Swiss Society of Toxicology, Basel, November, 2016
"Glyphosate Carcinogenicity", Concerned Scientists of Switzerland Annual Meeting, Zurich, December, 2015
"Should the precautionary principle be invoked for RF-EMF", BIOEM 2015, Asilomar, CA, USA, June 2015
"IARC Monograph Review Process and Glyphosate", Deutscher Bundestag, Berlin, Germany, June 2015
"The Exposome: Why does it matter for public health?", Association of Public Health Laboratories, Dr. Katherine Kelly Distinguished Lecture, Indianapolis, USA May 2015
"A bioinformatics/biostatistics approach to systems toxicology", Maastricht University, Maastricht, Netherlands, March, 2015
"Mechanistic Data, Cellular Pathways, and Cancer Classification", 39th Annual Toxicology Forum Meeting, Washington D.C., USA, January, 2015
"Current Issues in Environmental Public Health", Nicholls State University, Thibodaux, LA, April, 2014
"Review of Approaches to the Quantification of Risks", International Agency for Research on Cancer, Lyon, France, November, 2013
"The Gene-Environment-Disease Interactome", Maastricht University, September, 2013
"Toxicogenomics and Electromagnetic Fields", BEMS Annual Meeting, Thesaloniki, Greece, June 2013
"Toxicogenomics and Risk Assessment", International Symposium on Toxicogenomics and Human Health, Paris, France, May, 2013
"Extreme Weather, Climate and Health: Putting Science into Practice", Climate and Health Conference, Washington, DC, February, 2013
"Biofuels and Human Health: CDC's activities", Our Energy Future and Health, National Academy of Sciences, Washington, DC, USA, January, 2013

"Global Environmental Health", Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, January, 2013
"Addressing Superfund Sites", SBRP Annual Meeting, Washington, DC, October, 2012
"The future of cancer risk assessment", 6th NCC International Symposium- Management of Carcinogenic Hazard: Recent Progress and Future Perspectives, Seoul, Korea, June, 2012
"ATSDR Reorganization and New Directions", National Toxicology Program Executive Committee, Washington, DC, May, 2012
"Hydraulic Fracturing, National Concerns", Institute of Medicine Roundtable on Environmental Health, Washington, DC, April, 2012.
"Using Health Impact Assessment to Guide National Policy", National Health Impact Assessment Meeting, Washington, DC, April, 2012
"The Great Debate", Society of Toxicology Meetings, San Francisco, USA, March, 2012.
"CDC and Environmental Health", Society of Toxicology Meetings, San Francisco, USA, March, 2012.
"Keynote Address", National Climate Assessment Initial Workshop, Charleston, SC, February, 2012.
"Integration of Climate, Weather and Health", American Meteorological Society, New Orleans, USA, January, 2012.
"Biomonitoring and Environmental Health", CINVESTAV, Mexico Department of Health, Mexico City, Mexico, January, 2012.
"What is health risk assessment", International Conference on EMF and Health, Brussels, Belgium, November, 2012.
"Risks from multiple chemicals in polluted communities", International Conference on Chemical Mixtures, Wasington, USA, October, 2011.
"Healthy Homes: The Scientific Support", National Healthy Homes Conference, Denver, CO, June, 2011
"Climate Change and Human Health", Keynote Address, Yale School of Public Health Annual Alumni Day, New Haven, Ct, June, 2011
"Environmental Public Health", Keynote Address, International Conference on Sustainable Remediation, Amherst, MA, June, 2011
"The gene-environment disease interactome for humans", Society of Toxicology Annual Meeting, Washington, DC, March, 2011
"Environmental Exposure Science in the 21st Century", NAS Committee on Human and Environmental Exposure Science in the 21st Century, Washington, DC, February, 2011
"Human Health Effects and the Impact of Climate Change on Our Oceans", Annual National Conference on Science, Policy, and the Environment, Washington, Dc, January, 2011
"A Vision for the National Center for Environmental Health and Agency for Toxic Substances and Disease Registry", NAS Committee on Emerging Issues in Environmental Health, Washington, DC, December, 2010
"Predicting Health Risks Using Gene-Expression Data", EPA NextGEN Workshop, Research Triangle Park, NC, October, 2010
"Building Sustainable Environments", NAS Workshop: Pathways to Sustainable Development, Atlanta, GA, September, 2010
"Future Directions in Environmental Public Health", State Environmental Health Directors Annual Meeting, Portland, OR, September 2010
"The gene-environment disease interactome for humans", AACR Workshop on The Future of Molecular Epidemiology, Miami, Fl, June, 2010
"Emerging methods for determining chemical hazards", Keynote Address, Human Health Hazard Indicators Workshop, Sacramento, March, 2010.
"Dose-response and risk assessment considerations of melamine in infants", Society of Toxicology Annual Meetings, Sal Lake City, March, 2010
"The gene-environment disease interactome for humans", University of Queensland Centre for Clinical Research, Brisbane, Australia, February, 2010

"Research Needs for Climate Change and Human Health", Queensland Health and ENTOX, February, 2010

"Using systems biology to develop the gene-environment disease interactome for humans", ENTOX, Brisbane, Australia, December, 2009

"Quantifying the health risks of dioxins and dioxin-like compounds", ENTOX, January, 2010

"Epigenetics and its use in toxicology and risk assessment", Keynote Adress, Australian College of Toxicology and Risk Assessment Annual Meeting, Canberra, December, 2009.

"The changing shape of regulatory toxicology in the United States", Office of Chemical Safety & Environmental Health, Canberra, Australia, December, 2009

"The changing shape of regulatory toxicology in the United States", NICNAS, Sydney, Australia, December, 2009

"Development and Use of the Gene-Environment-Disease Interactome for Humans", 60th Anniversary of the Department of Biostatistics, University of North Carolina, Chapel Hill, NC, October, 2009

"Using systems biology to develop the gene-environment disease interactome for humans", Seventh World Congress on Alternatives and Animal Use in Life Sciences, Rome, Italy, September, 2009

"Use of 'Omics' Technologies to Enhance Risk Assessment", International Workshop on Genomics in Cancer Risk Assessment, Venice, Italy, August, 2009.

"Proteomics, Genomics and the Human Gene-Environment-Disease Interactome", First International Radiation Proteomics Workshop, Munich, Germany, May, 2009.

"Molecular Biology and Regualtory Toxicology", Society of Toxicology, Annual Meeting, Baltimore, Maryland, March, 2009.

"Using Modern Research Tools to Enhance Regulatory Toxicology", SOT Satelite Meeting on Development Of Toxicological And Environmental Public Health Infrastructures In Africa: Understanding The Premise And Mapping The Approach, Baltimore, MD, March 2009.

"Health Implications of Climate Change", Navy and Marine Public Health Conference, Norfolk, Va., March, 2009.

"Climate Change and Minority Health", Second Annual National Conference on Health Disparities, University of the Virgin Islands, St. Croix, December, 2008.

"Climate Change and Human Health", the Environmental Mutagen Society Annual Meetings, Puerto Rico, October, 2008.

"Climate Change and Human Health", The Puerto Rico Chamber of Commerce, October, 2008.

"Using Stem Cells in Environmental Health Research", California Stem Cells and Predictive Toxicology Initiative Workshop, Berkeley, CA, July, 2008.

"Developing the Disease-Environment Interactome", IMBA-FGF Workshop on Developing Omics Technologies to Assess Unclear Risks", Berlin, Germany, May, 2008

"Environmental Systems Biology", 40th Annual Interface Symposium on the interface between computer science and statistics, Durham, NC, May, 2008

"Environmental causes of childhood leukemia and modern environmental health research", Summary Address, ICNIRP/WHO/BS Symposium on Research Advances in Childhood Leukemia, Berlin, Germany, May, 2008.

"Using systems biology as a tool to understand environmental health", Atlantic Coast Symposium on the Mathematical Sciences in Biology and Medicine, Raleigh, NC, April, 2008.

"Biological networks and high-throughput screening", Society of Toxicology, Seattle, Washington, March, 2008.

"Environment and cancer: strategies for identifying new hazards". Workshop on the Environment and Cancer, American Cancer Society, Atlanta, Georgia, USA. January, 2008.

"A systems approach to human health risk assessment", Environmental Health Sciences Decision Making: Risk Management, Evidence and Ethics. US National Academy of Sciences, Washington, DC, USA. January, 2008.

"Finding targets for high-throughput screening linking genetics, genomics, pathways and human disease". NTP Biological Screening Program Seminar Series. January, 2008.

"The forest for the trees: A systems approach to environmental health research". Keynote Address, KTL-DEH Center of Excellence Program, Lamalo, Finland. December, 2007.
"Toxicology for the 21st Century", ECNIS Research Colloquium, Engelheim, Germany, October, 2007.
"Evidence-Based Decision Making in Public Health", First International Workshop on Evidence-Based Toxicology, Cuomo, Italy. October, 2007.
"Genes, Pathways and Diseases", World Health Organization Headquarters, Geneva, Switzerland. September, 2007
"Pharmacokinetics and dynamics of ketamine in horses", University of Bern, June, 2007
"Uncertainty and Variability in Risk Assessment", NAS Workshop on Characterizing Uncertainty: Subgroup on Uncertainty in Estimating Low-Dose Risk from High-Dose Data, June, 2007
"The utility and interpretation of high-throughput screening data in risk assessment with focus on the NTP programs", International Workshop on "Evaluating upstream endpoints for improved decision making and risk assessment", Berkeley, Ca. May, 2007
"Future directions of risk assessment at the World Health Organization", International Program for Chemical Safety Harmonization Steering Committee Meeting, Berlin, Germany, May, 2007
"Chipping away at environmental health risk assessment", GEMS annual meeting, Research Triangle park, NC, April, 2007
"The forest for the trees: A systems approach to environmental health", National Conference on Science, Policy and the Environment, Washington, DC, February, 2007
"Emerging technologies and their application in risk assessment", National Research Council Standing Committee on Risk Analysis Issues and Reviews, Washington, DC, December, 206
"Stochastic systems biology modeling", International Congress on Systems Biology, Tokyo, Japan, October, 2006
"Acceptable risk: environmental health research and public health", National Symposium on Acceptable Risk in Clinical Medicine, RTP, NC, September, 2006
"Stochastic Systems Biology", Society for Industrial and Applied Mathematics Annual Meeting, Raleigh, NC, August, 2006.
"Identifying and Quantifying Gene Interaction Networks", Academia Sinica, Tapei, Taiwan, April, 2006.
"Estimating Health Risks from Environmental Exposures", Medical School, Cheng Kung National University, Taiwan, April, 2006.
"Systems Biology and Environmental Health Research", National Institute of Environmental Studies, Tsukuba, Japan, April, 2006.
"Cancer Research and Risk Assessment: Looking to the Future", National Cancer Institute, Japan, April, 2006
"Cancer Research and Risk Assessment: Looking to the Future", Keynote Address, Cancer and the Environment Symposium, Duke University, March, 2006
"Environmental Systems Biology", Mount St Mary's College, Maryland, March, 2006.
"Bioinformatics in High Throughput Screening: A proposal", ILSI Annual Meeting, Puerto Rico, January, 2006.
"Gene Regulatory Networks in Cancer Risk Assessment, German Cancer Research Center, Heidelberg, Germany, December, 2005.
"Alternative Methods in Toxicology; Problems and Solutions", Keynote Address, Workshop on Alternative Methods in Toxicology, Baltimore, Maryland, November, 2005
"Future Directions of the National Toxicology Program", American Public Health Association Annual Meeting, New Orleans, Louisiana, November, 2005.
"Risk Assessment", A Mini-Course, University of Finland, Kuopio, Finland, October, 2005.
"Mechanism-Based Modeling as an Alternative to Animals in Toxicology", 5th World Conference on Alternatives To Animals Used in the Life Sciences, Berlin, Germany, August, 2005.
"Environmental Systems Biology", Toxicology Forum, Aspen, Colorado, July, 2005.
"Mechanistic Implications of Modifiers of Chemical Toxicity", Keynote Lecture, Workshop on Modifiers of Chemical Toxicity: Implications for Human Health Risk Assessment, Poros, Greece, June, 2005.

"Future Directions in Screening for Toxicants", Committee on the Future of Toxicology, National Academy of Sciences, Washington, DC, May, 2005.
"Toxicogenomics and the Future of Cancer Risk Assessment", International Agency for Research on Cancer, Lyon France, May, 2005.
"Statistical Contributions to Federal Advisory Committees", Eastern North American Region of the Biometrics Society Annual Meeting, Austin, Texas, March, 2005.
"The Future of Long-Term Animal Carcinogenicity Studies", Invited Debate, Society of Toxicology Annual Meetings, New Orleans, Louisiana, March, 2005.
"Future Directions of the National Toxicology Program", Society of Toxicology Annual Meetings, New Orleans, Louisiana, March, 2005.
"Role of the National Toxicology Program in Risk Assessment", Federal-State Oncology and Risk Analysis Committee, Madison, Wisconsin, October, 2004.
"Identifying and Quantifying Cancer Risks using Mechanistic Data", Cancer and The Environment: NCI Science Writers Seminar, National Institutes of Health, Bethesda, Maryland, October, 2004.
"Toxicogenomics and the Future of Risk Assessment", Office of Science and Technology Policy, Washington, DC, August, 2004
"A Vision for the National Toxicology Program", Toxicology Forum, Aspen, Colorado, June, 2004
"Health and Environment", Joint Program on Climate Variability and Human Health, Atlanta, Georgia, March, 2004
"Dose-Response Analysis of Toxicogenomic Data", NIEHS Toxicogenomics Faculty, Research Triangle Park, NC, December, 2003.
"Dose-Response Analysis of Toxicogenomic Data", DERT Retreat, Southern Pines, NC, December, 2003.
"Toxicogenomics and the Research Directions of the National Toxicology Program", Keynote Address, Conference on Toxicology in the 21st Century, Korean Food and Drug Administration, Seoul, Korea, November, 2003.
"Dioxin and Agent Orange: What is known and what is suspected", Keynote Address, NCST/NIEHS Conference of Environmental Mediation for Dioxin Soil Contamination, Hanoi, Vietnam, November, 2003.
"Dose-Response Analysis of Toxicogenomic Data", NCSU/NIEHS Workshop on Bioinformatics and Risk Assessment, Research Triangle Park, NC, October, 2003.
"Health Effects of Electric and Magnetic Fields: Current Research Directions", Joint WHO/Japanese Ministry of Health Public Meeting on Cellular Radiation, Tokyo, Japan, September, 2003.
"Future Directions in Toxicology and the National Toxicology Program", NIEHS Public Liaison Meeting, New York City, September, 2003.
"Chipping Away at Risk Assessment: Genomics, Proteomics, Metabonomics and Cancer Risk Assessment", Society of Toxicologic Pathology, Savannah, Ga. June, 2003.
"Cancer Modeling; An Overview", Statistical Methods in Cancer Research, Radiation Effects Research Foundation, Kyoto, Japan, March, 2003 (presented by H. Toyoshiba due to war in Iraq and US Govt. responsibilities)
"Statistical methods for evaluating population exposures using CDC's Environmental Report Card", CDC, Atlanta, Ga. March, 2003.
"Bystander Effects in Carcinogenesis", Society of Toxicology Meetings, Salt Lake City, Utah, March, 2003
"Validation and use of genetically-modified mouse models as alternatives in carcinogenicity testing", ILSI Workshop on Genetically Modified Mouse Models, Alexandria, Va., February, 2003.
"The Future of Genomics in Toxicology", Mississippi State University, Oxford, Mississippi, February, 2003
"NIEHS priorities in ecological research", USGS Director's Retreat, Washington, DC. January, 2003.
"The US National Toxicology Program", Keynote Lecture at Opening Ceremonies for the Korean National Toxicology Program, Seoul, Korea, November, 2002

"The NIEHS/NTP Initiatives on Alternative Models in Toxicology", Science Advisory Board Meeting of the Center for the Advancement of Alternatives in Toxicology, Johns Hopkins University, Baltimore, Maryland, November, 2002

"The Analysis and Interpretation of Two-Stage Liver Bioassays in the Rat", Workshop on Hepatic Preneoplasia: Quantitative Evaluation in Carcinogenesis Bioassays and Relevance for Human Hepatocarcinogenesis, Heidelberg, Germany, June, 2002

"Chipping Away at Risk Assessment: Genomics, Proteomics, Metabonomics and Cancer Risk Assessment", Office of Environmental Health Hazard Assessment, California Department of Health, Sacramento, California, June, 2002

"Mechanistic Modeling of Stochastic Endpoints", NIEHS Conference on Future Directions in Biostatistics, Research Triangle Park, North Carolina, May, 2002

"Mechanistic Models of Skin Carcinogenesis", North Carolina State University, Raleigh, North Carolina, May, 2002

"Endocrine Dismodulation and Cancer", Workshop on Light, Endocrine Systems and Cancer, University of Cologne, Cologne, Germany, May, 2002

"Mechanism-Based Quantitative Analysis of Carcinogenesis Data", New York Academy of Sciences, April, 2002.

"Emerging Issues in Cancer Risk Assessment", Sunrise Expert Seminar, American Association for Cancer Research Annual Meetings, San Francisco, California, April, 2002

"Quantitative Evaluation of Health Risks from Dioxin", Joint US-Vietnam Scientific Conference on the Health and Environmental Effects of Agent Orange/Dioxin in Vietnam, Hanoi, Vietnam, March, 2002

"Cancer Risk Assessment", Hanoi Medical School/Vietnam Environmental Protection Agency/Vietnam Ministry of Health Joint Seminar, Hanoi Vietnam, January, 2002

"Mechanism-Based Modeling of Genomics Data", University of Berne, Switzerland, October, 2001.

"Multistage Models of Carcinogenesis", International Biometrics Conference Satellite Meeting, Fukuoka, Japan, September, 2001. (given by H. Toyoshiba due to conflict in scheduling)

"Discussion of CDC's Report on Levels of Environmental Contaminants in Human Tissues", National Public Radio Talk of the Nation Science Friday, March, 2001.

"Mixtures and Models in Environmental Health Risk Assessment", *NIEHS/Colorado State University* conference on the Application of Technology to Chemical Mixture Research, January, 2001

"Biological and biophysical research at extremely low- and radio-frequencies", Forschungsgemeinschaft Funk, Bad Münstereifel, Germany, December 2000.

"Harmonization of study evaluation and health risk assessment", 2nd International EMF Seminar, Chinese Ministry of Health, WHO and ICNIRP, Xian, China, October 2000.

"QRA: extrapolations (animals to humans; high dose low dose)", First International Course on Scientific Basis of Carcinogen Assessment – Quo Vadis?, NIVA, Naantali, Finland, September 2000.

"Statistical and biological models and toxicological issues in risk assessment", Center for Environmental Health Risk Assessment (CERA) workshop on Future Needs in Risk Assessment, Stockholm, Sweden, September 2000.

"Innovative use of mechanistic considerations in forming quantitative risk assessment models", Workshop on Future Research For Improving Risk Assessment Methods, National Institute for Occupational Safety and Health, Aspen, Colorado, August 2000.

"Latest scientific findings on dioxin", Dioxin Summit, University of California at Berkeley, California, August 2000.

"Stochastic modeling in carcinogenesis and development", Virtual Human Workshop, Research Triangle Park, NC. June 2000.

"Evaluating health risks; methods and examples", Federal Office for Public Health, Bern, Switzerland. May 2000.

"Decisions about environmental health risks: What are the key questions and how does this apply to melatonin", Low frequency EMF, visible light, melatonin and cancer", International Symposium, University of Cologne and the German Research Society, Cologne, Germany. May 2000.

"Children's environmental health-risk assessment issues and challenges", California Environmental Protection Agency, Office of Environmental Health Assessment, Oakland, CA. April 2000.

"Children's environmental health risks", WHO/NIEHS Pacific Rim Meeting on Children's Health, Manila, April, 2000.

"Toxicology and environmental health seminar series 2000", University of Florida, Gainesville, Florida. April 2000.

"Biologically based population health risk assessment models", University of Ottawa, Department of Epidemiology and Community Medicine and the Institute of Population Health, Ottawa, Canada. March 2000.

"Molecular epidemiology: a new tool in cancer prevention", Applying science to regulatory policy and public health, Keystone Symposium, Taos, New Mexico. February 2000.

"Statistical methods used for evaluating chemical safety in the environment", Mathematical Research Institute, Oberwolfach, Germany. February 2000.

"Mechanism-based mathematical modeling in health risk assessment" NC State University, January, 2000.

"Methods for analyzing and quantifying EMF health risks", WHO/ICNIRP scientific meeting, Erice, Sicily, Italy. November 1999.

"Harmonization of cancer and non-cancer risk assessment", The Society of Toxicology, Washington, DC. November 1999.

"Risky business: evaluating the safety of environmental exposures", Illinois Environmental Health Association, 1999 Annual Education Conference, Peoria, IL. October 1999.

"Challenges in the use of experimental and epidemiological data in health risk assessment", Symposium on "Statistical methods in epidemiology and demography", Department of Biostatistics at the University of North Carolina in Chapel Hill, Chapel Hill, North Carolina. October 1999.

"Linking toxicokinetics and toxicodynamics in biologically-based dose response models", Dioxin 99, 19th International Symposium on Halogenated Environmental Organic Pollutants and Persistent Organic Pollutants (POPs), Venice, Italy. September 1999.

"How did WHO decide on a TDI for dioxin", Faculty of Environmental Studies in Nagasaki University and the Department of Medical Informatics in Kyushu Medical School, Nagasaki, Japan. September 1999.

"PBPK Models for Estrogen", Workshop To Evaluate Research Priorities For Endocrine Active Compound Risk Assessment Methods, CMA, EPA, NIEHS, Research Triangle Park, North Carolina. August 1999.

"Risk assessment activities in the National Toxicology Program; risk assessment methodology, and mechanistic modeling of endocrine disruptors and dioxins", Harvard Symposium on Persistent Organic Pollutants (POPS): A Public Health Perspective, Boston, Massachusetts. June 1999.

"Do extremely low frequency electric and magnetic fields pose a health risk?", 21st Annual Meeting of the Bioelectromagnetics Society, Long Beach, California. June 1999.

"Probabilistic assessment of cancer dose response data", Probabilistic Risk Assessment Workshop, Sarasota, Florida. February 1999.

"Linking toxicology and epidemiology: the role of mechanistic modeling", CDC and ATSDR Symposium on Statistical Methods, Emerging Statistical Issues In Public Health For The 21st Century, Atlanta, Georgia. January 1999.

"Evaluation Of Health Risks From Exposure To Electric And Magnetic Fields; Completion Of A 2-Year Review Process", Toxicology Round Table, Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, Virginia. January 1999.

Interagency Agreements and Intramural Research Grants

US Environmental Protection Agency (1993-1994). Development and implementation of a mechanistic model for 2,3,7,8-TCDD. $25K.

Agency for Toxic Substances and Disease Registry (1994-1996). Study of the relationship between chemical structure/activity and dose-response shape and magnitude for carcinogens and development of physiologically based pharmacokinetic models for risk assessment. $796K.

NIEHS, Intramural Research Grant (1995-1998). Development of a mechanistic model of the impact of electromagnetic fields on melatonin. $180K.

NIEHS, Interagency Coordinator for Risk Assessment, EMFRAPID Program (1996-1998). Evaluation of potential risks from exposure to electric and magnetic fields. $2 million.

US Environmental Protection Agency (1999). Update to Dose-Response Chapter, Dioxin Reassessment. $25K.

NIH, Office of Research on Minority Health (1999-2002) GIS/Resampling method for evaluating data on environmental justice. $70K.

Direction of Ph.D. Theses:

A Bailer. *The effects of treatment lethality on tests of carcinogenicity*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1986.

P Williams. *Estimating tumor incidence rates using the method of moments and maximum likelihood estimation combined*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1989.

G Carr. *The analysis of data on adverse reactions to chemicals in developmental toxicology*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1989.

S Liu. *Estimating parameters in a two-stage model of carcinogenesis using information on enzyme-altered foci from initiation-promotion experiments*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1993.

CD Sherman. *Multipath/multistage models of carcinogenesis*. Department of Statistics and Actuarial Sciences, University of Waterloo, Waterloo, Ontario, Canada, 1994.

C Lyles. *Cell labeling data: Models and parameter estimation*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 1995.

F Ye. *The equal slopes test for benchmark doses*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 2001

S Whitaker. *Development of a biologically-based mathematical model of fetal development*. Department of Mathematics, North Carolina State University, Raleigh, North Carolina, 2000.

R Helms. *Homeostatic feedback control of growth on multistage cancer models*. Department of Biostatistics, University of North Carolina, Chapel Hill, North Carolina, 2001.

Journal Articles: (peer reviewed)

1. Cote I, Andersen ME, Ankley GT, Barone S, Birnbaum LS, Boekelheide K, et al. The Next Generation of Risk Assessment Multi-Year Study-Highlights of Findings, Applications to Risk Assessment, and Future Directions. *Environ Health Perspect* (2016) **124**(11):1671-82. doi: 10.1289/EHP233. PubMed PMID: 27091369; PubMed Central PMCID: PMCPMC5089888.

2. Parham F, Portier CJ, Chang X, Mevissen M. The Use of Signal-Transduction and Metabolic Pathways to Predict Human Disease Targets from Electric and Magnetic Fields Using in vitro Data in Human Cell Lines. *Frontiers in public health* (2016) 4:193. doi: 10.3389/fpubh.2016.00193. PubMed PMID: 27656641; PubMed Central PMCID: PMCPMC5013261.

3. Portier CJ, Armstrong BK, Baguley BC, Baur X, Belyaev I, Belle R, et al. Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). *Journal of epidemiology and community health* (2016) **70**(8):741-5. doi: 10.1136/jech-2015-207005. PubMed PMID: 26941213; PubMed Central PMCID: PMCPMC4975799.

4. Sand S, Parham F, Portier CJ, Tice RR, Krewski D. Comparison of Points of Departure for Health Risk Assessment Based on High-Throughput Screening Data. *Environ Health Perspect* (2016). doi: 10.1289/EHP408. PubMed PMID: 27384688.

5. Scinicariello F, Portier C. A simple procedure for estimating pseudo risk ratios from exposure to non-carcinogenic chemical mixtures. *Archives of toxicology* (2016) **90**(3):513-23. doi: 10.1007/s00204-015-1467-z. PubMed PMID: 25667015.

6. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, et al. Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. *Environ Health Perspect* (2016) **124**(6):713-21. doi: 10.1289/ehp.1509912. PubMed PMID: 26600562; PubMed Central PMCID: PMCPMC4892922.

7. McPartland, J., Dantzker, H.C., Portier, C. J. Building a robust 21st century chemical testing program at the U.S. Environmental Protection Agency: recommendations for strengthening scientific engagement, Environ Health Perspect 2015. 123 (1): p. 1-5.

8. Smith, M.T., Gibbons, C.F., Fritz, J.M., Rusyn, I., Lambert, P., Kavlock, R., Hecht, S.S., Bucher, J., Caldwell, J.C., Demarini, D., Cogliano, V., Portier, C., Paan, R., Straif, K., Guyton, K.Z., Key Characteristics of Carcinogens and an Approach to using Mechanistic Data in their Classification, Environ Health Perspect 2015 (in press)

9. Thomas, R., Thomas, R.S., Auerbach, S. S., Portier, C. J., Biological networks for predicting chemical hepatocarcinogenicity using gene expression data from treated mice and relevance across human and rat species. PLoS One, 2013. **8**(5): p. e63308.

10. Scinicariello, F., Buser, M.C., Mevissen, M., Portier, C.J., Blood lead level association with lower body weight in NHANES 1999-2006. Toxicol Appl Pharmacol, 2013. 273(3): p. 516-23.

11. Thomas R, Portier CJ., Gene Expression Networks, Methods Mol Biol. 2013;930:165-78.

12. Aylward LL, Kirman CR, Schoeny R, Portier CJ, Hays SM., Evaluation of Biomonitoring Data from the CDC National Exposure Report in a Risk Assessment Context: Perspectives across Chemicals. Environ Health Perspect. 2012 Dec 11. [Epub ahead of print] PMID: 23232556

13. Sand, S., Portier, C.J., Krewski, D. A Signal-to-noise crossover dose as the point of departure for risk assessment. Environmental Health Perspectives. 119(12):1766-74, 2011

14. Gohlke, J.M., Thomas, R., Woodward, A., Campbell-Lundrum, D., Pruss-Ustun, A., Hales, S., Portier, C.J. Estimating the global public health implications of electricity and coal consumption. Environmental Health Perspectives 2011 119 (6): 821-6

15. McHale CM, Zhang L, Lan Q, Vermeulen R, Li G, Hubbard AE, Porter KE, Thomas R, Portier CJ, Shen M, Rappaport SM, Yin S, Smith MT, Rothman N. Global gene expression profiling of a population exposed to a range of benzene levels. Environ Health Perspect. 2011 May;119(5):628-34.

16. Prause AS, Guionaud CT, Stoffel MH, Portier CJ, Mevissen M. Expression and function of 5-hydroxytryptamine 4 receptors in smooth muscle preparations from the duodenum, ileum, and pelvic flexure of horses without gastrointestinal tract disease. Am J Vet Res. 2010 Dec;71(12):1432-42.

17. Luke, N.S., DeVito, M.J., Portier, C.J., El-Masri, H.A., Employing a mechanistic model for the MAPK pathway to examine the impact of cellular all-or-none behavior on overall tissue response, Dose-Response 2010 8(3): 347-67.

18. Crump, KS, Chen, C., Chiu, W.A., Louis, T.A., Portier, C. J., Subramaniam, R.P., Wgite, P.D., What role for biologically-based Dose-Response Models in Estimating Low-Dose Risk. Env. Health Persp. 2010 118(5):585-8

19. Parham F, Austin C, Southall N, Huang R, Tice R, Portier C. Dose-Response modeling of High-Throughput Screening Data. J Biomol Screen. 2009 **14**(10), 1216-27

20. Hines RN, Sargent D, Autrup H, Birnbaum LS, Brent RL, Doerrer NG, Cohen Hubal EA, Juberg DR, Laurent C, Luebke R., Olejniczak K, Portier CJ, Slikker W. Approaches for assessing risks to sensitive populations: lessons learned from evaluating risks in the pediatric population. Tox. Sci. 2010 **113** (4), 4-26.

21. Portier, C. Toxicological decision making on hazards and risks – status quo and the way forward: current concepts and schemes of science-driven decision making – an overview. *Human and Experimental Toxicology* 2009 **28**(2-3), 123-125

22. Prause, A.S., Stoffel, M.H., Portier, C.J., Mevissen, M., Expression and function of 5-HT7 receptors in smooth muscle preparation from equine duodenum, ileum, and pelvic flexure, *Research in Veterinary Science* 2009 **87**(2), 292-299

23. Boyd, W.A., Smith, M. V., Kissling, G. E., Rice, J., R., Snyder, D. W., Portier, C. J., Freedman, J. H. Application of a Mathematical Model to Describe the Effects of Chlorpyrifos on Caenorhabditis elegans Development, *PLoS ONE* 2009 **4**(9): e7024. doi:10.1371/journal.pone.0007024

24. Smith MV, Boyd WA, Kissling GE, Rice JR, Snyder DW, et al. A Discrete Time Model for the Analysis of Medium-Throughput C. elegans Growth Data. *PLoS ONE* 2009 **4**(9): e7018. doi:10.1371/journal.pone.0007018

25. Gohlke, J. M., Stockton, P.S., Sieber, S., Foley, J., Portier, C. J. AhR-mediated gene expression in the developing mouse telencephalon. *Reproductive Toxicology* 2009 (in press) doi:10.1016/j.reprotox.2009.05.067

26. Thomas, R., Gohlke, J., Parham, F., Smith, M., Portier, C. (2009) Choosing the right path: enhancement of biologically-relevant sets of genes or proteins using pathway structure. *Genome Biology* 2009 **10**(4), R44.

27. Julia M Gohlke, Reuben Thomas, Yonqing Zhang, Michael C Rosenstein, Allan P Davis, Cynthia Murphy, Carolyn J Mattingly, Kevin G Becker, Christopher J Portier, Genetic and Environmental Pathways to Complex Disease. *BMC Systems Biology* 2009 May 5, 3:46.

28. Schmitz, A., Portier, C. J., Thurmann, W., Theurillat, R., Mevissen, M. Stereoselective biotransformation of ketamine in equine liver and lung microsomes. *J. Vet. Pharm. And Therapeutics* 2008 **31** (5): 446-455

29. Xia, M; Huang, R; Witt, KL; Southall, N; Fostel, J; Cho, MH; Jadhav, A; Smith, CS; Inglese, J; Portier, CJ; Tice, RR; Austin, CP Compound cytotoxicity profiling using quantitative high-throughput screening. *Env. Health Perspectives* 2008 **116** (3): 284-291

30. Gohlke, J. M., Armant, O., Parham, F., M., Smith, M., V., Zimmer, C., Castro, D., S., Nguyen, L., Parker, J., S., Gradwohl, G., Guillemot, F., Portier, C. J. Characterization of proneural gene regulatory network during mouse telencephalon development., *BMC Biology* 2008 **6** (15)

31. Subramaniam, R. P., Chen, C., Crump, K. S., Devoney, D., Fox, J., F., Portier, C. J., Schlosser, P. M., Thompson, C. M., White, P. Uncertainties in Biologically-based modeling of formaldehyde-induced respiratory cancer risk: Identification of key issues. *Risk Analysis* 2008 28(4): 907-923

32. Buehler, M., Steiner, A., Meylan, M., Portier, C. J., and Mevissen, M., In vitro effects of bethanechol on smooth muscle preparations obtained from abomasal fundus, corpus and antrum of dairy cows. Research in Vet. Sci. **2008 84** (3), 444-451

33. Barton, H.A., W.A. Chiu, R.W. Setzer, M.E. Andersen, A.J. Bailer, F.Y. Bois, R.S. Dewoskin, S. Hays, G. Johanson, N. Jones, G. Loizou, R.C. Macphail, C.J. Portier, M. Spendiff, and Y.M. Tan, Characterizing Uncertainty and Variability in Physiologically-based Pharmacokinetic (PBPK) Models: State of the Science and Needs for Research and Implementation. *Toxicol Sciences* 2007 **99** (2) 395-402.

34. Pfeiffer, J.B., M. Mevissen, A. Steiner, C.J. Portier, and M. Meylan, In vitro effects of bethanechol on specimens of intestinal smooth muscle obtained from the duodenum and jejunum of healthy dairy cows. Am J Vet Res, 2007. **68**(3): p. 313-22.

35. Smith, M., Miller, C., Kohn, M., Walker, N.J., Portier, C. J., Absolute estimation of initial concentrations of amplicon in a real-time PT-PCR process, *BMC Bioinformatics* 2007 **8**(1), 409

36. Toyoshiba, H., Sone, H., Yamanaka, T., Parham, F., Irwin, R., Boorman, G., and Portier, C. Gene network analysis suggests differences between high and low doses of acetaminophen. Toxicology and Applied Pharmacology *2006* 215 (3), 306-316

37. Knobloch M, Portier CJ, Levionnois OL, Theurillat R, Thormann W, Spadavecchia C, Mevissen M. Antinociceptive effects, metabolism and disposition of ketamine in ponies under target-controlled drug infusion. Toxicology And Applied Pharmacology 2005 216 (3): 373-386

38. Portier, C.J., H. Toyoshiba, H. Sone, F. Parham, R.D. Irwin, and G.A. Boorman, Comparative analysis of gene networks at multiple doses and time points in livers of rats exposed to acetaminophen. Altex 2005 **23 Suppl**: p. 380-4.

39. Resnik, D.B. and C. Portier, Pesticide testing on human subjects: weighing benefits and risks. Environ Health Perspect. 2005 **113**(7): p. 813-7.

40. Walker, N. J., Crockett, P. W., Nyska, A., Brix, A. E., Jokinen, M. P., Sells, D. M., Hailey, J. R., Easterling, M., Haseman, J. K., Yin, M., Wyde, M. E., Bucher, J. R., and Portier, C. J. Dose-additive carcinogenicity of a defined mixture of "dioxin-like compounds". *Environ Health Perspect* 2005 113, 43-48.[1]

41. Boorman, G. A., Irwin, R. D., Vallant, M. K., Gerken, D. K., Lobenhofer, E. K., Hejtmancik, M. R., Hurban, P., Brys, A. M., Travlos, G. S., Parker, J. S., and Portier, C. J. Variation in the hepatic gene expression in individual male Fischer rats. *Toxicol Pathol* 2005 33, 102-110.

42. Toyoshiba, H., Walker, N.J., Bailer, A.J. and Portier, C.J. Evaluation of toxic equivalency factors for induction of cytochromes P450 CYP1A1 and CYP1A2 enzyme activity by dioxin-like compounds. *Toxicol Appl Pharmacol 2004 194*, 156-68.

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44. Bucher, J. R., and Portier, C. Human carcinogenic risk evaluation, Part V: The national toxicology program vision for assessing the human carcinogenic hazard of chemicals. *Toxicol Sci* 2004 82, 363-366.

45. Germolec, D. R., Kashon, M., Nyska, A., Kuper, C. F., Portier, C., Kommineni, C., Johnson, K. A., and Luster, M. I. The accuracy of extended histopathology to detect immunotoxic chemicals. *Toxicol Sci* 2004 82, 504-514.

46. Germolec, D. R., Nyska, A., Kashon, M., Kuper, C. F., Portier, C., Kommineni, C., Johnson, K. A., and Luster, M. I.. Extended histopathology in immunotoxicity testing: interlaboratory validation studies. *Toxicol Sci* 2004 78, 107-115.

47. Shelby, M., Portier, C., Goldman, L., Moore, J., Iannucci, A., Jahnke, G., and Donkin, S.. NTP-CERHR expert panel report on the reproductive and developmental toxicity of methanol. *Reprod Toxicol* 2004 18, 303-390.

48. Smith, M. V., Nyska, A., and Portier, C. Application of a statistical dynamic model investigating the short-term cellular kinetics induced by riddelliine, a hepatic endothelial carcinogen. *Toxicol Sci* 2004 80, 258-267.

49. Toyoshiba, H., Yamanaka, T., Sone, H., Parham, F. M., Walker, N. J., Martinez, J., and Portier, C. J. Gene interaction network suggests dioxin induces a significant linkage between aryl hydrocarbon receptor and retinoic acid receptor beta. *Environ Health Perspect* 2004 112, 1217-1224.[2]

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[1] Awarded outstanding published paper in 2005 by the Risk Assessment Specialty Section of the Society of Toxicology

[2] Awarded outstanding published paper in 2004 by the Risk Assessment Specialty Section of the Society of Toxicology

50. Yamanaka, T., Toyoshiba, H., Sone, H., Parham, F. M., and Portier, C. J. The TAO-Gen algorithm for identifying gene interaction networks with application to SOS repair in E. coli. *Environ Health Perspect* 2004 112, 1614-1621

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IPCS

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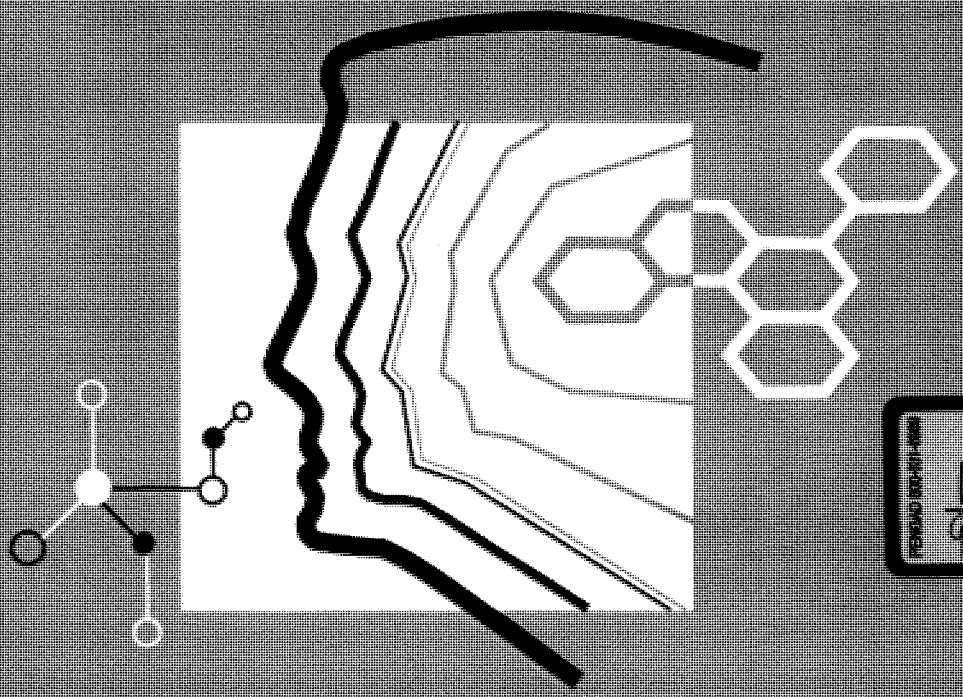
Principles for Modelling Dose–Response for the Risk Assessment of Chemicals



IOMC INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among UNEP, ILO, FAO, WHO, UNIDO, UNITAR and OECD

World Health Organization

Environmental Health Criteria 239

PRINCIPLES FOR MODELLING DOSE–RESPONSE FOR THE RISK ASSESSMENT OF CHEMICALS

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World Health Organization

The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO) and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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NOTE TO READERS OF THE CRITERIA MONOGRAPHS

Every effort has been made to present information in the criteria monographs as accurately as possible without unduly delaying their publication. In the interest of all users of the Environmental Health Criteria monographs, readers are requested to communicate any errors that may have occurred to the Director of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda.

Environmental Health Criteria

PREAMBLE

Objectives

In 1973, the WHO Environmental Health Criteria Programme was initiated with the following objectives:

(i) to assess information on the relationship between exposure to environmental pollutants and human health, and to provide guidelines for setting exposure limits;
(ii) to identify new or potential pollutants;
(iii) to identify gaps in knowledge concerning the health effects of pollutants;
(iv) to promote the harmonization of toxicological and epidemiological methods in order to have internationally comparable results.

The first Environmental Health Criteria (EHC) monograph, on mercury, was published in 1976, and since that time an ever-increasing number of assessments of chemicals and of physical effects have been produced. In addition, many EHC monographs have been devoted to evaluating toxicological methodology, e.g. for genetic, neurotoxic, teratogenic, and nephrotoxic effects. Other publications have been concerned with epidemiological guidelines, evaluation of short-term tests for carcinogens, biomarkers, effects on the elderly, and so forth.

Since its inauguration, the EHC Programme has widened its scope, and the importance of environmental effects, in addition to health effects, has been increasingly emphasized in the total evaluation of chemicals.

The original impetus for the Programme came from World Health Assembly resolutions and the recommendations of the 1972 UN Conference on the Human Environment. Subsequently, the work became an integral part of the International Programme on Chemical Safety (IPCS), a cooperative programme of WHO, ILO, and UNEP. In this manner, with the strong support of the new

partners, the importance of occupational health and environmental effects was fully recognized. The EHC monographs have become widely established, used, and recognized throughout the world.

The recommendations of the 1992 UN Conference on Environment and Development and the subsequent establishment of the Intergovernmental Forum on Chemical Safety with the priorities for action in the six programme areas of Chapter 19, Agenda 21, all lend further weight to the need for EHC assessments of the risks of chemicals.

Scope

Two different types of EHC documents are available: 1) on specific chemicals or groups of related chemicals; and 2) on risk assessment methodologies. The criteria monographs are intended to provide critical reviews on the effect on human health and the environment of chemicals and of combinations of chemicals and physical and biological agents and risk assessment methodologies. As such, they include and review studies that are of direct relevance for evaluations. However, they do not describe *every* study carried out. Worldwide data are used and are quoted from original studies, not from abstracts or reviews. Both published and unpublished reports are considered, and it is incumbent on the authors to assess all the articles cited in the references. Preference is always given to published data. Unpublished data are used only when relevant published data are absent or when they are pivotal to the risk assessment. A detailed policy statement is available that describes the procedures used for unpublished proprietary data so that this information can be used in the evaluation without compromising its confidential nature (WHO (1990) Revised Guidelines for the Preparation of Environmental Health Criteria Monographs. PCS/90.69, Geneva, World Health Organization).

In the evaluation of human health risks, sound human data, whenever available, are preferred to animal data. Animal and in vitro studies provide support and are used mainly to supply evidence missing from human studies. It is mandatory that research on human subjects is conducted in full accord with ethical principles, including the provisions of the Helsinki Declaration.

The EHC monographs are intended to assist national and international authorities in making risk assessments and subsequent risk management decisions. They represent a thorough evaluation of risks and are not, in any sense, recommendations for regulation or standard setting. These latter are the exclusive purview of national and regional governments.

Procedures

The following procedures were followed in the development and publication of this EHC. A designated IPCS Staff Member (Dr Sam Page and subsequently Dr A. Tritscher), responsible for the scientific content of the document, served as the Responsible Officer (RO). The IPCS editor was responsible for layout and language.

The WHO Planning Group for the IPCS Harmonization Project on Dose–Response Modelling met on 10 October 2002 in Geneva to develop an outline and proposed time frame for the project. A first draft working paper, including contributions from several additional authors, was prepared by Drs C. Carrington and M. Bolger and distributed to the Task Group prior to the Task Group meeting, which was held from 13 to 17 September 2004. The first draft working paper was revised during the Task Group meeting and during a subsequent internal Task Group Internet forum. This revised draft was available on the IPCS web site for external review and comment. Comments received are available on request from the WHO Secretariat. They were reviewed by the Task Group, and necessary additions and revisions to the document were made.

The Task Group members serve as individual scientists, not as representatives of any organization, government, or industry. All individuals who as authors, consultants, or advisers participate in the preparation of the EHC monograph must, in addition to serving in their personal capacity as scientists, inform the WHO Secretariat if at any time a conflict of interest, whether actual or potential, could be perceived in their work. They are required to sign a declaration of interest statement. The Chairpersons of Task Groups are briefed on their role and responsibility in ensuring that these rules are followed. Such a procedure ensures the transparency and probity of the process. Their function is to evaluate the accuracy, significance, and relevance of the information in the document. A

summary and recommendations for further research and improved safety aspects are also required. The composition of the Task Group is dictated by the range of expertise required for the subject of the meeting and, where possible, by the need for a balanced geographical distribution.

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PREFACE

The International Programme on Chemical Safety (IPCS) was initiated in 1980 as a collaborative programme of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). One of the major objectives of IPCS is to improve scientific methodologies for assessing the effects of chemicals on human health and the environment. As part of this effort, IPCS publishes a series of monographs, called Environmental Health Criteria (EHC) documents, that evaluate the scientific principles underlying methodologies and strategies to assess risks from exposure to chemicals.

This EHC is part of the ongoing review of the underlying scientific bases for decision-making in chemical risk assessment by IPCS. It involves specific consideration of the area of dose–response assessment in the evaluation of information from toxicological studies in animals and from human clinical and epidemiological studies. It covers toxicants with threshold effects and those for which there may be no practical threshold, such as substances that are genotoxic and carcinogenic. The discussions are concerned with that subset of cause–effect relationships commonly referred to as dose–response models, which are typically used to characterize the biological effects of intentional (e.g. drugs and nutrients) and unintentional (e.g. contaminants) exposure to chemicals.

This EHC is intended primarily to provide descriptive guidance for risk assessors in using dose–response modelling in hazard characterization. It will also provide mathematical modellers with an appreciation of issues to be considered when modelling in the context of the risk assessment process. Risk managers will be able to obtain a general understanding of the applications and limitations of dose–response modelling. For both risk assessors and risk managers, some considerations for communicating the results of risk assessments that use dose–response modelling are presented.

The efforts of all who helped in the preparation, review, and finalization of the monograph are gratefully acknowledged. Special thanks are due to Health Canada, the Ministry of Health of Japan, the United Kingdom Food Standards Agency and the United States

National Institute of Environmental Health Sciences for their financial support of the project.

ACRONYMS AND ABBREVIATIONS

ADI	acceptable daily intake
AIC	Akaike's information criterion
ALT	alanine aminotransferase
BMD	benchmark dose
BMD_{10}	benchmark dose at 10% risk
BMDL	lower confidence limit on the benchmark dose
BMDS	Benchmark Dose Software (United States Environmental Protection Agency)
BMR	benchmark response
CDF	cumulative distribution function
CSAF	chemical-specific adjustment factor
DDT	dichlorodiphenyltrichloroethane
DNA	deoxyribonucleic acid
DRM	dose–response modelling
EHC	Environmental Health Criteria
ED_{10}	effective dose for a 10% risk
EPI	exposure potency index
F	Frequency
FAO	Food and Agriculture Organization of the United Nations
f_x	dose–response function
f(x)	dose–response function
IPCS	International Programme on Chemical Safety
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD_{50}	median lethal dose
LED_{10}	lower bound on the effective dose resulting in a 10% increase in risk (ED_{10})
LL	log-likelihood
LOAEL	lowest-observed-adverse-effect level
MOE	margin of exposure
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
RfD	reference dose
SD	standard deviation

T_{25}	chronic daily dose that gives 25% of the animals tumours above background at a specific tissue site
TDI	tolerable daily intake
UF	uncertainty factor
WHO	World Health Organization

1. SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

1.1 Summary

Dose–response modelling (DRM), for use in quantitative risk assessment and ultimately for informing public health decisions about chemical exposures, can be described as a six-step process. The first four steps—data selection, model selection, statistical linkage, and parameter estimation—constitute dose–response analysis. These steps relate to the process through which a mathematical description of the data is obtained in order to evaluate predicted responses for known doses or to obtain dose estimates when a chosen response is of interest. The fifth step involves the integration of the results of the dose–response analysis with estimates of exposure for the purposes of guiding public health decisions. The final step, which can optionally be applied earlier in DRM, involves an assessment of the quality of the dose–response analysis and the sensitivity of model predictions to the assumptions used in the analysis.

The characterization of dose–response relationships in animal and human studies has been a major component of hazard characterization and has been used in the extrapolation of incidences of adverse effects in the range of human exposure levels. Over the years, a variety of methods have been developed to accommodate such relationships, for improving extrapolation to low doses and deriving health-based guidance values, such as acceptable daily intakes (ADIs), tolerable daily intakes (TDIs), and reference doses (RfDs). DRM may prove useful in risk assessments for making better use of available data and for providing tools to evaluate the quality of data and the ensuing uncertainties in dose–response estimates.

In general, DRM estimates are based on data from the entire dose–response curve for the critical effect. The standard no-observed-adverse-effect level (NOAEL) approach can be regarded as a special, simplified case of dose–response analysis, as it identifies a single dose that is assumed to be without an appreciable

adverse effect. The dose–response model reflects the characteristics of the dose–response curve, particularly in providing estimates of the slope. In the case of a regression framework, it provides standard error and confidence intervals for the model parameters. A disadvantage of using the NOAEL approach is that it is not possible to quantify the degree of variability and uncertainty that may be present, whereas other dose–response models can facilitate the analysis of sensitivity and uncertainty. Consideration of a dose–response model can optimize study design and clarify the need for additional studies. The NOAEL approach incorporates biological information through the application of "expert" but subjective judgement. Full DRM has the potential for a more "science-rich" analysis through the more formal quantitative inclusion of, for example, factors and covariates into the models. Estimates derived from DRM enhance the ability to compare quantitatively different experiments, effects, and compounds within a common framework. DRM can enhance risk and safety assessments as well as provide opportunities to consider the likelihood of effects outside the observable range.

The choice of the models to be used depends upon the type of data. The models should include a model for dose–response and a model for the variability of the data. Once models are fit to a data set, the degree to which they individually describe the data can be evaluated using goodness-of-fit measures. In addition, their ability to describe the data with respect to each other may be compared. Uncertainties about the inferences that result from such models fall into four main categories: statistical uncertainty of inferences due to variability among the responses of experimental subjects, experimental errors (e.g. imperfect randomization, dosing errors, unfavourable dose location), variability among experiments due to unavoidable differences in experimental execution, and uncertainty due to the fact that the "true model" for the data is unknown. Dose–response analysis needs to address all four sources of variability and uncertainty whenever possible.

One particularly important application of DRM is the calculation of benchmark doses (BMDs). These are doses at which it is inferred that a particular level of response would occur. When appropriate data are available, BMDs are an alternative to the NOAEL approach in the calculation of health-based guidance values. When extrapolation is necessary, the uncertainty associated

with a prediction should be represented. Here it is especially important to include model uncertainty.

Full DRM offers the potential to provide additional information for the risk manager. The output of DRM should be directed towards addressing specific questions about the likelihood of adverse health effects. It can be presented in three principal ways. Firstly, it can be used for the establishment of a health-based guidance value, such as an ADI, TDI, or RfD, analogous to current procedures based on a NOAEL or lowest-observed-adverse-effect level (LOAEL). DRM can be a more scientifically robust method for determining health-based guidance values. Secondly, the output from DRM can be used in risk management to estimate a margin of exposure (MOE), by calculation of the ratio of the dose corresponding to a given limit of response to a human exposure level. Thirdly, based on the modelled dose–response relationship, the output can be a quantitative estimation of the magnitude of the risk/health effect at the level of human exposure, with the generally accepted assumption that the uncertainty factors used cover the uncertainties about differences in sensitivity between individuals and species. DRM can provide better information on the likelihood of effects at low doses that are below the levels observed in biological systems and can also provide better estimates of the statistical uncertainties surrounding estimates of likely effects.

Two factors that can impact the type of outputs from DRM exercises and that may be of importance to the risk manager are multiple data sets and uncertainties. DRM can be used with exposure data to identify subpopulations at risk. DRM can also be used to assist risk managers in determining priorities and evaluating the consequences of proposed interventions aimed at reducing the risk. For risk communication, the use of DRM techniques offers opportunities and challenges. DRM evaluations can produce information in several formats, including dose–response functions that allow, along with estimates of exposure, the prediction of risks at specified exposure levels and functions that allow the estimation of exposure levels resulting in specified risks. This includes estimates of the possible risk at intakes above a health-based guidance value, such as an ADI. DRM evaluations also offer approaches to compare competing risks or benefits and provide a focus on uncertainties that can influence the predicted risk.

However, unless the situation of risk is viewed at the population level, there is the risk communication problem that while explaining the level of risk in those circumstances where there is no safe level of exposure, some percentage of the population will be predicted to experience some effect deemed to be adverse. It must be recognized that the use of DRM requires a certain quantity and quality of data, as well as specific expertise.

The potential "ongoing" use of the estimates from DRM can, from a risk management perspective, give an improved characterization for decision-making by:

- providing information about what happens above the health-based guidance value (magnitude and types of health impacts);
- showing benefits from different regulatory actions;
- giving the decision-maker a "more-than-one-point" appreciation of the data;
- promoting consistency in decisions, if appropriate adjustments are made for differences in effect, effect level, species, and study design; and
- allowing for an iterative interaction between the risk assessor and risk manager on a continuous and ongoing basis.

The use of DRM and probabilistic assessment techniques to quantitatively describe variability and uncertainty brings new challenges in risk communication. Some of these challenges are:

- explaining that some percentage of the population is predicted to exceed the safety level and/or experience an adverse effect;
- explaining the level of risk in those circumstances where there is assumed to be no safe level of exposure;
- comparing competing risks or benefits;
- providing a focus on uncertainties that influence the predicted risk; and
- explaining that a risk estimate pertains to what may occur at a population level, rather than the individual level, and noting that this is also the case for the ADI/TDI approach.

1.2 Conclusions

- Full DRM can be considered a more sophisticated or robust alternative to the NOAEL approach in all cases where suitable dose–response data are available (e.g. several dose groups with different response levels).

- For quantal dose–response data, the interest is often in low response (incidence) levels. This may call for low-dose extrapolation by several orders of magnitude (e.g. for tumour incidences). However, equally plausible dose–response risk models may result in highly divergent low estimates. A currently applied approach is to estimate a BMD_{10} (dose at 10% risk) and linearly extrapolate from that point downwards, as a conservative approach. Another option, currently under development, is to apply a Bayesian approach that considers the various models all together.

- For continuous dose–response data, two approaches of DRM exist. One is to transform the continuous data into quantal data. The other is to consider continuous dose–response data as information on the severity of the effect and therefore as a function of dose. In the latter approach, measurable changes of effect are often close to response levels considered as adverse (e.g. 10% inhibition of cholinesterase), and the low-dose extrapolation problem is minor or non-existent.

- For the purpose of deriving an ADI, TDI, or RfD, DRM may be used for deriving a BMD, to be used as a point of departure in the same way as the NOAEL is used (i.e. the same uncertainty factors would be applied to the BMD as to the NOAEL).

- DRM may also be used for estimating risks at a given (human) exposure level. For risks in terms of incidences (quantal data), this may involve low-dose extrapolation.

- DRM exercises can provide information on uncertainties associated with the data and identify factors contributing to uncertainties in risk estimates.

- Application of DRM for all end-points can be cost prohibitive, so it is efficient to pre-select the apparently more sensitive end-points. In some cases, however, it is not easy to identify the most sensitive end-points by visual inspection, so all of the end-points may need to be modelled.

- The BMD and the lower confidence limit of the BMD (BMDL) should always be reported, so that the quality of the data and the model fit are clear and potencies can be compared on the basis of the BMD.

- The output of the different models used in DRM should be presented.

1.3 Recommendations

- Toxicity testing protocols (e.g. Organisation for Economic Co-operation and Development guidelines) should be reviewed for optimization for BMD and other DRM approaches, including optimal designs for the number of animals and number of doses for different dose–response curves. Additional research is needed for the development of optimal study designs. Guidance should be developed for combining existing studies with a view to DRM.

- Better guidance needs to be developed for combined analysis of different data sets for more precisely estimating BMDs.

- Better understanding of when and how to use the benchmark response (BMR) needs to be developed.

- Better understanding of the shape of the dose–response curve at low doses needs to be developed. Additional research is needed to determine the biological basis for extrapolation (e.g. by using biomarkers, tumour precursors, genetically modified animals, and toxicokinetics for target dose estimation).

- Improved guidance needs to be developed for risk communication based on the results of DRM and probabilistic assessment techniques. This should include communication of

the types of uncertainty and the relation to statistical variability, imprecision, and the use of confidence intervals.

- The use of DRM should be reviewed and additional general principles for its use developed when more experience becomes available.

2. INTRODUCTION

The International Programme on Chemical Safety (IPCS) and other public health organizations have recognized the importance of the harmonization of procedures to enhance the quality of risk assessments, to improve the transparency of the risk assessment process, and to facilitate risk communication.

Public health decisions on the plausible risks of chemical exposures can include several possible outcomes. The ultimate goal is to implement a risk management action that will produce the desired reduction of risk. Among the first objectives of a risk assessment is the determination of the presence or absence of a cause–effect relationship. If there is sufficient plausibility for the presence of such a relationship, then dose–response information is needed and will be subject to an analysis of a dose–response relationship.

Extrapolation is a fundamental problem in the quantitative health risk assessment of exposures to chemicals that produce toxicity in experimental systems. Adverse health effects of chemicals are, in the absence of human data, typically evaluated in laboratory animals at significantly higher doses than the levels to which humans may be exposed. Also, for certain substances for which the exposure can be controlled, such as food additives and residues of pesticides and veterinary drugs, the quantification of the risk above the level of exposure that has been assessed to be safe (e.g. the acceptable daily intake [ADI]) can be difficult. This is particularly true in cases of temporary excursions above an ADI.

The use of mathematical and statistical approaches in hazard characterization is increasing. Although dose–response models have been available for some time, their use has been somewhat limited because of a lack of either appropriate scientific information or agreed-upon approaches and methods for how to obtain and use available dose–response information appropriately. Dose–response modelling (DRM) involves a number of choices based upon scientific experience, data availability, and mathematical tractability and can take on many different forms and be used in many different

ways. A recent review of the available quantitative approaches for hazard characterization noted that mathematical modelling of the dose–response relationship could improve the risk assessment process (Edler et al., 2002).

Dose–response models may improve and generate more reliable predictions, but they can never be proved to be completely correct. Therefore, it is necessary to rely on scientific judgement to determine the utility of risk predictions from DRM in making public health decisions. It is important to remember that risk numbers derived from DRM can be misleading for a variety of reasons; like any other tool used in science, DRM needs to be utilized in a broader context of all of the available scientific knowledge. Although mathematical and statistical rigor are important factors in risk assessment, the final standard that prevails remains biological plausibility. It is this inherent uncertainty and its communication for which modelling and quantitative risk assessment can be particularly valuable.

2.1 Background

This Environmental Health Criteria report (EHC) is intended primarily to provide descriptive guidance for risk assessors in using DRM in hazard characterization. It will also provide mathematical modellers an appreciation of the issues to be considered when modelling in the context of the risk assessment process. Risk managers will be able to obtain a general understanding of the applications and limitations of DRM. For both risk assessors and risk managers, some considerations for communicating the results of risk assessments that use DRM are presented.

2.2 Scope

This EHC is part of the ongoing review of the underlying scientific bases for decision-making in chemical risk assessment by IPCS. It involves specific consideration of the area of dose–response assessment in the evaluation of information from toxicological studies in animals and from human clinical and epidemiological studies; it does not include consideration of other aspects of quantitative risk assessment, such as physiologically based modelling. It covers toxicants with threshold effects and those for which there may be no practical threshold, such as substances

that are genotoxic and carcinogenic. The discussions are concerned with that subset of cause–effect relationships commonly referred to as dose–response models, which are typically used to characterize the biological effects of intentional (e.g. drugs and nutrients) and unintentional (e.g. contaminants) exposure to chemicals. Dose–response models are also commonly used in microbiological risk assessments (e.g. WHO, 2004a).

This document focuses primarily on experimental animal studies. In DRM of human epidemiological data, several important issues should be considered:

- *Impact of imprecision of the dose estimate*. This issue differs substantially from the situation with experimental animal studies. In observational studies, where the dose is not a matter of design, this imprecision is likely to be substantial.

- *Absence of a true control group*. In many observational studies, there may not be any subjects who are completely free from exposure. The response at zero exposure cannot be observed and has to be estimated.

- *Shape of the dose–response curve at low doses*. The shape may depend on both the outcome parameter and the toxicant. For most contaminants, insufficient information is available, and the impact on uncertainties must therefore be considered.

- *Confounder adjustment*. In epidemiological studies, confounder adjustment must be included. Decisions therefore need to be made as to which confounders to include in the DRM.

- *Meta-analysis*. If more than one study is available, a meta-analysis can provide improved information on the dose–response models.

Many of the considerations in this EHC are also relevant to ecotoxicological studies.

This EHC is intended to provide guidance in a number of areas relevant to DRM. Initially, there is a discussion of the risk analysis paradigm (chapter 3) and the basic concepts of DRM (chapter 4). In

chapter 5, the use of DRM is described, including comparing the no-observed-adverse-effect level (NOAEL) approach with the benchmark dose (BMD) modelling method. Chapter 6 provides the principles of DRM, including data considerations, model descriptions, model fitting and parameter estimation, model comparisons, and uncertainty. This chapter also includes discussion of BMD approaches. Chapter 7 discusses the provision of scientific advice by risk assessors to the risk managers. This chapter includes an explanation of the output of the dose–response analysis and the strengths and weaknesses of DRM. The final chapter, chapter 8, summarizes the conclusions of the EHC and provides recommendations for future research.

There is only limited treatment of the mathematical and statistical considerations for DRM. References and links are provided for more in-depth treatments, modelling tools, and examples.

3. RISK ANALYSIS

3.1 Decision paradigms

A risk analysis decision paradigm is a formal representation of a process that distinguishes the scientific bases from the risk management objectives and generally contains a component in which the probability of harm is estimated. This component of the decision paradigm is referred to as the risk assessment. As a probability calculation, a risk assessment will include both a statement of the objective under consideration (i.e. the harm) and the basis for the assertion that the harm may occur (i.e. the probability).

3.2 Risk analysis paradigms

The first risk analysis paradigm for public health was proposed by the National Academy of Sciences of the United States of America (NRC, 1983) and focused on assessing the risk of cancer from exposure to chemicals in food. The decision process was divided into three major steps: research, risk assessment, and risk management. The risk assessment process was further divided into hazard identification, dose–response assessment, exposure assessment, and risk characterization. Risk management is the decision-making process involving the consideration of political, social, economic, and technical factors with relevant risk assessment information relating to a hazard so as to develop, analyse, select, and implement appropriate risk mitigation options. Risk management comprises three elements: risk evaluation, emission and exposure control, and risk monitoring.

In the National Academy of Sciences paradigm, the principal steps were considered to be sequential, with the decision process commencing with research and concluding with the decision. A drawback of this sequential concept is an absence of the recognition of the influence that the risk analysis might have on data collection or of the impact that political, social, and economic objectives may have on the need to identify the hazard.

More recent examinations of risk assessment/analysis methodology have paid much closer attention to the influence of risk management on the risk assessment process (NRC, 1994, 1996; Presidential Commission, 1997; Renwick et al., 2003). Rather than insist that management be insulated from the risk assessment process for the sake of preserving scientific objectivity, it is acknowledged that risk management should interact with risk assessment for the scope of the analysis, particularly in problem formulation. The focus on this interaction leads to the notion that the relationship between risk assessment and risk management is an interactive, often iterative, and circular process (see Figure 1).

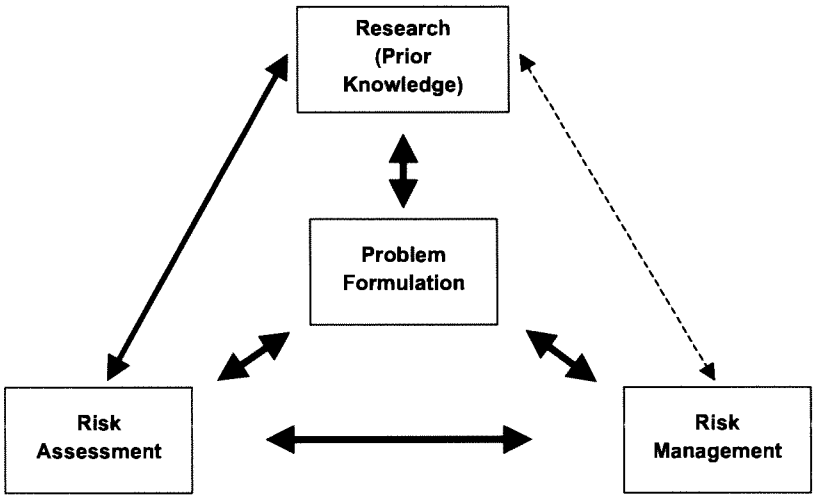


Fig. 1. Interactions of risk assessment with risk management.

As a general rule, formal risk assessments are preceded by preliminary risk assessments. These are usually subjective and informal and may be initiated from inside or outside the risk assessment and scientific communities. A key consideration of these preliminary risk assessments is whether or not a formal risk assessment is necessary. The transition process from preliminary assessments to formal risk assessments has been described as problem formulation (Renwick et al., 2003). It is an iterative process that facilitates the critical interface between risk assessment and risk management. Risk communication, with stakeholder involvement, is particularly essential during the problem formulation.

As the risk analysis paradigm evolved, the need for risk communication as an integral part was recognized (see Figure 2). Risk communication not only is the interactive exchange of information and opinions among risk assessors and risk managers, but necessarily includes all interested parties. The issues of risk, risk-related factors, and risk perceptions should involve interactive exchange throughout the risk assessment process. The communication of the results of the risk assessment as the basis of the risk management decisions demands transparency and appreciation for the uncertainties involved.

Fig. 2. The risk analysis paradigm.

3.3 Motivations and considerations for producing a formal risk assessment

There are several different reasons for preparing a formal risk assessment. The relative importance of these different motivations may influence the scope or the methodology used.

3.3.1 Transparency and justification

A major function of formal risk assessment is to serve as a transparent justification of a public health decision, whereby each step and assumption are clearly described. A key reason for undertaking such an assessment is to separate clearly scientific knowledge from values. Formal risk assessments are almost always

performed for notable public health issues where there is a wider interest in the political, social, and economic consequences of such assessments. Identifying the public health objectives before the technical analysis will allow participation in the debate of the other issues involved without necessarily requiring involvement in the scientific discussion. There may be areas of a risk assessment that can be obscure to someone not privy to their development. As a result, transparency is often audience dependent, relative to the level of comprehension and involvement. Since less can be taken for granted, the extent of the explanation required will increase as the audience broadens and its level of interest increases and sophistication decreases. Producing records of an assessment with varying degrees of technical detail may be a useful objective.

The World Trade Organization, under the Agreement on the Application of Sanitary and Phytosanitary Measures, has recognized the importance of harmonized science-based risk assessments. The World Trade Organization has specifically cited the standards, guidelines, and recommendations of the Codex Alimentarius Commission as reflecting international consensus regarding the requirements to protect human health from foodborne hazards. The Codex Alimentarius Commission has formally adopted the risk analysis paradigm in its decision-making (Codex Alimentarius Commission, 2003). Other organizations have also adopted this paradigm (European Commission, 2000).

3.3.2 *Public health and individual health*

A public health risk assessment is concerned with a population. The behavioural, environmental, or biological characteristics will vary among individuals in the population of concern. This variation is considered in probabilistic approaches and determines the statistical nature of health risk measures and conclusions made on populations. A risk assessment may need to describe or model these individual characteristics to produce a prediction of what might be expected to happen in the population. Specifying the population with which the risk assessment is concerned may be an important part of the problem formulation. In a public policy setting, the population will generally be defined by the risk managers, often in view of social, economic, and other considerations.

3.3.3 Quantification and computation

Public health issues often involve matters of degree, particularly in regard to level of exposure and risk, and may be defined by measures of quantity or statistical rates. If an uncertainty analysis is conducted, knowledge may be quantified as a matter of degree. Although judging matters of degree does not require the use of numbers, communication of degree does. Quantitative risk assessment approaches, including DRM, can be valuable in providing information to address these issues.

Formal risk assessments often involve the interaction of multiple quantitative measures that may lead to extensive and complicated calculations. Particularly in DRM, mathematical and statistical considerations are often complex. Although computers can carry out these calculations more accurately and quickly, knowledge of the scientific basis and experience with the applications of DRM are essential in order to avoid misinterpreting and incorrectly communicating the outcomes.

3.3.4 Cost of assessment

Risk assessments take time and effort to develop. The time and effort required will increase with the complexity of the problem and often with the degree of transparency that is required. The level of scientific detail addressed by the models and the level of documentation needed may vary with the nature and magnitude of the motivations for producing the risk assessment in the first place. In order to tailor the risk assessment to the decision problem, it may be desirable to develop the risk assessment by an iterative process that commences with the simplest possible statement of the problem and becomes more complicated as the risk assessment is developed.

3.4 Risk assessment

The risk assessment paradigm, incorporating problem formulation, is illustrated in Figure 3 (based on Renwick et al., 2003).

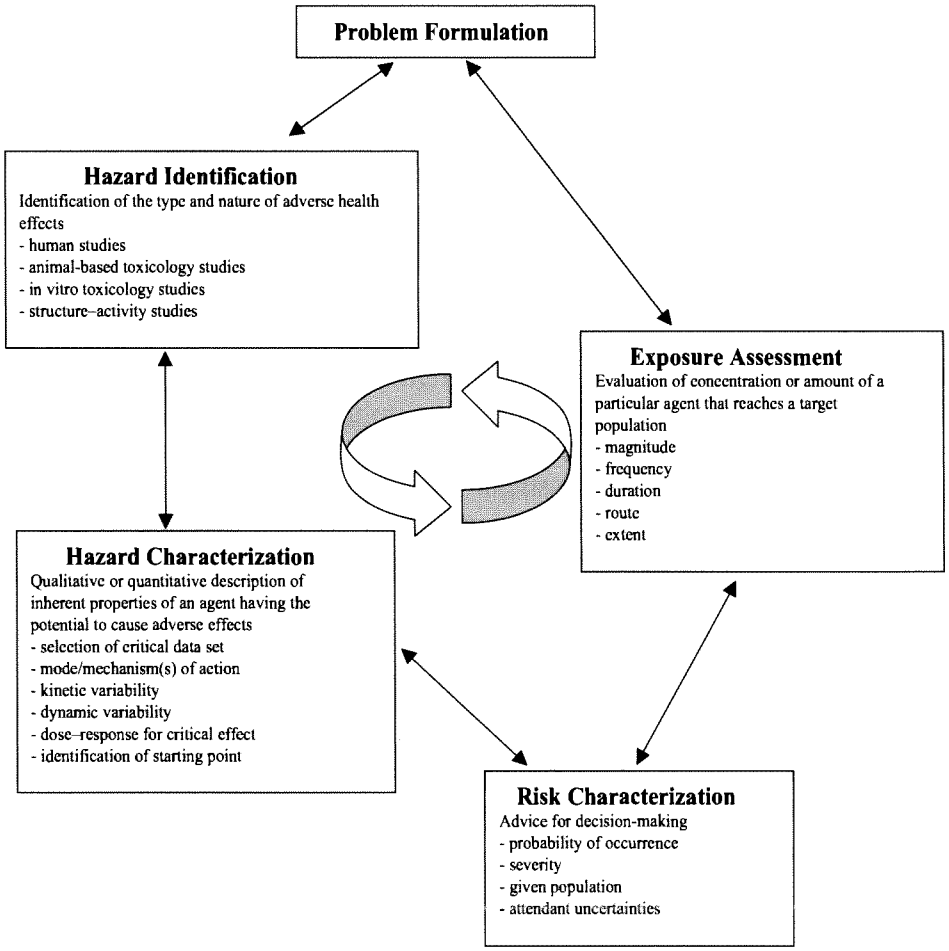


Fig. 3. Risk assessment (adapted from Renwick et al., 2003).

3.4.1 *Problem formulation*

Problem formulation is the initial phase in a risk assessment that determines if a detailed risk assessment is necessary and, if so, whether it is possible. Further, it serves as the transition from an informal risk assessment to a formal risk assessment. Problem formulation requires at least some preliminary consideration of the hazard identification, hazard characterization, and exposure assessment and usually proceeds in iterative stages. The output is a plan for the risk assessment process, which can be changed as the risk assessment progresses.

3.4.1.1 *Defining the question*

Among additional considerations are those that address who should be involved in the risk assessment and risk management processes. The transparency of a risk assessment will depend on how well these are described. It is not necessary to establish beyond all doubt that there is a cause–effect relationship in order to conduct a risk assessment. The suspicion that there may be such a relationship is sufficient. The consideration of the evidence for or against the supposition is often an integral part of the analysis. Identifying the problem may be politically controversial. That is, it may constitute a risk management issue that must be resolved before the risk assessment may be used as the justification for a decision. Non-scientific controversy may be diverted from the risk assessment by separating the valuation of the effect from the risk assessment per se (i.e. the risk assessment may be used as part of a cost–benefit analysis, but the cost–benefit analysis is not part of the risk assessment). Predicting the occurrence of an event is not part of an expression of the level of public health concern. However, suggesting that the problem is big enough to merit a formal risk assessment does imply that the risk may be of some significance.

3.4.1.2 *Prior knowledge*

Organizing information regarding public health issues that may involve many details and complex cause–effect relationships may benefit from the methodical collection and evaluation of prior knowledge of the agent, exposure to the agent, and possible biological effect(s) resulting from exposure to the agent. This is essential for determining the feasibility of a detailed assessment. Prior knowledge is also important for prioritizing and directing the risk assessment. Organization of information may also instigate and support specialization; different experts may produce or oversee different parts of the risk assessment. This information may in turn influence the conception of the problem (where management specifies the objective of the analysis) and also may influence additional research that may be needed.

3.4.1.3 *Desired outcomes*

The desired outcomes of the problem formulation are:

- explicit questions to be answered in the risk characterization to meet the needs of the risk manager;
- determination of the resources that are needed and available; and
- time frame for completing the assessment.

3.4.2 Risk assessment outcomes

The advice to risk managers that is formulated in the risk characterization may be qualitative or quantitative. Quantitative advice includes:

- health-based guidance values;
- estimates of the risks at different levels of exposure;
- exposure-based estimates used with low levels of exposure (e.g. threshold of toxicological concern); and
- risks at minimum and maximum intakes (e.g. nutrients).

Qualitative advice includes:

- statements/evidence that the agent is of no toxicological concern owing to the absence of toxicity even at high exposure levels (e.g. ADI "not specified");
- statements/evidence that the agent is "safe" in the context of a specified use; and
- recommendations for avoidance, minimization, or reduction of exposure.

Risk characterization should include all key assumptions and a clear explanation of the uncertainties in the risk assessment. It should also include information on susceptible subpopulations, including those with greater potential exposure and/or specific physiological conditions or genetic factors. At present, this is limited, and generic approaches have to be used (e.g. 10×10 uncertainty factors for interspecies differences and human variability). The advice to risk managers can be in the form of a comparison of the relative risks resulting from choosing different risk management options.

The risk assessment that is produced is followed by either a risk management decision or a request for further analysis, which may

influence the further research that is conducted. In one sense, the risk assessment process may never end. However, from a risk management standpoint, there is usually some imperative and timeline that conclude the process. Therefore, in another sense, the risk assessment ends when the risk management decision is made. The record produced by a risk assessment stands as a justification for a decision at the time the decision is made. However, with additional information, such as that which can reduce the uncertainties identified in the risk assessment, the risk assessment/analysis may be reopened. It is also possible that additional information can increase uncertainty.

4. DOSE–RESPONSE MODELLING: BASIC CONCEPTS

4.1 Introduction

Toxicology is the science of identifying and quantifying harmful or adverse effects of chemical and physical agents in the human environment. This can be accomplished by observations in humans (i.e. epidemiological and clinical studies), experimental studies using animal models (i.e. in vivo bioassays), or cellular and molecular studies. All these approaches have firmly established the principle of dose–response. Accordingly, dose–response toxicities of chemicals can be and have been expressed quantitatively (e.g. the median lethal dose, or LD_{50}).

However, scientific data alone are not sufficient to allow a decision to be made regarding the potential toxicity of chemicals and other agents that humans encounter; it is the analysis and interpretation of these data that lead to a scientifically supported decision regarding potential health effects. Many analytical processes have been developed to address the evaluation of the toxicities of chemicals, ranging from very simple approaches based solely upon the identification of the possibility of a hazard (NTP, 2002; Cogliano et al., 2004; USEPA, 2005) to much more complicated approaches incorporating biological mechanisms, complicated mathematical models, bioavailability in humans, and direct predictions of chemically induced changes in disease incidence in the affected human population (Portier & Kohn, 1996; Kim et al., 2002). All of these methods have two basic steps in common: analysis of the dose–response information and implementation of the results of that analysis to formulate a conclusion. The combined two-step approach will be referred to as DRM.

This chapter describes the elements that embody DRM. Most of the information presented is found in more extensive detail in other chapters of this guidance document. This chapter sets the stage for discussion of dose/exposure–response modelling by briefly

answering the questions: What is dose? What is response? What is a model? It then goes on to introduce the reader to the types of data and information that may have an impact on the development of dose–response models.

4.2 What is dose?

It is critical when performing dose–response analyses to have a clear concept of what is meant by "dose" and how it applies to the response. There are three basic types of "dose" that arise from scientific investigations: the administered or external dose, the internal (absorbed) dose, and the target or tissue dose. External dose denotes the amount of a chemical or other agent administered to an experimental animal or human in a controlled experimental setting by some specific route at some specific frequency. In the terminology used by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), intake (dietary exposure) refers to external dose. Internal dose is the amount determined by toxicokinetics to be systemically available. It is a consequence of absorption, distribution, metabolism, and excretion of the chemical. The tissue dose is the amount that is distributed to and present in a specific tissue of interest. The three are, of course, related, and each can be used to express dose–response.

Two other parameters are important: the dose frequency and duration of dosing. Dosing can be acute, subchronic, or chronic. For simplicity, the term dose in DRM will be used as an inclusive term referring to all three forms of dose described above. In general, units of dose should reflect the magnitude, frequency, and duration over which it applies. Dose can be expressed in a multitude of metrics. Some of these metrics include daily intake (e.g. ng/kg body weight per day), total body burden (e.g. ng/kg body weight), body burden averaged over a given period of time, or tissue concentration (ng/kg).

For humans, where dosing of xenobiotics is not intentional, the term exposure is used for the external dose. In epidemiological studies, exposure is rarely known, and best estimates are made using several assumptions and/or biomonitoring of tissue (usually blood) concentrations at very few time points, often many years

after what is believed to be the period of first/highest exposure. Sometimes, when laboratory animals are used for DRM, the dose used in the animal study is transformed to an equivalent human exposure prior to modelling. Exposure assessment is the qualitative and/or quantitative evaluation of the likely intake of chemical agents via food, as well as exposure from other sources, if relevant (WHO, 1997). In this situation, models of exposure linked to response data may be used to develop a dose–response model. However, limited knowledge of the events controlling absorption and tissue distribution (especially in humans at low levels of exposure), metabolism, and excretion and the other molecular and biochemical processes that ultimately lead to particular responses contribute to the uncertainty in these analyses.

4.3 What is response?

Response, in this context, generally relates to an observation or effect seen in a laboratory cell culture, an animal, or a human following exposure. These end-points cover a broad range of observations, from early responses, such as biochemical alterations, to more complicated responses, such as cancer and developmental defects. Responses can be either adaptive or adverse (e.g. Williams & Iatropoulos, 2002). The latter are defined as a change in the morphology, physiology, growth, development, reproduction, or lifespan of an organism or subsystem (e.g. subpopulation of cells) that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences. These are critical responses that are likely to underlie an adverse health effect in humans. The responses are sometimes species and/or tissue specific and have different degrees of variation across individuals. Nevertheless, there is some commonality across species, and there are known linkages between some responses (e.g. DNA damage is a precursor for mutations). DRM can address each response, provide insight into their quantitative similarity across species and tissues, and link responses in a mechanistically reasonable manner.

Response is generally considered to vary across experimental units (animals, humans, cell cultures) in the same dose group in a random fashion. This random variation is usually assumed to follow some statistical distribution describing the frequency of any given

response for a population. In general, statistical distributions are characterized by their central tendency (usually the mean or average value) and their effective range (usually based on the standard deviation). Most responses of interest in the context of dose–response assessment fall into one of four basic categories:

- *Quantal responses.* Quantal responses generally relate to the number of experimental units responding in a given period of time (e.g. the proportion of animals with a tumour in a cancer bioassay).

- *Counts.* Count data generally relate to a discrete number of items measured in a single experimental unit (e.g. number of papillomas on the skin).

- *Continuous measures.* Continuous measures generally take on any value in a defined range (e.g. body weight).

- *Ordered categorical measures.* Ordinal categorical measures generally take on one value from a small set of ordered values (e.g. tumour severity grades).

Sometimes it is useful to convert continuous data into proportions (e.g. number of animals outside a clinically relevant range for an immune system marker) or categories (e.g. measured degree of liver necrosis converted to minimal, moderate, or extensive).

For each of these different data types, there will be some differences in how they will be handled for DRM; as a general rule, however, the goal of DRM is to describe the mean and variance of the response as a function of exposure and/or time.

4.4 What is a model?

Dose–response models are mathematical models used to characterize the relationship between dose and response for a given set of scientific data. Mathematical models consist of three basic components: assumptions used to derive the model, a functional form for the model, and parameters that are components of the

functional form. For example, the simplest dose–response model is a linear model to describe a continuous response (see Figure 4).

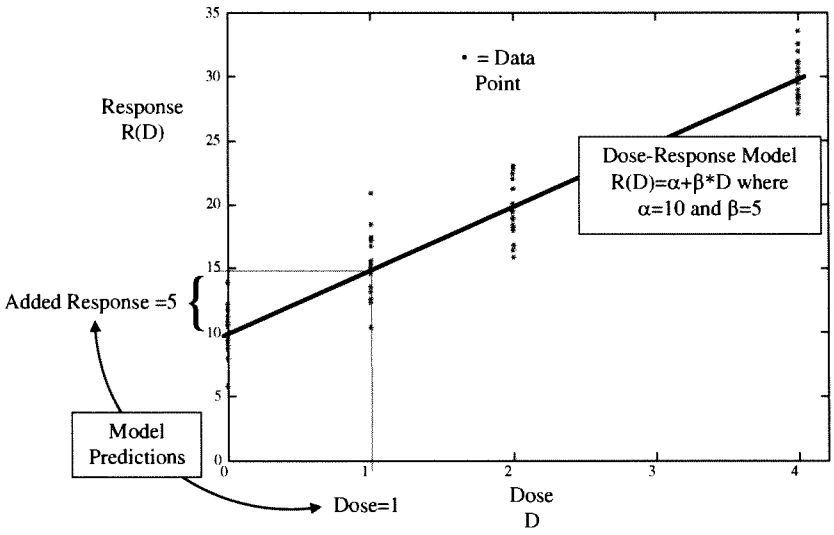


Fig. 4. Dose–response illustration displaying a linear model fit to continuous data for which prediction of the dose associated with an added response of 5 units (not designated) is a dose of 1 unit (not designated).

For this model, the key components are:

- *Assumptions*: Mean added response is proportional to dose.
- *Functional form*: $R(D) = \alpha + \beta \cdot D$, where R(D) is the mean response as a function of dose, denoted D.
- *Parameters*: α is a parameter describing the mean response in the control (unexposed) group, and β is a parameter describing the mean change in response per unit dose.

Dose–response models range from very simple models, such as the linear model described above, to extremely complicated models for which the eventual functional form cannot easily be expressed as a single equation (e.g. biologically based dose–response models). Models can also be linked, meaning that one model could describe part of the dose–response process while another describes the remainder of the process. For example, in most cases for chemical carcinogenesis, cancer risk is more closely linked to tissue

concentration than to administered dose. Given data on dose, tissue concentration, and tumour response, one can use a toxicokinetic model to relate dose to tissue concentration and use a multistage cancer model to relate tissue concentration to response. The two models combined are needed to describe the dose–response relationship.

Dose–response models may incorporate other information into the model form. Age and time-on-study are commonly used in DRM, but other factors, such as species/strain/human ethnicity, sex, body weight, etc., have also been used to expand the utility of dose–response models.

4.5 What is dose–response modelling?

DRM can be described by six basic steps, with a variety of options at each step (Table 1). The first four steps, which will be referred to as dose–response analysis, are aimed at the analysis of the data available for DRM. Dose–response analysis provides the linkage of a model to dose–response data for the purposes of predicting response to a given dose or predicting dose from a given response. The last two steps deal with implementation and evaluation of the analysis results.

Table 1. Basic steps in dose–response modelling

Step	Description	Options	Section links for chapter 6
1. Data selection	Determine the response to be modelled, and select appropriate data	End-point, data quality, sample size, data utility, data availability	6.1
2. Model selection	Choose the type of model to be applied to the data	End-point, data availability, purpose	6.2.1
3. Statistical linkage	Assumes that statistical distributions describe the response	End-point, data type, model choice, software availability	6.2.2
4. Parameter estimation	Combine the first three steps in an appropriate computer program to obtain estimates of the model parameters	Linkage function, software availability, variance	6.3
5. Implementation	Use the estimated model parameters and the model	Outputs, target selection, model predictions, BMD,	6.3

Step	Description	Options	Section links for chapter 6
	formula to predict response/dose as needed	direct extrapolation	
6. Evaluation	Examine the sensitivity of the resulting predictions to the assumptions used in the analysis	Model comparison, uncertainty	6.4, 6.5, 6.6

Step 1 involves selection of the appropriate data for DRM. The type of data available can have a marked impact on the complexity of the model that can be used. For example, whereas two points can be used to identify the slope of a line, it takes at least three points to identify the shape of a more complex dose–response relationship (e.g. straight line versus two connected lines). The issue of whether there are enough data to support a given model is quite complex (Portier, 1994) and is discussed in greater detail in section 6.1. In general, the data can restrict the type of model that can be used.

The second step is then to choose an appropriate model. Many choices exist for modelling dose–response data, and examples of some of the possible choices are presented in chapter 6. These models have been generally divided into two categories: empirical and biologically based models. Empirical models generally refer to functional forms for which there is limited mechanistic justification (e.g. the linear model above). Most of the DRM that has been done to date has focused on the use of empirical models. Biologically based models generally have functional forms that are derived from some basic principles about the onset and progression of disease in a biological system. These models are generally functionally complicated and require that experience in mathematics, statistics, and computer science be linked to experience with biological mechanisms. Mechanistic models also generally have greater data needs than do empirical models.

The third step requires the choice of a statistical linkage between the data and the model. The most common linkage method is to assume a statistical distribution for the response and use that distribution to derive a mathematical function describing the quality of the fit of the model to the data. However, a considerable amount of DRM has been done by simpler linkage functions, such as drawing a straight line through the data points. The advantage of

choosing a formal statistical linkage is the ability to test hypotheses and derive confidence intervals for model predictions.

In DRM, fitting the model to the data is the fourth step. Since the primary components of a model are the parameters that define the model, curve fitting simply involves choosing values for the parameters in the model. If a formal statistical linkage has been developed for linking the data to the model, then the parameters are chosen such that they "optimize" the value of the linkage function. For example, a common choice is to link the data to the model using the squared distance, denoted $[R(d_i) \bullet o_{ij}]^2$, between the predicted value from the model, denoted $R(d_i)$, and the observed value, denoted o_{ij}. These squared differences can be summed across all data points, and model parameters are chosen to minimize this sum; this is the common least-squares algorithm. Simpler methods can also be used to estimate model parameters. For example, by drawing a line through the data points, the parameters in the linear model can be estimated directly, since the value of can be estimated as the point where the line crosses the y-axis (zero dose) and the value of can be estimated by calculating the slope of the drawn line. Formal optimization is a better choice for modelling than ad hoc procedures, which often do not meet the criterion of transparency.

The fifth step in DRM is to make the inferences necessary to develop measures to protect public health. In its simplest form, a dose–response model allows the prediction of the response if the dose is known and the calculation of the dose if the aim is to target a specific level of response. In addition, implementation of the dose–response analysis (steps 1–4) also encompasses the extrapolation of results from the specific responses seen for the experiment being modelled to other exposure scenarios and other doses. This step can also involve an extrapolation from a laboratory species to humans. Usually, when making a prediction, the emphasis is on the change in response seen in the treated animals compared with the response seen in the controls. The different types of data (quantal, count, continuous, categorical) require different methods for predicting changes in response beyond the normal response. In general, the targets used for additional response fall into the categories of added response (simply subtract control

response), relative response (fold change relative to control response), and extra response (added response scaled to range from zero to the maximum possible response). Each of these choices can impact the final decision, so care should be taken to understand why a specific choice is made. Figure 4 illustrates some of the basic components of DRM for the simple linear model case and added response.

Measures used by public health agencies to prevent excess exposure to a hazardous agent generally fall into the categories of direct banning or limiting exposure. DRM could inform both choices, although its major impact is in the area of limiting exposure. Several methods on how to use DRM in this context have been proposed. The simplest is to use the predicted model to find the dose associated with a negligible (e.g. one in a million) or zero response over control. In general, this results in extrapolation far beyond the range of the data, which creates a great deal of uncertainty. A second approach is to use the dose–response model to identify a dose with a known response at or slightly below the observable range (the limit of scientific certainty) and use other models to get into a range where the response is assumed to be virtually unchanged relative to the control response. In this approach, a functional model structure can be used, such as a straight line, or something simpler, such as uncertainty factors (UFs), to identify a safe level of exposure. All of these options are discussed in chapter 6.

The basic steps in DRM shown in Table 1 can be repeated to consider other options in the process in order to understand the impact of choices on the predictions from DRM. This final step (step 6) in DRM is aimed at understanding the sensitivity of the analysis to specific choices and judging the overall quality of the final predictions. The simplest way to evaluate sensitivity is by considering several choices and determining if the results dramatically change. Depending on the degree of difference between choices, there could be value in performing a formal analysis of the quality of the fit of the model to the data. Other methods can also be used to assess the impact of choices used in the modelling on the eventual outcome, such as uncertainty analysis and Bayesian mixing. In some cases, step 6 is performed before step 5, with a focus on the assumptions used in the dose–response

analysis, and/or after step 5, with a focus on the assumptions used for implementation. These steps are further described in chapter 6.

4.6 Risk versus safety in dose–response modelling

Risk as used in this discussion is the direct estimation of the likelihood or degree of an event or its prevalence in a human population as a function of exposure. Given sufficient data in humans in the range of exposure where there is concern, it is possible to obtain scientifically supported estimates of risk. In most cases, the data used to develop dose–response models are not from studies in humans in the range of exposures that humans generally encounter. The most common type of data used for DRM comes from experiments in laboratory animals, generally at administered doses significantly exceeding the exposures that humans encounter. Even when human data are available and suitable for dose–response analysis, they are generally from selected populations, such as workers in occupational settings, whose exposures differ from those of the general population.

Thus, in many cases, dose–response analyses need to be extrapolated from an observable region where scientific support is available to a region where scientific support is weaker or non-existent. For dose–response analyses based on human studies, the extrapolation is generally a downward extrapolation to different exposure levels, but extrapolations can also be to different life stages (e.g. fetus, child) or to different populations with different environmental factors that might affect exposure (e.g. dietary differences). For dose–response analyses based upon laboratory data using animals, there is the additional problem of extrapolating from animals to humans.

Most of the methods used to implement the results of a dose–response analysis (step 5) address these extrapolation issues. The methods that have been used for extrapolation are diverse and sometimes contentious, with different countries, and even different agencies within a given country, using different approaches. The strategies used for extrapolation basically fall into two categories: those aimed at using estimates of risk for exposures outside of the

range of the data used in the dose–response analysis, and those aimed at establishing safety without using an estimate of risk.

Estimates of risk and the dose associated with that risk generally require extrapolation from the data on responses and doses to a lower dose range. These extrapolations can be done using the model (step 2) that was fit (step 4) to the data (direct estimation) or a different model, usually a line, extending from the lowest dose to a point of zero risk. The latter approach is generally envisioned to be conservative, assuming that the true risk is less than would be estimated by this second model at all doses below the dose for which scientific support is clear. In contrast, methods used to establish safety for a given dose without presenting an estimate of risk rely upon the concept that a dose that is sufficiently distant from the lowest dose associated with the observable range will be safe. This is generally done using uncertainty factors that have been developed over years of experience. In some cases where the general human exposure is estimated, however, the difference between the estimated exposure and the dose at the lowest edge of scientific support is used (margin of exposure, or MOE).

Regardless of how dose–response analysis is performed, additional methods are employed to extrapolate to humans. These methods are also varied, ranging from the use of additional uncertainty factors to more complicated modelling schemes based upon differences in toxicokinetics and toxicodynamics between humans and animals.

The term "risk assessment" is generally used to describe the entire process of making a public health decision regarding a specific chemical or agent. However, risk assessment can be defined further to differentiate between analyses aimed at establishing safety (as defined above) and analyses aimed at estimating risks. In this case, "safety assessment" would refer to the decision process aimed at establishing safety, whereas "risk assessment" would refer to assessments aimed at estimating risks that are part of a larger decision process. Safety assessments are more often used in cases where exposure can be controlled, such as for food additives and residues of pesticides and veterinary drugs in foods.

4.7 Summary

DRM, as used for informing public health decisions about chemical exposures, is a six-step process. The first four steps constitute dose–response analysis and relate to the process through which a mathematical description of the data is obtained in order to evaluate predicted responses for known doses or to obtain dose estimates when a chosen response is of interest. The fifth step involves the implementation of the results of the dose–response analysis for the purposes of guiding a public health decision. The final step, which can optionally be applied earlier in DRM, involves an assessment of the quality of the dose–response analysis and the sensitivity of model predictions to the assumptions used in the analysis. DRM, because it involves a large number of choices based upon scientific experience, can take on many different forms and be used in many different ways. The remaining chapters of this report focus on the range of choices available for each step in the process and some guidance to be used in making these choices.

5. DOSE–RESPONSE MODELLING: WHY AND WHEN TO USE IT

Dose–response analysis is a major part of the hazard characterization within the risk assessment paradigm and has been used in the past for both the characterization of dose–response relationships observed in animal bioassays as well as the low-dose extrapolation of incidences of adverse effects to the range of human exposure levels. Dose–response analysis includes the use of the NOAEL (pairwise testing) for deriving health-based guidance values such as the ADI and the use of DRM (fitting functions).

5.1 Historical perspectives

It has always been a challenge to extrapolate from effects observed in experimental animal bioassays to potential effects in humans in order to protect humans from potentially harmful chemical exposures. A variety of approaches have been developed.

The prototype chemical safety assessment uses the ADI methodology, which was introduced by Lehman & Fitzhugh (1954) and has come to be widely employed for the derivation of health-based guidance values (IPCS, 1987). The ADI was originally devised as a procedure for the regulatory approval of food additives. Since food additives are deliberately added, the process often defines what the regulatory agency is willing to accept as a legal standard of safety. The same methodology is used to derive health-based guidance values for chemical contaminants. However, because "acceptable" was deemed to be an inappropriate term for chemical contaminants, the term "tolerable" was used instead (i.e. tolerable daily intake, or TDI). Comparable terms that have been used are provisional maximum tolerable daily intake (IPCS, 1987) and reference dose (RfD) (Barnes & Dourson, 1988). Other similar methods exist for different types of exposures, such as for compounds with accumulating properties—for example, provisional maximum tolerable weekly intake or provisional maximum tolerable monthly intake (IPCS, 1987; WHO, 2002).

5.1.1 The no-observed-adverse-effect level approach to acceptable/tolerable daily intake

Calculation of the ADI based on the NOAEL approach for the case of quantal data is summarized in Table 2.

Table 2. NOAEL-derived ADI for the case of quantal data

Step	NOAEL-derived ADI
1. Data selection	Sufficient sample sizes, at least one dose with "no" effect and one dose with effect. Relevant end-points in a relevant species are important for any approach.
2. Model selection	Statistical method $R(D) = \begin{cases} 0 & \text{if response at dose D is not significantly different from control response} \\ 1 & \text{if response at dose D is significantly different from control response} \end{cases}$
3. Statistical linkage	Pairwise statistical tests between dose groups and control group.
4. Parameter estimation	Assessment of point of departure $NOAEL = D_{NOAEL}$ where $R(D) = 0$ for all $D \leq D_{NOAEL}$ and $R(D) = 1$ for all $D > D_{NOAEL}$ This procedure presupposes that all doses below the NOAEL are non-significant and all doses above the LOAEL are significant. This is often not the case.
5. Implementation	$ADI = \frac{NOAEL}{UFs}$ where UF is uncertainty factor.
6. Evaluation	Statistical power analysis should be performed to check if the test was sensitive enough to detect relevant effects.

Selecting the data needed to calculate the ADI based on the NOAEL approach (step 1) is similar to choosing the data to be used

for more complicated modelling; the better data sets have an appropriate number of relevant doses, sufficient sample sizes, and relevant end-points in a relevant species. The next step in calculating an ADI is to determine the NOAEL, which is the highest concentration or dose of a chemical, found by experiment or observation, that causes no detectable adverse effect, as defined above. This includes a statistical method (step 2), statistical linkage (step 3), and a method of assessment of a point of departure (step 4) that describes the identification of the NOAEL. Consider a response procedure, R(D), of the form:

$$R(D) = \begin{cases} 0 \text{ if response at dose D is not significantly different from control response} \\ 1 \text{ if response at dose D is significantly different from control response} \end{cases}$$

The statistical linkage (step 3) between this procedure and the data is represented by the statistical test used to determine if a response at any given dose is different from the control response. When the response is non-significant, we simply *act as if* the effect were in fact zero. Obviously, we cannot conclude that the effect actually *is* zero. When the NOAEL approach is chosen, the statistical test is used to decide upon the existence of a statistically significant increase (e.g. at the 5% level) over background (e.g. the control group) for each dose level separately. The selection of the NOAEL (step 4) is then achieved by choosing the largest dose, D_{NOAEL}, for which all smaller doses have R(D) = 0 and all larger doses have R(D) = 1. Mathematically, this assessment can be written as:

$$\text{NOAEL} = D_{NOAEL} \text{ where } R(D) = 0 \text{ for all } D \leq D_{NOAEL} \text{ and } R(D) = 1 \text{ for all } D > D_{NOAEL}$$

This procedure presupposes that all doses below the NOAEL are non-significant and all doses above the LOAEL are significant. This is not always the case.

The ADI methodology specifies that an acceptable dose of a chemical may be calculated by dividing the NOAEL by appropriate uncertainty factors (also called safety factors). Uncertainty factors are default factors used to account for both uncertainty and variability.

Historically, an uncertainty factor of 100-fold has been used to convert the NOAEL from an animal study into a health-based guidance value (Lehman & Fitzhugh, 1954; Dourson & Stara, 1983; IPCS, 1987). Additional uncertainty factors may be used to allow for database deficiencies, such as the absence of a chronic study (IPCS, 1994). The default 100-fold uncertainty factor may be seen to represent the product of two separate 10-fold factors that allow for interspecies differences and human variability (IPCS, 1987; Renwick & Lazarus, 1998). The recognition that the original 100-fold uncertainty factor could be considered to represent two 10-fold factors allowed some flexibility, because different factors could be applied to the NOAEL from a study in humans and from a study in animals. The concept of chemical-specific adjustment factors (CSAFs) (IPCS, 1994, 2005) was introduced to allow appropriate data on species differences and/or human variability in either toxicokinetics (fate of the chemical in the body) or toxicodynamics (actions of the chemical on the body) to modify the relevant default 10-fold uncertainty factor. The strategy used by WHO/IPCS in the NOAEL/ADI approach involves replacing the original 100-fold uncertainty factor with CSAFs where there are adequate data (IPCS, 1994, 2005).

Regardless of the quantities chosen for the uncertainty factor, the prediction (step 5) of the ADI from NOAEL-based DRM is given by the equation:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UFs}}$$

Step 6 can be extended to the evaluation of the sensitivity of the ADI to the assumed values of the uncertainty factors.

Some scientists have raised concerns regarding the use of the NOAEL to determine an ADI. The greatest concern is that the NOAEL tends to yield lower ADIs for chemicals for which there are more or better data. Therefore, stakeholders using usually more costly, better data are "punished" (Crump, 1984; Dourson et al., 1985; Kimmel & Gaylor, 1988; Barnes et al., 1995; Slob & Pieters, 1998).

5.1.2 *The benchmark dose approach to acceptable/tolerable daily intake*

The BMD concept was introduced as an alternative to the NOAEL approach (Crump, 1984; Kimmel & Gaylor, 1988). The BMD method has a number of advantages, including the possibility to extrapolate outside the experimental dose range and respond appropriately to sample size and the associated uncertainty.

Calculation of the ADI based on the BMD approach is summarized in Table 3 for the case of quantal data. A generic form of the BMD and benchmark dose lower confidence limit (BMDL) is presented in this table. In this document, a variety of response levels, such as 1%, 5%, and 10%, will be discussed.

Table 3. BMD-derived ADI (Weibull model) for the case of quantal data

Step	BMD-derived ADI
1. Data selection	Sufficient number of doses with different response levels and a sufficient number of *total* subjects.
2. Model selection	Fit dose–response model (e.g. Weibull model).
3. Statistical linkage	Predicted fractions are linked to observed fractions, and their "distance" is minimized by optimizing some fit criteria function (e.g. likelihood function based on assumed distribution).
4. Parameter estimation	Choose an appropriate response, p, in the range of experimental response. Estimate $BMDL_p$, the 95% lower confidence bound on the BMD_p, where $\frac{R(BMD_p) - R(0)}{1 - R(0)} = p$
5. Implementation	$ADI = \frac{BMDL_p}{UFs}$
6. Evaluation	Sensitivity of BMD to model choice can be checked by fitting various models.

In choosing the data (step 1) for BMD modelling, the same basic considerations apply as for the NOAEL method. In addition, studies showing a graded monotonic response with a significant dose-related trend work best. This is generally true for all DRM analyses.

Choosing a model (step 2) for the BMD method is dependent upon the types of data available and the characteristics of the response being modelled. Complicated models will require a larger number of dose groups than simpler models. Several models have been proposed for each type of data. In the United States Environmental Protection Agency's Benchmark Dose Software (BMDS) program, a number of routinely used models are cited (http://www.epa.gov/ncea/bmds/). As an example, assuming the availability of data that represent the proportion of animals responding to a given exposure with an adverse effect (e.g. cancer) from each dose group, one model choice could be the Weibull model, which has the form:

$$R(D) = \alpha + (1-\alpha)(1-e^{-(\beta * D)^{\gamma}})$$

where α is the proportion responding in the unexposed group, β describes the increase in probability of adverse effect per unit dose, and γ describes the shape of the dose–response curve (e.g. $\gamma >> 1$ implies threshold-like behaviour; $\gamma = 1$ implies log-linear behaviour).

The statistical linkage (step 3) between the data and the model can assume a number of different forms, as described previously (section 4.5) and in section 6.2. For quantal data, it is appropriate to assume that the data are binomially distributed for each dose group. Estimating model parameters (step 4) for the BMD method can also be based upon a variety of different methods. For the Weibull example, one routinely used approach would be to choose the parameters that maximize the binomial-based log-likelihood.

The concept of the BMD comes from the idea that it is desirable to use a dose–response model to capture the general pattern of response for all dose groups in the experimental data set, but there was some dose, the BMD, below which predictions would be tenuous. This BMD can be selected in a number of ways (e.g. Barnes et al., 1995; Murrell et al., 1998), but the most common way is to choose an excess response, the benchmark response, or BMR (p), below which there was insufficient support from the data. A common choice for BMR is p = 10%. Once the BMR (p) is selected, the BMD, specifically denoted BMD_p, is calculated according to the following equation, if the extra risk formula is used:

$$\frac{R(BMD_p) - R(0)}{1 - R(0)} = p$$

Empirical investigations showed for a large and representative set of compounds that the 95% statistical lower bound on the estimated BMD may be regarded as an analogue to a NOAEL, and substituting one with the other would result in similar ADIs (Crump, 1984; Barnes et al., 1995). As with all aspects of modelling, many choices exist for calculating confidence bounds, and these are discussed further in chapter 6.

Having chosen a method for estimating a 95% statistical lower bound on BMD_p, which can be called $BMDL_p$, the ADI can be calculated as follows:

$$ADI = \frac{BMDL_p}{UFs}$$

In this calculation, the values of the uncertainty factors could be the same as those used for the NOAEL or adjusted to account for a slightly different interpretation for the $BMDL_p$ relative to the NOAEL (Renwick et al., 2003).

The BMD method includes the determination of the response at a given dose, the dose at a given response, and their confidence limits. Using extrapolation of the dose–response model below the biologically observable dose range, the response at specified (lower) dose levels can be estimated as well as the dose corresponding to a specific response level.

5.2 Points of consideration

The use of DRM in general for hazard characterization is possible when a sufficient amount of dose–response information is available, either from an experimental animal bioassay or from a human study (epidemiological study or clinical trial). As shown in the previous section, the BMD can be considered as an alternative point of departure for deriving an ADI in those situations where a NOAEL would have been used as a point of departure in current procedures. In addition, DRM may be helpful in those situations

where there is a need for low-dose extrapolation (e.g. substances that are genotoxic and carcinogenic). It should be noted, however, that extrapolation from a single model that fits the data in the observed range cannot be justified, since other models fitting the data equally well may result in substantially different estimates of low-dose risk. Bayesian approaches are currently under development, which take into account both statistical uncertainties in the data and model uncertainty (see section 6.5). In practice, linear extrapolation from a BMD_{10} (or ED_{10}, effective dose for a 10% risk, approximately equal to BMD_{10}) is often applied as a simple method for low-dose extrapolation. This is considered a conservative approach. As another application, DRM may be used to estimate risks at any given (human) exposure level. Since human exposure levels are usually lower than the doses in the observed range in animal studies, methods for low-dose extrapolation may also be needed in this application.

5.2.1 General aspects of definition

The NOAEL is a parameter derived directly from the observed dose–response data and is defined as the highest administered dose at which the effect is still not significantly different from that at dose 0 (see section 5.1). The NOAEL is based on a multiple test procedure performed along the applied dose series. It lacks further detailed statistical properties compared with a parameter of a dose–response model, for which the precision of the estimate can be quantified.

The dependence of the NOAEL on the statistical significance test, however, tends to penalize chemicals for which there are more or better data by giving a higher estimate for those chemicals with less precise data. This problem does not occur in DRM. In fact, the opposite relationship holds: it penalizes studies with few or poor data.

The NOAEL approach can be formally considered a dichotomous procedure, where no effect is assumed to be present below the NOAEL and where an expression of the critical effect is present above the NOAEL (see section 5.1 and Table 2). Given the typical animal studies used in toxicology, the effect size that can be detected by a statistical test may be larger than 10% (additional

risk). Therefore, the NOAEL may be expected to be a dose at which the effect is in reality somewhere between 0% and 10% or more. In contrast, the BMD is a dose for which the size of the effect has been predefined, and thus it is under the control of the risk assessor. Furthermore, while the dichotomy of the NOAEL approach does not provide quantitative information about risk above the ADI, such information might be derived from fitted dose–response models, where such dichotomy does not exist.

In general, DRM estimates are based on data from the entire dose–response curve for the critical effect. The standard NOAEL approach can be regarded as a special, simplified case of dose–response analysis, as it identifies a single dose that is assumed to be without an appreciable adverse effect. The dose–response model thus reflects the characteristics of the dose–response curve, particularly in providing estimates of slope. In the case of a regression framework, it provides standard error and confidence intervals for the model parameters.

5.2.2 Estimation procedure

NOAELs are restricted by the set of doses used in the specific studies. An important consequence is that the NOAEL may be either below or above the threshold it aims to approximate, assuming one exists. When the true threshold is higher than the NOAEL, the distance between the two can be expected to be limited (related to the dose spacing used). However, when the true threshold is lower than the NOAEL, the distance between the two is unlimited: the true threshold could be anywhere between zero and the NOAEL.

The actual value of the NOAEL depends strongly on the following characteristics of the study design:

- *Group size.* The power to detect a NOAEL at some dose level is directly dependent on the sample sizes chosen at those dose levels (Gaylor, 1989). The larger the group size, the smaller the potential true effect size at the NOAEL.

- *Dose location.* Since the NOAEL is an applied dose that did not show significant effects, while the next higher dose applied did show significant effects, the NOAEL can only be one of the

doses actually applied in the study. A particularly disturbing disadvantage of the NOAEL approach is that in some cases no NOAEL can be assessed because the lowest applied dose showed effects.

- *Experimental variation*. Larger experimental variation between subjects will result in lower statistical power and, hence, higher NOAELs. In quantal data, this phenomenon is somewhat hidden, but in continuous data, it is directly visible: it is reflected by the scatter in the data per dose group. This experimental variation comprises various things: biological (e.g. genetic) variation between subjects, variation in experimental conditions (e.g. time of feeding, location in experimental room, time of section or interim measurements), and measurement errors.

DRM-derived estimates are based on interpolation, and these estimates are not restricted to the actually applied doses. DRM can also be used on a study where no NOAEL (only a LOAEL) can be defined, so in this situation another study may be unnecessary. A comparison of different models can be useful. When multiple models are fit to the same data and produce widely varying BMD estimates, caution should be used in interpreting the results, as this could indicate insufficient data for modelling (see chapter 6).

It should be noted that in comparison with the NOAEL approach, implementation of the full DRM approach may lead to differences between the NOAEL and the BMD in individual data sets. However, on average, BMDs that represent the lower confidence interval on the dosage giving a BMR of 5% or 10% tend to be quite similar to the NOAELs (Allen et al., 1994). Therefore, in data sets where DRM cannot be applied, the NOAEL may serve as a reasonable surrogate of the BMD.

5.2.3 Uncertainty

A modelling approach facilitates both sensitivity and uncertainty analyses. Uncertainty (see section 6.5) can be expressed numerically when the doses and responses are linked by a model. Such numerical analyses can also be subject to sensitivity analyses, to test the contribution of different aspects of the database or of

model characteristics to the overall uncertainty. The uncertainty in the risk estimates that arises from aspects of study design, such as dose spacing, sample size, and biological variability, can be assessed in a dose–response model. While uncertainty factors are amenable to uncertainty analysis (Slob & Pieters, 1998), the threshold procedure of the NOAEL is not readily amenable to quantitative estimation of uncertainty or to a sensitivity analysis.

A disadvantage of using the threshold procedure of the NOAEL for the estimation of a point of departure ("starting point") for formulating advice to risk managers is that it is not possible to quantify the degree of variability and uncertainty that may be present. The NOAEL is assumed to be a dose without biologically significant effects. This assumption is more likely to be valid in toxicological studies with larger sample sizes.

5.2.4 Study design

A design optimal for the NOAEL approach could limit the use of DRM, and vice versa. While the NOAEL approach requires sufficient sample sizes within dose groups (to warrant statistical power), the DRM approach requires a sufficient number of dose groups (to warrant a description of the whole dose–response). Given the restrictions on the total number of animals used in a single study, these two requirements may not be compatible.

An important point to bear in mind is that DRM can be used on studies carried out in the past and based on the traditional designs (with three dose groups and a control). Some have argued that optimal designs for dose–response models may have the advantage for animal welfare that fewer animals could be used (Slob et al., 2005).

While DRM provides uncertain estimates when the number of dose groups is too small, the determination of both the BMD/BMDL and the NOAEL may prove inadequate at different points when the number of animals per dose group is too small. For example, when the critical effect is seen in a larger experimental animal, such as the dog, with few animals per dose group, the NOAEL may be high owing to the insensitivity of the test. The BMD/BMDL approach, however, can be used to evaluate sparse dose–response data and quantify the inherent uncertainty. However,

even here, where an apparent dose–response relationship in the data remains, the BMD/BMDL may also provide very uncertain estimates. Therefore, a typical four-dose study with a few animals per dose may in practice be unreliable whatever method, NOAEL or BMD, is applied. However, the advantage of DRM is that this uncertainty is made visible, whereas in the NOAEL approach it remains hidden.

DRM reduces the need for more experiments when a small degree of extrapolation is needed (e.g. when the doses used are near the human exposure level). In contrast, the NOAEL approach may require further experiments where no clear NOAEL (or LOAEL) can be identified. This can be illustrated by the study of Allen et al. (1996) on developmental risk assessment in rats exposed to boric acid in their diet. This study failed to establish a NOAEL; however, the BMD approach could have been applied, thereby avoiding the need for repeat studies (see also section 5.2.2 above). Distributing the total number of animals over more dose groups does not result in poorer performance, despite the smaller number of animals per dose group, as shown by Slob et al. (2005). The above example of Allen et al. (1996) suggests that the BMD approach provides a reasonable basis for appropriately comparing and combining studies, as opposed to ad hoc combinations of study results.

A major advantage of DRM is the ability to estimate risks within the observable range of effects. In animal studies, it is possible to estimate risk over the full range of doses used. Estimation of risks outside the observable range will be more and more unreliable when risks get smaller and smaller (Murrell et al., 1998). Some studies (e.g. Sand et al., 2002) have investigated the effect of model dependence at different response levels.

Some experts have argued that extrapolation to risk levels outside the observable range might be warranted when there are indications that the same toxicological mechanism is active in both the extrapolation region and the experimental region of the model fit. However, mathematical models that adequately describe the full complexity of the mechanisms involved are very rare; even then, it needs to be additionally assumed that the parameters estimated from the data (i.e. the observable range) are adequate for the low-dose

range and have sufficient precision to make the prediction (see also section 6.5.3).

5.2.5 Biological information

The NOAEL approach incorporates biological information through the application of "expert" but subjective judgement. Full DRM has the potential for a more "science-rich" analysis through the more formal quantitative inclusion of factors/covariates into the models, in the case of both human epidemiological and animal data.

Such an approach can lead to more certain estimates, centred on a toxicologically based concept of estimating the dose–response relationship on the basis of all available biological knowledge, using empirical data and applying statistical inference. More complicated models can be developed on the basis of toxicokinetics and toxicodynamics.

5.2.6 Comparison of experimental results

NOAELs derive from an algorithmic analysis of the results of a single experiment. Meta-analysis on data such as NOAELs across a range of studies on a specific chemical is possible, such as when data are insufficient to build a dose–response model, but may be limited by the statistical properties of the NOAEL estimates.

Estimates derived from full DRM, however, enhance the ability to compare different experiments, effects, and compounds using a common framework. The estimates obtained may provide a test of consistency among different studies that may use different dose levels. DRM methodology can be used to describe dose–response relationships in different studies (e.g. rat and mouse, chronic and subchronic exposure, healthy and diseased animals) if suitable data sets exist.

Rules for combining studies, however, need to be developed. Descriptions of the dose–response on the same end-points in different studies may be integrated to provide a cohesive picture of the chemical's toxicity. The values obtained using DRM may result in estimates for each end-point on the basis of biological and functional relevance.

5.2.7 Risk management perspectives

The potential use of the estimates from DRM can, from a risk management perspective, give an improved characterization for decision-making by:

- giving the decision-maker a "more-than-one-point" appreciation of the data;
- providing information about what happens above the safety level (magnitude and types of health impacts);
- quantifying benefits in risk reduction from different regulatory actions;
- promoting consistency in decisions, if appropriate adjustments are made for differences in effect, effect level, species, and study design; and
- allowing for an iterative interaction between the risk assessor and risk manager on a continuous and ongoing basis.

5.3 Implementation issues

In the case of the BMD, there are a number of decisions to be made in applying the method and determining a BMDL: for example, which mathematical model to use; what degree of confidence to use in calculating confidence limits; what response level to predetermine as the BMR (e.g. BMR = 1%, 5%, or 10% incidence of an effect, or a 5% or 10% change in a continuous endpoint, such as body weight or red blood cell counts). It is often not clear what response level (BMR) can be considered as non-adverse. For example, should a 5% decrease in red blood cell counts be considered as adverse, or should a smaller (or larger) change be chosen? Should up to a 5% increased incidence in hepatocellular hypertrophy be considered as acceptable in an animal study, or is a maximum of 10% increase adequate? These and other choices need additional discussion among toxicologists and clinicians. Although an explicit statement on the BMR is an improvement compared with the generally unknown response level associated with a NOAEL, choices of a BMR need consensus building.

5.4 Summary

The characterization of dose–response relationships in animal and human studies has been a major component of hazard characterization. Over the years, a variety of methods have been developed to accommodate such relationships. DRM may be regarded as the most adequate approach for analysing dose–response data, provided that a suitable data set of animal or human dose–response data is available.

The standard NOAEL approach identifies a single dose that is assumed to be without appreciable effect, whereas the BMD is based on data from the entire dose–response curve, estimated for the critical effect. Although the effect at the NOAEL is assumed to be zero, it will be non-zero in many cases, although to what extent remains unknown. The size of the effect at the BMD is made explicit and, as far as possible, is based on toxicological knowledge. While the uncertainty in a NOAEL cannot be quantified, the uncertainty in a BMD can be quantified by a confidence interval. The use of DRM may call for different guidelines for optimal study designs, as the number of dose groups should be sufficiently large. Distributing the total number of animals over more dose groups may be done without loss of precision. DRM can more effectively compare different experiments, effects, and compounds. While risks above the ADI based on a NOAEL cannot be quantified, such may be possible for exposures exceeding the ADI based on DRM. For estimating risks below the observable range, extrapolation based on a single fitted model is unwarranted. Here, linear extrapolation may be considered as a conservative approach. Currently, more advanced methods are being developed (e.g. Bayesian approaches) for low-dose extrapolation based on DRM.

6. PRINCIPLES OF DOSE–RESPONSE MODELLING

6.1 Data

6.1.1 Selection of data

When considering which data to use from a set of available toxicity studies on a particular compound, it may not be effective to do a dose–response analysis for each observed end-point in each study. As a first step, one may omit studies that have obviously larger NOAELs compared with the other studies. In this way, one may, for example, select for a given type of toxic response (e.g. chronic, developmental) for the most sensitive species. For a given study, many end-points may have been measured. End-points not showing a clear dose–response on visual inspection can be omitted. Then, based on the toxicological impact together with the apparent magnitude of the response, a selection of end-points can be made as candidates for modelling. It would be very helpful if submitted studies included an annex with plots (in addition to tables) of observed data points for each end-point, possibly with fitted curves to the plots, to enhance the process of selecting end-points. At a minimum, these should be included for end-points showing evident effects.

After selecting the potentially relevant end-points, one must decide whether each dose–response data set is actually amenable for a dose–response analysis. Generally, it is desirable to have at least three or four different doses (including controls). In addition, the associated effect levels need to be different from each other; it is preferable to have at least three different response levels.

6.1.2 Data types

There are various types of response data, and these can be categorized in various ways. The main distinction relevant for effects is that between quantal and continuous data. Quantal data relate to an effect that is observed or not in each individual subject (laboratory animal or human). Hence, for each dose, the number of subjects responding out of the number of subjects available is

reported. In continuous data, a quantitative measurement is associated with each individual subject. As an intermediate type of data, ordinal data reflect (ordered) severity categories—that is, they are qualitative data but with a rank order (e.g. histopathological severity data). When the categories are non-ordered, they are called categorical data, but these are rare for response data. Finally, count data form another class of data (i.e. discrete data), but in practice they can often be treated as continuous data (see also section 4.3).

Although the type of data is important for statistical reasons (see section 6.2.2 on distributions), the distinction between quantal and continuous data also has a crucial impact on interpretation of results and their ensuing use in risk assessment. In the case of quantal dose–response data, information on the change of incidence with dose is available at one particular degree of effect. For example, the incidence of cleft palate may increase as dose increases, but under the categories "no cleft palate" and "cleft palate", there is no information about the degree of the effect. In ordinal and continuous data, in contrast, information on both the degree of effect and the incidence is available as a function of dose. So, for example, cleft palate might be categorized into an ordinal variable with levels "no clefting", "mild clefting", "moderate clefting", and "severe clefting", or it might be quantified in a continuous variable as, for example, the fraction of closure. The relationship between the average response and dose gives information about how exposure changes the degree of effect. For instance, a plot of (average) red blood cell count may show the decrease in mean red blood cell count (i.e. the degree of the effect) as a function of dose. By also considering the individual data points, information on the incidence can be derived as well. For example, an estimate of the fraction of individuals with red blood cell counts less than some critical value can be derived.

When using animals as a model for human response, the observed dose–response information is assumed to mimic the dose–response in humans to some approximation. It might be argued that this assumption is more plausible for degree of effect than for incidence. The problem is that the observed dose–incidence relationship for animals largely reflects the variation in the animals used, which is highly controlled in a laboratory experiment. Hence, it may not mimic the human variation.

6.2 Models and distributions

6.2.1 Dose–response models

6.2.1.1 Continuous dose–response models

The models listed in Table 4 are some of the forms that may be used to describe the relationship between dose and the magnitude of a response on a continuous scale in an individual. When combined with a statistical distribution (e.g. normal or lognormal), these equations can also be used to describe the relationship between dose and a continuous response in a population, where the continuous model corresponds to the central estimate.

Dose–response data are often adjusted by subtracting the (mean) control value from each individual observation. However, this procedure does not account for the fact that the background response level in the controls is, like the response level in the experimental groups, subject to sampling error. A better approach is to account for the background response in the model with a parameter that needs to be estimated from the data. Among the many ways in which this can be done, the following are three of the simplest:

1. $y = a + f_x(D)$
2. $y = a \times f_x(D)$
3. $y = f_x(a + D)$

where D is dose, a is the background term, and f_x may be any dose–response function. For some assessments, there may be mechanistic information that makes one form preferable to another. For example, the first form is preferable for modelling an influence that produces the effect independently, the second corresponds to the idea of normalizing the response as a fraction of the background response, and the third reflects a contribution from another agent acting by the same mechanism.

Table 4. Continuous dose–response models

Name(s)	Notes	Equation for response	Parameter explanations
Michaelis-Menten law of mass action	A theoretical account of enzyme- or receptor-based activity where the rate of action is a function of the rate of association (ka) and the rate of dissociation (kd).	$= \text{RMax}\frac{[S]}{K_M + [S]}$	RMax is the maximum rate of the reaction, [S] is the substrate concentration, and K_M is the Michaelis-Menten constant, which is equal to ka/kd.
Hill equation log-logistic	A modification of the Michaelis-Menten equation that supposes that the occupation of multiple sites or receptors is required for the production of an effect.	$= \text{RMax}\frac{D^n}{K_D{}^n + D^n}$	RMax is the maximum response, D is the dose, K_D is the reaction constant for the drug–receptor interaction, and n is the number of (hypothetical) binding sites.
First-order exponential	If the interaction between a chemical and a target site is irreversible, then the rate of the reaction is determined by the rate of association (ka) only.	$= \text{RMax}\left(1 - e^{-rD}\right)$	RMax is the maximum response, D is the dose, and r is the exponential rate constant.
Power	Simple exponential model.	$= \beta D^{\alpha}$	D is the dose, α is the shape parameter, and β is the scale parameter.
Linear	Although there is usually no biological theory to suggest it, linear models are often justified by their simplicity; linear models have but a single parameter.	$= mD$	D is the dose and m is the slope.

6.2.1.2 *Quantal dose–response models*

Quantal dose–response functions describe the relationship between dose and the frequency of a particular outcome in a population (see Table 5). For a group of homogeneous or nearly identical individuals, the relationship between dose and frequency can be described with a step function where all subjects either respond or fail to respond at any given dose. However, because variability is ubiquitous in living organisms, quantal dose–response data typically show gradually increasing incidence with dose. One interpretation of this is that individual subjects differ in tolerance to the agent, which can be described by a statistical tolerance distribution. Hence, any cumulative distribution function may be used as a quantal dose–response function. Other models have been derived from statistical assumptions about how the agent might exert its effect in an organism, such as the gamma multi-hit model.

Background response rates should, just as in the case of continuous data, be accounted for by incorporating an additional parameter in the dose–response model. The two simplest ways of doing this are:

1. $y = a + (1 - a)\, f(x)$
2. $y = f(x + a)$

where f(x) is any dose–response function (varying from 0 to 1). As with continuous data, correcting the data for background response prior to the dose–response analysis is statistically unsound. The background response level should be estimated simultaneously with the dose–response model and be treated in the same way as the observed responses in the other dose groups.

6.2.1.3 *Thresholds*

The term "threshold" can be used in three different senses. First, it is used in a scientific sense to indicate a level of exposure at which no effect occurs (e.g. there is a physical stimulus, but there is no response). Second, a threshold may be thought of as a level at which there may or may not be an effect, but it is too small to be observed (e.g. a NOAEL). In this case, it is the perceptual limitation of an observer or analyst, rather than the actual subject of the experiment, that is being described. As a third meaning, a "practical

Table 5. Quantal dose–response models

Name(s)	Theoretical basis	Equation for frequency (F)	Parameter explanations
Step function	No variability.	If $D < T$, $F = 0$ If $D \geq T$, $F = 1$	D is the dose and T is the threshold parameter.
One-hit (single-hit)	Hit theory models employ the use of a rate to describe the interaction between a group of causal agents (e.g. molecules) and a group of targets (e.g. a human population).	$= 1 - e^{-(\alpha+\beta D)}$	D is the dose, e is Euler's constant, α is a location parameter, and β is the slope parameter.
Gamma multi-hit	An expansion of the one-hit model, which is based on the notion that multiple hits or events are required to produce a particular effect.	$= \Gamma(\text{gamma}*D, k)$	Γ() is the incomplete gamma CDF, D is the dose, gamma is a rate parameter, and k is the number of hits required to produce the effect.
Probit normal	A descriptive model based on a normal or Gaussian distribution.	$= \Phi(\alpha + D*\beta)$	Φ() is the normal CDF, D is the dose, α is a location parameter, and β is the slope parameter.
Logistic	The statistical logistic model is also a descriptive tool with no theoretical basis.	$= \frac{1}{1 + e^{-\alpha - D \times \beta}}$	D is the dose, α is a location parameter, and β is the slope parameter.
Weibull	A flexible descriptive model originally developed to describe survival data in demography.	$= e^{-(\alpha + (\beta \times D)^{\gamma})}$	D is the dose, α is the background parameter, β is the slope parameter, and γ is an exponent.

CDF, cumulative distribution function

threshold" is a response where the consequences are determined to be trivial and not worth further consideration.

A threshold in the first sense may be incorporated into a model. The introduction of a threshold parameter truncates the dose–response relation at a threshold dose:

- Below threshold, the effective dose is zero.
- Above threshold, the effective dose is the dose minus threshold.

Threshold terms generally are difficult to estimate accurately and have large confidence limits.

6.2.1.4 Severity (degree of effect)

The severity of toxic responses is rarely used in DRM other than in a qualitative manner (e.g. tumour formation vs reduced fertility). However, one may also consider severity or degree of response in a quantitative way at the level of a single end-point. As noted above, the dose–response of continuous end-points may be directly interpreted as a dose-related change in degree of effect—for example, a per cent decrease in haematocrit (Woutersen et al., 2001) or a per cent change in body weight (see Figure 5, which represents the dose–response relationship between body weight and exposure to the mycotoxin deoxynivalenol) (Pieters et al., 2004). Here, a certain degree of effect (5% reduction in body weight) is chosen for deriving the BMD. The BMDL is then defined as the dose associated with a particular (e.g. 5%) change in degree of effect for that end-point.

An important advantage of defining a BMR in terms of degree of effect based on continuous response data is that values for the BMR that may be considered non-adverse are within or close to the range of observations. Therefore, low-dose extrapolation may not be needed or needed only to a small extent when continuous end-points are considered.

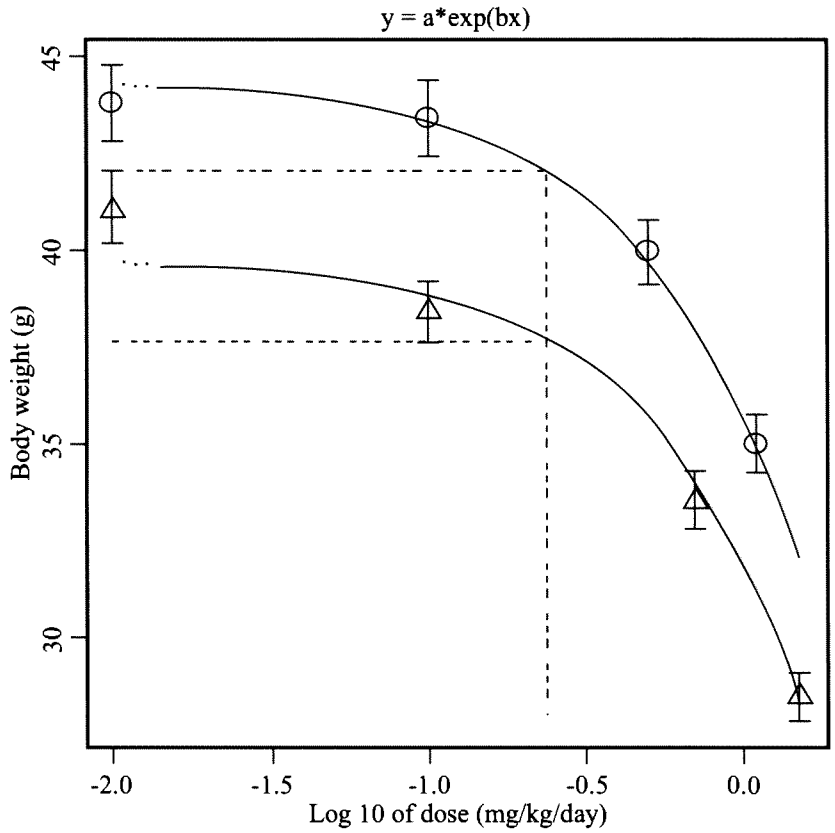


Fig. 5. Dose–response model fitted to male (circles) and female (triangles) body weights plotted against log dose (exposure to the mycotoxin deoxynivalenol). The plotted marks represent the (geometric) means of about 40 mice, with 90% confidence intervals. The BMD associated with a BMR of 5% is estimated at 0.24 mg/kg body weight (log equivalent = −0.62), with a lower confidence bound of 0.22 mg/kg body weight (log equivalent = −0.66). The latter value can be considered as a BMDL for this end-point (adapted from Pieters et al., 2004).

In the case of a histopathological end-point resulting in ordinal data, a dose–response function may be fit using categorical regression, and the BMDL associated with a particular degree of effect (e.g. minimal or mild) may be estimated (e.g. Piersma et al., 2000; Woutersen et al., 2001).

Categorical regression may also be applied at a higher level—that is, in an analysis of multiple studies (Hertzberg & Miller, 1985; Hertzberg, 1991; Hertzberg & Wymer, 1991). In this application of categorical regression, severity categories are defined covering disparate end-points. Most of these applications focus on estimating

the likelihood that a given category of severity may occur at a given dose level.

6.2.1.5 *Modelling with covariates*

In some circumstances, it is desirable to include variables in addition to an exposure variable in dose–response models. For example, in epidemiological studies, it is common to model disease risk in terms of not only exposure, but also age, sex, socioeconomic status, smoking status, and other measurements that may be relevant to the disease state. These other factors may be correlated with exposure status because of the way in which the sample was taken. Then, unless the proper covariates are included in a model for the relationship between exposure and the health end-point, the effect of exposure will be incorrectly estimated. In bioassay studies, in which animals are randomized to treatment groups, this sort of confounding cannot, in principle, occur, but it may be useful to include a covariate such as sex to account for some of the variability in a related measure (see Figure 6).

6.2.1.6 *Biologically based dose–response models*

While biological considerations may motivate the choice of one or several empirical models, the level of biological detail in such models is minimal. Thus, their credibility for interpolating and extrapolating a data set derives mainly from their fit to the data, as evaluated statistically. Another class of model, the biologically based dose–response model, is much more complicated and is explicitly designed to model the biological details that lead from initial exposure to a toxicant to the ultimate pathological outcome. Typically, such a model includes a physiologically based toxicokinetic model to describe the distribution and metabolism of the parent compound and toxic metabolites and other mechanistic, or toxicodynamic, models that link target tissue concentration to the ultimate response. The toxicodynamic part of the models may be relatively simple (e.g. when the outcome is inhibition of acetylcholinesterase in the model for chlorpyrifos; Timchalk et al., 2002) or as complicated as a fully elaborated stochastic model for carcinogenesis (Sherman & Portier, 1998). Such a model is really a quantitative expression of a set of biological hypotheses and, when rigorously tested against critical experiments, becomes a credible tool for extrapolating from experimental results into exposure

realms that are difficult or expensive to reproduce in controlled experiments. Such models are quite expensive to construct both in resources and in time and thus would be expected to be developed fully only for exposures and toxicities of the highest concern.

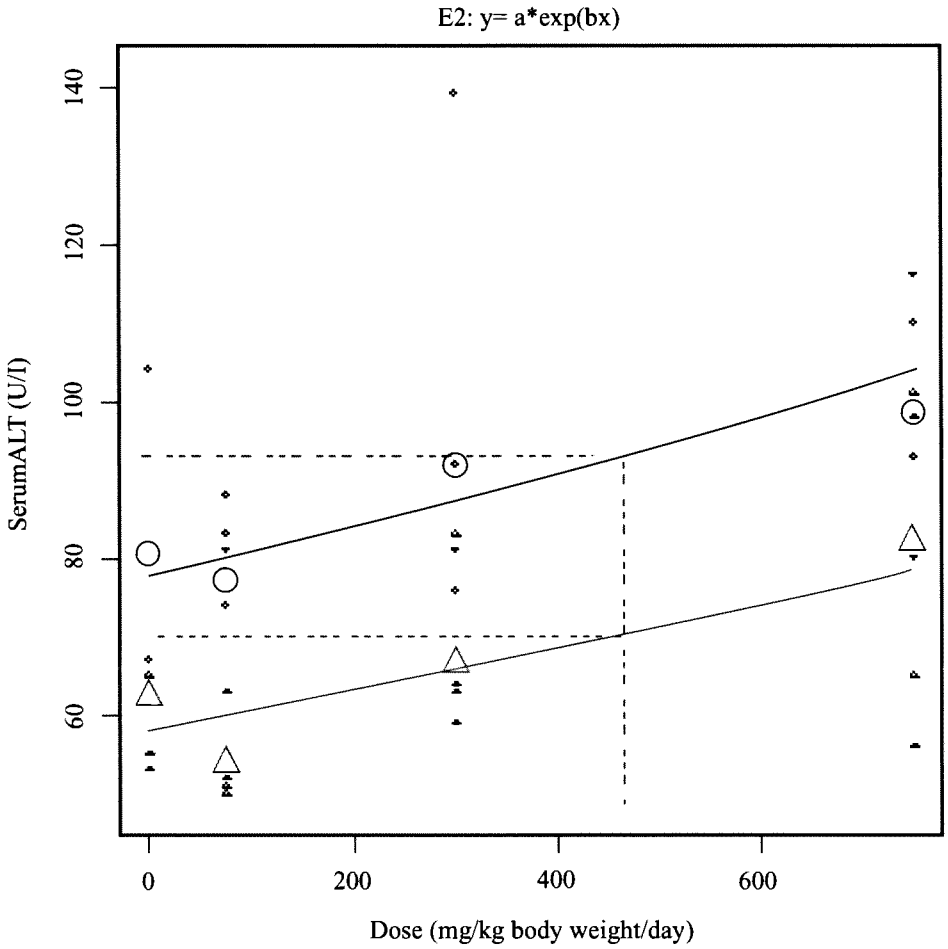


Fig. 6. Dose–response model fit to serum alanine aminotransferase (ALT) levels observed in males (circles) and females (triangles), where sex is treated as a covariate. In this case, the parameter a (background response level) differs between sexes, whereas parameter b and the residual variance (var) for the log(data) do not differ between sexes.

6.2.2 Statistical distributions

6.2.2.1 Continuous distributions

The normal or Gaussian distribution is symmetrical and defined from minus to plus infinity. It has two parameters: the mean and standard deviation, which control the location and scale of the distribution, respectively. Because sums of large numbers of small effects tend to be approximately normally distributed, this distribution is often used to describe variability and the variation of measurement error.

The lognormal distribution has two parameters: the geometric mean and the geometric standard deviation. It can be considered as a derivative of the normal distribution where the logarithms of the observed or predicted values are assumed to be normally distributed. This produces a skewed distribution on the original scale. Another consequence of using a lognormal distribution is that it will not generate negative values, which makes it more suitable for describing positive-only data sets and unsuited for values with negative values. Since many distributions are skewed and contain only positive numbers, the lognormal distribution often provides a good description. In addition, products of a large number of small effects tend to be approximately lognormally distributed. Since effects in biological measures tend to be multiplicative (proportional) rather than additive, the lognormal distribution is generally more suitable for biological measures.

The Weibull distribution is most commonly used to represent the survival or "lifetime" distribution of physical systems/products or biological systems, depending upon the context. In many applications, there is no explicit theoretical reasoning indicating that a Weibull distribution is appropriate or should be used, although the distribution does have some theoretical underpinning within the class of extreme value distributions. From a curve-fitting standpoint, the functional form of the distribution is simply a power transformation of the exponential model, which gives the model more flexibility for describing data. The multi-hit model is a special case of the Weibull model.

A more complete list of continuous distributions is given in Evans et al. (1993).

6.2.2.2 *Discrete distributions*

Discrete distributions describe responses on a finite or infinite scale, preferably count data; a special case is a response with a dichotomous quantal outcome of 0 or 1.

A Bernoulli distribution has an outcome of 1 or 0, corresponding to the occurrence or absence of an event that occurs with frequency f over an infinite sequence of trials. The Bernoulli distribution is then simply "1" with frequency f and "0" with frequency 1 − f. The Bernoulli trial is the basis of the binomial distribution, the definition of which subsumes the former.

The binomial distribution is defined as the distribution of a sum of a given number of Bernoulli trials with outcome of 1 or 0, denoting the occurrence or absence of a specified event, respectively. In toxicological applications, the number of trials is fixed by the experimental design, and the proportion of subjects in which the specified event occurs is the response to be estimated. As a result, the binomial distribution is the distribution typically used to estimate quantal response model parameters.

The Poisson distribution is a one-parameter distribution for a positive and discrete valued response. The domain of the response variable is any positive integer. The distribution was originally derived as a distribution of rare events: specifically, the number (n) of events occurring in a sequence of Bernoulli trials where the number of trials is large and the probability (P) of events per trial is small. Consequently, the Poisson distribution can be used as an approximation of the binomial distribution when n is large and P is small. The Poisson distribution is commonly used in analyses of epidemiological data when the study design involves prospectively following a cohort of subjects over a time period for which the expected incidence of adverse events is small relative to the cohort size.

A more complete list of discrete distributions can be found in Evans et al. (1993).

6.3 Model fitting and estimation of parameters

The general principles of parameter estimation and model fitting have been discussed in chapter 4. Two basic methodologies are available for model fitting: conventional, in which parameters are selected to minimize or maximize an objective function, and Bayesian, in which information in a data set is combined with prior information about model parameters, resulting in a posterior distribution for those parameters that reflects the degree of uncertainty about those parameters. For historical and computational reasons, "user-friendly" software designed for carrying out dose–response analysis and non-linear modelling in general has been restricted to using conventional methodologies, whereas Bayesian methods are implemented in packages that require more extensive programming and substantially greater understanding of the statistical details (for further details on Bayesian approaches, see Hasselblad & Jarabek, 1995; Gelman et al., 2004). While such software requires substantial statistical understanding for successful use of Bayesian methods and is thus beyond the scope of this document, even conventional methods require an understanding of some basic principles before outcomes from applying the software can be properly interpreted. Some general remarks are given below.

6.3.1 Criterion function

The general approach of fitting a model is to find parameter values for the model that optimize the fit of the model to the data. To that end, a criterion function is defined, reflecting the fit of the model. The goal is to find the parameter values that optimize the value of the criterion. For many models typically used, this can be achieved only by an iterative "trial and error" approach (see below).

In many applications, the logarithm of the likelihood function is used as the criterion. The likelihood directly derives from the distribution assumed for the scatter in the data. For quantal data, the binomial likelihood is typically used. For continuous data, the normal likelihood is often used, be it for the observed responses themselves or for the log-transformed responses. Note that maximizing the likelihood function for data that are assumed to be

normally distributed is in fact equivalent to minimizing the sum of squares.

6.3.2 *Search algorithms*

Computer software employs algorithms to find parameter values that optimize the fit of the model to the data, and the user does not need to worry about the exact nature of the calculations. However, some basic understanding of the search process is required in order to interpret the outcomes.

An iterative search algorithm tries to find "better" parameter values in a process by evaluating whether the fit can be improved by changing the parameter values through a trial and error process. More advanced algorithms operate by evaluating the slope of the likelihood at which the fit is improved for one or more parameter value changes (basically using the slope to "climb the likelihood function" as quickly as possible to find the top value). The algorithm can start searching only when the parameters have values to start with. Although the software often gives a reasonable first guess for the starting values, the user may have to change these. It is not unusual (in particular when the information in the data is hardly sufficient to estimate the intended parameters) that the end result depends on the starting values chosen, and the user should be aware of that.

The algorithm keeps on varying the parameter values until criteria for stopping are satisfied. There are two major reasons for the algorithm to stop the searching process:

1. The algorithm has converged (e.g. it has found a clear maximum in the log-likelihood function). In this case, the associated parameter values can be considered as the "best" estimates—e.g. the maximum likelihood estimate—if the likelihood was maximized. However, it can happen that the log-likelihood function has not one but more (local) maxima. This means that one may get other results when running the algorithm again, but with other start values. This can be understood by remembering that the algorithm can only "feel" the slope locally, so that it usually finds the optimum that is closest to the starting point.

2. The algorithm has not converged (i.e. the algorithm was not able to find a clear optimum in the likelihood function, but it stops because the maximum number of iterations [trials] is exceeded). This may occur when the starting values were poorly chosen, such that the associated model would be too far away from the data. Another reason could be that the information in the data is poor relative to the number of parameters to be estimated. For example, a dose–response model with five unknown parameters cannot be estimated with a study with four dose groups. As another example, the variation between the observations within dose groups may be large compared with the overall change in the dose–response. In these cases, the likelihood function may be very flat, and the algorithm cannot find a point where the function changes between increasing and decreasing. The user may recognize such situations by high correlations between parameter estimates (i.e. changing the value of one parameter may be compensated by another), leaving the model prediction practically unchanged.

6.4 Model comparison

The fundamental criterion for judging a model is that the selected model should describe the data, especially in regions of the dose–response where inferences are needed. Most fitting methods provide a global goodness-of-fit measure, usually providing a p-value. These measures quantify the degree to which the model predictions correspond to the data. Small p-values indicate a poor fit to the data. Since it is particularly important that the data be adequately described, it is recommended that a p-value of 0.1 be used to compute the critical value for goodness of fit, instead of the more conventional values of 0.05 or 0.01.

Another way to detect the form of these deviations from fit is with graphical displays. Plots should always supplement goodness-of-fit testing. For continuous data, it would be extremely helpful for plots that include data points to also include a measure of dispersion of those data points. In certain cases, the typical models used in DRM cannot fit the observed data, such as when the data are not monotonic or when the response rises abruptly after some lower doses that give only the background response. In these cases,

adjustments to the data (e.g. a transformation of dose) or the model (e.g. adjustments for unrelated deaths) may be helpful.

When fitting many different models to the same data, they generally will not all result in the same fit, and some care must be taken in choosing which model or models will be considered. In applying a statistical theory to this problem, one of four possible situations may arise:

1. The models form a nested series of models in the same family, in the sense that there is a "full" model, and other "restricted" models are derived from that full model by setting successively more parameters to a fixed value or, conversely, successively incorporating more parameters into the model. Likelihood ratio tests can be used to evaluate whether the improvement in fit afforded by estimating additional parameters is justified. The general form of the test is to calculate $2 \times (LL_{full} - LL_{restricted})$, where LL is log-likelihood, and compare this with a critical value from the chi-squared distribution with $P_{full} - P_{restricted}$ degrees of freedom (where P_x is the number of parameters estimated in model x).

2. The models are from the same family, but do not form a nested series. Some statistics, notably Akaike's information criterion (AIC is $-2LL + 2P$, where LL is the log-likelihood at the maximum likelihood estimates for the parameters, and P is the number of model degrees of freedom) can be used to compare models (Akaike, 1973; Burnham & Anderson, 2002). In this case, the model with the smallest AIC value is selected, although models with similar AIC values (differing by no more than about 4) are probably equivalent (Burnham & Anderson, 2002).

3. The models are not from the same family, but are fit using the same assumptions about the underlying probability distributions (e.g. all using a lognormal likelihood or all using a normal likelihood). In this case, Burnham & Anderson (2002) argue that AIC can still be used to identify the best model, but this appears to be a controversial point. Sand et al. (2002) have shown that it may be difficult to discriminate between the commonly used quantal dose–response models based on the AIC, which may be due to the fact that these models are quite

similar in their structure and include a similar number of parameters. In general, this case is still the subject of statistical research. At present, it will probably be adequate to use AIC to select a model as in the previous case, recognizing that this guidance may change.

4. Models do not use the same probability distribution. In this case, little formal statistical guidance is available. The plausibility of assumptions about the distribution of data needs to be examined by looking at the distribution of individual data. However, continuous data are often aggregated and reported as means and standard deviations, which eliminates the possibility of examining distributional assumptions. In these situations, the best that can be done is to rely on past experience with the end-points being modelled and select a reasonable probability distribution.

6.5 Representing uncertainty

Any parameters or predictions estimated from a given model are only point estimates and, to a larger or smaller extent, uncertain. This uncertainty arises from at least three sources:

1. *Sampling error*—the sampling error arising from inferences about a larger population from a single experiment;
2. *Study error*—the reality that dose–response estimates often differ among experiments with different experimental design, protocol, or uncontrolled circumstances; and
3. *Model error*—the fact that the "true" model is not known, which results in additional uncertainty when interpolating between doses, but even more so when extrapolating outside the dose range containing observations.

These three sources of uncertainty are briefly discussed below.

6.5.1 Sampling error

Uncertainty arising from sampling error with a single experiment is perhaps the easiest to evaluate and report. It may typically be quantified by a standard error or, preferably, by a

confidence interval. Confidence intervals may be calculated in several ways:

- plus or minus twice the parameter's standard error (provided by most dose–response software), which is estimated by the second derivative of the likelihood function (Hessian or information matrix);
- based on the profile of the log-likelihood function, using the chi-square approximation of the log-likelihood;
- bootstrap methods (see, for example, Efron, 1987; Efron & Tibshirani, 1993); and
- Bayesian methods, in particular if one has some preliminary knowledge of the plausible range of the parameter.

Various studies have compared the first three methods and concluded that the first may result in inaccurate intervals, whereas the second and third methods give similar results (see, for example, Moerbeek et al., 2004).

6.5.2 *Study error*

Uncertainty about the true value of a parameter that stems from variability among experiments can often be handled by treating the experiments as comprising an additional level of hierarchy, when the experiments are very similar in design and intent (e.g. same agent on the same end-point in the same strain and species). To characterize uncertainty in a statistical framework, it can be assumed that there is a population of experiments from which the ones at hand were selected (e.g. Davidian & Giltinan, 1995). As a result, the prediction or parameter of interest varies around a mean value among the members of that population of experiments, and an estimate of the mean and the degree of confidence can be derived. It should be noted that, even if data from only one experiment are available for analysis, this source of uncertainty still exists—it may be possible to quantify this uncertainty by analogy.

6.5.3 *Model error*

The third area of uncertainty, model uncertainty, is reflected by the question: to what extent do the data, possibly along with other knowledge about dose–response shape, constrain the set of possible dose–response shapes? A statistical model completely hinges on the

dose–response data, and the quality of the data is in fact the crucial aspect. In the fitting process, a model tries to hit the response at the observed doses. However, when a model is used to make inferences, interpolation between observed doses and extrapolation beyond the non-control doses are possible approaches. Thus, the model must also predict the response in the non-observed dose range. In other words, there are two aspects in evaluating the fitted model: one should assess not only if the model succeeded in describing the observed responses, but also if the model can be trusted to describe the non-observed responses where it is desirable to make inferences. The former aspect focuses on the quality of the model, the latter on the quality of the data. The following discussion elaborates on how to deal with the second of these two aspects (the first was addressed in section 6.4, Model comparison).

There are two ways to evaluate whether the data provide sufficient information to constrain the model and allow inference in some defined range outside of the range of the data. The fitted dose–response model should be visually inspected, to check if the data provide sufficient information to confine the model. Here, the question should be asked: if a curve is drawn through the data points by hand, could that be done in disparate ways? For instance, in the top panel of Figure 7, three curves have been drawn through the data points, each of which might be close to the true dose–response curve in the range between 2 and 5. In the bottom panel, however, it is very difficult to imagine that the true dose–response relationship would be very different from the (single) curve drawn here in the same range.

Another way to deal with this question is by comparing the outcomes from different fitted models. If the data do contain sufficient information to confine the shape of the dose–response relationship, different models fitting the data (nearly) equally well will result in similar fits and similar inferences. As an illustration, Figure 8 shows two different models fit to the same (continuous) data. Owing to the good quality of the data, they result in very similar estimated dose–response relationships. Inferences from dose–response models bear an additional level of uncertainty in proportion to the degree with which those inferences depend on the model used.

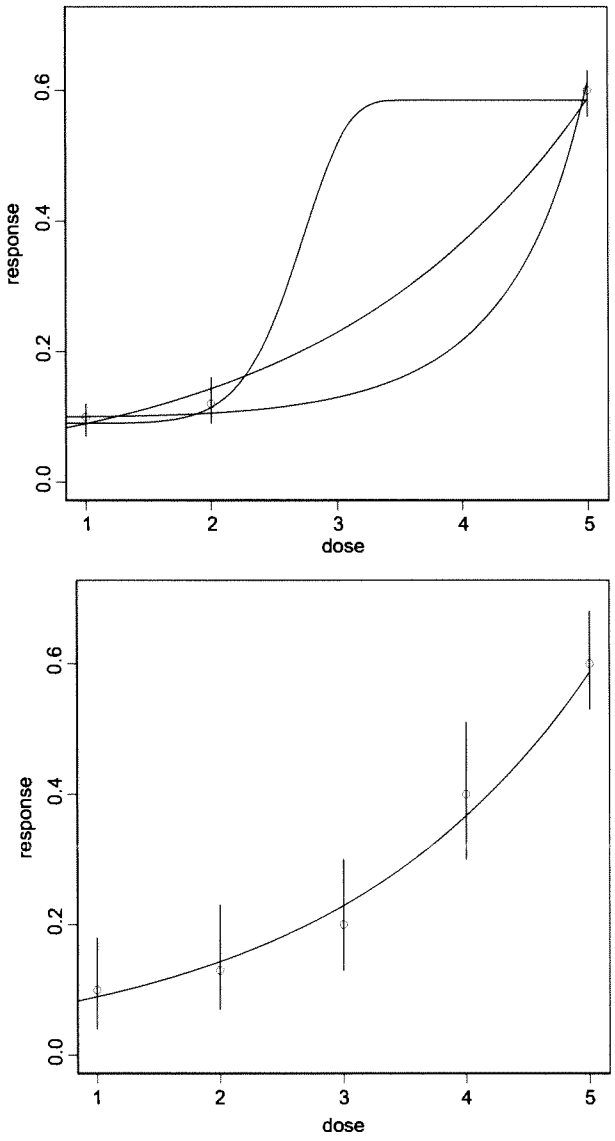


Fig. 7. Two data sets illustrating the idea of model uncertainty. In the top panel, the data (either quantal or continuous) do not contain sufficient information to confine the dose–response relationship in the range between 2 and 5: one may imagine various disparate curves that are all in agreement with the data, and hence they all might represent the true dose–response relationship. In the bottom panel, the data points prohibit the possibility of drawing disparate curves between 2 and 5.

In current practice, there is a tendency to focus only on goodness of fit, and passing a formal goodness-of-fit test is often

regarded as sufficient evidence that the model is acceptable. This is unfortunate, since a goodness-of-fit test tends to be more easily passed for data with few dose groups or when few dose-related responses are noted and therefore non-observed responses are important or dominate. In addition, a goodness-of-fit test assumes that the experiment was carried out perfectly (i.e. perfectly random with respect to all potentially relevant experimental factors and actions). Clearly, this assumption is not realistic.

It is re-emphasized that a dose–response model, as long as it is not based on the mechanism of action of the particular chemical, serves only to smooth the observed dose–response relationship and to provide for a tool to assess confidence intervals. A statistical regression model itself has little, if any, biological meaning, and the choice of the model is to some extent arbitrary. It is the data, much more than the model, that should determine the dose–response relationship and any inferences derived from it. When different models (with similar goodness of fit and equal number of parameters) result in different estimates, this reflects a component of uncertainty that needs to be quantified and communicated with the estimate.

Dose–response models that are based on the mechanism of action of a particular chemical stand in opposition to statistical models as described here. Such mechanistic models contain information gleaned from biological theory and typically multiple experiments and therefore are less sensitive to data gaps (between dose groups). However, they do contain unknown parameters that need to be estimated from the data and thus require the resulting uncertainties to be quantified. Since such models are typically complex and idiosyncratic, little further general advice can be given, and it is suggested that professional statistical advice be sought in such cases.

Model uncertainty is particularly relevant to the issue of low-dose extrapolation. Here, the problem is that there may well be several models that are consistent with the data, as shown in the top half of Figure 9, and so give similar predictions in the range of the data, but whose predictions diverge at the low end of the dose range, as depicted in the lower half of Figure 9. One way to collect and represent model uncertainty in a risk assessment is through the

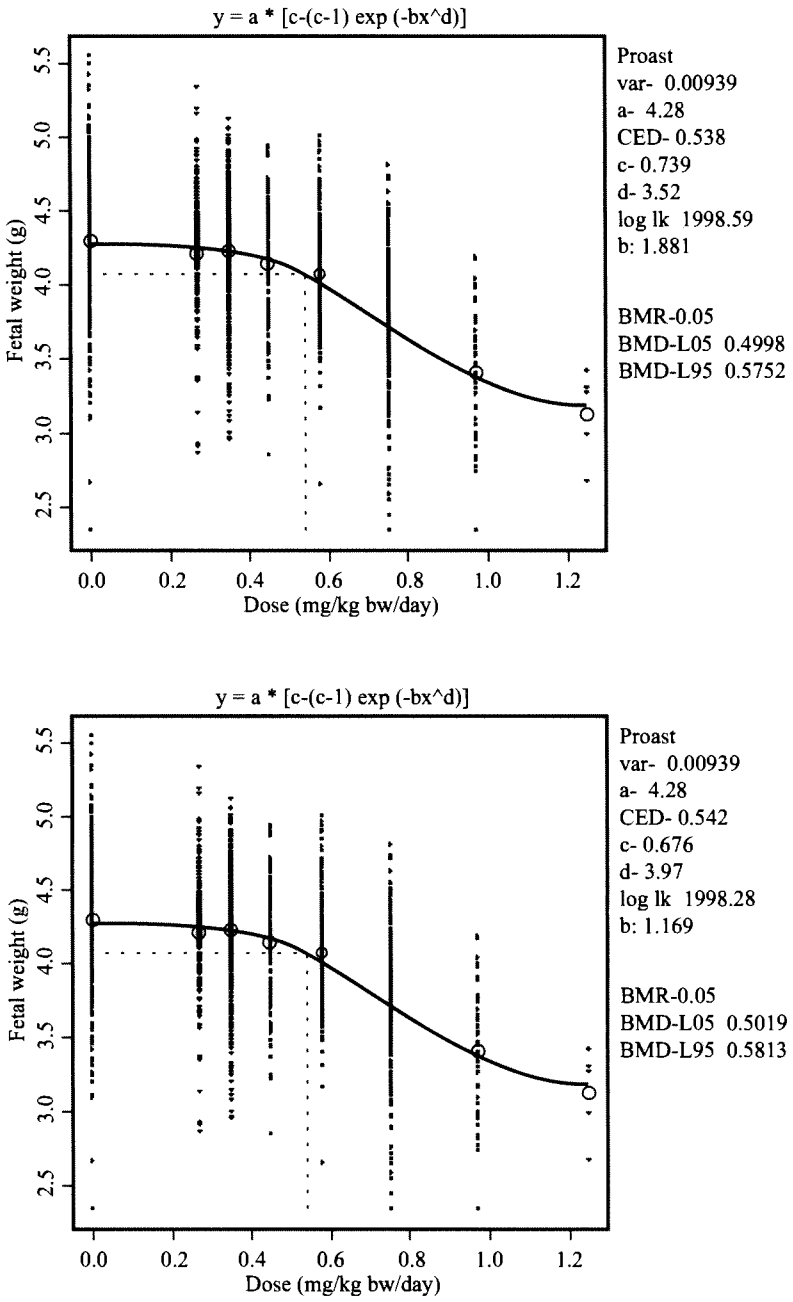


Fig. 8. Two different models (both with four parameters) fitted to the same data set resulting in similar dose–response relationships and similar BMD(L)s. Small circles indicate individual observations, large circles (geometric) group means.

use of probability trees (Rescher, 1969; Hacking, 1976). A probability tree is a logical construct that may be used to represent a set of mutually exclusive propositions. For example, if the three models depicted in the top panel of Figure 8 were equally well supported, then each model would have a probability of 0.33. If one model had a weight that was 6 times greater than the others, then it would have a probability of 0.75, whereas the others would have a probability of 0.125. Note that the probability of a model does not depend only on the strength of evidential support; it also depends on what other models are being considered. A model with little support may have a high probability if all the alternatives under consideration have even less support. Quantitative measures of model preference may be combined to produce an overall rank or to provide a formal measure of the weight of the evidence.

To some extent, all quantitative methods for assigning model probabilities rely on untestable assumptions or elements of judgement. Therefore, the simplest and most straightforward method for assigning probabilities to models is to simply give them all the same weight. This approach is implicit when the predictions from different models are simply listed (e.g. Ghani at al., 2000). Another relatively simple approach is to ask the experts to identify plausible theories and then apply probabilities to them (Evans et al., 1994; IPCS, 2000). These probabilities can then be updated to incorporate additional information in the data by using Bayesian methods. However, there are many formal techniques for assigning weights or probabilities to models (Bozdogan, 1987; Raftery et al., 1997). A semiformal approach may be used in which the same criteria discussed in the section for selecting models (section 6.2.1) may also be used to weight and assign probabilities to each alternative model considered (e.g. Carrington & Bolger, 2000). Model uncertainty may also be integrated with sampling error by using bootstrapping techniques. This involves repeatedly drawing random samples from the data set and refitting each data set with a set of models. The best models from each bootstrap are then retained in a probability tree to represent both parameter and model uncertainty.

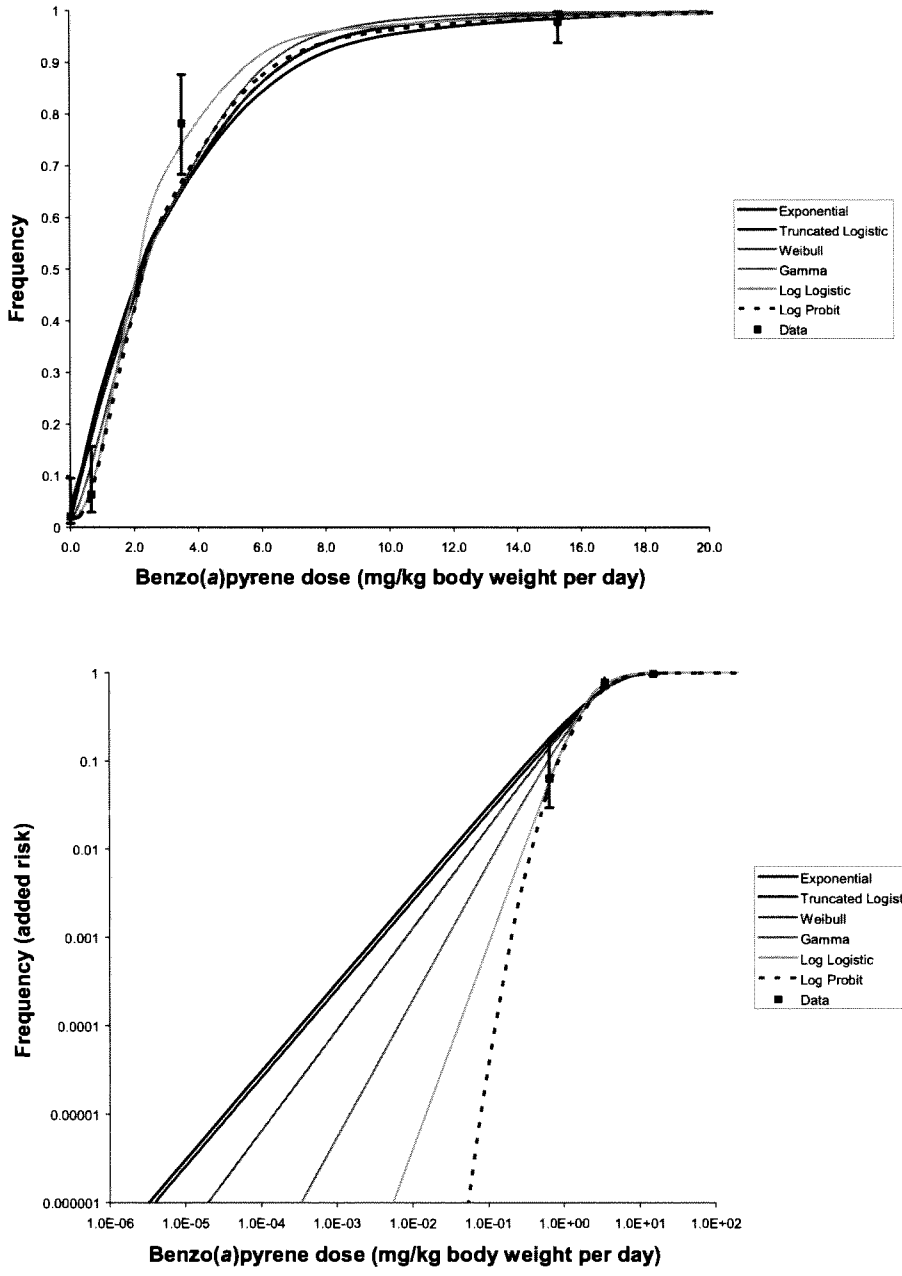


Fig. 9. Model uncertainty in low-dose extrapolation. Different models may all fit the data reasonably well (top), but yield highly divergent response estimates at low doses (bottom). The data and models are taken from Fitzgerald et al. (2004).

Alternatively, some people have addressed this uncertainty by choosing a subset of the models that appear to fit the data well. From these models, those with adequate fits are summarized with a range and associated variance. When choosing a final value for the BMD, these values can be aggregated by taking a mean or geometric mean to provide a central point estimate (National Health and Medical Research Council, 1999) or a value simply chosen through expert judgement (WHO, 2006).

6.6 Benchmark dose and benchmark response selection

One important use of DRM is the calculation of BMDs. A BMD is the dose at which it is inferred that a particular, prespecified level of response would occur. The methodology was introduced in Crump (1984) as an alternative to the use of NOAELs and LOAELs in dose–response assessment for determining quantities such as ADIs. The main advantages of the use of the BMD over NOAELs and LOAELs stems from the more complete use of dose–response data by BMD methods and from the fact that uncertainties about the value of a BMD can be quantified using statistical methodology. The uncertainty of a BMD may be expressed as a confidence interval, in which case the lower end of a one-sided 95% confidence interval is termed the BMDL, or as a full Bayesian posterior distribution.

The BMR is the response for which the BMD is to be calculated. There are both technical and policy aspects associated with selecting the BMR. The technical aspects have to do with just how the BMR is expressed; different types of end-points, such as quantal and continuous, require different treatments. Also, in somewhat more complicated situations, such as when covariates have been used in the modelling, the BMD depends on the BMR and possibly on the values of the covariates. Policy issues have to do with just how high or low down the dose–response curve the BMR should be. This section discusses the technical issues surrounding the choice of BMR and some of the consequences that need to be considered in making the policy decision about where to set the BMR, but it does not directly address the choice of its particular value.

The way in which the BMR is expressed depends upon the kind of response variable being modelled. For end-points with two states (affected/not affected), the BMR is usually expressed in a way that adjusts for background. Two equations are common. One is that of added risk (AR):

$$BMR_{AR} = f(BMD) - f(0)$$

where f_x represents the dose–response function evaluated at dose x. The other, which is probably most widely used, is extra risk (ER):

$$BMR_{ER} = \frac{f(BMD) - f(0)}{1 - f(0)}$$

where added risk is divided by the non-affected fraction of the non-exposed population. The response at the BMD_{ER} is always smaller than the response at the BMD_{AR} for the same numerical value of BMR when there is a background incidence. However, for small to moderate background response, the difference is small.

A third equation, common in epidemiological analyses, but applicable to animal studies as well, is relative risk (RR):

$$BMR_{RR} = f\left(BMD\right) / f\left(0\right)$$

BMRs for continuous end-points can be expressed directly in terms of changes in the mean response level or indirectly in terms of the fraction of experimental animals that exceed (or drop below) some critical level. For example, the BMD for mean adult body weight might be selected to be the dose at which the mean body weight drops below 90% of the body weight in controls or at which brain acetylcholinesterase activity is inhibited by 10% relative to control levels (this is often termed the critical effect size). One might also specify a fixed value or fixed drop in the mean, selecting, for example, the dose at which the mean nerve conduction velocity drops below a fixed rate or a fixed difference from that in unexposed individuals. For end-points that demonstrate a sigmoidal response, as does enzyme induction, it has been suggested (Murrell et al., 1998; see Gaylor & Aylward, 2004, for a contrary argument) that a formulation similar to extra risk be used: for these end-points, the authors suggest that the BMD is best characterized as the dose at

which the response is a specified fraction of the total dynamic range (e.g. the difference between background and maximum possible induction) of the response. The Gaylor & Aylward (2004) approach considers a certain setting within the definition of the response (i.e. a 1% change) and compares the uncertainties in the resulting BMD with the uncertainties in BMDs estimated using the specific setting in the "hybrid" approach. Thus, their conclusion may not hold in general terms (e.g. considering a 5% or 10% change in response relative to the total dynamic range).

Indirect or "hybrid" approaches have been advocated by Crump (2002) and Gaylor and his co-authors (Gaylor & Slikker, 1994; Kodell et al., 1995). In indirect approaches, the relationship between the mean of a continuous variable and dose is modelled, in the same manner as in the direct approaches. Next, a critical value for the continuous variable is determined that is to be considered as adverse, and an extra (or additional) risk BMR is selected for which to calculate a BMD. It is preferable that the critical value be based upon biological considerations, but it may otherwise be a value in the tail of the distribution of values in the control group. As the mean response increases, so will the fraction of subjects that exceed the previously determined critical value. The BMD is the dose at which the fraction exceeding the critical value corresponds to the fraction of affected animals associated with the BMR as defined for quantal data (e.g. BMR_{ER}).

It is possible to approximate the BMD as calculated in the previous paragraph (Crump, 1995) for a critical value corresponding to a "small" (e.g. 0.1–2%) risk in the control group and extra risk in the vicinity of 10%. This BMD corresponds approximately to the dose at which the mean of the response variable differs from the control mean by an amount equal to the standard deviation of the control group. This gives another way to specify a BMR for continuous variables, based on the variability of the animals used in the bioassays.

Both hybrid methods based on variability discussed above require that the variability be true interindividual variability, and not be due to large assay errors. They depend critically on the idea that extreme quantiles of an unexposed population may be thought of as affected in the same sense as an individual with the same value from

an exposed population. Sand et al. (2003) examined how the hybrid approach depends on the estimate of variance. Gaylor & Slikker (2004) discussed how different sources of variability may be separated.

In some cases, the dose is not the only independent variable in a dose–response model. For example, in epidemiological studies, often many covariates that help characterize an individual and that might influence the response variable and be incidentally associated with the exposure variable are included in analyses in an attempt to reduce bias in the estimates of the effects of exposure (see section 6.2.1.4). In developmental bioassays, characteristics of the dam or the litter as a whole (e.g. number of implantation sites) may be used as a covariate in the modelling to help explain some of the additional variation among litters usually seen in such studies. Even adult-only rodent bioassays are usually segregated by sex. Typically, then, the assessor needs to decide for which values of the covariates BMDs need to be calculated. When there are few, discrete covariates, it may make sense to calculate a separate BMD for each set of values (e.g. a BMD for both males and females). When covariates are continuous (or treated as such, as in number of implantation sites), in an animal bioassay, it is usual to pick a typical value in the control group. However, if BMD changes with the value of the continuous variable, a detailed analysis of the dependency should be undertaken (e.g. modelling the BMD as a function of that covariate). If the variable makes sense for extrapolation to the human situation, it might be informative to calculate the BMDs for several values of the covariate, to evaluate the sensitivity of the BMD to the range of covariate values for humans.

6.7 Summary

Data sets for DRM generally need to be selected to reflect the more sensitive end-points available, just to reduce potential workload. Models used depend upon the type of data (continuous, ordered categorical, quantal, or counts) and include a model for dose–response and a model for the variability of the data. Once models are fit to a data set, the degree to which they individually describe the data is evaluated using goodness-of-fit measures; in addition, their ability to describe the data with respect to each other may be compared using measures such as the AIC.

Uncertainty about the inferences that result from such models fall into three main categories: statistical uncertainty of inferences due to variability among responses in experimental subjects, variability among experiments due to unavoidable differences in experimental execution, and uncertainty due to the fact that different models yield different approximations of the true dose–response relationship. Dose–response analysis needs to address all three sources of uncertainty whenever possible.

One particularly important application of DRM is the calculation of BMDs, doses at which it is inferred that a particular level of response would occur. When data are available, BMDs are a better alternative than NOAELs or LOAELs in the calculation of guidance values such as ADIs or TDIs. When extrapolation is necessary, the uncertainty associated with any predictions made should be represented. It is often especially important to include model uncertainty.

7. COMMUNICATING THE RESULTS OF DOSE–RESPONSE MODELLING

7.1 Introduction

Risk communication has been defined as the "interactive exchange of information about (health or environmental) risks among risk assessors, managers, news media, interested groups and the general public" (IPCS, 2004). Risk communication has evolved with the rest of the risk analysis paradigm to embrace the "interactive" nature of the processes. The transition from monologue to reflexive dialogue in risk communication has necessitated awareness that risk perception issues are extremely important. The scientific, political, and social perspectives of bench scientists, risk assessors, risk managers, media, and the public can result in considerable misunderstandings and misinterpretations (Garvin, 2001). The preconception that scientific and technical knowledge and their application in risk analysis are value free and objective has often resulted in the marginalization of insights from other sources.

General public perception, resulting from health-based guidance approaches and terminology such as "ADI", "TDI", and "threshold", is that there is a bright line between "safe" and "unsafe". These approaches are not designed to incorporate risk and benefit dynamics and may not require or even allow an outside audience to become engaged in the decision process. For many considerations of chemical exposures, these dynamics do not have to be dealt with because the outcome of the safety/risk assessment provides a perfectly useful and acceptable answer to the risk manager. However, there are instances where these dynamics will need to be considered and evaluated.

The use of DRM and other probabilistic assessment techniques to quantitatively describe variability and uncertainty brings new challenges in risk communication. Some of these challenges are:

- explaining that a certain percentage of the population is predicted to experience some effect;

- explaining the level of risk in those circumstances where there is no safe level of exposure;
- comparing competing risks or benefits;
- providing a focus on uncertainties that are attendant to the predicted risk; and
- explaining that the risk generally is described at the population level, rather than the individual level, noting that this is also the case for the ADI/TDI approach.

In addition, one of the limitations of the current health-based guidance approach is that it gives no information about risk when the ADI/TDI is exceeded. For example, some subpopulations may exceed the health-based guidance value for dioxins, and the DRM approach may provide additional information that is useful for the risk manager and communicator.

An appreciation of the variability in most populations clearly impacts risk communication. This is particularly true for genotoxic carcinogens and other substances, such as lead, that are unavoidable contaminants and may be toxic at low levels. Using a point estimate to depict an entire population in the context of risk communication can be misleading, because it can suggest that the risks are larger for the entire population than they really are if upper percentile point estimates are used, and it ignores the fact that some portion of the population does have a somewhat higher level of risk. Becoming involved in a public decision requires a transformation from concern for an individual to concern for a population and thinking about variability as an inherent part of the problem rather than just a source of uncertainty.

In risk communication, uncertainties can facilitate dialogue. Uncertainty analysis can inform all the parties of what is known, what is not known, and the weight of evidence for what is only partially understood. However, there are currently no general criteria for the application of weight-of-evidence approaches. An appreciation of uncertainty, including uncertainty about variability, can lead to better consideration of the options for seeking better information, using a value-of-information approach (Thompson, 2002). However, in risk communication, "uncertainty" can be a double-edged sword. When the results of a probabilistic risk assessment are presented, uncertainty is specifically described rather

than managed by the use of a default factor. Since the responsibility for managing the uncertainty is left to the discretion of the management process, communicating the uncertainty to the participants in that process is very important.

The application of DRM and other probabilistic risk assessment techniques has the potential for improving risk analysis and public risk perception. There must be an acknowledgement of the limitations and weaknesses of the technical knowledge in addition to its strengths. There should also be the realization that there may be difficulties with risk comparisons and that social perceptions can drive precautionary considerations. There may not be agreement on how to interpret new information or on the appropriate criteria for making or reversing risk decisions. The critical contribution of probabilistic approaches is that they can improve the processes of risk assessment and risk management and thereby facilitate communication. As a result, participation in the decision process will be broadened.

7.2 Incorporation of the outputs of dose–response modelling into risk assessment

The output of dose–response analysis can be used in various ways, depending on problem formulation and the nature of the effect modelled. An output may be presented in three principal ways as the basis for advice on the possible health implications of human exposure:

1. establishment of a health-based guidance value, such as an ADI or TDI, which is a daily intake over a lifetime that is considered to be without appreciable health risk (this would be analogous to current procedures based on a NOAEL or LOAEL);
2. estimation of the MOE as the ratio between the dose–response output and the estimate of human exposure; and
3. quantitative estimation of the magnitude of the risk at the level of human exposure, derived from the modelled dose–response relationship.

The discussion below assumes that the dose used in the dose–response model was the external dose expressed in milligrams per kilogram body weight. The use of internal or target organ dose estimated by a physiologically based toxicokinetic model would

reduce the uncertainties of interspecies extrapolation, because kinetics are a major source of species differences, such that a reduced uncertainty factor would be required.

7.3 Derivation of health-based guidance values

Traditionally, a health-based guidance value for threshold effects has been derived from a NOAEL or LOAEL divided by an appropriate composite uncertainty factor, either default values or CSAFs (IPCS, 2005), on the assumption that the NOAEL represents an intake close to the threshold for the adverse effect. In practice, the limit of detection for the incidence of adverse effects in animal experiments depends on the sample size, and more than 100 animals may be needed to achieve confidence intervals in the range of ±5%.

Many studies have shown that the BMDL for a 5% response is similar to the experimental NOAEL (Allen et al., 1994). Fowles et al. (1999) came to a somewhat different conclusion. They examined acute inhalation lethality data and compared NOAELs with BMDs corresponding to 1%, 5%, and 10% response incidences. Similarly to the "quantal" parts of the results of the Allen et al. (1994) studies, BMDLs based on 10% incidence corresponded approximately to NOAELs. However, because the dose–response for lethality is so steep, BMDLs for 5% and 1% incidences were very close to those for 10% incidence. As a result, the BMDLs for a 1% incidence were on average only about 1.6 or 3.6 times smaller than a NOAEL, depending on whether a log-probit or Weibull model was used. This possibly can be explained by the smaller sample sizes in these experiments, not by the difference in end-points.

Given the uncertainty in the relationship of the NOAEL and the threshold of the adverse effect, finding a BMR such that the resulting BMD and BMDL correspond numerically (on average) to a NOAEL may not be relevant and is certainly not necessary for the application of BMD approaches. Also, the use of the BMDL to set a health-based guidance value would need to take into account the same uncertainties as when a NOAEL is used as the basis for establishing an ADI/TDI.

7.4 Estimation of the margin of exposure

The normal default uncertainty factor of 100 has a long history of use for threshold effects and can be regarded as the margin between two points—the NOAEL or BMDL from the experimental data and a level of human intake/exposure that would be without appreciable health risk. Because this is based on a NOAEL or BMDL, the ratio is equivalent to a margin of safety, and there would be negligible risk providing that the intake was at or less than the ADI/TDI.

In the case of adverse effects that are considered not to show a biological threshold in their dose–response, the BMDL could not be considered to represent an intake close to a threshold, but is simply the confidence interval on the BMD. Consequently, the margin between the BMDL and the estimated human intake/exposure would not be a margin or safety and is therefore termed an MOE. The MOE is calculated as the ratio between two experimental estimates, the BMDL and the predicted or estimated human intake/exposure. Calculation of an MOE does not require extrapolation of the data beyond the range of observations (IPCS, 1999; Edler et al., 2002).

Uncertainties related to interspecies differences and human variability, which are the basis for the usual 100-fold uncertainty factor used in the derivation of an ADI/TDI, would be equally applicable to an MOE based on animal data, but there would be additional uncertainties related to the nature of the dose–response relationship below the experimental/observable range, the impact of genetic polymorphisms in the processes critical to the production of a mutated cell, and the subsequent clonal expansion and progression into a cancer. Consequently, an MOE of 100 would be inadequate to reflect the fact that the starting point (the BMDL) cannot be regarded as a threshold or the additional uncertainties related to the mode of action.

Application of linear low-dose extrapolation using the BMDL for a 5% response (see below) to estimate a one in a million lifetime risk is equivalent to an MOE of 50 000.

7.5 Quantitative estimations of the magnitude of the risk at levels of human exposure

The results of a dose–response model can be used to estimate the possible risks at intakes/exposures above a health-based guidance value such as the ADI and at very low levels of human exposure or to estimate intakes/exposures associated with predefined levels of risk, such as a one in a million lifetime risk of cancer.

Estimation of risks of intakes/exposures above a health-based guidance value, derived by the application of uncertainty factors to a BMDL from a study in either animals or humans, would need to use the slope characteristics in the dose–response model. For example, if an intake is of concern because it is above the health-based guidance value, then the extent of any risk could be estimated by reference back to the modelled animal dose–response relationship. Traditionally, an estimate of the possible risk has not been made, and intakes above the ADI/TDI have been considered to have eroded the uncertainty factor. However, if one assumes that the dose–response relationship in humans has a similar shape to that in the animal study, the ADI is set with default uncertainty factors that will obscure any quantitative estimates of the risk above the ADI (the risk at the ADI is assumed to be negligible). More accurate estimates of differences in sensitivity between humans and animals would be required for such calculations.

Estimation of risks at very low levels of human exposure or of exposures associated with responses below the BMR requires extrapolation outside the data used to generate the dose–response model. Extrapolation outside the observed range—for example, from an incidence of about 5% to one in a million—will require extrapolation over many orders of magnitude. Low-dose extrapolation may be undertaken using the dose–response relationship defined by the model that was fitted to the experimental data or by application of a standardized mathematical approach, such as linear extrapolation, to the starting point. An advantage of using a model is that the risk estimates can be compared across different compounds. The major uncertainty associated with such estimates is the biological relevance of the model in the region of extrapolation.

7.6 Presentation of results

In a scientific or logical sense, the risk assessment is finished when the conclusions have been drawn. However, when the conclusions are simulation results, some distillation or condensation is often necessary in order to make the results comprehensible. Since there is always some danger that crucial information may be lost, care must be exercised to ensure that the summary process does not omit information that is important for the decision.

7.6.1 Tables

Precise communication of quantitative information requires numbers. More numbers will portray more information than fewer numbers, but will take longer to assimilate. Tables 6–10 give examples of the range of options, from high to low complexity, that may be considered, all taken from the same simulation results for exposure. It is recommended that, in case of effects of concern or a single effect found in several studies, all quantitative results be summarized in a table. The risk assessor should sort out the most relevant results and present the data to the risk manager in a clear and understandable way.

7.6.2 Graphs

Although they may allow quick comparison, tables inherently compare one value at a time. Graphing or visualization is in some ways a better means of digesting the entire distribution. A one-dimensional simulation will produce a frequency distribution (when simulating variability) or a likelihood distribution (when representing uncertainty). There are two ways of plotting frequency or likelihood curves (see Figure 10). The first is to plot density against value, which emphasizes the values that are the most common or likely. The second is to plot cumulative percentiles against value, which allows the percentile corresponding to a particular value to be read from the plot. A graphical presentation of the dose modelling in relation to the experimental data may also be helpful in deciding which dose descriptor should be used for lifetime risk.

Table 6. Population percentiles from a two-dimensional simulation

		Uncertainty												
		Average	SD	Minimum	P1	P5	P10	P25	Median	P75	P90	P95	P99	Maximum
Variability	Average	0.457	0.063	0.234	0.236	0.366	0.403	0.456	0.462	0.497	0.502	0.503	0.510	0.874
	Minimum	0.047	0.061	0.000	0.000	0.000	0.000	0.016	0.055	0.076	0.076	0.076	0.076	0.874
	P1	0.094	0.065	0.000	0.000	0.000	0.007	0.072	0.101	0.129	0.129	0.130	0.131	0.874
	P5	0.146	0.068	0.000	0.000	0.000	0.069	0.144	0.148	0.178	0.179	0.180	0.180	0.874
	P10	0.188	0.074	0.000	0.000	0.000	0.116	0.187	0.205	0.216	0.216	0.217	0.218	0.874
	P25	0.274	0.083	0.000	0.000	0.119	0.207	0.287	0.291	0.317	0.320	0.320	0.327	0.874
	Median	0.401	0.105	0.000	0.000	0.267	0.352	0.399	0.404	0.471	0.476	0.476	0.484	0.874
	P75	0.586	0.064	0.388	0.394	0.519	0.531	0.561	0.568	0.651	0.657	0.657	0.667	0.874
	P90	0.808	0.030	0.760	0.762	0.774	0.776	0.784	0.790	0.843	0.847	0.848	0.858	0.874
	P95	0.949	0.024	0.874	0.923	0.930	0.931	0.941	0.944	0.953	0.963	1.014	1.056	1.058
	P99	1.247	0.086	0.874	1.138	1.142	1.147	1.149	1.287	1.296	1.321	1.403	1.462	1.473
	Maximum	2.192	0.483	0.875	1.573	1.579	1.584	1.599	2.559	2.592	2.608	2.619	2.663	2.670

Pxx = xxth percentile; SD = standard deviation.

Table 7. Population percentiles with confidence intervals

Percentile	Average (confidence interval)
Average	0.457 (0.366, 0.503)
Minimum	0.047 (0.000, 0.076)
1st percentile	0.094 (0.000, 0.130)
5th percentile	0.146 (0.000, 0.180)
10th percentile	0.188 (0.000, 0.217)
25th percentile	0.274 (0.119, 0.320)
Median	0.401 (0.267, 0.476)
75th percentile	0.586 (0.519, 0.657)
90th percentile	0.808 (0.774, 0.848)
95th percentile	0.949 (0.930, 1.014)
99th percentile	1.247 (1.142, 1.403)
Maximum	2.192 (1.579, 2.619)

Table 8. Population percentiles with standard deviations

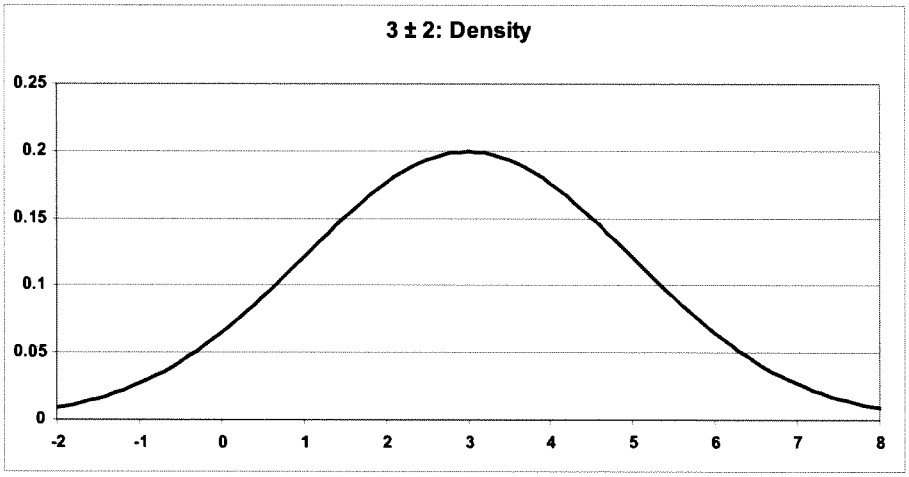
Percentile	Average ± standard deviation
Average	0.457 ± 0.063
Minimum	0.047 ± 0.061
1st percentile	0.094 ± 0.065
5th percentile	0.146 ± 0.068
10th percentile	0.188 ± 0.074
25th percentile	0.274 ± 0.083
Median	0.401 ± 0.105
75th percentile	0.586 ± 0.064
90th percentile	0.808 ± 0.030
95th percentile	0.949 ± 0.024
99th percentile	1.247 ± 0.086
Maximum	2.192 ± 0.483

Table 9. Selected population percentiles with confidence intervals

Percentile	Average (confidence interval)
Average	0.457 (0.366, 0.503)
Median	0.401 (0.267, 0.476)
90th percentile	0.808 (0.774, 0.848)
95th percentile	0.949 (0.930, 1.014)
99th percentile	1.247 (1.142, 1.403)

Table 10. Population mean with uncertainty estimate

	Average ± standard deviation
Average	0.457 ± 0.063



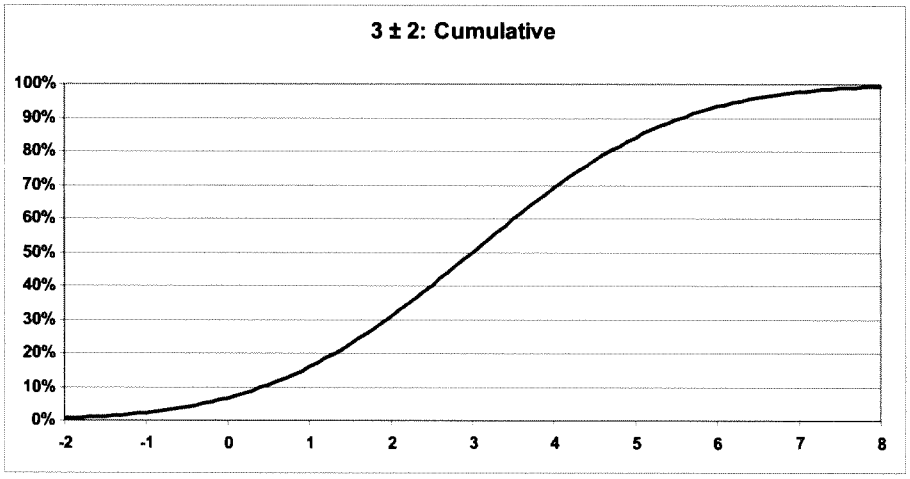
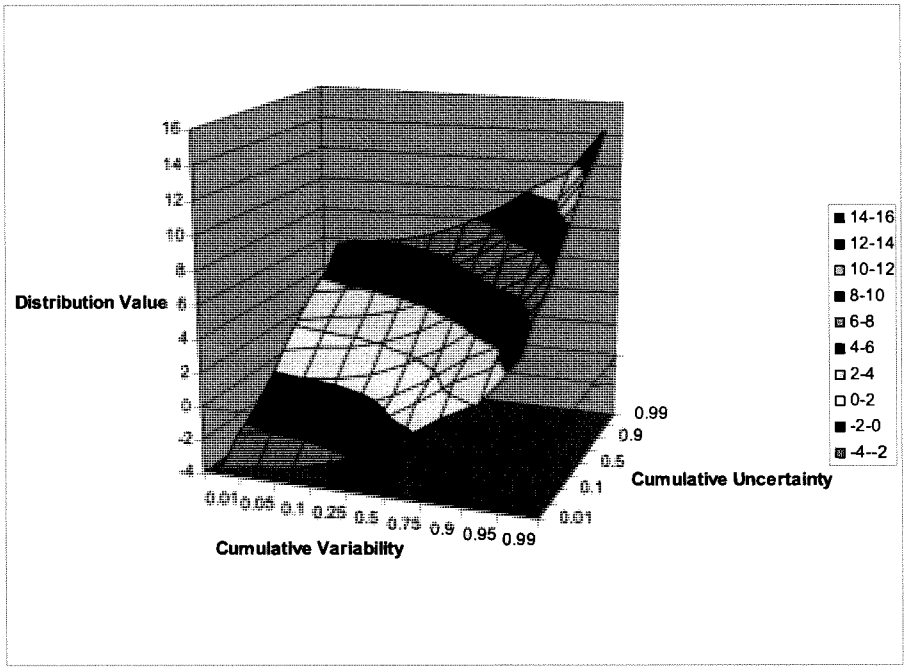


Fig. 10. Plotting frequency distributions.

Two-dimensional results are more difficult to display. Two strategies for adding an extra dimension are illustrated in Figure 11. The first uses three-dimensional perspective to portray the third dimension. The second uses shading, where darker hues are used to represent either higher density or more central values. This is particularly of use for displaying uncertainty, as the less well defined (more uncertain) parts of a curve appear fuzzy.



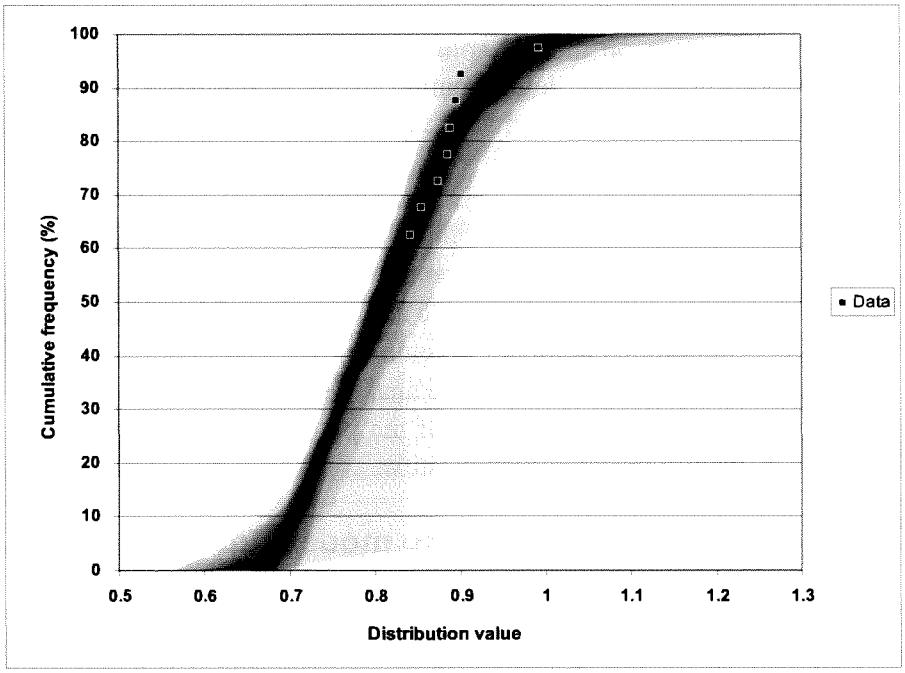


Fig. 11. Plotting results of three-dimensional simulations.

7.7 Risk assessment context and questions

The output of the DRM should be directed towards addressing specific questions about the likelihood of adverse health effects in response to exposure to chemicals. This would build on conventional risk assessment procedures that have been accepted internationally as the indicator for determining acceptable levels of exposure. These rely on the identification of a NOAEL/no-observed-effect level (NOEL) for a critical end-point in the effect data and incorporation of uncertainty factors to allow for interspecies and interindividual variation.

DRM offers the potential to provide additional information for the risk manager, specifically a more scientifically robust method for determining the health-based guidance values (e.g. ADI) using the BMD and better information on the likelihood of effects at low doses that are below the levels observed in biological systems. The mathematical models will also provide estimates of the statistical uncertainty surrounding estimates of likely effect.

Whether traditional safety-based assessments or DRM assessments are carried out, the risk manager will still require information on the toxicology of the adverse health effect and the robustness of the determination of the health-based guidance value to help inform the management options. This may include the following:

- a discussion of the strength and weight of evidence;
- uncertainties and gaps in the data;
- information on the nature and severity of the (critical) effect;
- limitations in the interpretation;
- assumptions made in the analysis; and
- qualitative assessment of the potential effects of exceeding the health-based guidance value.

7.8 Synopsis of approach to modelling

DRM involves six basic steps: data selection, model selection, statistical linkage, parameter estimation, implementation, and evaluation (see chapter 4, Table 1). In undertaking a DRM exercise,

two factors that will impact the types of outputs and that may be of importance to the risk manager are briefly described below.

7.8.1 Data sets

Traditional safety assessments focus primarily on a single critical end-point, whereas DRM gives the potential for separating out multiple end-points. Modelling outcomes may be based on data from single or multiple experiments. In the latter situation, meta-analysis may integrate the results of several independent studies that are considered to be "combinable".

The risk manager could see four types of data from the modelling evaluations: namely, quantal, count, continuous, and ordinal categorical data. The risk manager will need to understand what data sets were modelled and, if quantitative information from more than one data set is presented, will need guidance on the rationale for forwarding the additional data set information and for synthesizing this additional information. This guidance may include information about the consistency (or inconsistency) of the quantitative response across the end-points. Such information could be used by the risk manager to strengthen (or weaken) his or her confidence in the quantitative evaluation of the potential for health impacts.

If DRM information is available from human epidemiological evaluation, then an understanding of both the strengths as well as the possible limitations (often in the quantitative exposure information) of the data set may also temper or strengthen the qualitative or quantitative assessment from the animal studies.

7.8.2 Uncertainty

DRM should capture the relative uncertainties in the estimates of risk. This information will allow the generation of confidence limits on health-based guidance values. However, such confidence limits will still capture only one part of the uncertainty inherent in these estimates. The risk manager will need to know what uncertainty is accounted for in the information provided, and the risk assessment information will need to clearly indicate what uncertainty is not accounted for in a quantitative assessment.

One approach that has been used to capture variability in population response is calculation of population percentiles. Availability of dose–response functions when linked with population-based exposure assessments has allowed risk managers to calculate percentiles of populations above target exposure or intake levels. Likewise, dose–response functions have also been utilized to calculate percentiles of the population above target risk levels.

One of the advantages of DRM is that the confidence limit around the BMD can be calculated. From the conservative point of view, the lower limit of the dose is most important. However, this is not the same as to say that the confidence limit of the health-based guidance values can be calculated, as the uncertainty factors will obscure such estimates.

7.9 Explaining/interpreting the output of the dose–response analysis

Advice to the risk manager should describe the uncertainties inherent in such an approach to the use of dose–response data, such as uncertainties in the slope estimate in animals, the relevance of this slope to humans (such an approach is more appropriate if the response is a continuous variable, rather than quantal), and the appropriateness of the uncertainty factor applied to allow for species differences and human variability.

7.9.1 Outputs in the observable biological range

The output of the analysis takes the form of a numerical quantity—at present, commonly a TDI or ADI derived from a NOAEL, which is a single point in the dose–response relationship. The dose–response analysis uses more of the available information by fitting a mathematical model to all the data in the observable biological range and then determining the dose associated with a specified response level. A statistical lower bound (e.g. the 95% lower bound on the dose) is often used to account for statistical uncertainties (a BMDL) and for the level of health protection required by the risk manager. As with the NOAEL, the BMDL can be used as the starting point for deriving a health-based guidance value and/or MOE. However, unlike the NOAEL, the BMD

approach uses the whole range of experimental dose–response data, and therefore it is not limited by the doses selected by the investigators.

7.9.1.1 Health-based guidance values

On the basis of current practice, it appears that the BMD approach leads to doses that are usually quite similar to NOAELs for the studies in question (see section 7.3). In the same way as for the derivation of the ADI/TDI, uncertainty factors, for example 100, are applied to the BMDL to obtain the health-based guidance value. However, the confidence intervals that are possible in the case of the BMD-derived health-based guidance value provide the risk manager with an increased understanding of the uncertainty associated with the risk assessment. This allows a more informed decision to be made when choosing among risk management options.

7.9.1.2 Margin of exposure

An MOE is determined by comparing the point of departure (the BMDL) with the actual or estimated human exposure. The MOE is used when limited toxicological or human data exist but the hazard identification and characterization data are insufficient to set a health-based guidance value. Alternatively, the MOE approach is used when it is inappropriate to derive a health-based guidance value owing to the nature of the effect, such as for substances that are genotoxic and carcinogenic.

The acceptability of an MOE depends on its magnitude and is ultimately a risk management decision. To aid that decision, the risk assessor should provide information on the nature of the toxicity involved and nature and magnitude of the uncertainties, from both the toxicological and exposure perspectives. Although the risk assessor should not provide an assessment of the acceptability of the MOE, guidance on its adequacy, taking into account the severity/nature of the toxicity, uncertainties, and variability, should be given—for example, in terms of high, medium, or low concern. The use of all the data by the dose–response analysis enables the uncertainties to be better defined. The MOE can also be used by the risk manager for priority setting.

There is no internationally accepted value for an MOE for a genotoxic and carcinogenic compound such that the exposure would not be a significant health risk. However, several institutions and countries have used the MOE approach, and their conclusions provide examples of MOE values that have been considered acceptable:

- The National Health and Medical Research Council in Australia concluded that a guideline dose for carcinogens present in soil could be calculated by application of uncertainty factors up to 50 000 to the BMD (not BMDL). The factor applied in any particular case would depend on the nature of the effects (National Health and Medical Research Council, 1999).

- The reciprocal of the MOE, the exposure potency index (EPI), has been used by Health Canada for genotoxic and carcinogenic compounds in their *Human Health Risk Assessment for Priority Substances* under the Canadian Environmental Protection Act (Health Canada, 1994). MOE values of <5000, 5000–500 000, and >500 000 indicate high, medium, and low priority, respectively.

- The Committee on Carcinogenicity in the United Kingdom considered derivation of the minimal risk level for a genotoxic and carcinogen compound. One proposal was that an adequate MOE for carcinogenicity might be 10 000 (Gaylor et al., 1999; Gold et al., 2003). A particular carcinogenic impurity posed a negligible carcinogenic risk if an uncertainty factor of 10 000 was applied to the estimated 5% BMD (BMD_5) (Committee on Carcinogenicity, 2003). The MOE for average intakes for acrylamide in men in Norway has been estimated using the T_{25} value[1] and the LED_{10} (the lower bound on the effective dose for a 10% increase in risk) (approximately equivalent to $BMDL_{10}$) methods. These approaches result in MOE values of 1306 and 1225 for T_{25} and LED_{10}, respectively.

[1] The tumorigenic descriptor T_{25} is the chronic daily dose that will give 25% of the animals tumours above background at a specific tissue site. The T_{25} is determined by linear interpolation from the lowest dose giving a statistically significant increase in tumours (Dybing et al., 1997).

- The 64th (WHO, 2006) and 67th (WHO, 2007a) meetings of JECFA used MOE approaches for the evaluation of several substances that were genotoxic and carcinogenic. The 64th JECFA developed general considerations for the formulation of advice on compounds that are both genotoxic and carcinogenic. This meeting established MOEs for acrylamide, ethyl carbamate, polybrominated diphenyl ethers, and polycyclic aromatic hydrocarbons. The 67th JECFA established an MOE for 1,3-dichloro-2-propanol.

- A joint European Food Safety Authority/WHO conference on the risk assessment of substances that are both genotoxic and carcinogenic (Barlow et al., 2006) compared the approaches that are currently used. "This conference concluded that the MOE approach was a useful and pragmatic option...."

- O'Brien et al. (2006) presented a critical appraisal of the approaches to the risk assessment of genotoxic carcinogens in food and concluded that "Overall, MOE is the most appropriate default approach because it combines information on potency and exposure, without the generation of numerical risk estimates of unknown reliability." They presented case-studies on the calculation of MOEs for acrylamide, aflatoxin B_1, benzo(*a*)pyrene, dimethylnitrosamine, ethyl carbamate, and 2-amino-1-methyl-6-phenylimidazo(4,5*b*)pyridine.

7.9.2 *Outputs outside the observable biological range*

DRM evaluations can produce information in several formats, including dose–response functions that allow, along with estimates of exposure, the prediction of risks at specified exposure levels and functions that allow the estimation of exposure levels resulting in specified risks. In addition, DRM exercises can provide uncertainty analyses. The availability of such outputs from DRM exercises can provide both opportunities for additional assessment as well as challenges in interpretation for the risk manager.

Three different methods have been used or proposed for quantitative risk assessment by regulatory authorities in the United States and Europe for non-threshold (genotoxic) carcinogens. In the area of food safety, the United States Food and Drug Administration has used a simple, direct method for low-dose

cancer risk assessment. A point on the dose–response curve is chosen below which the data no longer appear to be reliable (e.g. 1–10% tumour incidence), and a straight line is drawn from the upper confidence limit on risk at that point to the origin (Gaylor et al., 1997). The linearized multistage model was previously extensively used by the United States Environmental Protection Agency (USEPA, 1986). The LED_{10} method was later proposed by the USEPA (1996), and the T_{25} (Dybing et al., 1997; Sanner et al., 2001) method has been used in Europe (European Commission, 1999; SCCNFP, 2003). Lifetime cancer hazards may be estimated by linear extrapolation using LED_{10} and T_{25} as starting points. The results obtained with these extrapolation methods are in most cases nearly indistinguishable (Sanner et al., 2001). A measure for an assessment of concern may be arrived at by comparing the calculated risks for some specific scenario of human exposure to such substances, with some default policy-determined risk level.

7.9.2.1 Prediction of risks at specified exposure levels

One type of output from DRM is the prediction of risks at specified exposure levels. This output can take the generic form of predicting "X number of health-impacted individuals at exposure Y". Examples of such estimates have been used to predict the number of excess lung cancer deaths due to smoking two packs of cigarettes per day, the number of excess skin cancers from arsenic-contaminated water, and the number of excess mortality cases due to air pollution. In the optimal case, such estimates are supported by parallel assessments that describe the uncertainty in such estimates, by providing additional information on the range of estimates, rather than a single value. The risk manager can then make such statements as "Up to X individuals may be impacted by exposure Y". This same information can allow the risk manager to see how low the estimates of the health impact may be; when confidence limits are included in such estimates, many uncertain health impacts can be shown to include the potential for no health impacts. Assumptions inherent in such estimates that can impact interpretation by the risk manager include choice of models, choice of end-points, and limitations in initial data sets that were extrapolated.

One use of such information has been to evaluate the effect of different maximum limits for a chemical on risks. This type of consideration was included when JECFA evaluated aflatoxin B_1 and the impact of different maximum limits on risk (WHO, 1999, 2007b). Similar assessments have also been performed for lead and fumonisins B_1 and B_2 (Carrington et al., 1996; Humphreys et al., 2001). For example, the health impacts of current particulate standards (WHO, 2000, 2003) have been estimated. Availability of such estimates can provide additional information for risk managers to conduct cost–benefit analyses, risk–benefit assessments, and evaluations of public health interventions.

7.9.2.2 *Prediction of exposure levels producing specified risk levels*

Another type of output from DRM is risk level estimates. In these estimates, a specific level of risk is evaluated and the amount of exposure that would be estimated to result in that risk is determined. For example, a common level of risk related to carcinogen exposures that has been evaluated in the United States has been 10^{-6} over a lifetime. Estimates of exposure that would result in that level of risk have been determined, and such estimates have been made for approximately 100 environmental pollutants (http://www.epa.gov/iris). For the risk manager, availability of such estimates can allow for development of risk-based consistency in proposed regulatory actions.

7.9.2.3 *Uncertainty analyses*

A third type of output from DRM is that linked with uncertainty analysis. One example of such approaches is when the DRM output is linked with distributions of population effects with confidence intervals. The result from such analysis is a distribution of potential population risks. For example, in Figure 12, the outputs for three models and two data sets were used to generate a set of 3000 different model parameters (two data sets, three models, 500 bootstraps).

One approach that has been used to extrapolate dose–response models beyond bioassay data has focused on the use of biomarker data to extend the dose–response curve 1–2 orders of magnitude closer to environmentally relevant exposures. Such approaches can be facilitated when DRM data are available.

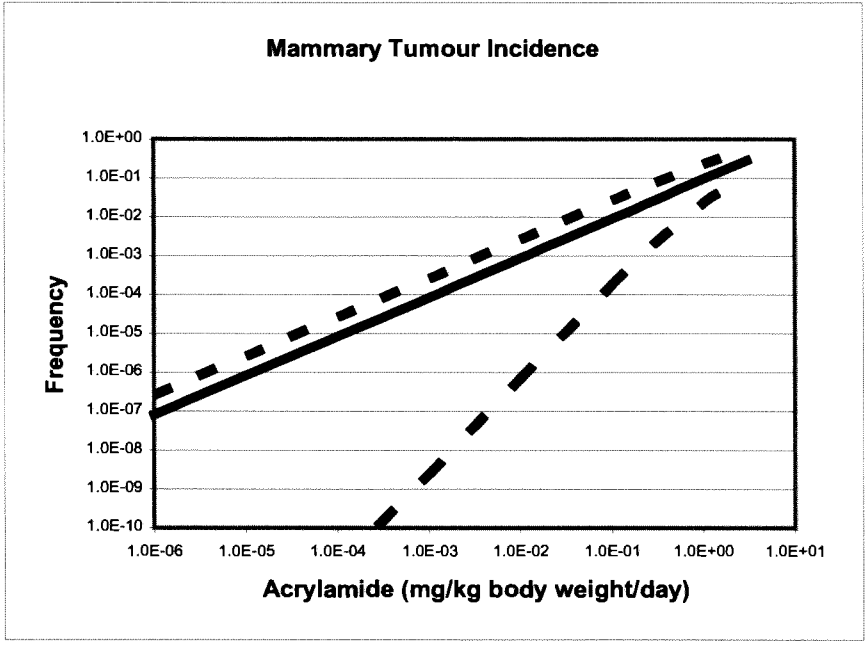


Fig. 12. Integrated uncertainty analysis for mammary tumours. The dark line is the central (median) estimate, and the dotted lines are the 5% and 95% confidence limits.

All these modelling approaches exhibit similar limitations and difficulties. A benefit is that DRM allows for the transfer of more quantitative toxicological data into risk manager assessment methods such as cost–benefit and risk–benefit analyses. The limitation is the question of whether the model outputs are accurate and representative of public health impacts.

7.10 Issues for risk managers

7.10.1 Risk assessment issues

7.10.1.1 Population versus individual effects

The potential health effect at the population level can be informed by DRM. However, as the behaviour, environment, or biological characteristics may vary among individuals, a dose–response model may need to describe or model these characteristics to produce a prediction of adverse health effects in the population.

The output of the dose–response model should identify the degree of any subpopulation effects.

7.10.1.2 Risk characterization

The actual risk to the population of an adverse health effect requires consideration of both the likelihood and severity of the effect, as determined from the dose–response model when combined with the exposure to the chemical in the population under consideration. The exposure may be determined from consumption surveys, measurement of environmental media, direct contact information, or biomarkers (e.g. IPCS, 2000; Kroes et al., 2002).

Consideration of the DRM data together with exposure data will help identify populations at risk. This information, together with knowledge about the severity of the adverse health effects, will inform the risk management options.

7.10.2 Risk management issues

7.10.2.1 Risk management options

A risk assessment can be used to establish that a risk is of a sufficient magnitude that regulation or other type of intervention may be warranted. DRM can then be used to evaluate the consequences of possible interventions that aim to reduce the risk. That is, a model may be used to estimate change in the likelihood of the adverse health effect occurring following implementation of a particular intervention. To date, alternative risk management options have been evaluated using DRM in a limited number of cases. For example, at the request of the Codex Committee on Food Additives and Contaminants, the 49th JECFA analysed the application of two hypothetical standards for aflatoxin contamination in food in model populations (WHO, 1999).

A range of risk management interventions are available, with the types of interventions varying from a ban on a particular product (e.g. carcinogenic antibiotics, DDT), establishing regulatory limits (e.g. aflatoxins), advice on consumption or use patterns (e.g. consumption of predatory fish that accumulate high levels of methylmercury), and control at source of production (e.g. emissions of dioxins).

7.10.2.2 *Cost–benefit and risk–benefit analyses*

While health risk management decisions should be based on risk assessments, a number of other factors will influence the final decisions. In particular, it may also be necessary to undertake a cost–benefit analysis (e.g. health costs to the community from exposure to aflatoxins versus the cost of implementation of a management strategy) and/or risk–benefit analysis (e.g. risk associated with methylmercury in fish versus nutritional benefits of fish consumption) and to assess the feasibility of the intervention, availability of alternatives, and loss of products of economic value. These factors are beyond the scope of the assessment of the risks and will need to reflect wider societal factors.

7.10.2.3 *Acceptable level of risk*

Different institutions and countries may make different risk management decisions based on different perceptions of the risk that is deemed to be acceptable to society. The ADI, which usually incorporates a composite uncertainty factor of 100 when based on animal studies, has been accepted by international institutions and countries as a health-based guidance value. Although DRM can give a prediction of the risk at various exposures, there is no international agreement on how to interpret this new information, the appropriate criteria for making or reversing risk decisions, or the acceptable level of risk determined using this technique.

A predicted risk level, such as 10^{-6}, determined from dose–response analysis has been used by some countries and institutions as being not appreciable or negligible (virtually safe dose). Variations around the calculated risk by a factor of about 10 trigger further consideration of the qualitative aspects of the risk assessment, such as variability and uncertainty (Sanner et al., 2001; SCCNFP, 2003). In the case of compounds in drinking-water considered to be genotoxic carcinogens, WHO has assigned guideline values associated with an estimated upper-bound excess lifetime cancer risk of 10^{-5} determined by a mathematical model (WHO, 2004b). The United States Occupational Safety and Health Administration has considered a lifetime cancer risk for workers higher than 10^{-3} to represent an unacceptably high risk, and its goal is to reduce this risk to less than 10^{-5} (OSHA, 1983, 1984).

Proposals for the application of lifetime risk estimates in establishing tolerable risk levels have also been published in Europe (Bos et al., 2004).

8. CONCLUSIONS AND RECOMMENDATIONS

8.1 Conclusions

- Full DRM can be considered a more sophisticated or robust alternative to the NOAEL approach in all cases where suitable dose–response data are available (e.g. several dose groups with different response levels).

- For quantal dose–response data, the interest is often in low response (incidence) levels. This may call for low-dose extrapolation by several orders of magnitude (e.g. for tumour incidences). However, equally plausible dose–response risk models may result in highly divergent low estimates. A currently applied approach is to estimate a BMD_{10} and linearly extrapolate from that point downwards, as a conservative approach. Another option, currently under development, is to apply a Bayesian approach that considers the various models all together.

- For continuous dose–response data, two approaches of DRM exist. One is to transform the continuous data into quantal data. The other is to consider continuous dose–response data as information on the severity of the effect and therefore as a function of dose. In the latter approach, measurable changes of effect are often close to response levels considered as adverse (e.g. 10% inhibition of cholinesterase), and the low-dose extrapolation problem is minor or non-existent.

- For the purpose of deriving an ADI, TDI, or RfD, DRM may be used for deriving a BMD, to be used as a point of departure in the same way as the NOAEL is used (i.e. the same uncertainty factors would be applied to the BMD as to the NOAEL).

- DRM may also be used for estimating risks at a given (human) exposure level. For risks in terms of incidences (quantal data), this may involve low-dose extrapolation.

- DRM exercises can provide information on uncertainties associated with the data and identify factors contributing to uncertainties in risk estimates.

- Application of DRM for all end-points can be cost prohibitive, so it is efficient to pre-select the apparently more sensitive end-points. In some

cases, however, it is not easy to identify the most sensitive end-points by visual inspection, so all of the end-points may need to be modelled.

- The BMD and the BMDL should always be reported, so that the quality of the data and the model fit are clear and potencies can be compared on the basis of the BMD.

- The output of the different models used in DRM should be presented.

8.2 Recommendations

- Toxicity testing protocols (e.g. Organisation for Economic Co-operation and Development guidelines) should be reviewed for optimization for BMD and other DRM approaches, including optimal designs for the number of animals and number of doses for different dose–response curves. Additional research is needed for the development of optimal study designs. Guidance should be developed for combining existing studies with a view to DRM.

- Better guidance needs to be developed for combined analysis of different data sets for more precisely estimating BMDs.

- Better understanding of when and how to use the BMR needs to be developed.

- Better understanding of the shape of the dose–response curve at low doses needs to be developed. Additional research is needed to determine the biological basis for extrapolation (e.g. by using biomarkers, tumour precursors, genetically modified animals, and toxicokinetics for target dose estimation).

- Improved guidance needs to be developed for risk communication based on the results of DRM and probabilistic assessment techniques. This should include communication of the types of uncertainty and the relation to statistical variability, imprecision, and the use of confidence intervals.

- The use of DRM should be reviewed and additional general principles for its use developed when more experience becomes available.

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ANNEX 1: TERMINOLOGY

Acceptable daily intake (ADI)/tolerable daily intake (TDI)/reference dose (RfD): Estimated maximum amount of an agent, expressed on a body mass basis, to which an individual in a (sub)population may be exposed daily over the individual's lifetime without appreciable health risk.

Acceptable risk: A risk management term. The acceptability of risk depends on scientific data, on social, economic, and political factors, and on the perceived benefits arising from exposure to an agent.

Additional risk (extra risk): The additional proportion of total animals that respond in the presence of the dose, or the probability of response at dose d, P(d), minus the probability of response in the absence of exposure, P(0).

Adverse effect: Change in the morphology, physiology, growth, development, reproduction, or lifespan of an organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.

Akaike information criterion: A statistical procedure that provides a measure of the goodness of fit of a dose–response model to a set of data.

Assessment factor: Numerical adjustment to extrapolate from experimentally determined (dose–response) relationships to estimate the exposure to an agent below which an adverse effect is not likely to occur (see *Safety factor* and *Uncertainty factor*).

Benchmark concentration (BMC): The concentration of a substance that is associated with a specified low incidence of risk of a health effect, or the concentration associated with a specified measure or change of a biological effect.

Benchmark dose (BMD): A dose of a substance associated with a specified low incidence of risk, generally in the range of 1–10%, of a health effect; or the dose associated with a specified measure or change of a biological effect.

Benchmark dose lower confidence limit (BMDL): A lower one-sided confidence limit on the BMD.

Benchmark response (BMR): The response, generally expressed as in excess of background, at which a benchmark dose or concentration is desired.

Bernoulli distribution: A theoretical distribution of the number of successes in a finite set of independent trials with a constant probability of success. It is a discrete distribution having two possible outcomes labelled by $n = 0$ and $n = 1$, in which $n = 1$ ("success") occurs with probability p and $n = 0$ ("failure") occurs with probability $q \equiv 1 - p$, where $0 < p < 1$.

Binomial distribution: The statistical distribution of the probabilities of observing 0, 1, 2, … , n events in a sample of n independent trials each with the same individual probability that the event occurs.

Bootstrap: A statistical technique based on multiple resampling with replacement of the sample values or resampling of estimated distributions of the sample values that is used to calculate confidence limits or perform statistical tests for complex situations or where the distribution of an estimate or test statistic cannot be assumed.

Cancer potency (cancer slope factor): A number that estimates the cancer risk (incidence) for a lifetime exposure to a substance per unit of dose, which is generally expressed as mg/kg body weight per day.

Categorical data: Results obtained where observations or measurements on individuals or samples are stratified according to degree or severity of an effect (e.g. none, mild, moderate, or severe).

Categorical default factor: A factor based on common characteristics of a group of compounds (e.g. physical/chemical properties or pathways of metabolism).

Chemical-specific adjustment factor (CSAF): A factor based on quantitative chemical-specific toxicokinetic or toxicodynamic data, which replaces some or all of the default uncertainty factor.

Chi-square test: A statistical test used to examine the deviation of an observed number of events from an expected number of events.

Clustered data: Measurements collected on some grouping of individuals (e.g. litters in reproductive and developmental studies).

Confidence interval (one-sided): An interval below the estimated upper confidence limit, or an interval above the estimated lower confidence limit, that is expected to include the true value of an estimated parameter with a specified confidence (percentage of the time).

Confidence interval (two-sided): An estimated interval from the lower to upper confidence limit of an estimate of a parameter. This interval is expected to include the true value of the parameter with a specified confidence percentage (e.g. 95% of such intervals are expected to include the true values of the estimated parameters).

Confidence limit: An estimated value below (or above) which the true value of an estimated parameter is expected to lie for a specified percentage of such estimated limits.

Constrained dose–response model: Estimates of one or more parameters of the model restricted to a specified range (e.g. equal to or greater than zero).

Continuous data: Effects measured on a continuum, e.g. organ weight or enzyme concentration, as opposed to quantal or categorical data, where effects are classified by assignment to a class.

Convergence: A parameter approach that estimates a single value with increasing sample size or increasing number of computer iterations.

Covariate: An independent variable other than dose that may influence the outcome of an effect (e.g. age, body weight, or polymorphism).

Critical effect: The adverse effect, or its known precursor, that is relevant to human risk assessment and that occurs in the dose/concentration scale in the most sensitive animal species.

Degrees of freedom: For dose–response model fitting, the number of data points minus the number of model parameters estimated from the data.

Default value: Pragmatic, fixed, or standard value used in the absence of relevant data.

Dichotomous data: Quantal data where an effect for an individual may be classified by one of two possibilities (e.g. dead or alive), with or without a specific type of tumour.

Dispersion: Variation (differences) from a central (mean or median) value.

Dose: Total amount of an agent administered to or taken up or absorbed by an organism, system, or (sub)population.

Dose–response: Relationship between the amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the change developed in that organism, system, or (sub)population in reaction to the agent.

Dose–response assessment: Analysis of the relationship between the total amount of an agent administered to, taken up by, or absorbed by an organism, system, or (sub)population and the changes developed in that organism, system, or (sub)population in reaction to that agent, and inferences derived from such an analysis with respect to the entire population.

Dose–response model: A mathematical relationship (function) that relates (predicts) a measure of an effect to a dose.

Dose–response trend: Relationship between incidence or severity of a biological effect and a function of dose. Simply the slope for a linear dose–response.

ED_x: Effective dose associated with a biological effect in x% of the individuals. Dose may be the external exposure often expressed in milligrams of the substance per day per kilogram body weight raised to a power (generally 1, 3/4, or 2/3) or area under the curve (AUC) in blood or target tissue where the substance remains in the body over a period of time.

Estimate: An empirical value derived from data for a parameter.

Exposure: Concentration or amount of a particular agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration.

Gamma distribution: A unimodal statistical distribution (relative proportion of responders as a function of some measure) restricted to effects greater than or equal to zero that can describe a wide variety of shapes (e.g. flat, peaked, asymmetrical).

Gaussian (normal) distribution: A unimodal symmetrical (bell-shaped) distribution where the most prevalent value is the mean (average) and the spread is measured by the standard deviation. Mathematically, the distribution varies from minus infinity with zero probability to plus infinity with zero probability.

Goodness of fit: A statistic that measures the dispersion of data about a dose–response curve in order to provide a test for rejection of a model due to lack of an adequate fit (e.g. a p-value < 0.1).

Hazard identification: The identification of the type and nature of adverse effects that an agent has an inherent capacity to cause in an organism, system, or (sub)population.

Hill equation: A dose–response curve, frequently used for enzyme kinetics, that monotonically approaches an asymptote (maximum value) as a function of dose raised to a power.

Hybrid model: For continuous data, establishes abnormal values based on the extremes in controls (unexposed individuals or animals) and estimates the risk of abnormal levels as a function of dose.

Incidence: Proportion or probability of individuals or animals exhibiting an effect that varies from zero to one, sometimes expressed as a percentage from 0% to 100%.

Independence: The result in one animal or individual does not influence the result in another animal or individual.

Intercept term: The estimated value at zero dose or the dose corresponding to a zero effect.

Least squares: A statistical procedure that estimates the values of dose–response parameters such that the sum of squares of deviations of data points from their estimated values is minimized (i.e. minimizes the estimated variance).

Likelihood function: Relative probabilities that various values of population parameters would arise from the sample observations.

Likelihood ratio: Ratio of the probability that the observed data arise from a set of model parameters relative to the maximum probability that arises from the set of maximum likelihood estimates.

Linear dose–response model: The amount of change in a response is proportional to the amount of change in some function of dose.

Linearized multistage model: Dose–response model based on the multistage model of carcinogenesis that is restricted to a form that is approximately linear at low doses.

Local maximum: Mathematical solution that maximizes a function in a region that may not be the overall global maximum.

Logistic model: A sigmoidal (S-shaped) function that relates the proportion of individuals with a specified characteristic to an independent variable.

Lognormal distribution: A mathematical description where the natural logarithm of a random variable has a normal distribution.

Log transformation: Logarithm of raw data.

Lowest-observed-adverse-effect level (LOAEL): The lowest concentration or dose of a substance, found by experiment or observation, that causes an adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Lowest-observed-effect level (LOEL): The lowest concentration or dose of a substance, found by experiment or observation, that causes any alteration of morphology, functional capacity, growth, development, or lifespan of the target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Margin of exposure (MOE): Ratio of the no-observed-adverse-effect level (NOAEL) or benchmark dose lower confidence limit (BMDL) for the critical effect to the theoretical, predicted, or estimated exposure dose or concentration.

Maximum likelihood estimate: Estimate of a population parameter most likely to have produced the sample observations.

Mechanism of action: A detailed description of the precise chain of events from the molecular level to gross macroscopic or histopathological toxicity.

Michaelis-Menten equation: A dose–response curve, frequently used for enzyme kinetics, with maximum slope at zero dose that approaches a maximum asymptote at increasing dose.

Mode of action: A series of events that may lead to induction of the relevant end-point of toxicity for which the weight of evidence supports plausibility.

Monotonic dose–response: A dose–response that never decreases as dose increases. A monotonic function may be flat (constant) up to a threshold dose or may be flat at high doses if a biological limit (e.g. saturation) is attained.

Multinomial: Animals or individuals may be classified by more than two (binomial) categories (e.g. in a reproductive study, fetuses may be dead, alive normal, or alive abnormal).

Negligible risk: A risk management term. In cases where a quantitative risk estimate has been made, it is any risk less than an upper-bound incremental lifetime risk calculated using conservative risk assessment techniques such as the benchmark dose.

Non-linear dose–response model: Mathematical relationship that cannot be expressed simply as the change in response being proportional to the amount of change of some function of dose.

No-observed-adverse-effect level (NOAEL): The highest concentration or dose of a substance, found by experiment or observation, that causes no detectable adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organisms under defined conditions of exposure.

No-observed-effect level (NOEL): The highest concentration or dose of a substance, found by experiment or observation, that causes no detectable alteration of morphology, functional capacity, growth, development, or lifespan of the target organisms under defined conditions of exposure.

Normal distribution: A mathematical description where a continuous random variable x with a mean μ and a variance σ^2 has a probability density function:

$$P(x) = \frac{1}{\sigma\sqrt{2\pi}} e^{-(x-\mu)^2/(2\sigma^2)}$$

Objective function: Choice of function that is optimized for maximum likelihood estimation.

Ordinal data: Integers designating the rank, order, or counts.

Parameter: A value used to numerically describe a population of values (e.g. the mean and standard deviation); or a value used to describe a dose–response curve (e.g. the intercept and the slope of a linear dose–response).

Point of departure: The point on a dose–response curve established from experimental data (e.g. the benchmark dose), generally corresponding to an estimated low effect level (e.g. 1–10% incidence of an effect). Depending on the mode of action and available data, some form of extrapolation below the point of departure may be employed for low-dose risk assessment, or the point of departure may be divided by a series of uncertainty factors to arrive at a reference dose. Points of departure include the BMD, BMDL, LOAEL, and carcinogenic potency estimates, such as the T_{25}.

Polynomial: A mathematical function of the sum of a constant, linear term, quadratic term, cubic term, etc.

Probability: The proportion (on a scale of 0 to 1) of cases for which a particular event occurs. Zero indicates the event never occurs, and one indicates the event always occurs.

Probability distribution: A mathematical description of the relative probabilities of all possible outcomes of a measurement.

Probit function: Assumes that the relative probabilities of effects as a function of dose are described by a normal distribution. The cumulative probability as a function of dose has a sigmoidal shape.

Profile likelihood: A plot of the likelihood function versus the estimated value of a parameter.

P-value: In testing a hypothesis, the probability of a type I error (false positive). The probability that the sample (experimental) results are compatible with a specific hypothesis.

Quadratic term: A quantity in a mathematical formula that is raised to the second power (squared).

Quantal data: Dichotomous (binomial) classification where an individual or animal is placed in one of two categories (e.g. dead or alive, with or without a particular type of tumour, normal or abnormal level of a hormone).

Quantile: Percentile (cumulative probability) of a distribution that ranges from zero to the 100th percentile.

Regression analysis: A statistical process that produces a mathematical function (regression equation) that relates a dependent variable (biological effect) to an independent variable (e.g. dose rate, duration of exposure, age).

Repeated measures: A biological end-point is measured for the same individual or animal at different times (ages).

Response: Change developed in the state or dynamics of an organism, system, or (sub)population in reaction to exposure to an agent.

Residual variance: The variance in experimental measurements remaining after accounting for the variance due to the independent variables (e.g. dose rate, duration of exposure, age). Typically referred to as the inherent unaccountable experimental variation.

Risk: The probability of an adverse effect in an organism, system, or (sub)population caused under specified circumstances by exposure to an agent.

Risk assessment: A process intended to calculate or estimate the risk to a given target organism, system, or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system.

Risk characterization: The qualitative and, wherever possible, quantitative determination, including attendant uncertainties, of the

probability of occurrence of known and potential adverse effects of an agent in a given organism, system, or (sub)population, under defined exposure conditions.

Safety factor: Composite (reductive) factor by which an observed or estimated no-observed-adverse-effect level (NOAEL) is divided to arrive at a criterion or standard that is considered safe or without appreciable risk (see *Assessment factor* and *Uncertainty factor*).

Severity: The degree to which an effect changes and impairs the functional capacity of an organ system.

Shape parameter: The exponent on dose in a dose–response function that dictates the curvature of the function.

Threshold: Dose or exposure concentration of an agent below which a stated effect is not observed or expected to occur.

Threshold of toxicological concern: An exposure threshold value below which there is a very low probability of an appreciable risk to human health.

Toxicodynamics: The process of interaction of chemical substances with target sites and the subsequent reactions leading to adverse effects.

Toxicokinetics: The process of the uptake of potentially toxic substances by the body, the biotransformation they undergo, the distribution of the substances and their metabolites in the tissues, and the elimination of the substances and their metabolites from the body. Both the amounts and the concentrations of the substances and their metabolites are studied. The term has essentially the same meaning as *pharmacokinetics*, but the latter term should be restricted to the study of pharmaceutical substances.

Uncertainty: Imperfect knowledge concerning the present or future state of an organism, system, or (sub)population under consideration.

Uncertainty factor: Reductive factor by which an observed or estimated no-observed-adverse-effect level (NOAEL) is divided to

arrive at a criterion or standard that is considered safe or without appreciable risk (see *Assessment factor* and *Safety factor*).

Unconstrained dose–response model: No restrictions imposed on the estimates of parameters.

Upper-tail probability: Probability that a variable exceeds a specified value.

Validation: Process by which the reliability and relevance of a particular approach, method, process, or assessment is established for a defined purpose.

Variability: Observable diversity in biological sensitivity or response and in exposure parameters.

Variance: Measure of variability, standard deviation squared.

Weibull: Form of a dose–response curve characterized by a relatively shallow slope at low doses that increases sharply as dose increases before levelling off at high doses.

Weighted least squares estimate: Parameter estimate obtained by minimizing the sum of squares of observed and estimated values weighted by a function, frequently the reciprocal of the variance of an observation.

RESUME, CONCLUSIONS ET RECOMMANDATIONS

1. Résumé

La modélisation de la relation dose-réponse (DRM), destinée à évaluer quantitativement les risques et enfin à étayer les décisions de santé publique concernant les expositions à des produits chimiques, peut être décrite comme un processus en six étapes. Les quatre premières étapes – sélection des données, choix du modèle, mise en relation statistique et estimation des paramètres – constituent une analyse de la relation dose-réponse. Ces étapes composent le processus permettant d'obtenir une description mathématique des données, en vue de prédire les réponses à des doses connues ou d'établir des estimations de doses à partir d'une réponse donnée. La cinquième étape réalise une synthèse des résultats de l'analyse dose-réponse et des estimations de l'exposition afin de guider les décisions de santé publique. L'étape finale, qui peut éventuellement intervenir plus tôt dans la DRM, évalue la qualité de la relation dose-réponse et la sensibilité des prédictions aux hypothèses ayant servi à l'analyse.

La caractérisation de la relation dose-réponse dans les études chez l'homme et chez l'animal constitue une composante majeure de la caractérisation des dangers et sert à extrapoler les incidences des effets nocifs sur la gamme de niveaux d'exposition humaine. Au cours des années, diverses méthodes ont été mises au point pour traiter de telles relations, améliorer l'extrapolation pour les faibles doses et dériver des valeurs guides reposant sur des considérations sanitaires telles que les doses journalières admissibles (DJA), les doses journalières tolérables (DJT) et les doses de référence (D_{ref}). La DRM peut s'avérer utile dans les évaluations des risques en permettant un meilleur usage des données disponibles et en fournissant des outils pour évaluer la qualité des données et les incertitudes résultantes sur les estimations de la relation dose-réponse.

D'une manière générale, les estimations obtenues par DRM sont établies à partir de données provenant de l'ensemble de la courbe dose-réponse pour l'effet critique. L'approche standard reposant sur la dose sans effet nocif observé (DSENO) peut être considérée comme un cas spécial et simplifié d'analyse de la

relation dose-réponse, dans la mesure où elle identifie une dose unique supposée ne pas avoir d'effet nocif appréciable. La modèle DRM reflète les caractéristiques de la courbe dose-réponse, en permettant notamment d'estimer sa pente. Dans le cas d'un cadre de régression, il indique l'écart-type et l'intervalle de confiance pour les paramètres de modélisation. L'un des inconvénients de l'approche DSENO réside dans l'impossibilité de quantifier les degrés de variabilité et d'incertitude, alors que d'autres modèles de la relation dose-réponse peuvent faciliter l'analyse de ces grandeurs. L'utilisation d'un modèle dose-réponse peut permettre d'optimiser la conception de l'étude et de préciser les besoins en matière d'études supplémentaires. L'approche DSENO intègre des informations biologiques à travers l'application d'un jugement d'expert, néanmoins subjectif. Une DRM complète est en mesure de fournir une analyse plus « riche en éléments scientifiques » grâce à l'inclusion quantitative plus formelle dans les modèles de facteurs et de covariables, par exemple. Les estimations obtenues à partir de cette DRM facilitent la comparaison dans un cadre commun entre des expériences, des effets et des composés qui diffèrent sur le plan quantitatif. La modélisation DRM peut aussi conduire à de meilleures évaluations des risques et de l'innocuité et offre la possibilité d'étudier les probabilités d'effets se manifestant en dehors de la plage observable.

Le choix des modèles à utiliser dépend du type de donnée. Il faut sélectionner un modèle dose-réponse et un modèle décrivant la variabilité des données. Une fois qu'on dispose de modèles adaptés à un jeu de données, on peut évaluer leur degré de représentativité pour ces données par des mesures de la qualité de l'ajustement. On peut en outre comparer leur capacité à décrire les données. Les incertitudes portant sur les inférences tirées de ces modèles se répartissent dans quatre catégories : incertitudes statistiques sur les inférences dues à la variabilité des réponses entre les sujets des expériences, erreurs expérimentales (randomisation imparfaite, erreurs de dosage, localisation défavorable de la dose, par exemple), variabilité d'une expérience à l'autre due aux différences inévitables dans l'exécution de l'expérience et incertitude due au fait que l'on ne connaît pas le « vrai modèle » décrivant les données. L'analyse de la relation dose-réponse doit, dans la mesure du possible, prendre en compte l'ensemble de ces quatre sources de variabilité et d'incertitude.

Le calcul des doses de référence (BMD) est une application particulièrement importante de la DRM. Les BMD sont les doses pour lesquelles on détermine par déduction qu'il se produira un niveau donnée de réponse. Lorsqu'on dispose de données appropriées, les BMD offrent une alternative à l'approche DSENO pour le calcul de valeurs guides reposant sur des considérations sanitaires. Lorsqu'une extrapolation s'avère nécessaire, il convient de représenter l'incertitude associée à la prédiction. Il est dans ce cas particulièrement important d'indiquer l'incertitude liée au modèle.

Une DRM complète peut apporter des informations supplémentaires au gestionnaire de risques. La sortie du modèle doit être conçue pour répondre à certaines questions concernant la probabilité d'effets sanitaires nocifs. Elle peut être présentée essentiellement de trois façons. Premièrement, elle peut servir à établir des valeurs guides reposant sur des considérations sanitaires telles que les DJA, les DJT ou les D_{ref}, d'une manière analogue aux procédures actuellement appliquées à partir de la DSENO ou de la dose minimale avec effets nocifs observés (DMENO). La DRM peut être une méthode plus sûre sur le plan scientifique pour déterminer ces valeurs guides. Deuxièmement, la sortie de la DRM peut être utilisée en gestion des risques pour estimer une marge d'exposition (ME), par détermination du rapport de la dose correspondant à une limite donnée de la réponse à un niveau d'exposition humaine. Troisièmement, sur la base de la relation dose-réponse modélisée, cette sortie peut être une estimation quantitative de l'ampleur du risque ou de l'effet sanitaire pour un niveau d'exposition humaine, moyennant l'hypothèse généralement acceptée que les facteurs d'incertitude utilisés couvrent les incertitudes associées aux différences de sensibilité entre individus et espèces. La DRM peut fournir de meilleures informations sur la probabilité des effets pour les doses faibles et inférieures aux niveaux observés dans les systèmes biologiques, ainsi que de meilleures estimations des incertitudes statistiques entachant les estimations des effets probables.

La multiplicité des jeux de données et des incertitudes peut influer sur le type de sortie des exercices de DRM et avoir de l'importance pour les gestionnaires de risques. On peut utiliser la DRM avec des données d'exposition pour identifier les sous-

populations à risque. Elle peut aussi aider les gestionnaires dans la détermination des priorités et dans l'évaluation des conséquences d'interventions proposées pour réduire les risques. Pour la communication à propos des risques, l'application des techniques de DRM offre des opportunités, mais comporte aussi des difficultés. Les évaluations par DRM peuvent produire des informations sous plusieurs formats, et notamment sous forme de fonctions dose-réponse permettant, avec les estimations de l'exposition, de prédire les risques pour des niveaux d'exposition donnés, ainsi que de fonctions permettant inversement d'estimer les niveaux d'exposition à l'origine de risques donnés. On obtient ainsi notamment des estimations du risque potentiel d'absorption plus importante qu'une valeur guide reposant sur des considérations sanitaires, DJA par exemple. Ces évaluations offrent aussi des approches pour comparer les risques ou les bénéfices concurrents et s'intéresser aux incertitudes susceptibles d'influer sur les risques prédits. Toutefois, à moins que la situation en termes de risque ne soit envisagée à l'échelle de la population, il existe un problème de communication à propos du risque car lorsqu'on présente le niveau de risque dans des situations où aucun niveau d'exposition n'est dépourvu de risque, la modélisation prévoit qu'un certain pourcentage de la population subira des effets jugés nocifs. Il faut reconnaître que l'utilisation de la DRM impose aux données des exigences en termes de qualité et de quantité et nécessite des compétences spécifiques.

L'utilisation courante des estimations tirées der la DRM pourrait, du point de vue de la gestion des risques, permettre une meilleure caractérisation avant la prise de décisions en :

- apportant des informations sur les valeurs guides (ampleur et types des impacts sanitaires) ;
- montrant les bénéfices de différentes actions réglementaires ;
- fournissant au décideur une appréciation des données « plus que ponctuelle » ;
- favorisant la cohérence dans les décisions, moyennant des ajustements appropriés pour tenir compte des différences entre les effets, les niveaux d'effet, les espèces et les types d'étude ; et en
- permettant en continu et en permanence des interactions itératives entre l'évaluateur et le gestionnaire de risques.

L'utilisation de la DRM et des techniques d'évaluation probabiliste pour décrire quantitativement la variabilité et l'incertitude génère de nouvelles difficultés dans la communication à propos des risques. Ces difficultés résident notamment dans :

- l'explication de la prévision, pour un certain pourcentage de la population, d'un dépassement du niveau de sécurité et/ou de l'apparition d'effets nocifs ;
- l'explication du niveau de risque dans les cas où on suppose qu'aucun niveau d'exposition n'est dépourvu de risque ;
- la comparaison entre risques ou bénéfices concurrents ;
- la mise en lumière d'incertitudes influant sur le risque prédit ; et
- l'explication du fait qu'en matière de risque, une estimation indique ce qui peut se passer au niveau d'une population, plutôt qu'à celui d'un individu, ce qui, notons le, vaut aussi pour l'approche DJA/DJT.

2. Conclusions

- La DRM complète peut être considérée comme une alternative plus élaborée et plus robuste à l'approche DSENO dans tous les cas où l'on dispose de données appropriées sur la relation dose-réponse (pour plusieurs groupes de dose et différents niveaux d'exposition, par exemple).

- Pour les données dose-réponse ponctuelles, on s'intéresse souvent aux faibles niveaux de réponse (d'incidence). Il est parfois nécessaire, dans cette perspective, d'extrapoler sur plusieurs ordres de grandeur (pour l'incidence des tumeurs, par exemple). Cependant, des modèles également plausibles de la relation dose-réponse peuvent fournir des estimations fortement divergentes pour les faibles valeurs. Une approche actuellement appliquée en tant que méthode prudente consiste à estimer la BMD_{10} (dose pour un risque de 10 %) et à extrapoler linéairement à partir de ce point vers les valeurs descendantes. Une autre solution, actuellement en cours de développement, applique une approche bayésienne, considérant globalement les divers modèles.

- Pour les données dose-réponse continues, il existe deux approches de type DRM. L'une comprend la transformation des

données continues en données ponctuelles. L'autre considère les données dose-réponse continues comme des informations sur la gravité de l'effet et donc comme une fonction de la dose. Dans cette dernière approche, des variations mesurables de l'effet sont souvent proches des niveaux de réponses considérés comme nocifs (par exemple, inhibition de 10 % de la cholinestérase) et le problème de l'extrapolation à faible dose est mineur ou ne se pose pas.

- Pour dériver une DJA, une DJT ou une Dref, on peut faire appel à la DRM pour déterminer une BMD, qui sera utilisée comme point de départ de la même façon qu'une DSENO (c'est-à-dire qu'on appliquera les mêmes facteurs d'incertitude à la BMD qu'à la DSENO).

- La DRM peut aussi être employée pour estimer les risques correspondant à un niveau d'exposition (humaine) donné. Pour évaluer les risques en termes d'incidence (données ponctuelles), cette opération peut devoir inclure une extrapolation aux faibles doses.

- Les exercices de DRM peuvent apporter des informations sur les incertitudes associées aux données et identifier des facteurs contribuant aux incertitudes sur les estimations des risques.

- L'application de la DRM à tous les points finaux peut être extrêmement onéreuse, il est donc plus efficace de présélectionner les points finaux apparemment les plus sensibles. Dans certains cas cependant, il n'est pas facile d'identifier visuellement ces points de sorte qu'il peut être nécessaire de modéliser tous les points finaux.

- La BMD et la borne inférieure de l'intervalle de confiance de la BMD (BMDL) doivent toujours être indiquées de manière à ce que la qualité des données et de l'ajustement du modèle apparaisse clairement et que l'on puisse procéder à une comparaison de puissances à partir de la BMD.

- Il convient de présenter la sortie des différents modèles de DRM.

3. Recommandations

- Les protocoles d'évaluation de la toxicité (par exemple les Lignes directrices de l'Organisation de coopération et de développement économiques) doivent être examinés pour optimiser l'approche utilisant la BMD et d'autres approches de type DRM, notamment pour choisir au mieux les nombres d'animaux et de doses pour les différentes courbes dose-réponse. Des recherches supplémentaires sont nécessaires pour développer des types d'étude optimaux. Il faut également élaborer des conseils pour combiner les études existantes en vue d'une DRM.

- Il faut mettre au point des recommandations pour l'analyse combinée de différents jeux de données en vue d'une estimation plus précise des BMD.

- Il faut aussi parvenir à mieux comprendre quand et comment utiliser la réponse de référence (BMR).

- La forme de la courbe dose-réponse aux faibles doses doit être mieux interprétée. Des recherches supplémentaires sont nécessaires pour déterminer la base biologique de l'extrapolation (en faisant appel, par exemple, à des marqueurs biologiques, à des précurseurs de tumeur, à des animaux génétiquement modifiés ou à la toxico-cinétique, pour estimer la dose cible).

- Il faut élaborer de meilleures recommandations pour la communication à propos des risques sur la base des résultats de la DRM et des techniques d'évaluation probabiliste. Cette communication devra couvrir les types d'incertitude, leur relation avec la variabilité statistique, l'imprécision et l'utilisation des intervalles de confiance.

- L'utilisation de la DRM doit faire l'objet d'un bilan et des principes généraux supplémentaires devront être développés à mesure que l'on disposera de plus d'expérience.

RESUMEN, CONCLUSIONES Y RECOMENDACIONES

1. Resumen

La creación de modelos de la relación dosis-respuesta, para su utilización en la evaluación cuantitativa del riesgo y en último término para documentar las decisiones en materia de salud pública, se puede describir como un proceso en seis etapas. Las cuatro primeras etapas—selección de datos, selección del modelo, vinculación estadística y estimación de los parámetros—constituyen el análisis de la relación dosis-respuesta. Estas etapas están relacionadas con el proceso mediante el cual se obtiene una descripción matemática de los datos, a fin de evaluar respuestas previstas para dosis conocidas u obtener estimaciones de la dosis cuando lo que interesa es una respuesta determinada. La quinta etapa consiste en la integración de los resultados del análisis de la relación dosis-respuesta en las estimaciones de la exposición, con el objetivo de orientar las decisiones relativas a la salud pública. La última etapa, que se puede elegir aplicar antes, consiste en una evaluación de la calidad del análisis de la relación dosis-respuesta y de la sensibilidad de las predicciones de los modelos con respecto a las hipótesis utilizadas en el análisis.

La caracterización de las relaciones dosis-respuesta en estudios realizados en animales y personas ha sido un componente importante de la caracterización del peligro y se ha utilizado en la extrapolación de incidencias de efectos adversos en la gama de los niveles de exposición humana. Durante años se han elaborado diversos métodos para ajustar dichas relaciones, mejorar la extrapolación a dosis bajas y obtener valores guía basados en la salud, como la ingesta diaria admisible (IDA), la ingesta diaria tolerable (IDT) y las dosis de referencia. La creación de modelos puede ser útil en las evaluaciones del riesgo para utilizar mejor los datos disponibles y para suministrar instrumentos de evaluación de la calidad de los datos y las consiguientes incertidumbres en las estimaciones de la relación dosis-respuesta.

En general, las estimaciones de los modelos de la relación dosis-respuesta se basan en los datos obtenidos de la totalidad de la

curva correspondiente a dicha relación para el efecto crítico. El método normalizado de la concentración sin efectos adversos observados (NOAEL) se puede considerar como un caso especial simplificado de análisis de la relación dosis-respuesta, puesto que identifica una dosis única que se supone que no tiene un efecto adverso apreciable. El modelo de la relación dosis-respuesta refleja las características de la curva de dicha relación, en particular porque proporciona estimaciones de la pendiente. En el caso de un marco de regresión, proporciona el error estándar y los intervalos de confianza para los parámetros del modelo. La utilización del método de la NOAEL tiene el inconveniente de que no es posible cuantificar el grado de variabilidad e incertidumbre que puede haber, mientras que otros modelos de la relación dosis-respuesta pueden facilitar el análisis de la sensibilidad y la incertidumbre. El examen de un modelo de dosis-respuesta puede mejorar al máximo la formulación del estudio y aclarar la necesidad de estudios adicionales. El método de la NOAEL incorpora información biológica mediante la aplicación de un parecer "experto", pero subjetivo. La creación de modelos de la relación dosis-respuesta completos permitiría un análisis más "científico", por ejemplo mediante la inclusión cuantitativa más oficial de factores y covariantes en los modelos. Las estimaciones derivadas de los modelos de dosis-respuesta mejoran la capacidad para comparar experimentos, efectos y compuestos con diferencias cuantitativas en el ámbito de un marco común. Los modelos pueden mejorar las evaluaciones del riesgo y de la inocuidad, ofreciendo al mismo tiempo oportunidades para examinar la probabilidad de los efectos fuera de la gama observable.

La elección de los modelos que se van a utilizar depende del tipo de datos. Dichos modelos deben incluir un patrón para la relación dosis-respuesta y otro para la variabilidad de los datos. Una vez ajustados los modelos a una serie de datos, se puede evaluar el grado en que los describen individualmente utilizando medidas de la precisión del ajuste. Además, se puede comparar entre ellos la capacidad para describir los datos. Las incertidumbres sobre las consecuencias que puedan derivarse de dichos modelos entran en cuatro categorías principales: incertidumbre estadística de las consecuencias debida a la variabilidad entre las respuestas de los sujetos objeto de experimentación, errores experimentales (por ejemplo, distribución al azar imperfecta, errores de dosificación,

localización desfavorable de las dosis), variabilidad entre experimentos debida a diferencias inevitables en su realización e incertidumbre debida al hecho de que no se conoce el "verdadero modelo" para los datos. Siempre que sea posible, en el análisis de la relación dosis-respuesta hay que abordar las cuatro fuentes de variabilidad e incertidumbre.

Una aplicación particularmente importante de los modelos de dosis-respuesta es el cálculo de las dosis de referencia. Son las dosis con las cuales se deduce que se producirá un determinado nivel de respuesta. Cuando se dispone de datos apropiados, las dosis de referencia son una alternativa al método de la NOAEL para calcular los valores guía basados en la salud. Cuando es necesaria una extrapolación, se debe representar la incertidumbre asociada con una predicción. En este caso es particularmente importante incluir la incertidumbre del modelo.

La creación de modelos de la relación dosis-respuesta completos ofrece la posibilidad de proporcionar información adicional a los gestores del riesgo. Los resultados de los modelos se deben orientar hacia el examen de cuestiones específicas relativas a la probabilidad de efectos adversos en la salud. Se pueden presentar de tres maneras principales. En primer lugar, se pueden utilizar para el establecimiento de un valor guía basado en la salud, por ejemplo una IDA, una IDT o unas dosis de referencia, de manera análoga a los procedimientos actuales basados en la NOAEL o la concentración más baja con efectos adversos observados (LOAEL). Los modelos de dosis-respuesta pueden ser un método más sólido desde el punto de vista científico para determinar valores guía basados en la salud. En segundo lugar, los resultados de dichos modelos se pueden utilizar en la gestión del riesgo para estimar un margen de exposición, mediante el cálculo de la relación entre la dosis correspondiente a un límite determinado de respuesta y un nivel de exposición humana. En tercer lugar, sobre la base de la relación dosis-respuesta obtenida mediante el modelo, el resultado puede ser una estimación cuantitativa de la magnitud del riesgo/efecto en la salud para el nivel de exposición humana, con la hipótesis generalmente aceptada de que los factores de incertidumbre utilizados incluyen las incertidumbres relativas a las diferencias de sensibilidad intraespecíficas e interespecíficas. Los modelos de dosis-respuesta pueden proporcionar mejor información sobre la probabilidad de efectos con dosis bajas, inferiores a los

niveles observados en los sistemas biológicos, y pueden proporcionar asimismo mejores estimaciones de las incertidumbres estadísticas de los efectos probables.

Dos factores que pueden influir en el tipo de resultados obtenidos de la aplicación de los modelos de dosis-respuesta y que pueden ser importantes para el gestor del riesgo son las series de datos múltiples y las incertidumbres. Los modelos se pueden utilizar con datos de exposición para identificar las subpoblaciones en situación de riesgo. También se pueden emplear para ayudar a los gestores del riesgo a establecer prioridades y evaluar las consecuencias de las intervenciones propuestas encaminadas a reducir el riesgo. Para la comunicación del riesgo, la utilización de técnicas con modelos de dosis-respuesta ofrece oportunidades y retos. Las evaluaciones con estos modelos pueden generar información de varios tipos, como funciones de la relación dosis-respuesta que permiten, junto con las estimaciones de la exposición, la predicción de los riesgos con niveles específicos de exposición y funciones que permiten la estimación de los niveles de exposición que dan lugar a riesgos determinados. Esto incluye las estimaciones del posible riesgo de ingestas por encima de un valor guía basado en la salud, por ejemplo la IDA. Las evaluaciones con los modelos de dosis-respuesta también ofrecen métodos para comparar riesgos o beneficios competitivos y permiten concentrar la atención en las incertidumbres que pueden influir en el riesgo pronosticado. Sin embargo, salvo que la situación del riesgo se examine en la población, su comunicación presenta el problema de que, aun explicando el nivel de riesgo en esas circunstancias en las que no hay un nivel inocuo de exposición, cabe predecir que cierto porcentaje de la población va a registrar algunos efectos considerados adversos. Hay que reconocer que la utilización de los modelos de la relación dosis-respuesta requiere cierta cantidad y calidad de datos, así como conocimientos técnicos específicos.

El uso potencial "continuo" de las estimaciones derivadas de los modelos de dosis-respuesta puede, desde una perspectiva de gestión del riesgo, mejorar la caracterización para la adopción de decisiones, porque:

- facilita información sobre lo que ocurre por encima del valor guía basado en la salud (magnitud y tipos de efectos en la salud);
- demuestra los beneficios de distintas medidas normativas;
- ofrece a los encargados de la adopción de decisiones una apreciación de los datos desde más de un punto de vista;
- promueve la coherencia en las decisiones, si se hacen ajustes apropiados para las diferencias en los efectos, el nivel de los efectos, las especies y la formulación del estudio; y
- facilita una interacción iterativa entre el asesor del riesgo y el gestor del riesgo de manera continua e ininterrumpida.

La utilización de modelos de la relación dosis respuesta y de técnicas de evaluación probabilística para describir de manera cuantitativa la variabilidad y la incertidumbre incorpora nuevos retos a la comunicación del riesgo. Algunos de ellos son los siguientes:

- explicar que se prevé que un cierto porcentaje de la población superará el nivel de inocuidad y/o sufrirá un efecto adverso;
- explicar el nivel de riesgo en esas circunstancias en las que se supone que no hay un nivel inocuo de exposición;
- comparar los riesgos o los beneficios en pugna;
- prestar una atención especial a las incertidumbres que influyen en el riesgo pronosticado; y
- explicar que una estimación del riesgo se refiere a lo que puede ocurrir a la población, más que a nivel individual, y señalar que esto es lo que ocurre también con el enfoque de la IDA/IDT.

2. Conclusiones

- La creación de modelos de la relación dosis-respuesta completos se puede considerar un método alternativo más complejo o válido que el de la NOAEL en todos los casos en que se disponga de datos apropiados de la relación dosis-respuesta (por ejemplo, para varios grupos de dosis con distintos niveles de respuesta).

- Para los datos cuantales de la relación dosis-respuesta, el interés radica con frecuencia en los niveles bajos de respuesta (incidencia). Esto puede exigir una extrapolación a dosis más

bajas en varios órdenes de magnitud (por ejemplo, para las incidencias de tumores). Sin embargo, los modelos del riesgo de la relación dosis-respuesta que sean igualmente admisibles pueden dar lugar a estimaciones bajas muy divergentes. Un método aplicado actualmente, considerado prudente, consiste en estimar una dosis de referencia$_{10}$ (dosis con un riesgo del 10%) y hacer una extrapolación de manera lineal descendente desde ese punto. Otra opción, todavía en preparación, consiste en aplicar un método bayesiano, que examina los distintos modelos en conjunto.

- Para la obtención de datos continuos de la relación dosis-respuesta hay dos sistemas de utilización de los modelos. Uno consiste en transformar los datos continuos en datos cuantales. El otro en considerar los datos continuos de la relación dosis-respuesta como información de la gravedad del efecto y, por consiguiente, como una función de la dosis. En el segundo sistema, los cambios mensurables de los efectos suelen estar cerca de los niveles de respuesta considerados adversos (por ejemplo, la inhibición del 10% de la colinesterasa) y el problema de la extrapolación a dosis bajas es insignificante o inexistente.

- Con el fin de obtener un valor de la IDA, la IDT o las dosis de referencia, se pueden utilizar los modelos de dosis-respuesta para derivar una dosis de referencia, que se utilizará como punto de partida de la misma manera que se utiliza la NOAEL (es decir, se aplicarían a la dosis de referencia los mismos factores de incertidumbre que a la NOAEL).

- También se pueden utilizar modelos de la relación dosis-respuesta para estimar los riesgos en un determinado nivel de exposición (humana). Para los riesgos expresados como incidencias (datos cuantales) puede ser necesaria la extrapolación a dosis bajas.

- El uso de modelos de dosis-respuesta puede proporcionar información sobre las incertidumbres asociadas con los datos e identificar los factores que contribuyen a ellas en las estimaciones del riesgo.

- La aplicación de modelos de la relación dosis-respuesta a todos los efectos finales puede tener un costo prohibitivo, de manera que sería útil realizar una selección previa de los efectos finales aparentemente más sensibles. Sin embargo, en algunos casos no es fácil identificar los más sensibles mediante una inspección visual, de manera que hay que aplicar el modelo a todos ellos.

- Se debería notificar siempre la dosis de referencia y su límite inferior de confianza, de manera que la calidad de los datos y el ajuste del modelo sean claros y se puedan comparar sus potencias basándose en la dosis de referencia.

- Se deben presentar los resultados de los distintos métodos utilizados en los modelos de dosis-respuesta.

3. Recomendaciones

- Se deben examinar los protocolos de las pruebas de toxicidad (por ejemplo, las directrices de la Organización de Cooperación y Desarrollo Económicos) para conseguir unos resultados óptimos de las dosis de referencia y demás métodos basados en modelos de la relación dosis-respuesta, por ejemplo las formulaciones óptimas correspondientes al número de animales y el número de dosis para diferentes curvas de la relación dosis-respuesta.

- Hay que elaborar mejores orientaciones para el análisis combinado de distintas series de datos, a fin de estimar las dosis de referencia con mayor precisión.

- Es necesario fomentar un mayor conocimiento de cuándo y cómo se ha de utilizar la respuesta de referencia.

- Hay que tratar de conocer mejor la forma de la curva de la relación dosis-respuesta a dosis bajas. Se requieren nuevas investigaciones para determinar la base biológica de la extrapolación (por ejemplo, utilizando biomarcadores, precursores de tumores, animales modificados genéticamente y la tóxicocinética para la estimación de dosis específicas).

- Es necesario elaborar orientaciones mejores para la comunicación del riesgo basada en los resultados de los modelos dosis-respuesta y de las técnicas de evaluación probabilística. Deben incluir la comunicación de los tipos de incertidumbre y la relación con la variabilidad estadística, la imprecisión y la utilización de intervalos de confianza.

- Se debe examinar la utilización de modelos de la relación dosis-respuesta y se han de elaborar principios generales adicionales para su uso cuando se disponga de más experiencia.

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Mouse models of human B lymphoid neoplasms

HERBERT C MORSE III, JERROLD M WARD AND MICHAEL A TEITELL

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INTRODUCTION

The identification of T cells and B cells as subsets of lymphocytes readily distinguished by phenotype and function heralded a new era for the field of immunology. This milestone also marked the end of an epoch in which hematologic malignancies were categorized primarily on the basis of their cytology, histology, and clinical presentation. Classification schemes founded on recognition of microscopic features were gradually replaced by those emphasizing cell lineage and state of differentiation as defined by immunophenotyping. Identification of distinctive chromosomal abnormalities in metaphase spreads foresaw the wealth of molecular genetic approaches that now belong to the armamentarium of a modern department of human hematopathology. The sum of approaches to diagnosis provided by clinical features, morphology, immunophenotype, and genetic characteristics was brought to bear in the 2001 World Health

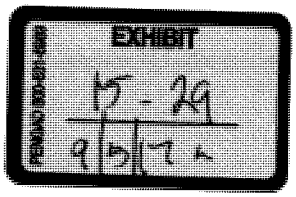

Table 18.1 Relationships between classification of mouse and human B cell-lineage lymphomas

Human B cell neoplasm	Mouse B cell neoplasm
Precursor B cell neoplasm	Precursor B cell neoplasm
Precursor B lymphoblastic leukemia/lymphoma	Precursor B lymphoblastic leukemia/lymphoma
Mature B cell neoplasms	Mature B cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Small B cell lymphoma/leukemia
B cell prolymphocytic leukemia	
Lymphoplasmacytic lymphoma	
Splenic marginal zone lymphoma	Splenic marginal zone lymphoma
Hairy cell leukemia	
Plasma cell myeloma	
Solitary plasmacytoma of bone	
Extraosseus plasmacytoma	Extraosseus plasmacytoma
Extranodal marginal zone B cell lymphoma of mucosal-associated lymphoid tissue	
Nodal marginal zone lymphoma	
Follicular lymphoma	Follicular B cell lymphoma
Mantle cell lymphoma	
Diffuse large B cell lymphoma	Diffuse large B cell lymphoma
Morphologic variants:	Morphologic variants:
Centroblastic	Centroblastic
Immunoblastic	Immunoblastic
T cell/histiocyte-rich	Histiocyte associated
Subtypes:	Subtypes:
Mediastinal (thymic) large B cell lymphoma	Mediastinal (thymic) large B cell lymphoma
Intravascular large B cell lymphoma	
Primary effusion lymphoma	
Burkitt lymphoma/leukemia	
	Diffuse high-grade B cell blastic lymphoma/leukemia

Organization (WHO) classification of human hematopoietic neoplasms,[1] which has recently been updated.

An appreciation of the diversity and pathogenesis of mouse hematopoietic neoplasms has historically lagged far behind that of seemingly similar human malignancies. The spur to changing the *status quo* came from the remarkable progress made in manipulating the mouse genome. The use of transgenic (TG), knockout, knockin, and mutagenized mice to model human diseases has yielded a wealth of new strains, many of which unexpectedly develop hematologic malignancies. In addition, the rate at which the scientific community is generating mouse models of human cancer that require validation has grown almost exponentially. To optimize the utility of mouse models of human lymphoma and leukemia, community standards were developed for classifying both lymphoid and nonlymphoid neoplasms using systems that parallel the WHO schemes for human diseases.[2] These 'Bethesda proposals' were recognized to have inherent limitations due to lack of information on specific disorders and were designed to be open to revision with the development of new data.

This chapter will focus exclusively on B cell–lineage lymphomas, except for plasma cell–related neoplasms, which are covered in Chapter 14. The classification scheme to be used here differs from that published in the Bethesda proposals, with changes suggested by information garnered from the literature and the experiences of our laboratories. The classification defines individual disease entities based on morphology, immunophenotype, genetic features, and state of differentiation in relation to a presumed cell of origin.

Table 18.1 lists the mouse lymphoma types distinguished by these characteristics and their closest human counterpart. This comparison shows that many disease entities recognized in humans do not have parallels in the mouse for either spontaneous diseases or those appearing in genetically engineered mice. Several factors are likely to have contributed to this discrepancy. First, much of our detailed knowledge about mouse B cell lymphomas comes from studies of a limited number of strains. The best-studied strains are NFS.V$^+$ congenic mice[3] and the AKXD recombinant inbred (RI) strains.[4–6] The NFS congenics and most of the RI strains express ecotropic murine leukemia viruses (MuLV) from endogenous germ-line loci at high levels from early in life. When MuLV infect somatic cells, their insertion into genomic DNA is inherently mutagenic.

Some of these mutagenic insertions result in the unprogrammed activation of cellular genes, some of which are protooncogenes that can participate in the process of transformation.[7] These contributions to disease pathogenesis in the mouse have no direct parallels in human B lymphomas that instead feature activation of protooncogenes induced by balanced chromosomal translocations. Translocations resulting in protooncogene activation do occur in the mouse, being found in almost all pristane-induced plasmacytomas of BALB/c mice[8] and rarely in diffuse large B cell lymphomas,[9] but they are certainly not the rule.

Second, there are significant differences between mouse and human immune systems in their development, structure, phenotype, and function.[10,11] For example, expression of CD23 and CD5 is mutually exclusive on mouse but not on human B cell subsets, and CD38 is downregulated on mouse germinal center (GC) B cells but upregulated in humans.[12] More important, perhaps, is that the spleen is the major secondary lymphoid organ of the mouse, whereas lymph nodes fill that niche in humans. In addition, the mouse spleen is responsible for extramedullary hematopoiesis throughout the animal's lifespan, while hematopoiesis in humans is confined to the bone marrow.

Finally, the genetic and epigenetic alterations required for neoplastic transformation sometimes differ for mouse and human.[13] As one example, programmed telomere shortening is viewed as a tumor-suppressor pathway in humans, with activation of telomerase being a requirement for averting replicative senescence. In contrast, telomerase is not repressed in murine somatic cells, and the cellular response to telomere damage differs for mice and humans.[14] A second example comes from studies of mice with targeted mutations of tumor-suppressor genes in which the phenotypes of mutant mice are sometimes highly discordant with the effects of the mutation in humans.[15] Species-specific differences in the immune system and the molecular circuitry required for transformation could thus make it difficult to model some human diseases in mice.

This difficulty is exemplified by efforts to develop a mouse model of Burkitt lymphoma by generating 'simple' *MYC* transgenics,[16–19] yeast artificial chromosome (YAC) transgenics with *MYC* inserted into the IgH locus[20,21] and, most recently, a knockin mouse with *MYC* inserted into the IgH locus in an orientation characteristic of most translocations in endemic Burkitt lymphoma and mouse plasmacytomas.[22] All these mice developed lymphomas with varying latency. Analyses of immunoglobulin (Ig) gene rearrangements and phenotypic analyses showed that the Eμ-Myc lymphomas included pre-B as well as IgM^+ IgD^- lymphomas, a phenotype consistent with immature or transitional B cells. The λ-Myc lymphomas were also found to have features of immature or transitional B cells and had non-mutated Ig genes. Approximately 25 percent of the Myc knockin lymphomas were lymphoblastic with a starry-sky appearance and expression of Bcl-6, a phenotype very much like human Burkitt lymphoma;[22] however, the Ig genes of these lymphomas did not contain somatic hypervariable region mutations,[23] whereas all human Burkitt lymphoma Ig genes contain such mutations to varying extents. Could some mouse B cells passage the GC without being mutated? Can Ig gene mutation occur outside the GC? The answer to the latter question has recently been shown to be 'yes.'[24] Answers to questions such as this will be critical for fully assessing the validity of a mouse model for a human disease.

These concerns are important to those involved in basic research efforts to understand the pathogenesis of mouse lymphomas or to develop mouse models of human cancers. Other scientific communities need only determine whether mice presented to them have a neoplasm and, if so, how to classify that tumor. In the former circumstance, many approaches can be applied to make diagnoses that contribute to understanding B cell pathogenesis. In the latter, histologic analysis of fixed sections stained with hematoxylin and eosin will sometimes be the only material available for diagnosis. The classification system described below for each lymphoma class is intended to be useful for both the basic research and applied science communities.

PRECURSOR B CELL LYMPHOBLASTIC LYMPHOMA/LEUKEMIA

Definition

Precursor B cell lymphoblastic lymphoma/leukemia (pre-B LBL) is a high-grade neoplasm of small to medium-sized, round, uniform precursor B cells arising in the bone marrow. A leukemic phase and spread to peripheral lymphoid and nonlymphoid tissues is frequently present.

Synonyms

Lymphoblastic lymphoma; lymphoblastic leukemia

Epidemiology of spontaneous disease

SL/Kh is a recombinant congenic mouse strain, derived from proto-SL and AKR strains, that develops pre-B LBL.[25,26] Tumors arise from a combination of host genetic factors and reintegration of endogenous MuLV provirus into several loci that include *Stat5a, Stat5b, Evi3, c-Myc,* and *n-Myc.*

Crosses between AKR and DBA/2 mice created 24 distinct AKXD RI strains with distinct MuLV proviral integration sites, most of which develop lymphoma.[4–6] Tumors classified as pre-B LBL on the basis of lymphoblastic cytology and the presence of clonal IgH rearrangements without detectable IgL clonality morphology arise in at least ten different AKXD RI strains, although analysis of additional phenotypic features of pre-B LBL have not yet been performed.[6]

Epidemiology of disease in genetically engineered mice

BCR-ABL^{p210} *retrovirus-transduced bone marrow cells*:[27–29] Infection of bone marrow (BM) cells from mice treated with 5-fluorouracil with a BCR-ABL^{p210}-expressing retrovirus followed by injection of lethally irradiated hosts yielded pre-B LBL in DBA/2 recipients, T cell acute lymphocytic leukemia (T-ALL) in C57BL/6 recipients, and other hematopoietic tumors in BALB/c recipients.

Metallothionein-1 promoter-BCR-ABL^{p190} *TG*:[30,31] Transgenic mice developed either chronic myeloid leukemia (CML) in blast crisis or pre-B LBL.

IgV_H-promoter-Eμ or retroviral LTR-bcr/v-abl TG:[32] Transgenic mice expressing a synthetic BCR-ABL gene created by fusing *bcr* with *v-abl* sequences developed either pre-B LBL or probably pre-T LBL.

BCR-ABL^{p190} knockin:[33] BCR-ABL inserted in-frame into exon 1 of the endogenous *bcr* locus by homologous recombination mimics half of the reciprocal translocation seen in Philadelphia (Ph)-positive cases. These *BCR-ABL^{p190}* 'knockin' mice developed pre-B LBL.

Eμ-myc TG:[16] These mice developed pre-B LBL together with more mature lymphomas. Most tumors lacked IgL gene rearrangements and were surface immunoglobulin (sIg)$^-$. Crossing Eμ-*myc* TG with Eμ-*pim1* TG mice, which develop low-frequency pre-T LBL, resulted in congenital pre-B LBLs that were B220$^+$ and sIg$^-$.[34]

Eμ-Blk TG:[35] Blk is a Src family tyrosine kinase that associates with and signals from the pre-BCR and BCR.[36] Mice with a constitutively active Blk (Y495F) flanked by a H-2K promoter and Eμ developed pro-B and pre-B LBL along with intermediate single positive–stage thymic pre-T LBL. B cell–lineage tumors occurred in 45 percent of mice by 6 months. Activating lesions for the *Blk* homolog in human B and T cell tumors have not yet been described.

LTR-TEL/AML1 retrovirus-transduced BM cells:[37–39] A t(12;21)(p13;q22) occurs in 25 percent of pediatric and 3 percent of adult B-ALL cases, resulting in a *TEL/AML1* oncogene. TEL/AML1 retains the amino portion of the TEL protein fused to the AML1 DNA binding domain. TEL/AML1 may cause B-ALL by direct repression of AML1 target genes or by TEL inhibition of other ETS family proteins via binding through its pointed domain.[40–42] Transduction of wild-type or *p16^{Ink4a}*/p19^{Arf} null BM retrovirus was followed by adoptive transfer into lethally irradiated C57BL/6 mice. A low frequency of pre-B-ALL and T-ALL from the transduced wild-type donor cells and a higher frequency of an undetermined leukemia type was seen with the *p16^{Ink4a}*/p19^{Arf}-deficient cells.

Aiolos knockout:[43] Aiolos is a member of a kruppel-like zinc finger transcription factor family that binds DNA and regulates lymphocyte development and function. A knockout of Aiolos causes hyperproliferation and constitutive B cell activation followed by lymphadenopathy and evolution into probable B-LBL in 20 percent of mice. Alternatively, spliced Aiolos isoforms lacking a full complement of DNA binding domains in normal and leukemic human B cells have been reported, but their role in B cell transformation is not resolved.[44,45]

p16^{INK4a}/p19(p14)^{ARF} *knockouts*:[46] The *p16^{INK4a}/p19(p14)^{ARF}* genes overlap in the genome and encode tumor suppressor proteins that inhibit cancer formation.[47] Mice deficient in *p16^{Ink4a}/p19^{Arf}* developed mainly soft tissue sarcomas or B220$^+$ B cell lymphomas with prominent nucleoli that effaced lymph nodes. Although not further characterized, these features suggest a pre-B LBL phenotype. Deletion of *p16^{INK4a}*/p14^{ARF} occurs in 20 percent of B-ALL and 60 percent of T-ALL arising during childhood.[48] Also, DNA methylation of the *p16^{INK4a}* (but not of the *p14^{ARF}*) locus occurs in multiple types of non-Hodgkin lymphoma (NHL) and acute myeloid leukemia (AML), accompanied by loss of *p16^{INK4a}* expression.[49]

IL-7 TG:[50–53] Interleukin-7 (IL-7) and the IL-7/γcR regulate lymphopoiesis. Four distinct transgenic strains were generated to aberrantly express IL-7. A major histocompatibility complex (MHC)-II E_α promoter–IL-7 transgene causes λ5 and EBF-expressing pre/pro-B/pro-B LBL with germ-line Ig genes.[53] Clonality is difficult to establish, and femurs are packed with lymphoid blast cells. There is accompanying lymphadenopathy. The tumor incidence varies by strain, with almost 100 percent of BALB/c and 25 percent of C57BL/6 mice developing morbid disease. Human lymphoid malignancies from IL-7 dysregulation have not been reported.

Histologic features

Pre-B LBL forms sheets of small to medium-sized blast cells in the bone marrow or infiltrated organs. The nuclei appear round to oval with condensed chromatin and a central, prominent nucleolus. There is a high nuclear:cytoplasmic ratio, with scant eosinophilic cytoplasm. A high mitotic index and abundant apoptosis can provide a 'starry-sky' appearance from macrophages stuffed with apoptotic debris (tingible body macrophages) that is histologically indistinguishable from that seen with pre-T LBL or more mature sIg$^+$ diffuse high-grade blastic B cell lymphoblastic lymphomas (DBLL), previously referred to as Burkitt-like.[2] Distinction is made from pre-T LBL, which are CD3$^+$ and B220$^-$, and DBLL, which are sIg$^+$ and contain rearranged IgL. Gross presentation may include lymphadenopathy without splenomegaly, a relatively unique occurrence for B cell lineage mouse tumors.

Immunologic features

Precursor B cells that by flow cytometry (fluorescence-activated cell sorting; FACS) are sIg$^-$, B220$^+$, CD19$^+$, CD43$^{+/-}$, Ly6d (ThB)$^+$, and by immunohistochemistry (IHC) are TdT$^+$.

Molecular features

Clonal population of precursor B cells with IgH gene rearrangement, typically of one allele and germ-line configuration of κ and λ IgL.

Postulated cell of origin

Bone marrow precursor B cell lymphoblast.

Comments

Mice containing BCR-ABL–infected BM or mice expressing either form of BCR-ABL (or bcr-v-abl) using transgenic, tetracycline-inducible or knockin technologies develop pre-B LBL with variable penetrance and strain dependence.[54] The p210 isoform of BCR-ABL generally does not result in B-ALL in humans. The human counterpart malignancies are pro-B and pre-B acute lymphoblastic leukemia (B-ALL) or B lymphoblastic lymphoma (B-LBL). Pre-B LBL shows similar histologic, cytologic, phenotypic, and molecular features in mice and humans.

SMALL B CELL LYMPHOMA/LEUKEMIA

Definition

A neoplasm of small, round, monomorphic B cells in the spleen and lymph nodes, sometimes admixed with prolymphocytes and paraimmunoblasts in pseudofollicles. Cases without leukemia (i.e., lymphoma) are more common than cases with leukemia.

Synonyms

Lymphocytic lymphoma; small lymphocytic lymphoma; chronic lymphocytic leukemia; well-differentiated lymphocytic lymphoma.

Epidemiology of spontaneous disease

Frequency was ~1 percent in AKXD RI strains and ~12 percent of all B cell lineage lymphomas in NFS.V$^+$.[55] The average age at diagnosis was ~400 days in NFS.V$^+$ mice. Uncommon in most commonly used mouse strains and stocks.

Epidemiology of disease in genetically engineered mice

Eμ-TCL1 TG:[56] Mice exhibited involvement of bone marrow at 2 months, spleen at 5 months, and leukemia at 5 months with CD5$^+$CD11b$^+$Bcl-6$^-$ clonal B cells. Spleens often exhibited marked expansion of the marginal zone.

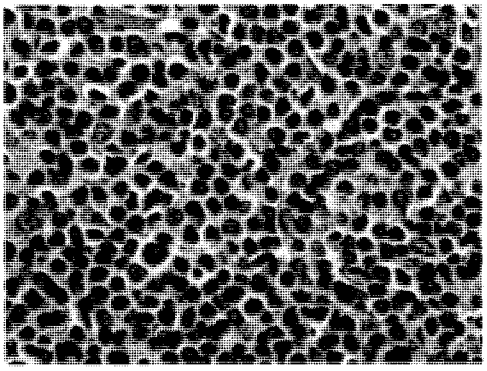

Figure 18.1 Small B cell lymphoma showing a uniform population of small lymphocytes similar to those of the normal mantle zone. There are few mitotic figures, apoptotic bodies, or tingible body macrophages.

TRAF2DN/BCL-2 TG:[57] Transgenic mice exhibited splenic involvement at 10–16 months often associated with leukemia, ascites, and pleural effusion with CD5$^{+/-}$ CD11b$^+$Bcl-6$^-$ B cells. Splenic marginal zone expansion was often present.

IL-5 TG:[58] Forty percent of mice presented with clonal CD5$^+$ B cell leukemia by 22 months of age.

Histologic features

Enlarged splenic white pulp filled with small lymphocytes and some larger prolymphocytes, with few mitotic or apoptotic figures (Fig. 18.1). Isolated accumulations of [AQ1] cells with features of immunoblasts can form proliferation centers similar to those seen in human chronic lymphocytic leukemia (CLL). A readily evident blood phase with predominantly small lymphocytes is seen in about 25 percent of cases. Extensive, diffuse infiltration of lymph nodes, lung, liver, and kidney can occur in the presence or absence of leukemia. Progression to immunoblastic lymphoma is rare, with immunoblasts and small lymphocytes cohabiting isolated areas, a possible parallel to Richter's transformation in human CLL.

Immunologic features

NFS.V$^+$ lymphomas were usually IgM$^+$B220^d CD5^d CD11b$^{+/-}$ by FACS and PAX-5$^+$Bcl-6$^-$ by IHC.

Molecular features

Clonal IgH rearrangements. No major structural rearrangements of protooncogenes or tumor suppressor genes were identified in mice with spontaneous disease.

Postulated cell of origin

Not known. Immunoglobulin V-region sequencing required to determine whether pre- or post-GC.

Comments

Strains NZB and NZW, and genetically engineered strains including those listed above under induced diseases, regularly exhibit age-related expansions of populations of $CD5^+$ B cells in the peritoneum, spleen, and blood, sometimes sequentially. Expression of CD5 on mouse B cells is usually confined to a substantial proportion of B cells in the peritoneum and ~2 percent of B cells in the spleen.

SPLENIC MARGINAL ZONE B CELL LYMPHOMA

Definition

A neoplasm of cells from the splenic marginal zone presenting as low-, intermediate-, or high-grade disease that arises in the spleen and is almost always restricted to the spleen.

Synonyms

Splenic marginal zone lymphoma.

Epidemiology of spontaneous disease

The frequency of marginal zone lymphoma (MZL) was ~7 percent in NZB mice.[59] Marginal zone lymphoma accounted for ~35 percent of all neoplasms in $NFS.V^+$ and ~18 percent in AKXD strains.[55] The mean latency in NZB mice was ~450 days. In $NFS.V^+$ mice, the average age at diagnosis for low-, intermediate-, or high-grade disease was ~400 days.[60] In AKXD RI strains, the mean latency of predominantly low-grade disease was ~500 days.[6] A significant number of one-year-old TAN mice, a strain derived from a cross between NZB and NZW, also had MZL. Frequency is less than 1 percent in most commonly used mouse strains and stocks.

Epidemiology of disease in genetically engineered mice

In *p53* knockouts,[61] MZL was diagnosed in ~35 percent of ex-breeder mice.

Histologic features

Three levels of progression have been described: MZL, [AQ1] MZL+, and MZL++ (Fig. 18.2, Fig. 18.3, and Fig. 18.4). Marginal zone lymphoma is characterized by a substantially

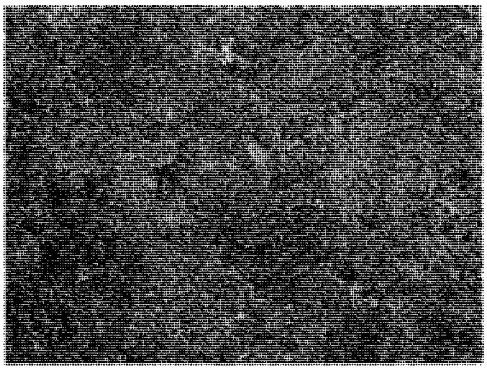

Figure 18.2 Splenic marginal zone lymphoma. Note atrophic white pulp and a halo of normal-appearing marginal zone lymphoid cells fingering out into the red pulp. Mitoses and apoptotic bodies are uncommon at this stage.

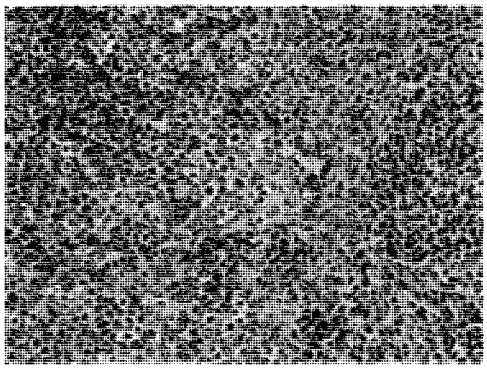

Figure 18.3 Splenic marginal zone lymphoma. The marginal zone is replaced by neoplastic lymphocytes adjacent to atrophic white pulp. Cells retain the features of normal marginal zone cells with an ovoid nucleus featuring fine chromatin, small, often inconspicuous nucleoli, and plentiful cytoplasm.

widened marginal zone comprising cells with normal cytology yielding a halo-like appearance around the follicles. Early lesions include hyperplastic marginal zone B cells with abundant eosinophilic cytoplasm and uniformly shaped nuclei. At this stage, mitoses are rare. With progression to MZL+, there is a merging of the marginal zones and the cells have taken on centroblastic features. Infiltration of the red pulp is often extensive, but follicles are usually intact. By the MZL++ stage, the spleen can be almost completely taken over by cells with centroblastic or, more rarely, immunoblastic morphology. The white pulp is usually rudimentary, consisting only of a periarteriolar lymphoid sheath (PALS). Mitoses are common. The lymphoma occasionally extends to the splenic node and rarely

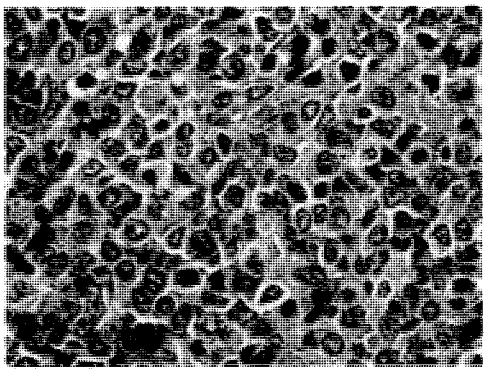

Figure 18.4 Marginal zone lymphoma with pleiomorphic population of lymphocytes with moderate amount of eosinophilic cytoplasm.

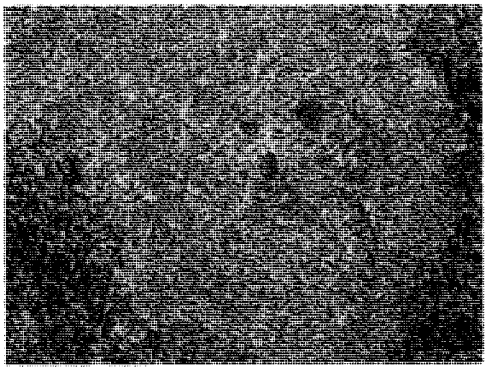

Figure 18.5 Follicular lymphoma. Depletion of normal darker T lymphocytes in the periarteriolar lymphoid sheath and replacement of white pulp by lymphoma.

disseminates to the liver or other tissues. A leukemic phase is extremely rare.

Immunologic features

By FACS analysis, MZL – regardless of grade – expressed IgM at varying levels and little to no IgD.[60] Almost all cells expressed CD5 and CD45R(B200) at low levels and CD38 at high levels but were $CD23^-$. Nearly half of cases expressed CD11B at low levels. By IHC, cases were consistently $IgM^+CD45R(B220)^{dull}$ IgD^-CD5^-.

Molecular features

Clonal for Ig gene rearrangements, with oligoclonality being more common among MZL than MZL+ or MZL++.[60,61] Rearrangements of cellular loci identified in MZL of AKXD RI strains included *Nmyc1*, *Pim1*, and *Evi1* in ~16 percent of cases.[6] Marginal zone lymphoma of $NFS.V^+$ mice studied for common proviral integration sites identified three or more integrations at *Stk10*, *Abcc5*, *Sox4*, *Mela*, and *Edh2*.[62] *Gfi1* was also identified as a common integration site (CIS) and was expressed at elevated levels in all grades of MZL.[62]

Postulated cell of origin

Splenic marginal zone B cell.

Comments

Non-splenic MZL in humans is associated with autoimmune diseases including, most prominently, Sjögren syndrome and Hashimoto thyroiditis.[63] Marginal zone lymphoma also occurs in association with infections caused by *Helicobacter pylori*, *Chlamydia psittaci*, and other agents. The observation that MZL occurs in autoimmune NZB mice and in the TAN strain, derived from a cross between NZB and NZW, suggests a possible etiologic link with human MZL. Shared low-affinity reactivity with autoantigens or repetitive bacterial antigens could be that tie. Autoimmune disease is generally not associated with these lymphomas in mice.

FOLLICULAR B CELL LYMPHOMA

Definition

Follicular B cell lymphoma (FBL) is a neoplasm comprising a mixture of B-lineage cells with cytologic features of centrocytes and centroblasts in varying proportions (Fig. 18.5 and Fig. 18.6). [AQ1]

Synonyms

Follicular lymphoma; centroblastic/centrocytic lymphoma; follicular center cell lymphoma, mixed; reticulum cell sarcoma, type B; lymphoma-pleiomorphic.

Epidemiology of spontaneous disease

This is the most common neoplasm in aging mice of many inbred strains. It accounts for 6 percent of cases in $NFS.V^+$ mice, 35 percent of cases in CFW strains, and 8 percent of cases in AKXD RI strains.[55] The average age at diagnosis is ~435 days for $NFS.V^+$ and ~400 days for the AKXD RI strains but ranges from 18 to 24 months in most other strains and stocks.

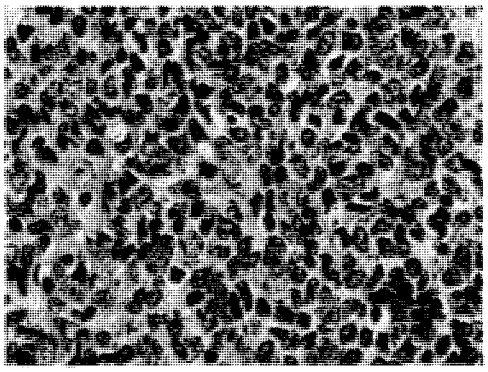

Figure 18.6 Follicular lymphoma showing a pleiomorphic population of centroblasts and centrocytes. Centrocytes feature irregularly shaped, often elongated, relatively dense nuclei with little cytoplasm. Centroblasts are marked by larger, vesicular nuclei with more prominent nucleoli, often with two appended to the nuclear membrane.

Epidemiology of disease in genetically engineered mice

Eμ-BCL-2 TG:[64,65] Both TG lines of mice were reported to develop follicular hyperplasia that progressed to overt lymphoma. No increase in lymphoma incidence was found in later studies of the same strains.

Mcl1 *TG*:[66] About 65 percent of mice presented with lymphoma by two years of age, most presenting with splenomegaly and lymphadenopathy. Around 20 percent of cases were FBL.

VavP-Bcl-2 TG:[67] Approximately 60 percent of mice not dying previously with autoimmune disease succumbed to lymphoma between 10 and 18 months of age. Lymphoma development was preceded by increases in the number and size of GC and class-switched B cells with mutated Ig genes. The expanded GC phenotype was totally dependent on the presence of $CD4^+$ T cells.

Histologic features

Animals present most commonly with gross lesions of splenomegaly and varying degrees of enlargement of the mesenteric lymph node and Peyer's patches. In the spleen, the white pulp is expanded, appearing as white nodules that coalesce as the disease progresses. Occasionally, there is only a solitary large white nodule in the spleen. The smaller nodules are enlarged, sometimes with fused follicles with centrocytes and centroblasts as the chief cellular constituents. Normal small follicular B cells are pushed to the periphery, and the T cell zone is reduced or eliminated. In some mouse strains, tumors may arise within the PALS or inactive white pulp with

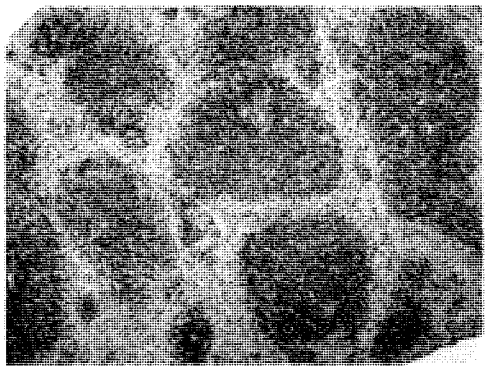

Figure 18.7 Immunohistochemistry of follicular lymphoma B cells expressing CD45R(B220) on the cell surface.

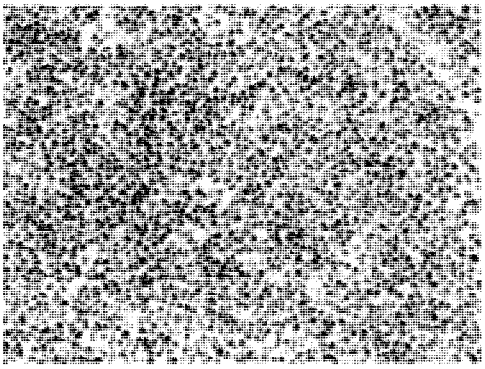

Figure 18.8 Immunohistochemistry of follicular lymphoma expressing PAX-5 (B cell lineage specific activator protein; BSAP) at high levels in the nucleus of lymphoma cells.

no apparent relation to the GC. The proportions of centrocytes and centroblasts vary from case to case. The proportion of blasts should be less than 50 percent to differentiate the condition from diffuse large B cell lymphoma (DLBCL).

Immunologic features

By FACS, both the centrocytes and centroblasts in spontaneous cases were most often $IgM^+IgD^-CD5^{dull}CD45R(B220)^{dull\ to\ normal}$. By IHC, both populations were IgM^+B220^+ (Fig. 18.7 and Fig. 18.8).[68] [AQ1]

Molecular features

All cases examined in $NFS.V^+$ and AKXD mice were mono- or oligoclonal for Ig gene rearrangements.[3,6] No rearrangements in Bcl-2 were seen in large panels of FBL

from NFS.V$^+$ mice or other inbred strains.[2] Genomic rearrangements of oncogenes or tumor suppressor genes were seen only for *Evi1* in AKXD mice.[6]

Postulated cell of origin

Germinal center centrocytes and centroblasts.

DIFFUSE LARGE B CELL LYMPHOMA

Definition

Diffuse large B cell lymphoma is a B cell neoplasm characterized by a diffuse proliferation of cells with large nuclei and distinctive cytologic features characteristic of each of the variants seen in spontaneous disease: centroblastic (CBL), immunoblastic (IBL), and histiocyte associated (HA) DLBCL.

DLBCL – centroblastic

SYNONYMS

Large cleaved follicular center lymphoma; centroblastic lymphoma.

EPIDEMIOLOGY OF SPONTANEOUS DISEASE

Centroblastic DLBCL accounted for ≈12 percent of cases in NFS.V$^+$ mice and 17 percent in CFW mice but were not observed among AKXD RI strain lymphomas.[55] The average age at diagnosis was ≈400 days in NFS.V$^+$ mice. The disease is uncommon in most commonly used strains and stocks of inbred mice.

HISTOLOGIC FEATURES

The white pulp is greatly expanded, with a population of cells with round nuclei, often with two nucleoli attached to the nuclear membrane, and a moderate amount of [AQ1] basophilic cytoplasm (Fig. 18.9). These are admixed to varying extents with smaller cells with characteristics of centrocytes. The diagnosis is readily made when over 70 percent of the cells are blasts. When the proportions of centrocytes and blasts range from 40 percent to 70 percent and the ratio varies in different fields, a distinction between FBL and DLBCL is difficult. In the classification system of Fredrickson and Harris,[68] CBL is subdivided into follicular, marginal zone, and diffuse to identify distinct regional origins for the first two and CBL of uncertain origin for the last. The lymphoma frequently infiltrates the lung, liver, and kidney and, less frequently, the bone marrow.

IMMUNOLOGIC FEATURES

By FACS, the tumors are IgM$^+$ or IgG$^+$, CD19$^+$, and B220$^+$ and often express CD5 at low levels. The tumors are almost uniformly Bcl-6$^+$ PAX-5$^+$IRF-8$^+$PU.1$^+$ by IHC, but CD138$^-$XBP-1$^-$IRF-4$^-$BLIMP$^-$.

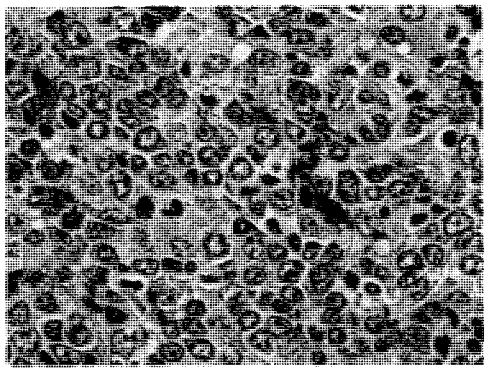

Figure 18.9 Diffuse large B cell lymphoma (DLBCL), centroblastic. Centroblasts have chromatin along the nuclear membrane and prominent nucleoli.

MOLECULAR FEATURES

The tumors are clonal for Ig gene rearrangements, and rare cases have structural changes in Bcl-6.[9] Oligonucleotide microarray analyses have shown no clear distinctions between CBL subclassified as follicular or diffuse, suggesting similar origins from follicular B cells for both. By this methodology, both are readily distinguished from the centroblastic form of MZL, MZL++.

POSTULATED CELL OF ORIGIN

Germinal center dark zone centroblasts.

DLBCL – immunoblastic

SYNONYMS

Immunoblastic lymphoma.

EPIDEMIOLOGY OF SPONTANEOUS DISEASE

Immunoblastic lymphoma comprised ~8 percent of cases in NFS.V$^+$ mice and 4 percent in CFW mice, but was not observed among AKXD strain lymphomas.[55]The average age at diagnosis in NFS.V$^+$ mice was ~400 days.

HISTOLOGIC FEATURES

These are highly aggressive tumors populated by cells with large nuclei having dispersed chromatin and large, frequently bar-shaped nucleoli (Fig. 18.10). The cells are [AQ1] frequently admixed with centroblasts and centrocytes

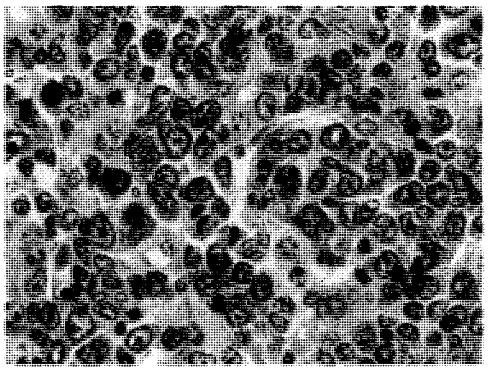

Figure 18.10 Diffuse large B cell lymphoma (DLBCL), centroblastic-immunoblastic. Central nucleoli can be seen in some of the large blast cells. Immunoblasts often have large, magenta, bar-shaped nucleoli appended to the nuclear membrane on one side.

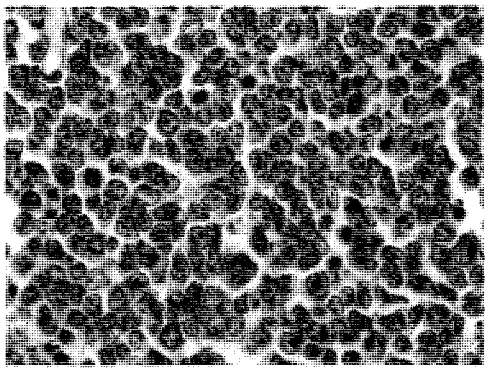

Figure 18.11 Diffuse high-grade lymphoblastic lymphoma of mature B cells. Cells are of intermediate size with scant cytoplasm and often having a prominent central nucleolus. Mitoses and apoptotic bodies are common and tingible body macrophages in many cases can give a starry-sky appearance.

reflecting their probable origin in FBL or from a post-GC immunoblast.

IMMUNOLOGIC FEATURES

By FACS, surface Ig levels are very low and they are $B220^{dull}$. By IHC, almost all cases are Bcl-6^+ and PAX-5^+ but IRF-8^-XBP-1^-IRF-4^-PU.1^-BLIMP$^-$.

MOLECULAR FEATURES

Clonal for Ig gene organization.

PRESUMED CELL OF ORIGIN

Post-GC immunoblast.

DLBCL – histiocyte associated

SYNONYMS

Diffuse large cell lymphoma, histiocyte associated (DLCL[HS]).

EPIDEMIOLOGY OF SPONTANEOUS DISEASE

In AKXD RI strains, ~20 percent of lymphomas were HA, while only ~1 percent of NFS.V^+ lymphomas were diagnosed as such.[55] The average age at diagnosis for the AKXD RI strains was ~500 days. The disease is uncommon in commonly used strains and stocks of mice.

HISTOLOGIC FEATURES

All mice present with splenomegaly associated with a marked expansion of macrophages (histiocytes) with frothy eosinophilic cytoplasm and, usually, quite limited numbers of lymphocytes. The histiocytes often occupy the entire white pulp, obliterating the PALS and normal follicular structure, leaving patches of B cells pushed to the periphery. Most often, the lymphocytes have features characteristic of FBL or CBL although rare cases with features of MZL, small B cell lymphoma (SBL), or IBL have been observed. Lymphadenopathy was seen in about half of the cases and was associated with diffuse histiocytic infiltration.

IMMUNOLOGIC FEATURES

The histiocyte population is frequently positive for EMR1 (F4/80) and LGALS3 (Mac-2) by IHC, with the B cell populations clearly delineated by exclusive expression of PAX-5.

MOLECULAR FEATURES

Frequently, the diagnosis can be made only after evaluating Ig gene organization and IHC staining. The presence of clonal Ig gene rearrangements and PAX-5^+ populations of cells associated with a histologic picture dominated by histiocytes is diagnostic. The differential diagnosis is true histiocytic sarcoma. In some cases, clonal rearrangements of T cell receptor (TCR)β have also been observed.

PRESUMED CELL OF ORIGIN

Germinal center B cells for the B cell component, in most cases; tissue macrophages for the histiocytic component.

DLBCL in genetically engineered mice

T and B cell–lineage lymphomas and autoimmunity are among the most common unexpected features of transgenic

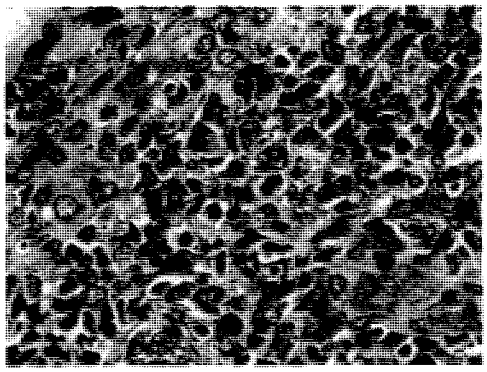

Figure 18.12 Diffuse large B cell lymphoma (DLBCL), histiocyte-associated, showing large eosinophilic histiocytes in association with large blastic B lymphoma cells and normal erythroid cells with small dark nucleoli. The B cell component is most often centroblastic or follicular, but cases with malignant immunoblasts, plasma cells, marginal zone B cells or, rarely, small B cells, are seen.

and knockout mice.[69] The B cell neoplasms appearing in individual lines of such mice may span several histologic types, ranging from FBL to CBL and IBL and histiocyte-associated DLBCL (Fig. 18.12). They may resemble the spontaneous lymphomas of older mice of commonly used strains while developing in younger animals than in wild-type mice and having a more aggressive phenotype. It is important to distinguish induced from spontaneous tumors in genetically engineered mice. The genetic manipulation may simply accelerate the development of a disease seen in wild-type mice or may induce novel diseases not seen in conventional strains and stocks.

[AQ1]

FEATURES OF GENETICALLY ENGINEERED MICE WITH DLBCL

Riz1 knockout:[70] About 37 percent of −/− and 19 percent of +/− mice killed between 18 and 22 months of age had clonal B cell lymphomas with histologic and cytologic features of centroblastic DLBCL.

H2-L^d-Il6 *TG:*[71] Between 6 and 19 months of age, many TG mice developed FBL or CBL that sometimes coexisted with plasmacytomas. The lymphomas were IgM$^+$CD19$^+$ CD45R(B220)$^+$. Several of the lymphomas had t(12;15) IgH/Myc translocations detectable by polymerase chain reaction (PCR) and/or Southern blotting.

Eμ-TCL1 *TG:*[72] Transgenic mice averaging ~12 months of age presented with splenomegaly and often with lymphadenopathy due to lymphomas. The tumors were classified as FBL, DLBCL(HA), CBL, and DBLL. The neoplasms were clonal, had mutated Ig genes, and were Bcl-6$^+$.

Bad *knockouts:*[73] About 20 percent of mice homozygous for a null allele developed clonal B cell lymphomas between 18 and 24 months of age. The lymphomas were surface IgM$^+$ or IgG$^+$ and were Bcl-6$^+$.

*Iμ*BCL-6 *knockins:*[74] Mice with *Bcl-6* knocked into the IgH locus developed DLBCL and FBL beginning at 13 months of age. The lymphomas were clonal with mutated IgG genes and variably expressed some late GC markers such as IRF-4. Trisomy 15 was common.

*Eμ*Myc *knockins:*[22,23] Mice with *Myc* knocked into the IgH locus 5′ of Eμ developed DLBCL between 6 and 21 months of age. Other B cell-lineage neoplasms included FBL, plasmacytomas, and DBLL. The DLBCL were clonal and Bcl-6$^+$IgM$^+$CD45R(B220)$^+$CD19$^+$.

PRESUMED CELL OF ORIGIN

Germinal center B cells.

DIFFUSE HIGH-GRADE BLASTIC B CELL LYMPHOMA/LEUKEMIA

Definition

Diffuse high-grade lymphoblastic lymphoma/leukemia is a highly aggressive neoplasm characterized by a uniform population of medium-size B cells usually associated with a high mitotic rate and extensive apoptosis, sometimes with a leukemic phase.

Synonyms

Lymphoblastic lymphoma; Burkitt and Burkitt-like lymphoma; DLBCL of lymphoblastic lymphoma subtype (DLBCL[LL]).

Epidemiology of spontaneous disease

Diffuse high-grade lymphoblastic lymphoma/leukemia accounted for ~20 percent of cases in NFS.V$^+$ mice and ~30 percent in AKXD RI strains and CFW mice.[55] The average age at diagnosis for NFS.V$^+$ mice was ~280 days and for AXKD RI strains was ~350 days. This disease is not frequent among commonly used inbred strains and stocks.

Epidemiology of disease in genetically engineered mice

Eμ-Myc *TG:* All TG mice with a particular construct[16] died with clonal lymphoma by 84 weeks of age, with a median time to diagnosis of ~90 days, while mice with a different construct[18] died with clonal lymphoma, with a mean time to diagnosis of ~115 days.

IgH/c-myc YAC and EΔIgH/c-myc YAC TG:[20,21] All mice died with clonal lymphoma before 20 weeks of age.

λ-*MYC TG*:[19] All mice died with clonal lymphoma with an average age at diagnosis of ~125 days.

Histologic features

Cases present with lymphadenopathy and variable involvement of the spleen. Affected tissues are infiltrated with lymphoblasts: uniform cells of medium size with little cytoplasm, moderately dispersed chromatin, and indistinct nucleoli. These are associated with many mitotic figures and often with large numbers of tingible body macrophages ingesting apoptotic cells and leading to a starry-sky appearance (Fig. 18.11). In lymph nodes, early infiltration of the deep cortex progresses to total replacement of normal cells, with growth outside the capsule and into the fat. The spleen, when involved, exhibits diffuse infiltration of the red and white pulp. Perivascular and peribronchial infiltrates of the lungs and periportal live infiltrates are common.

[AQ1]

Immunologic features

Diffuse high-grade lymphoblastic lymphoma/leukemia has a spectrum of surface phenotypes ranging from patterns similar to those of normal immature or transitional B cells – $IgM^+IgD^-CIQR1(AA4.1)^+$ – to that of cells that are Ig class switched and mutated for Ig V-region sequences. The less mature phenotype is characteristic of most lymphomas of Eμ-*Myc*, IgH/*c-myc* YAC, EΔIgH/c-myc YAC, and λ-MYC transgenic mice. More mature phenotypes are characteristic of many spontaneous DBLL of $NFS.V^+$ mice and some lymphomas of Eμ-*TCL1* TG and E*μMyc* knockin mice along with many other genetically engineered mice.

Molecular features

The lymphomas are clonal for IgH and IgL rearrangements. Structural rearrangements of cellular genes, most due to proviral insertions, were found in pooled studies of $NFS.V^{+3}$ and AKXD RI^6 lymphomas for *Zfp521* (*Evi3*) (11.9 percent), *Pim1* (5.6 percent), *Evi1* (4.8 percent), and *Myc* (0.8 percent). Lymphomas of λ-MYC were characterized by chromosomal instability and frequent biallelic deletions of *Cdkn2a* (p16).[19] Lymphomas of Eμ-*Myc* mice had frequent changes in the $p19^{ARF}$-MDM2-p53 tumor suppressor axis.[22]

Presumed cell of origin

Immature or transitional B cells for Eμ-*Myc*, IgH/*c-myc* YAC, EΔIgH/c-myc YAC, and λ-MYC transgenic mice. Probable GC or early post-GC cells for those with features similar to the DBLL of Eμ-*TCL1* transgenic mice.

Comments

B cell-lineage lymphomas with lymphoblastic cytology but distinct from precursor B lymphoblastic neoplasms are seen at low to high frequency in many strains of genetically engineered mice and a number of conventional inbred strains. The lymphomas of λ-MYC transgenic mice were previously designated Burkitt lymphoma,[2] but the findings that Ig genes are not mutated and that they have a surface phenotype of transitional or immature B cells indicate that they differ from most human Burkitt lymphoma cases, suggesting that another designation is warranted. Mouse cases with similar histology and cytology occurring in mice other than the λ-MYC transgenic mice were previously designated Burkitt-like.[2] The findings that they rarely have structural alterations in *Myc* and do not overexpress *Myc* distinguish them from human Burkitt-like lymphomas.[1]

KEY POINTS

- Mouse B cell-lineage lymphomas comprise a spectrum of tumor types that can be distinguished through studies of their histologic, immunophenotypic, and molecular features and their relationship to a presumed cell of origin.
- Most detailed information on these lymphomas has come from studies of a limited number of mouse strains that express murine leukemia viruses at high levels, with the viruses acting as insertional mutagens.
- Some mouse lymphoma classes identified in high-virus mice exhibit many similarities to distinct lymphoma types in humans, whereas others appear to be species specific. There are many human B cell-lineage neoplasms that have no known counterpart in mice.
- Efforts to model human lymphomas in the mouse through genetic engineering have generally failed to produce accurate replicas but have generated invaluable information on the functions of oncogenes and tumor suppressor genes in normal B cell biology and their contributions to the transformed state in mice.
- The true utility of any mouse model will only be known when it has been rigorously dissected using the combined powers of histologic, immunophenotypic, genetic, and epigenetic analyses.

ACKNOWLEDGMENTS

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● = Key primary paper
◆ = Major review article

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Detail of Query
Figure call-outs have been added through the text (marked with [AQ1]); please ensure that these are all located in the required position
NOTE Based on text order, should Figures 18.11 and 18.12 be renumbered so that the image currently labeled 18.12 appears with text for DLBCL, histiocyte-associated; then the image currently labeled 18.11 appears last, close to text on diffuse high-grade blastic B cell lymphoma/leukemia?

Expert Report
Christopher J. Portier, Ph.D.

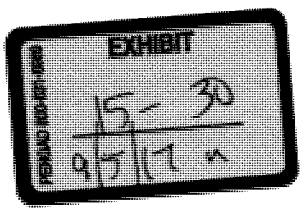
Charge

Glyphosate acid is a colorless, odorless, crystalline solid. Glyphosate is the term used to describe the salt that is formulated by combining the deprotonated glyphosate acid and a cation (isopropylamine, ammonium, or sodium). This expert report is intended to review the available scientific evidence relating to the potential of glyphosate and glyphosate-based formulations (GBFs), including Roundup®, to cause Non-Hodgkin's Lymphoma (NHL) in humans.

Qualifications

I received an undergraduate degree in mathematics in 1977 from Nicholls State University and a Master's degree and Ph.D. in biostatistics from the University of North Carolina School of Public Health in 1979 and 1981 respectively. My Ph.D. thesis addressed the optimal way to design a two-year rodent carcinogenicity study to assess the ability of a chemical to cause cancer[1, 2]; the optimal dosing pattern from my thesis is still used by most researchers. My first employment following my doctoral degree was a joint appointment at the National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP) to conduct research on the design and analysis of experiments generally employed in toxicology. After 5 years with NIEHS/NTP, I developed my own research group which eventually became the Laboratory of Quantitative and Computational Biology and then the Laboratory of Computational Biology and Risk Assessment (LCBRA). One highlight during this period was the development of the Poly-3 Test for survival adjustment of data from two-year carcinogenicity studies in rodents[3, 4]; this test is used as the main method of analysis of these studies by the NTP and many others. We also did a complete analysis of the historical controls animals from the NTP studies[5, 6]. The LCBRA focused on the application of computational tools to identify chemicals that are toxic to humans, to develop tools for understanding the mechanisms underlying those toxicities and to quantify the risks to humans associated with these toxicities. The main toxicological focus of the LCBRA was cancer and my laboratory developed many methods for applying multistage models to animal cancer data and implemented the use of these models in several experimental settings[7-19]. In my last few years at the NIEHS/NTP, my research focus expanded to the development of tools for evaluating the response of complex experimental and human systems to chemicals[20-24] and the name of the laboratory shifted to Environmental Systems Biology.

Over my 32 years with the NIEHS/NTP, I was involved in numerous national priority issues that went beyond my individual research activities. After Congress asked NIEHS to work with the Vietnamese government to address the hazards associated with Agent Orange use during the Vietnamese War, I was given the responsibility of working with



my counterparts in Vietnam to build a research program in this area[25]. Congress also tasked NIEHS with developing a research program (EMF-RAPID) to address concerns about the risks to humans from exposure to power lines and to report back to Congress on what we found. I was in charge of evaluating all research developed under this program and was responsible for the final recommendations to Congress on this issue[26-28].

While at the NIEHS/NTP, I also had administrative positions that relate to my qualifications. From 2000 to 2006 I was the Director of the Environmental Toxicology Program (ETP) at NIEHS. The ETP included all of the toxicology research laboratories within the NIEHS Intramural Research Program. It was my responsibility to ensure the research being done was pertinent to the mission of the NIEHS, addressing high priority concerns about toxic substances and human health and that the NIEHS had adequate resources to complete this research.

During this time I was also Associate Director of the NTP, a position in which I was the scientific and administrative director of the NTP (The Director of the NTP was also the NIEHS Director and gave me complete autonomy in the management and science of the NTP). These two positions were historically always combined at the NIEHS and the NTP so that one person was in charge of all toxicological research at the NIEHS/NTP. The NTP is the world's largest toxicology program, routinely having 15 to 25 active two-year carcinogenicity studies, numerous genetic toxicology studies and many other toxicological studies being conducted at any given time. The NTP two-year carcinogenicity studies and their technical reports are also considered the "gold standard" of cancer studies due to their extreme high quality, their tremendous utility in evaluating human health hazards and the rigor and transparency they bring to the evaluation of the data. All data from NTP two-year cancer studies are publicly available including data on individual animals and images from the pathology review of each animal. The NTP is also home to the Report on Carcinogens, the US Department of Health and Human Services official list of what is known or reasonably anticipated to be carcinogenic to humans. It was my responsibility to decide what items eventually went onto this list while I was Associate Director of the NTP. In 2006, I became an Associate Director of the NIEHS, a senior advisor to the director and the director of the Office of Risk Assessment Research (ORAR). ORAR focused on stimulating new research areas on the evaluation of health risks from the environment and addressed major risk assessment issues on behalf of the NIEHS/NTP. For example, in this capacity, I lead a multiagency effort to understand the health risks to humans from climate change and to develop a research program in this area[29].

I left the NIEHS/NTP in 2010 to become the Director of the National Center for Environmental Health (NCEH) at the Centers for Disease Control and Prevention and simultaneously Director of the Agency for Toxic Substances and Disease Registry (ATSDR). NCEH does research and supports activities aimed at reducing the impact of environmental hazards on public health. One well-respected research effort of the NCEH is the National Biomonitoring Program. This program tests for the presence of hundreds of chemicals in human blood and urine in a national sample of people in the

United States. ATSDR advices the Environmental Protection Agency (EPA) and communities on the potential health impacts from toxic waste dump sites (superfund sites). ATSDR is required by law to produce ToxProfiles. These are comprehensive reviews of the scientific literature for specific chemicals generally found at superfund sites. They also provide an assessment of the safety of these chemicals. As part of my activities at ATSDR, I began a modernization of the ToxProfiles to use systematic review methods in their assessments; this effort was linked to a similar effort that I had helped to implement at the NIEHS/NTP.

Aside from my official duties in my various federal jobs, I also served on numerous national and international science advisory panels. Most notable, for my qualifications for this statement, are my serving as Chair from 2005 to 2010 of the Subcommittee on Toxics and Risk of the President's National Science and Technology Council, member and chair of EPA'S Science Advisory Panel from 1998 to 2003 (focused specifically on advising their pesticides program) and chair of the International Agency for Research on Cancer (IARC) advisory group that updated and improved its rules for reviewing scientific data to ensure that conclusions on the carcinogenicity of human exposures are the best possible (Preamble)[30]. As part of my work on science advisory panels, I have served on EPA's Science Advisory Board, as an advisor to the Australian Health Council on risk assessment methods, as an advisor to the Korean Food and Drug Administration on toxicological methods, and served on several World Health Organization (WHO) International Program on Chemical Safety scientific panels dealing with risk assessment. Besides the guidelines for evaluating cancer hazards used by the IARC, I have either chaired or served as a member of scientific panels developing guidance documents for other organizations including the EPA.

I have received numerous awards, most notably the Outstanding Practitioner Award from the International Society for Risk Analysis and the Paper of the Year Award (twice) from the Society of Toxicology Risk Assessment Specialty Section. I am a fellow of the American Statistical Association, the International Statistical Institute, the World Innovation Foundation and the Ramazinni Institute. I have published over 250 peer-reviewed scientific papers, book chapters and technical documents on topics in toxicology and risk assessment.

Finally, I have served on numerous national and international committees tasked with evaluating the risk and/or hazard of specific environmental chemicals, including glyphosate. For example, I have contributed to risk assessments for EPA, the Food and Drug Administration, the Centers for Disease Control and Prevention, the National Institutes of Health, the WHO and IARC.

Reliance List

During the course of my preparation for this report, I have reviewed the following materials:

a. All epidemiological data relating to the ability of glyphosate formulations to cause NHL in humans.

b. Scientific papers on the cellular origins of NHL
c. Peer-reviewed scientific data relating to the carcinogenicity, genotoxicity and oxidative stress caused by glyphosate
d. Technical reports relating to the carcinogenicity of glyphosate provided by the defendant to the lawyers for the plaintiff
e. The USEPA, the European Food Safety Authority (EFSA), the German Federal Institute for Risk Assessment, the European Chemical Agency, the IARC and the WHO/Food and Agriculture Organization Joint Meeting on Pesticide Residues reviews of the scientific literature relating to the potential for glyphosate to cause cancer.
f. Technical documents available from EFSA regarding animal carcinogenicity data on glyphosate prepared by organizations other than the defendant
g. Various other documents produced in the litigation

A complete list of my reliance materials is at the end of this report.

Methodology for Causality Evaluation

The evaluation of whether glyphosate and/or GBFs can cause NHL in humans requires the review and synthesis of scientific evidence from studies of human populations (epidemiology), animal cancer studies, and studies investigating the mechanisms through which chemicals cause cancer. Many different approaches[31, 32] are used to synthesize these three areas of science to answer the question "Does this chemical cause cancer in humans?" In any of these three science areas, the quality of the individual studies has to be assessed and summarized to make certain the studies included in the overall assessment are done appropriately. Once the quality of the individual studies has been assessed, a judgment needs to be made concerning the degree to which the studies support a finding of cancer in humans. To do this, the EPA, IARC, the European Chemical Agency (EChA), the US Report on Carcinogens, and many others use guidelines[30, 33-35] that rely upon aspects of the criteria for causality developed by **Hill (1965)**[36].

Hill listed nine (9) aspects of epidemiological studies and the related science that one should consider in assessing causality. The presence or absence of any of these aspects is neither sufficient nor necessary for drawing inferences of causality. Instead, the nine aspects serve as means to answer the question of whether other explanations are more credible than a causal inference. As noted by Hill:

> *"None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question — is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"*

The nine aspects cited by Hill include consistency of the observed association, strength

of the observed association, biological plausibility, biological gradient, temporal relationship of the observed association, specificity of the observed association, coherence, evidence from human experimentation and analogy. These are briefly described below.

An inference of causality is strengthened when several of the studies show a **consistent positive association** between cancer and the exposure. This addresses the key issue of replication of studies which is critical in most scientific debates. If studies are discordant, differences in study quality, potential confounding, potential bias and statistical power are considered to better understand that discordance.

An inference of causality is strengthened when the **strength of the observed association** in several studies are large and precise. These large, precise associations lessen the possibility that the observed associations are due to chance or bias. A small increase in risk of getting cancer does not preclude a causal inference since issues such as potency and exposure level may reduce the ability of a study to identify larger risks. Meta-analyses provide an objective evaluation of the strength of the observed association across several studies with modest risks to help clarify strength of the observed associations.

An inference of causality is strengthened when there is data supporting **biological plausibility** demonstrated through experimental evidence. Animal carcinogenicity studies, in which tumor incidence is evaluated in experimental animals exposed to pure glyphosate, play a major role in establishing biological plausibility. There are numerous types of mechanisms that can lead to cancer[37], most of which can be demonstrated through experimental studies in animals, human cells, animal cells, and/or other experimental systems. Occasionally, occupational, accidental or unintended exposures to humans allow researchers to evaluate mechanisms using direct human evidence.

An inference of causality is strengthened when there is a **biological gradient** showing a reasonable pattern of changing risk with changes in exposure (e.g. risk increases with increasing exposure or with longer exposure). In many epidemiological studies, this aspect cannot be examined due to limitations in the study design or due to a lack of clarity in the presentation of the results. When a study does address an exposure-response relationship, failure to find a relationship can be due to a small range of exposures, insufficient sample size or a changing exposure magnitude over time that has not been accounted for.

An inference of causality is strengthened when there is a **temporal relationship** in which the exposure comes before the cancer. This aspect is necessary to show causality; if it is not present, a causal inference is not plausible. Because the latency period for cancers can be long (years), evaluation of studies should consider whether the exposure occurred sufficiently long ago to be associated with cancer development.

An inference of causality is strengthened when the exposure is **specific** for a given cancer. This would mean that the disease endpoint being studied is only due to the cause being assessed. This issue is seldom applicable and, since NHL has other causes, specificity is not applicable to the determination of causality for glyphosate.

An inference of causality is strengthened when other lines of experimental evidence are **coherent** with a causal interpretation of the association seen in the epidemiological evidence. To evaluate coherence, information from animal carcinogenicity studies, mechanistic investigations and information on the metabolism of the chemical being studied would be considered.

An inference of causality is strengthened when there is **experimental evidence in humans** supporting a causal interpretation. Seldom is this type of information available when addressing the toxicity of chemicals. However, experiments in which an individual reduces or limits exposures and the risk of cancer is reduced would carry considerable weight in the evaluation (e.g. studies evaluating the cancer risks of people who stop cigarette smoking compared with continuing smoking have demonstrated reduced lung cancer risks). No such data are available for glyphosate.

Finally, an inference of causality is strengthened when there are other chemical agents with **analogous** structures showing similar effects in humans and/or animals and/or showing similar biological impacts in mechanistic studies. No such data are available for glyphosate.

The most logical approach to developing an inference of causality is to step through each of the aspects of causality developed **by Hill (1965)**[36] and apply them to the available data for glyphosate and for glyphosate formulations. This is done in the sections that follow.

Consistency of the Associations seen in Human Epidemiological Studies

Relevant Epidemiology Studies

In their meta-analysis, **Chang and Delzell (2016)**[38] performed a systematic literature search of all scientific literature up to June, 2015, to identify all epidemiological studies that were pertinent to evaluating an association between glyphosate and NHL. They identified 12 relevant epidemiology studies[39-50]. Their search agrees with all current reviews of glyphosate and I will use their findings from the literature up until 2015. To cover from June 2015 to the present (April 1, 2017), I used their searching algorithm and identified 117 additional published studies, none of which were new epidemiology studies. These same 12 studies will be considered for use in this evaluation. Other experts will be discussing the studies as well as their strengths and their weaknesses; I will focus on using the results of these studies in evaluating causality so I will only briefly describe each study.

Cantor et al. (1992)[39] did an in-person interview study comparing 622 white men, newly diagnosed with NHL, to 1245 population-based controls in Iowa and Minnesota. They originally identified 780 cases, of which 694 (89%) were interviewed. After pathology review, only 622 were found to have NHL, the remaining cases having leukemia or other diseases. Three different sources of controls were used, random digit dialing (76.7% response rate), Health Care Financing Administration rolls (79% response

rate) and deceased controls with eligible proxies (77% response rate). Both cases and controls were questioned regarding their use of agricultural products including Roundup® and any other glyphosate-based formulations. For deceased or incompetent controls (184) and cases (number not given), proxy interviews were done with a close relative. When cases in farmers were compared to cases in non-farmer controls, 26 cases (out of 266) and 49 controls (out of 547) had handled herbicides containing glyphosate yielding an odds ratio[1] (OR) of 1.1 (95% confidence interval 0.7-1.9). This analysis controlled for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations and high-risk exposures in a logistic analysis. The authors noted there was "minimal evidence for confounding of results for any single pesticide by exposure to pesticides belonging to other chemical families." Because the exposure is determined based on interviews in cases and controls, this study has the potential for recall bias[2]. However, the authors note that the bias could both increase or decrease the OR because of non-differential exposure misclassification[3] because of difficulties in accurate recall of past pesticide exposures for both controls and treated individuals. This study will not be included separately into the evaluation since it overlaps with **De Roos et al. (2003)**[43]

Two additional studies conducted by **Zahm et al. (1990)**[51] in Nebraska and **Hoar et al. (1986)**[52] in Kansas collected information on pesticide and herbicide use, but did not report specifically on the effects of glyphosate. **De Roos et al. (2003)**[43] pooled the data from these two studies with the data from **Cantor et al. (1992)**[39] to examine pesticide exposure to glyphosate in farming as risk factors for NHL. The three case-control studies[39, 51, 52] had slightly different designs. The design for the Minnesota study[39] is

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[1] The odds ratio (OR) is calculated as the proportion of exposed cases with disease to exposed controls divided by the proportion of non-exposed cases to non-exposed controls. For rare diseases, this value approximates the population risk ratio (PRR) which is the probability of having the disease in exposed individuals divided by the probability of having the disease in non-exposed individuals. If the PRR is 1, then there is no difference in the probability of having the disease regardless of your exposure. Values of PRR greater than 1 imply the risk is higher in the exposed population. Because the OR is an estimate of the PRR for rare diseases, it is usually accompanied by a 95% confidence interval that describes the probable range of the estimate. If the OR is greater than 1, then the exposure is associated with the disease. If the lower 95% confidence bound for the OR is greater than 1, this is typically used to say the association is statistically significant.

[2] Recall bias occurs when cases are more likely to say they are exposed to glyphosate than controls or when controls are more likely to say they are exposed to glyphosate than cases. The recall must be different for the cases than the controls for this to cause a bias; errors in recalling past exposures that happen for both cases and controls would not be recall bias.

[3] Non-differential exposure misclassification occurs when the probability of an error in determining whether an individual is exposed or not is the same for both cases and controls.

provided directly above. In Nebraska[51], the cases were identified through the Nebraska Lymphoma Study Group and area hospitals for 66 counties and included all white men and women diagnosed with NHL between July 1, 1983 and June 30, 1986. Controls were obtained by random-digit dialing, Medicare records or state mortality files depending upon age and vital status. All study participants were over age 21 and even though this study included a few women, they were excluded from the **De Roos et al. (2003)** analysis. The response rates for cases and controls were 91% and 87% respectively. In Kansas[52], cases were randomly sampled from a registry at the University of Kansas of white men, over age 21, diagnosed between 1979 and 1981. The response rates for cases and controls were 96% and 94% respectively. Controls were population-based matched on age and vital status. As for the Nebraska study, controls for live cases were obtained from Medicare records for cases 65+ and by random-digit dialing for cases <65 years; controls for deceased patients came from state mortality records. The resulting pooled case-control study had 870 cases and 2569 controls (for analyzing the relationship between glyphosate and NHL, there were only 650 cases and 1933 controls following exclusion of subjects with missing data). For any glyphosate exposure, there were 36 exposed cases and 61 exposed controls with an OR (95% confidence interval) of 2.1 (1.1-4.0) in a logistic regression analysis controlling for all other pesticides reported, age and study site. The authors also analyzed the data using a Bayesian hierarchical regression analysis yielding an OR (95% confidence interval) of 1.6 (0.9-2.8) controlling for the same parameters as the logistic regression. They also conducted an analysis of "potentially carcinogenic" pesticides which included glyphosate. When just one of these pesticides was used by subjects, the logistic regression OR was 1.6 (0.8-3.1), two to four pesticides yielded an OR of 2.7 (0.7 to 10.8) and when more than five were used, the OR was 25.9 (1.5-450.2) in the logistic regression analysis and 1.1 (0.8-1.7), 1.3 (0.7-2.3) and 2.0 (0.8-5.2) respectively for the Bayesian analysis. Removing glyphosate from the list of "potentially carcinogenic" pesticides yielded equivalent ORs of 1.2 for one pesticide, 1.2 for two to four pesticides and 1.1 for five or more pesticides. The authors note that the positive results seen in their study are not likely due to recall bias since there were few associations seen over the 47 pesticides they studied. Also, although some of the positive results could be due to chance, the use of the hierarchical regression analysis theoretically decreases the chance of false positive findings. In the Kansas study[52], suppliers for 110 subjects with farming experience were identified and provided information on the subjects' crops and pesticide purchases. In general, the suppliers reported less pesticide use than the subjects of the study with no consistent differences in agreement rates between cases and controls. The agreement between suppliers and subjects improved when pesticide use during the last 10 years was considered. This supports a reduced role of recall bias in these studies and a possible role of non-differential exposure misclassification. The reduced ORs when using the Bayesian analysis as compared to the logistic regression is not surprising because the authors used a non-informative prior rather than a less conservative prior. In addition, adjustment for 47 pesticides is also likely to reduce the significance of the observed ORs for pesticides that are associated with NHL as demonstrated by the analysis of "potentially carcinogenic" pesticides (this model is possibly over-parameterized since it

includes over 47 dependent variables for only 36 exposed cases; this can significantly reduce the ORs and increase the confidence bounds). This pooled case-control study is the strongest study with sufficient power (3.8% of subjects exposed) and will be included in the evaluation of causation.

Lee et al. (2004)[44] pooled data from **Zahm et al. (1990)**[51] and **Cantor et al. (1992)**[39] (previously described) to evaluate whether asthma acts as an effect modifier of the association between glyphosate exposure and NHL. Women were included in this analysis whereas **De Roos et al. (2003)**[43] excluded women. The final study published by Lee included 872 cases and 2336 controls of which 45 cases and 132 controls had been told by their doctors they had asthma. The OR of association between glyphosate and NHL in non-asthmatics was 1.4 (0.98-2.1) and 1.2 (0.4-3.3) in asthmatics when controlling for age, vital status and state (geographical location). This study completely overlaps with the study by **De Roos et al. (2003)**[43] with the exception of the inclusion of the few women in the study by **Zahm et al. (1990)**[51]. Since this study only looks at effect modification due to asthma, it does not contribute to the overall evaluation of causality and it will be excluded from further evaluations.

Nordstrom et al. (1998)[40] conducted a population-based case-control study of hairy cell leukemia (HCL); a subtype of B-cell NHL) in Sweden that included an evaluation of exposures to glyphosate. The study included 111 men with NHL reported to the Swedish Cancer Registry between 1987 and 1992 (with one patient from 1993 accidentally included). Controls (400 in total) were drawn from the National Population Registry matched for age and county with the cases. The response rates were 91% for cases (10 refused to participate out of the original 121) and 83% (84 controls refused to participate out of 484 selected). Almost all questionnaires were answered by the subject of the study (4 cases and 5 controls were answered by proxies). The study reported an OR for glyphosate exposure and HCL of 3.1 (0.8-12) controlling only for age. This study had very limited power for detecting an association because there were only four cases and five controls with glyphosate exposure (1.8% of the total study population). In addition, because they failed to adjust for other exposures, the potential for confounding in this study is greater than those presented previously. The authors noted that they attempted to minimize recall bias by only using living cases in the analysis. Also, even though matching was performed to identify the controls, this matching was not used in the final analysis. This study was later used in a pooled analysis of HCL and NHL[42] and will not be considered independently in the evaluation for causation but will be used in the context of the pooled analysis.

Hardell and Eriksson (1999)[41] conducted a population-based case-control study of all male patients older than 25 years diagnosed with NHL between 1987 and 1990 in the four most northern counties of Sweden. After excluding misdiagnosed cases, they included 442 cases of which 404 answered their questionnaire (most by proxy) for a response rate of 91%; 192 of these cases were deceased. For each living case, two male matched controls were chosen from the National Population Registry and matched on age and county. For each deceased case, two male controls were chosen from the National Registry for Causes of Death, matched for age and year of death. The response

rate for the controls was 84% (741 out of 884 identified). Study subjects were sent a detailed questionnaire and, in most cases, this was supplemented with a phone interview. A complete working history was obtained with questions regarding exposure to numerous chemicals to avoid a focus on pesticides and organic solvents, the focus of the study. Exposure was defined as at least one full day of exposure more than one year before diagnosis. For glyphosate exposure, the authors identified four cases and three controls with exposures and a univariate OR of 2.3 (0.4-13). A multivariate analysis of both glyphosate and phenoxy herbicides produced an OR of 5.8 (0.6-54). The study has limited power for detecting an effect because the exposure frequency is very low (0.6% exposed). This study was later used in a pooled analysis of HCL and NHL[42] and will not be considered independently in the evaluation for causation but will be used in the context of the pooled analysis.

Hardell et al. (2002)[42] conducted a pooled analysis of NHL and HCL by combining the studies of **Nordstrom et al. (1998)**[40] and **Hardell and Eriksson (1999)**[41]. This study fully overlaps with the previous two studies. The analysis controlling for age, study, county and vital status yielded an OR of 3.04 (1.08-8.52) based on eight exposed cases and eight exposed controls. A more extensive analysis additionally controlled for other pesticides and yielded a smaller OR of 1.85 (0.55-6.20). As for the study by **De Roos et al. (2003)**, the analysis may be over-parameterized (more than eight dependent variables with only eight exposed cases) which could lead to a reduction in the ORs and larger confidence bounds. Even with the pooled data, **Hardell et al. (2002)** had limited power to detect an effect because the exposure frequency for cases and controls was very low (1% exposed). This study is a valid case-control study and will be used in the evaluation of causality.

In a later study, **Eriksson et al. (2008)**[46] conducted a population-based case-control study where cases were identified as NHL patients aged 18-74 years diagnosed in four major hospitals in Sweden from December 1, 1999 until April 30, 2002. In total, 995 cases were identified as matching the study parameters with 910 (91%) answering the questionnaire shortly after diagnosis. All cases were classified into subgroups with 810 B-cell, 53 T-cell, and 38 unspecified lymphomas. Controls (1,108) were randomly selected from the population registry and matched on health service, region, sex and age and interviewed in several periods during the conduct of the study; 1,016 controls responded to the questionnaire (92% response rate). Study subjects were sent a detailed questionnaire and, in many cases, a phone interview followed. Exposure was defined as at least one full day of exposure more than one year before diagnosis. The univariate analysis, adjusting for age, sex and year of diagnosis (cases) or enrollment (control) yielded an OR of 2.02 (1.10-3.71) based on 29 exposed cases and 18 exposed controls. When cases and controls were divided into those with ≤10 days per year exposure and those with >10 days per year exposure, the ORs were 1.69 (0.70-4.07) and 2.36 (1.04-5.37) respectively. When diagnoses were grouped into various subtypes of NHL, the results did not change dramatically except for small lymphocytic lymphoma and chronic lymphocytic lymphoma which showed an increased OR of 3.35 (1.42-7.89). A multivariate analysis of glyphosate controlling for other agents with statistically

increased odds ratios and/or odds ratios greater than 1.5 yielded an OR of 1.51 (0.77-2.94). In a similar analysis to the multivariate analysis, latency periods of one to ten years showed an OR of 1.11 (0.24-5.08) and >10 years had an OR of 2.26 (1.16-4.40). This study was much larger than the previous Swedish studies (2.3% exposed) and, although there may have been confounding from other pesticides, this was addressed in the multivariate analysis and the latency analysis. This study is a valid case-control study and will be used in the evaluation of causality.

McDuffie et al. (2001)[50] recruited incidence cases of NHL in men 19 years or older from six Canadian provinces with a first diagnosis between September 1, 1991 and December 31, 1994. Each provincial Cancer Registry or, in the case of Quebec, hospital, had a target number of cases and ended recruitment when the case number was reached. Controls were men 19 years or older selected at random from provincial health insurance records, computerized telephone listings or voter registration lists, depending upon the province. Cases and controls were sent questionnaires with surrogates ineligible to answer the questionnaires for deceased cases or controls. Each subject who reported 10 hours per year or more of pesticide exposure and a random sample of 15% who reported less exposure were interviewed by telephone to obtain details on pesticide use. A pilot study was conducted to obtain an improved version of the telephone interview questionnaire used by **Hoar et al. (1986)**[52] and **Zahm et al. (1990)**[51] that would provide accurate pesticide exposure assessment in the form of a screening questionnaire and a telephone interview questionnaire. This was followed by a validation study (27 farmers) where the final questionnaires used to screen and include potential cases and controls were administered and the answers regarding pesticide usage showed excellent concordance with purchases through their local agrochemical supplier. The screening questionnaire was returned by 517 cases of NHL (67.1% response rate) and 1506 controls (48% response rate). Following analysis of the screening questionnaire, the telephone interview was administered to 179 cases and 456 controls to obtain more detailed exposure information. The OR for glyphosate exposure and NHL was 1.26 (0.87-1.80) stratified by age group and province of residence and the OR was 1.20 (0.83-1.74) when the analysis also controlled for significant medical variables (51 exposed cases and 133 exposed controls). An exposure-response evaluation was performed where the OR for exposure between zero to two days per year was 1.0 (0.63-1.57) and for greater than two days per year was 2.12 (1.20-3.73) with the latter group having 23 exposed cases and 36 exposed controls. This study had excellent sample size and power (8.1% of subjects exposed), but a low response rate to the screening questionnaire. Also, by adjusting for significant medical variables, this study ruled out many confounders but did not adjust for other pesticide exposures. The effort to validate the recall of pesticide usage for farmers supports a lack of recall bias in the study. This study is a valid case-control study and will be used in the evaluation of causality.

Hohenadel et al. (2011)[48] re-analyzed the data of **McDuffie et al. (2001)**[50] to specifically investigate the impact of exposure to multiple pesticides on NHL. Four cases of NHL were excluded from this evaluation following a pathology review. They reported associations with the use of glyphosate with and without malathion but not with

glyphosate overall. The OR for glyphosate (ever used) without malathion (ever used) was 0.92 (0.54-1.55) and the OR for glyphosate (ever used) with malathion (ever used) was 2.1 (1.31-3.37). **Chang and Delzell (2016)**[38] combined the ORs from the glyphosate only analysis with the glyphosate and malathion analyses using random-effects meta-analysis to get a combined OR for glyphosate of 1.4 (0.62-3.15). This study was specifically targeted to interactions of various pesticides and does not substantively contribute to an evaluation of glyphosate. Since it is a refined analysis of **McDuffie et al. (2001)**[50], it will be included in the evaluation of causation only in the context of the combined analysis provided by **Chang and Delzell (2016).**

Orsi et al. (2009)[47] conducted a hospital-based case-control study of men and women diagnosed with lymphoid neoplasms in five hospitals in France between 2000 and 2004 who were aged 20-75 years (the abstract gives the age range as 18-75 years). All diagnoses were cytologically or histologically confirmed. The evaluation only included men and questionnaires/interviews were completed by 491 cases (95.7% response rate) which included 244 cases with NHL. Controls were patients in the same hospital (mostly orthopedic or rheumatological patients) with no prior history of lymphoid neoplasms and excluding patients admitted to the hospital for cancer or a disease directly related to occupation, smoking or alcohol abuse. The controls were matched to cases by hospital and age. Of the 501 candidate controls, 456 participated (91% response). Exposure was evaluated differently for subjects who had non-occupational exposures from those who had occupational exposures. For both, the subjects had to fill out a questionnaire/interview on occupations and home gardening pesticide exposures. For those who had worked professionally as farmers or gardeners for at least 6 months, a specific agricultural occupational questionnaire/interview was administered and exposure was determined on the basis of this extra data. The OR for occupational use of glyphosate and NHL was 1.0 (0.5-2.2) with 12 exposed cases and 24 exposed controls stratified by age and center category. A further analysis was done by individual subtypes of NHL with an OR of 1.0 (0.3-2.7) for diffuse large cell lymphoma, 1.4 (0.4-5.2) for follicular lymphoma, 0.4 (0.1-1.8) for chronic lymphocytic leukemia (CLL) and 1.8 (0.3-9.3) for HCL. No separate analysis of non-occupational use of glyphosate was provided, nor does it seem specific data on glyphosate usage was ascertained for subjects who were not professional farmers or gardeners. This could lead to non-differential misclassification of exposure which could reduce the ORs of the study. Barring this, the sample size was sufficient to detect an effect (5.3% with occupational exposure) and this study will be included in the evaluation of causality.

Cocco et al. (2013)[49] evaluated data from a multi-center case-control study of lymphoid neoplasms in six European countries from 1998 to 2004. Cases included only adult patients diagnosed with lymphoma during the study period drawn from participating centers. Controls were either selected by sampling from the general population on sex, age group, and residence area (Germany, Italy), or from hospital controls matched to the patient excluding patients with cancer, infectious diseases, and immunodeficiency diseases (Czech Republic, France, Ireland, Spain). The study included 2348 lymphoma cases (88% participation) and 2462 controls (81% response rate in hospital-based controls and 52% in population-based controls). Exposures were derived using an

occupational exposure matrix developed by industrial hygienists and occupational experts from the research centers. Only 35 individuals (cases and controls not broken out) in the study were exposed to carbamates (glyphosate was grouped with the carbamates). No results were provided for NHL and the only OR provided for glyphosate was for B-cell lymphoma where the OR was 3.1 (0.6-17.1) based on four exposed cases and two exposed controls. No information was provided on the total number of cases for each type of lymphoma evaluated. This study has very limited power to evaluate an association between NHL and glyphosate and provides only information on B-cell lymphomas with very few exposed cases and controls. As has been done by most researchers evaluating these data, this study will receive very little weight in the evaluation of causality.

De Roos et al. (2005)[45] reported results on the association of glyphosate and cancer incidence from the Agricultural Health Study (AHS), a prospective cohort study in Iowa and North Carolina, which included 57,311 private and commercial applicators who were licensed to apply restricted-use pesticides at the time of enrollment. Recruitment occurred between 1993 and 1997 and cohort members were matched to cancer registry files to identify cases and the National Death Index (1999) to ascertain vital status. Incident cancers were identified from the date on enrollment until 31 December, 2001, with the average follow-up time being 6.7 years. Comprehensive use data was obtained by self-administered questionnaire for 22 pesticides, ever/never use for 28 additional pesticides, and general information on work practices. Applicators were given a second self-administered questionnaire on occupational exposures and lifestyle factors. They used three exposure metrics in their analyses: a) ever personally mixed or applied pesticides containing glyphosate; b) cumulative exposure days of use of glyphosate (years of use times days per year); and c) intensity weighted cumulative exposure days (years of use times days per year times intensity of use). Persons whose first primary tumor occurred before the time of enrollment (1074) were excluded from the analysis as were those who were lost to follow-up (298), did not provide age information (7) or information on glyphosate use (1678) leaving 54,315 subjects for inclusion. There were 92 cohort members with a diagnosis of NHL during the study period of which 77.2% had ever used glyphosate resulting in a rate ratio[4] (RR) of 1.2 (0.7-1.9) when controlling for age and an RR of 1.1 (0.7-1.9) when controlling for age, lifestyle factors, demographics and five other pesticides for which cumulative-exposure-day variables were most highly associated with glyphosate cumulative-exposure-days (2,4-D, alachlor, atrazine, metalochlor, and trifluralin) or, for chemicals with only ever/never exposure information that were most highly associated with glyphosate ever/never use (benomyl, maneb, paraquat, carbaryl and diazinon). When cumulative exposure days in exposed individuals are divided into tertiles and RRs examined using the lowest exposed tertile as

[4] The rate ratio (RR) is estimated as the incidence in the exposed population divided by the incidence in the unexposed population. Incidence is calculated as the number of events in a fixed period of time divided by the person years at risk. Unlike the OR, the RR does not require the assumption of a rare disease to serve as a good estimate of the population risk ratio (PRR).

the reference group, the RRs drop with values of 0.7 (0.4-1.4) and 0.9 (0.5-1.6) for tertiles 2 and 3 respectively controlling for demographic and lifestyle factors and other pesticides (30,699 subjects). When intensity-weighted exposure days are examined again using exposed tertile 1 as the reference group, the RRs drop with values of 0.6 (0.3-1.1) and 0.8 (0.5-1.4) for tertiles 2 and 3 intensity-weighted exposure days respectively controlling for demographic and lifestyle factors and other pesticides (30,699 subjects). Analyses are not shown for the evaluation of the exposed tertiles against never exposed because the authors felt that never exposed and exposed subjects differed in terms of socio-economic factors and other exposures like smoking[45].

This is a typical cohort study, but has some limitations in terms of its interpretation. The majority (75.5%) of subjects in the cohort reported having ever personally mixed or applied products containing glyphosate and was composed primarily of male, middle-aged, private applicators. For glyphosate, reliability of the answers by subjects on the use of glyphosate between the first and second questionnaire were evaluated in the AHS[53]: 82% agreement for whether they had ever mixed or applied glyphosate, 53% agreement on years mixed or applied, and 62% agreement on days per year mixed or applied and 62% agreement on decade first applied. They saw no differences in over versus under reporting between the two questionnaires suggesting this could lead to non-differential exposure bias and reduce the RRs in this study. Another weakness, noted by the authors, is that the small number of incident cases during follow-up period hindered precise effect estimates. Also, the high frequency of exposure to many pesticides (e.g. 73.8% were exposed to 2,4-D) means subjects unexposed to glyphosate were likely to be exposed to other agents that may also induce NHL, reducing the RRs. Also, as noted by the EPA's FIFRA Science Advisory Panel (SAP)[54] in their review of the EPA's issue paper on the carcinogenicity of glyphosate and as noted in a critique[55] of the European Food Safety Agency's risk assessment for glyphosate, the follow-up time in this cohort study may not be long enough to produce a sufficient sample size for evaluation of the association between NHL and glyphosate. Like other studies, this study has few exposed cases and controls, but the authors adjust their analysis for many other pesticides which could reduce ORs and increase confidence bounds limiting the ability of the study to show positive results. This study could also suffer from a survival bias because pesticide applicators were recruited as case participants after their exposure had begun and those with a cancer prior to enrollment were excluded.

This study will be included in the evaluation of causality.

Consistency of Associations

Hill (1965)[36] defines consistency as the answer "yes" to the question "Has it repeatedly been observed by different persons, in different places, circumstances and times?" For these studies, the answer is indeed yes.

If the population relative risk (PRR) for an association of glyphosate with NHL were equal to 1 (no effect), then one would expect very few statistically significant results in multiple studies and that about half of the studies would have ORs or RRs below one

and half above one. As noted by both the **IARC Monograph 112 (2015)**[56] and by **Chang and Delzell (2016)**[38], when comparing studies, the most reasonable comparison is to use the most-fully-adjusted risk estimates. I will mostly limit my comments to these most-fully-adjusted risk estimates.

Consistency of the associations across several epidemiology studies is not simply a matter of seeing how many were statistically significant and how many were not but must also address the consistency of the direction of the responses. Figure 1 shows a forest plot of all ORs and RRs from the epidemiology studies discussed previously. Each horizontal line in the forest plot shows the mean estimate of the OR/RR as a black square and the 95% confidence interval around this estimate as whiskers extending left and right from the black square.

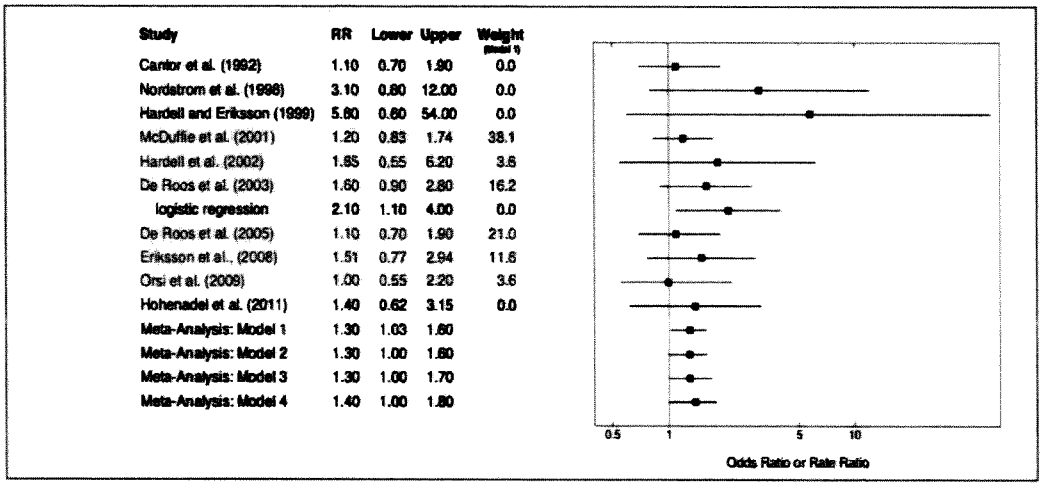
The first obvious conclusion to be drawn from Figure 1 is that all of the mean OR/RR estimates (black squares) are consistently ≥1. This implies that all of the studies are pointing in the same direction toward a positive effect. In their meta-analyses, **Schinasi and Leon (2014)**[57], **IARC (2015)**[56] and **Chang and Delzell (2016)**[38] all identified 6 papers (highlighted in red in Figure 1) as being the most reliable for evaluation of the ability for glyphosate to induce NHL in people: **McDuffie et al. (2001)**[50], **Hardell et al. (2002)**[42], **De Roos et al. (2003)**[43] and **(2005)**[45], **Eriksson et al. (2008)**[46] and **Orsi et al. (2009)**[47]. I will refer to these papers as the six core epidemiology studies. As noted above, if the true underlying risk ratio was 1 (no effect), you would expect about half of the findings to be below 1 and half to be equal to 1 or greater. Using only the results from the 6 core studies, you can see that all are ≥1; the probability of this happening is $(0.5)^6$ or 0.016, strongly suggesting the studies do not agree with an underlying PRR=1 and that they consistently support a positive effect.

A second way in which consistency can be evaluated is to combine the individual studies using meta-analysis to obtain a combined analysis using both the ORs and the RR (CRR) and test for heterogeneity in the studies. The meta-analysis done by **Chang and Delzell (2016)** includes the same analysis as that done by the **IARC (2015)** and is an improvement over **Schinasi and Leon (2014)**, so I will focus my comments on using the **Chang and Delzell (2016)** meta-analysis. **Chang and Delzell (2016)** did four separate meta-analyses on the glyphosate epidemiology studies using two different methods (random-effects and fixed-effects models). In their first analysis (model 1)[5], they combined the most-fully-adjusted risk estimates from the six core studies to yield a CRR of 1.27 (1.01-1.59) for both random-effects and fixed-effects models supporting an association between NHL and glyphosate exposure in these studies. In a second analysis (model 2), they replace the results of the Bayesian analysis in **De Roos et al. (2003)** with the results of the logistic regression analysis and get the same CRR of 1.30 (1.03-1.64) for both random-effects and fixed-effects models. In a third analysis (model 3), they replace from model 1 the **McDuffie et al. (2001)** results in with a combined meta-

[5] **Chang and Delzell (2016)** provided only one significant digit to the right of the decimal point in their confidence bounds; the EPA SAP (2017) re-calculated models 1-4 of **Chang and Delzell (2016)** to provide two significant digits – these are presented here.

analytic result they derived from analyses by **Hohenadel et al. (2011)** (this study reanalyzed the same data as **McDuffie et al. (2001)**, splitting results between asthmatics and non-asthmatics) resulting in a CRR of 1.32 (1.00-1.73) for both random-effects and fixed-effects models. Finally, in a fourth analysis (model 4), they use model 3 but replaced the Bayesian analysis in **De Roos et al. (2003)** with the logistic regression analysis yielding a CRR of 1.37 (1.04-1.82) for both random-effects and fixed-effects models. In essence, none of the different meta-analyses rejected the notion of a combined, statistically significant positive effect.

Figure 1: Odds Ratios and Rate Ratios from the most-fully-adjusted risk estimates from selected epidemiology studies and from the meta-analyses of **Chang and Delzell (2016)**[38]. "RR" refers to the OR or RR from the study, "Lower" refers to the 95% lower bound, "Upper" to the 95% upper bound and "Weight" refers to the weight applied to that specific study in Model 1 of the meta-analysis (Table 3 in Chang and Delzell). For **De Roos et al. (2003)**, the first row is for the Bayesian model analysis and the second row, labelled "logistic regression" is from the logistic model analysis.



As stated above, another way to evaluate consistency in the epidemiological data would be to evaluate the heterogeneity in the studies. Heterogeneity may be due to differences in participants, outcomes, exposure metrics, methods for questioning study subjects, sex of the subjects, etc. **Chang and Delzell (2016)** formally tested for heterogeneity of the responses from the six core studies using Cochran's Q statistic and the I^2 statistic[58]. For models 1 to 4, the p-values from Cochran's Q test are 0.84, 0.59, 0.85, and 0.63 respectively (typically you reject the concept of homogenous studies in favor of heterogeneous studies if $p<0.10$). The I^2 statistic for all four models are 0.0% (values for I^2 can range from 0-100% with concern for heterogeneity above 50%). The fact that the fixed-effects models and random-effects models gave the same results also supports a lack of heterogeneity in the data. There is no indication of heterogeneity in these six core studies. Lack of heterogeneity supports the interpretation of the meta-analyses as showing a positive association and strong consistency of the findings across the six core studies.

Chang and Delzell (2016) also evaluated the association between subtypes of NHL and glyphosate exposure where possible. For B-cell lymphomas, they combined the results of **Eriksson et al. (2008)**[46] with those of **Cocco et al. (2013)**[49] and saw a CRR (random-effects and fixed-effects) of 2.0 (1.1-3.6) with an I^2 of 0 and a Cochran's Q test p-value of 0.58. For diffuse large B-cell lymphomas, they combined the results of **Eriksson et al. (2008)**[46] with those of **Orsi et al. (2009)**[47] and saw a CRR (random-effects and fixed-effects) of 1.1 (0.5-2.3) with an I^2 of 0 and a Cochran's Q test p-value of 0.79. For combined chronic lymphocytic leukemia and small lymphocytic lymphoma, they combined the results of **Eriksson et al. (2008)**[46] with those of **Orsi et al. (2009)**[47] and saw a CRR using the random-effects model of 1.3 (0.2-10) and for the fixed effects model 1.9 (0.9-4.0) with an I^2 of 83.7% and a Cochran's Q test p-value of 0.01. For follicular lymphomas, they combined the results of **Eriksson et al. (2008)**[46] with those of **Orsi et al. (2009)**[47] and saw a CRR (random-effects and fixed-effects) of 1.7 (0.7-3.9) with an I^2 of 0 and a Cochran's Q test p-value of 0.73. And finally, for HCL, they combined the results of **Nordstrom et al. (1998)**[40] with those of **Orsi et al. (2009)**[47] and saw a CRR (random-effects and fixed-effects) of 2.5 (0.9-7.3) with an I^2 of 0 and a Cochran's Q test p-value of 0.63. These subtype analyses are based upon small numbers of cases and only two studies making them unreliable, when considered individually, to address the question of consistency in the data. However, when they are combined with the results for the meta-analyses of the core studies of NHL, these studies add support to the conclusion that these data are consistent.

Chang and Delzell (2016) also performed a sensitivity analysis by only doing meta-analyses on studies with similar characteristics. Using only the five case-control studies, the CRR was 1.3 (1.0-1.7). Breaking them into the type of control used, there were four studies using population controls with a CRR of 1.4 (1.0-1.8). There were four studies with males only with a CRR of 1.3 (1.0-1.7) and two studies with males and females with a CRR of 1.2 (0.8-1.8). Three studies were done in North America with a CRR of 1.2 (1.0-1.6), three in Europe with a CRR of 1.3 (0.8-2.1); two of the three studies were in Sweden with a CRR of 1.6 (0.9-2.8). All of the resulting meta CRRs were the same for the fixed-effects model and the random-effects model. This sensitivity analysis shows that the results do not differ significantly from the main CRR for the six core studies combined adding support to the findings being consistent across the different studies.

In case-control studies, selection bias arises when the reasons cases and controls choose to participate in the study could lead to systematic biases that might result in a positive or negative finding independent of the exposure being studied. For example, if cases with exposure are more likely to participate than controls with exposure, the result would be higher OR values; however, this difference has to be differential and not simply a difference in participation rates. It is possible that in a few of these studies, the method by which controls were selected could contribute to selection bias that might lead to increased ORs. However, given the diverse types of cases and controls used in the five core case-control studies, this is unlikely to explain the consistent findings seen from these studies. It is also possible that the lack of complete data on cases versus controls could result in selection bias if the reasons for not completing the questionnaire/interview are different between cases and controls and relates to

exposure. There is no indication of this type of selection bias in these reports, and this is unlikely to explain the consistency seen in these data.

Exposure misclassification can lead to increases or decreases in the OR or RR values seen in both case-control and cohort studies. For example, in case-control studies, if cases are more likely to say they were exposed to glyphosate than controls, this would inflate the OR values; this is one type of recall bias. This type of bias is less likely in cohort studies. In all six of the core studies, this issue was discussed by the authors. In every case, they concluded there was bound to be some exposure misclassification, but that it was most likely non-differential, meaning that the misclassification was random; this would likely reduce the OR/RRs seen in the studies rather than increase them.

Confounding occurs when there is an exposure or some other factor that is tightly associated with both glyphosate exposure and NHL diagnosis that, if controlled for, could explain the results. The most likely source of confounding in these studies would be exposures to other pesticides. Four[42, 43, 45, 46] of the six core studies controlled for exposure to other pesticides and saw basically the same findings as the other two studies. Another concern for confounding would be if the cases had immune deficiencies that could be linked to NHL; in all of the case-control studies, such cases were excluded. Finally, other agricultural exposures (e.g. animals, other chemicals, infectious agents) could be correlated with glyphosate exposure and may be linked to NHL; none of the studies controlled for these factors. However, not all exposed cases were farmers; if confounding via other agricultural exposures is occurring, it is not possible to determine the magnitude or direction of such an effect from these data.

In conclusion, we have six core epidemiology studies done on two different continents by four different research groups using different designs, questionnaires and study populations that are highly consistent with no obvious bias or confounding that would explain the results. **There is a consistency of associations across the six core studies.**

Strength of the Association seen in Human Epidemiological Studies

To explain strength of association, **Hill (1965)** gives the classic example of John Snow and the cholera epidemic of 1855 where the risk ratio of dying if you drank water from the Southwark and Vauxhall Company (polluted by sewage) compared to drinking from the Lambeth Company water (sewage free) was 14. Yet, for the six core studies, the OR/RR ranges from 1.0 to 1.85 for the most-fully-adjusted risk estimates and to 2.1 if you include the fully adjusted risk estimate from De Roos et al. (2003)[45] using logistic regression. These are moderate OR/RR estimates making it conceivable they are individually due to either chance or bias. Thus, with the exception of the logistic regression analysis in **De Roos et al. (2003)**[45], none of the core studies demonstrate large, precise risks as envisioned by **Hill (2016)**[36]. However, **Hill (1965)** was not expressing himself in statistical terms where the significance of an association is dependent upon the precision of the observations. If the statistical variation around an OR/RR estimate is large relative to the estimate itself, the estimate is not very precise

and generally would not be statistically significant. The result from the study by **Hardell and Eriksson (1999)** shown in Figure 1 is an example of an estimate with very large statistical variation. On the other hand, a very small (in value), precise OR or RR estimate could be statistically significant and prove important in deciding causation. The meta-analyses shown in Figure 1 all demonstrate estimates of OR/RR that are significantly different from 1 rejecting the concept that the overall association is due to chance. The statistically significant estimate of the OR/RR for B-cell lymphomas in the meta-analysis support this finding as well.

In summary, we have six core epidemiology studies that all show approximately the same, modest increase in OR/RR that, when combined, demonstrate a significant strength of association. **There is a strong association across the six core studies**

Biological Plausibility

The range of data one can use to determine biological plausibility is quite diverse and can be exceptionally complicated. For simplicity, it can be divided into the types of assays that can be used in this evaluation: animal cancer bioassays, toxicokinetic studies, studies from accidental exposures in humans, and studies of specific biological mechanisms in animals or cells derived from humans or animals. Animal cancer bioassays are intended to test whether glyphosate can cause cancers in mammals, thus supporting the concept that the chemical could cause cancer in humans. Toxicokinetic studies provide insight into the degree to which glyphosate is absorbed by humans, distributed to various organs in the body, what happens to the chemical once it is in the body (metabolism), and, finally, how it is eliminated from the body. Studies from accidental exposures in humans can provide some information on the effects of glyphosate through changes in the chemistry and cellular structure of human blood. Studies of biological mechanisms are generally addressing what effects the chemical may have on human and animal cells under controlled, laboratory conditions. Some of the studies in this section were done with technical grade (virtually pure) glyphosate and some with the glyphosate formulations that humans encounter in occupational and environmental settings. I will summarize the literature in each of these areas and offer an opinion to their support of biological plausibility of NHL in humans.

Animal Cancer Bioassays

Typical animal cancer bioassays will expose animals (generally rats or mice) to a chemical for a substantial proportion of the animal's life (generally 2 years) then kill the animal and examine its organs and tissues for tumors. There are guidelines on how to conduct and analyze these studies. Typically, chemical registrants conduct cancer bioassays for pesticide approval pursuant to guidelines developed under the guidance of the Organization for Economic Cooperation and Development (OECD[59]). Other groups[30, 33, 34] provide guidance on how to analyze these studies based upon methodology papers from the published literature. These studies are conducted in a way that controls for everything in the animal's environment (e.g., food type, water quality, how often the animals are handled) leaving only the exposure to explain

differences in tumor formation between control and exposed animals. Even then, non-cancer endpoints can also be modified by the chemical and these may have an impact on tumor rates in the animals (e.g., survival, death from some other toxic effect of the chemical); these must be accounted for when reaching conclusions from the study.

Studies generally use four groups of animals, one group receiving no exposure (control) and the remaining three groups are test animals, with each group receiving different dose exposures to the chemical[60]. Doses generally above human experience are used in animal carcinogenicity studies because only relatively small numbers of animals are being used to evaluate risk for a large human population and because even the best known human carcinogens do not cause cancer in large fractions (say 20%) of the human population. The basic underlying premise of this design consideration is that, as the dose increases, so does the risk of getting a tumor. By exposing animals to the highest dose possible, you increase the ability of the study to identify a risk if one is present. However, one must be careful not to use a dose that is so high it will cause cancers by processes that would never work at lower doses. To avoid this, studies are designed around a maximum tolerated dose (MTD) or limit dose. This dose is generally determined based upon a subchronic study (90 days) in the same animals and is usually the maximum dose that can be tolerated by the animals without any signs of significant toxicity in the exposed animals (e.g., weight loss, tissue damage). The OECD and EPA provide guidelines[33, 59] on how to choose this top dose. These guidelines are in general agreement with the scientific literature[60].

The guidelines also address the methods by which the data should be analyzed. For example, the EPA guidelines[61] state that:

"A trend test such as the Cochran-Armitage test (Snedecor and Cochran, 1967) asks whether the results in all dose groups together increase as dose increases. A pairwise comparison test such as the Fisher exact test (Fisher, 1950) asks whether an incidence in one dose group is increased over that of the control group. By convention, for both tests a statistically significant comparison is one for which p is less than 0.05 that the increased incidence is due to chance. Significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result."

In fact, most guidelines and peer-reviewed publications come to the same conclusion[30, 59, 60, 62] on what tests to use, as did EPA's FIFRA Scientific Advisory Panel (SAP) in their review of the EPA's issue paper of the carcinogenicity of glyphosate[54]. The US National Toxicology Program (NTP) uses both a trend test[3, 4, 63] and Fisher's exact test for analyzing carcinogenicity data. Unless otherwise noted in this document, all p-values presented in this section on animal cancer studies were recalculated on my computer and are the exact one-sided p-values for the Fisher test (p_{Fisher}) and/or the Cochran-Armitage linear trend test (p_{Trend}) where appropriate. In cases where the data is pooled and the numbers of tumors are large, the approximate p-value based upon the normal distribution is used for the trend test to avoid excessive computation time; these are noted as p_{TrendA}. The approximation (p_{TrendA}) is generally equivalent to the exact p-value (p_{Trend}) when there are more than 10 animals with tumors[64].

To avoid doing large numbers of tests and over-analyzing the data, my comments will generally rely upon the use of the trend test with the results from Fisher's exact test serving as a descriptive discussion of the findings. This is in agreement with SAP comments[54] and is generally accepted in the evaluation of animal cancer studies.

Even with the high doses used in these studies, it is sometimes necessary to use "historical controls" to evaluate a given response. Historical controls are generally the historical collection of tumor responses from untreated control groups from studies in the same laboratory within two to three years of the study being evaluated[30, 34, 59, 65, 66]. Evaluation of the data using the historical controls should be done rigorously to correctly evaluate the responses seen in a given study. Where a valid historical control dataset was available, I used the mean tumor response in the controls to calculate the probability of observing the trend seen in the study or a more significant trend if the true probability of response is the historical control average; this is labeled p_{Hist}. In all cases, the guidelines and literature support the use of the control in the current study as the most appropriate control group to use unless there is a specific need to address historical responses. Many guidelines[30, 33, 34, 67] suggest historical controls be used for evaluating rare tumors and findings in assays that appear to be unusual. It is explicitly noted that significant increases in tumors over what is seen in the concurrent control should not be rejected simply because the tumors are in the range of the historical controls[30]. Nor is it recommended to reject significant increases in tumor responses because the control response is on the low end of the historical range. Animals are randomly assigned to control and exposure groups and any low response in controls is likely to also reflect similar response patterns in treated animals. This is in agreement with SAP comments[54] on the EPA issue paper on glyphosate[61] and with all guidelines for analyzing animal carcinogenicity data.

There are 13 animal carcinogenicity studies in rats[68-80] and eight in mice[81-88]. Only two studies[71, 77] appear in the peer-reviewed literature; the remaining studies are partially available through several sources. For three of the rat studies[70, 74, 78] and two mouse studies[83, 86], technical reports from the performing laboratory are available from documents provided by the registrant. For the remaining unpublished studies, data was obtained from the EPA review of glyphosate[61], the European Food Safety Authority review of glyphosate[89, 90] and supplemental material from a review of the carcinogenicity of glyphosate by a panel of scientists on behalf of Monsanto[91].

Many additional endpoints, other than cancer incidence and related toxicities, were evaluated in these studies; I will only provide comments on the tumor incidence data and related data where relevant to the cancer findings.

It is unusual to have multiple carcinogenicity studies in the same experimental animal model arising from different laboratories. Methods for the combined analysis of multiple animal cancer bioassays are not available in the scientific literature. However, pooled analyses, as conducted in epidemiology[92, 93] are applicable for combining animal carcinogenicity studies. The basic concept is to pool all data from the same sex/species/strain into one study and analyze it appropriately. The basic steps are: 1) select the studies to be pooled; 2) merge the data for analysis; 3) estimate study specific

effects; 4) estimate pooled effects; 5) explain the differences between the pooled effects and the individual study effects; 6) do a sensitivity analysis if possible. These steps will be used to analyze pooled data from animal carcinogenicity studies where pooling is done by sex, species, strain and duration of exposure to limit heterogeneity across pooled studies. In their recommendations to the EPA regarding EPA's issue paper on the carcinogenicity of glyphosate[54], the FIFRA Science Advisory panel strongly supported the use of a pooled analysis to address the question of consistency citing my comments to the EPA[94].

Rat Studies

Reyna and Gordon (1974)[76] exposed Albino rats (probably Sprague-Dawley) to ammonium salt of glyphosate (13.85% purity) in a two-year chronic feeding study. Only EPA[61] reported on this study and provided no details other than to report there were approximately 70 animals per group and there was insufficient reporting on the histopathology findings. Insufficient detail is available on this study.

This study is inadequate for use in deciding on causality.

Burnett et al. (1979)[70] exposed male and female albino rats to an aqueous monosodium salt solution of glyphosate by oral intubation (purity not given). There were 90 animals per group and doses were 0, 3, 10 and 30 mg/kg/day for 24 months. EPA[61] reported that no histopathological alterations were observed; no additional information was available on this study. This study had severely reduced sensitivity to observe any cancer findings because the highest dose used in this study is very low compared to the MTDs in the other rat studies. This study does not contribute to the evaluation of cancer causation in laboratory animals and will be excluded from any further discussion.

Lankas et al. (1981)[74] exposed groups of 50 male and 50 female Sprague-Dawley rats to glyphosate (98.7% purity) in feed (see Table 1 for doses) for 26 months. This study is not in concordance with OECD guidelines (they were not available at the time of this study), but as noted by EFSA[89], it was in general accordance with the 1981 OECD guidelines. Information on this study was available from EPA[61], EFSA[89], Greim et al.[91], the original study report from Bio/dynamics Inc.[95] and memos from Monsanto to EPA provided by Monsanto.

There were no survival differences in this study and there was no indication that the highest dose used exceeded the maximum-tolerated dose.

Table 1 shows the statistically significant trend in testicular interstitial cell tumors that was observed (p_{Trend}=0.009). Historical controls were provided in the study report for five studies with response rates of 4/116, 5/75, 4/113, 6/113 and 5/118 for a mean response of 4.5% (24/535). Comparing this historical control mean to the observed response yields p_{Hist}=0.006, showing that this result is significant, even when comparing it to the historical control dataset. **Lankas et al. (1981)** argued that the tumor rates at sacrifice were not statistically significant from control suggesting this finding is not related to glyphosate. However, by reducing the numbers of animals to only those at

terminal sacrifice, the power to find an effect was significantly reduced. Also, if the tumor increases the animal's chances of dying, then some animals with tumors will die early, which could bias results only seen at terminal sacrifice. This type of analysis is simply never done; it appears to have been developed for this case to dismiss the effects seen in the study. **Lankas et al. (1981)** also suggested the control response was low compared to the historical rates, but the concurrent control is always the best control group to use unless it is clearly flawed[33, 34, 59]; in this case, there was no apparent problem with the controls because the probability of seeing 0/50 if the true background response is 4.5% is about 10% and this control group is not significantly different than the historical controls. **EFSA**[89] noted rates for interstitial cell hyperplasia (a potential precursor for the interstitial cell tumors) and saw no dose-response trend (Table 1). However, these very low rates would suggest that the tumors arising in the 10 animals that did get interstitial cell tumors are independent of a mechanism involving interstitial cell hyperplasia. The tumor response for interstitial cell tumors was not monotonic (tumor rates increasing as dose increases), but was still within statistical variation. The EPA SAP agrees, concluding that "requiring visual confirmation of a monotonic trend in scatter plots of data ... is known to be a poor way of assessing trend"[54].

An increase in Thyroid C-cell carcinomas (Table 1) was observed in female rats (p_{Trend}=0.003) but combining adenomas and carcinomas was only marginally significant (p_{Trend}=0.072). Independent pathologists brought in by Monsanto argued these tumors were not treatment related. The authors provided historical control data for both carcinomas and carcinomas combined with adenomas from nine control groups with mean responses of 4/453=0.9% for carcinomas and 46/453=10.2% for the combined tumors. The significance of both results was unchanged using the historical control data.

The authors also mentioned that the incidence of lymphocytic hyperplasia in the thymus and lymph nodes were slightly elevated above controls (p_{Trend}=0.143). The middle dose group was significantly different from controls (p_{Fisher}=0.018).

This study also had a statistically significant increase in pancreatic islet cell tumors in the lowest dose (p_{Fisher}=0.028) in males (Table 1), but not any of the other doses; the trend test was not significant (p_{Trend}=0.312).

The highest dose used in this study in Sprague-Dawley rats is far below the MTD. Even though EFSA[89] noted that this study was in general accordance with the 1981 OECD guidelines, they dismissed it for not meeting current guidelines due to the low-doses used. EPA[61] also excluded this study from consideration. However, the study saw an increase in testicular tumors in males and Thyroid C-cell carcinomas in females that should be carefully evaluated in determining causality. Also, this is the study with the longest exposure (26 months) and provides unique information to the overall evaluation.

Additional tumors seen to have significant increases in other studies using Sprague-Dawley Rats are also included in Table 1.

Table 1: Tumors of interest in male and female Sprague-Dawley rats the 26-month feeding study of **Lankas (1981)**[74]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	3.05	10.30	31.49	
	Female	0	3.37	11.22	34.02	
Testicular interstitial cell tumors	Male	0/50	3/50	1/50	6/50**	P_{Trend}=0.009 P_{Hist}=0.006
Interstitial cell hyperplasia	Male	1/50	1/50	1/50	0/50	P_{Trend}=0.830
Thyroid C-cell Carcinomas	Female	1/47	0/49	2/50	6/47	P_{Trend}=0.003 P_{Hist}=<0.001
Thyroid C-cell Adenomas and Carcinomas	Female	6/47	3/49	8/50	9/47	P_{Trend}=0.072 P_{Hist}=0.072
Pancreas Islet Cell Tumors	Male	0/50	5/50*	2/50	3/50	P_{Trend}=0.312
lymphocytic hyperplasia, thymus and lymph nodes	Female	27/50	35/50	38/50*	35/50	P_{Trend}=0.143
Thyroid C-cell Adenomas and Carcinomas	Male	1/47	2/49	4/49	4/49	P_{Trend}=0.122
Thyroid Follicular-cell Adenoma	Male	5/47	1/49	2/49	2/49	P_{Trend}=0.748
Liver Neoplastic Nodule	Male	3/50	5/50	1/50	3/10	P_{Trend}=0.630
Kidney Adenoma	Male	1/50	5/50	0/50	0/50	P_{Trend}=0.979

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

In conclusion, this study shows positive result for testes interstitial cell tumors and hepatocellular adenomas in male Sprague-Dawley rats and a positive response for thyroid c-cell carcinomas in female Sprague-Dawley rats and will be included in the overall evaluation of causation.

Stout and Ruecker (1990)[78] exposed groups of 50 male and 50 female Sprague-Dawley rats to glyphosate (98.7% purity) in feed (see Table 2 for doses) for 24 months. This study was done under OECD guidelines.

There were no survival differences in this study and there was no indication that the highest dose used exceeded the maximum-tolerated dose.

Pancreatic islet cell tumors were increased in all dose groups relative to the controls in male rats and statistically significant for the lowest (p_{Fisher}=0.015) and highest (p_{Fisher}=0.032) dose groups (Table 2). However, these rates include the 10 animals that were sacrificed at one year. Due to the short duration of exposure, the rats terminated at one year were likely not at risk of developing this tumor; it is very unusual to include these animals in the final tumor counts (EPA[61] also excluded these animals). In the pathology tables for this study, there were no tumors in any of the 10 animals at the interim sacrifice. Removing these 10 animals does not alter the p-values for trend or

Fisher's exact test. Historical control data for this tumor in this laboratory was reported as 23/432 or 5.3%[96] and a trend comparison against this control rate was not significant (p_{hist}=0.15). The lack of a trend is driven by the up and down nature of the response. Assuming the historical rate of 5.3% is correct, the chances of seeing eight or more tumors in 47 animals is 0.003. Similarly, for the mid- and high-doses, this probability is 0.124 and 0.014, respectively. Females did not show an increase in this tumor. The authors provided a table with the combined results for pancreatic islet-cell adenomas and carcinomas from this study with the tumor counts from the **Lankas et al. (1981)**[74] study arguing the results do not show a dose-related increase. Animals studied for 26 months versus 24 months can have very different responses to the same chemical and very different control incidence.

In male rats, there was a statistically significant trend (p_{Trend}=0.015) after removal of interim-sacrificed animals for hepatocellular adenomas but a significant increase for adenomas and carcinomas combined (p_{Trend}= 0.05, Table 2) and not in females (not shown). Liver carcinomas are generally also provided in a separate analysis, but these data were not provided by the authors (the data would suggest the hepatocellular carcinomas would have a negative trend).

There was also a significant increase in thyroid C-cell adenomas in the female rats (p_{Trend}=0.049) and a marginal increase[6] in adenomas and carcinomas combined (p_{Trend}=0.052) regardless of whether interim sacrificed animals are included (Table 2). In males, the trend for adenomas was p_{Trend}=0.084 and for adenomas and carcinomas was p_{Trend} =0.091. Adenomas were seen in male rats at the interim sacrifice demonstrating that male rats at the interim sacrifice were at risk for this tumor. If these animals are added back into the analysis, the trend test in males has p_{Trend}=0.063 for adenomas and p_{Trend}=0.068 for adenomas and carcinomas combined.

Several other tumors demonstrating significant findings in other studies of Sprague-Dawley rats are included in Table 2 and do not show significant effects.

In conclusion, the finding of an increased incidence of pancreatic islet-cell tumors in this study cannot easily be ruled out as a chance finding. Findings of significant increases in liver adenomas in male rats with no increases in carcinomas could be due to chance. The findings of significant increases in thyroid c-cell tumors in males and females should be compared with other studies. This study will be included in the overall evaluation of causation.

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[6] In statistics, it is common to refer to p-values in the range of 0.10>p-value>0.05 as marginal when the target p-value is ≤0.05; this is done to avoid missing trends in data reflected by almost significant findings

Table 2: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of Stout and Ruecker (1990)[78]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	89	362	940	
	Female	0	113	457	1183	
Pancreas Islet Cell Tumors (with interim sacrifice)	Male	1/58	8/57*	5/60	7/59*	P_{Trend}=0.147 P_{Hist}=0.140
Pancreas Islet Cell Tumors (without interim sacrifice)	Male	1/48	8/47*	5/50	7/49*	P_{Trend}=0.147 P_{Hist}=0.150
Hepatocellular adenomas (without interim sacrifice)	Male	3/50	2/50	3/50	8/50	P_{Trend}=0.015
Hepatocellular Adenomas and Carcinomas (without interim sacrifice)	Male	6/50	4/50	4/50	10/50	P_{Trend}=0.050
Thyroid C-Cell Adenomas (with interim sacrifice)	Female	2/60	2/60	6/60	6/60	P_{Trend}=0.050
Thyroid C-Cell Adenomas (without interim sacrifice)	Female	2/50	2/50	6/50	6/50	P_{Trend}=0.049
Thyroid C-Cell Adenomas and Carcinomas (with interim sacrifice)	Female	2/60	2/60	7/60	6/60	P_{Trend}=0.053
Thyroid C-Cell Adenomas and Carcinomas (without interim sacrifice)	Female	2/50	2/50	7/50	6/50	P_{Trend}=0.052
Thyroid C-Cell Adenomas (with interim sacrifice)	Male	2/60	4/60	8/60	7/60	P_{Trend}=0.063
Thyroid C-Cell Adenomas (without interim sacrifice)	Male	0/50	4/50	8/50**	5/50*	P_{Trend}=0.084
Thyroid C-Cell Adenomas and Carcinomas (with interim sacrifice)	Male	2/60	6/60	8/60*	8/60*	P_{Trend}=0.068
Thyroid C-Cell Adenomas and Carcinomas (without interim sacrifice)	Male	0/50	6/50*	8/50**	6/50*	P_{Trend}=0.091
Testis Interstitial Cell Tumors	Male	2/50	0/50	3/50	2/50	P_{Trend}=0.296
Kidney Adenomas	Males	0/50	2/50	0/50	0/50	P_{Trend}=0.813
Thyroid Follicular Adenoma/Carcinoma	Males	2/50	1/48	3/48	3/50	P_{Trend}=0.225

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Atkinson et al. (1993)[68] conducted a combined chronic toxicity/carcinogenicity study of glyphosate (98.9% pure). They used 50 Sprague-Dawley rats in each group for both sexes with dietary exposures given in Table 3. An additional 35 rats/sex/dose were included for interim sacrifices.

There were no survival differences in this study and there was no indication that the highest dose used exceeded the maximum-tolerated dose.

Table 3: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of Atkinson et al. (1993)[68]

Tumor	Sex	Doses (mg/kg/day)					p-values
	Male	0	11	112	320	1147	
	Female	0	12	109	347	1134	
Thyroid Follicular Adenomas and Carcinomas	Male	0/50	0/21	0/17	2/21	2/49	P_{Trend}=0.099
Thyroid Follicular Adenomas and Carcinomas (adding terminal sacrifice animals to denominator)	Male	0/50	0/50	0/50	2/50	2/49	P_{Trend}=0.034
Thyroid C-cell Adenomas and Carcinomas	Female	8/50	1/27	1/29	1/29	7/49	P_{Trend}=0.197
Thyroid C-cell Adenomas and Carcinomas	Male	9/50	1/21	1/17	2/21	9/49	P_{Trend}=0.183
Testes Interstitial Cell Tumors	Male	3/50	1/25	0/19	0/21	2/50	P_{Trend}=0.580
Kidney Adenomas	Males	1/50	0/50	0/50	0/50	0/50	p_{Trend}=1
Hepatocellular Adenomas	Males	2/50	1/50	1/50	2/50	3/50	P_{Trend}=0.155
Pancreas Islet-Cell Adenoma	Male	0/50	0/50	0/50	0/50	1/50	P_{Trend}=0.200

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

The authors reported no significant effects, as do **EPA**[61] and **EFSA**[89]. The study did not do detailed histopathological examination on all animals in all groups for every tumor type, but did examine all control and high dose animals, all animals that died before study termination and animals showing macroscopic tumors at study termination; liver, kidney and lungs were examined for all animals. This severely weakens the study for addressing dose-response trends. However, in reviewing the pathology tables provided in **Greim et al. (2015)**[91], thyroid follicular adenomas and carcinomas were found to be marginally significant (p_{Trend}=0.099) by the trend test. If the three middle exposure groups had seen no other tumors and the denominators were the entire 50 animals on study, the trend analysis becomes significant (p_{Trend}=0.034).

Without examination of the animals free of gross tumors at terminal sacrifice, the findings from this study will be given less weight in the overall evaluation of causation.

Brammer (2001)[69] conducted a two-year carcinogenicity study in Wistar rats in which groups of 52 animals were exposed to glyphosate (97.6% pure) at doses provided in

Table 4 . An additional 12 animals were sacrificed at one-year.

A significant positive trend in survival was noted by the EPA (p=0.03), however this trend was not accomplished using a Kaplan-Meir test[97] (the appropriate test), but simply a test relating to the percent surviving to terminal sacrifice. There was no indication that the highest dose used exceeded the maximum-tolerated dose.

EPA[61], but not **EFSA**[89], noted there was a statistically significant trend of hepatocellular adenomas in male rats with the highest dose also being statistically significant from the control. Trend analysis gives p_{Trend}=0.008 and the Fisher's exact test comparison of high dose to control is p_{Fisher}=0.027. EPA dismissed this finding as potentially due to a slight difference in the number of animals at the terminal sacrifice in this study versus controls. However, no formal statistical evaluation of survival is provided and it cannot be assumed from these numbers that survival was significantly impacted in these animals. **Greim et al. (2015)**[91] used slightly different numbers for this tumor because three animals (one in the control group, one in the low-dose group and one in the mid-dose group) in the interim sacrifice group died before their sacrifice time and, from the pathology tables provided in their paper, these could not be separated from others. These numbers have been included in Table 4, but it does not change the significance of the findings. **Greim et al. (2015)**[91] dismissed these findings, partly because of the same survival argument used by the EPA and partly because they had a historical control dataset where the range of historical response was from 0-11.5%; they did not provide the mean response or the individual tumor responses for these historical controls. As mentioned earlier, dismissing results because they are in the range of the historical controls is an unacceptable method for using historical controls to evaluate a study, and in this case, there is no reason to question the concurrent controls.

Table 4: Tumors of interest in male and female Wistar rats from the 24-month feeding study of Brammer (2001)[69]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	121	361	1214	
	Female	0	145	437	1498	
Hepatocellular Adenoma	Male	0/52	2/52	0/52	5/52*	P_{Trend}=0.008
Hepatocellular Adenoma (from Greim et al., 2015[91])	Male	0/53	2/53	0/53	5/52*	P_{Trend}=0.008 P_{Hist}=0.006
Mammary Gland Adenomas and Adenocarcinomas	Female	3/51	2/51	0/51	2/51	P_{Trend}=0.575
Skin Keratocanthoma	Male	1/51	0/51	1/51	1/51	P_{Trend}=0.392

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

I obtained historical control data from 16 control groups in Wistar rats from Charles River Laboratories for the years 2003 to 2011[98]. Although these are outside of the optimal time range for the animals used in the **Brammer (2001)** study, they can serve as an illustration of why using a range can be misleading. There were 52 liver adenomas

seen in 1217 control animals for a mean response of 4.27% with a range of 0% to 17.5% (individual study findings of 6/100, 0/60, 1/60,1/50,1/80, 14/112, 1/65, 0/60, 21/120, 0/50, 1/50, 2/60, 0/50, 1/100, 1/150, 2/50; 13 studies with ≤2% response). Assuming the underlying probability of having a tumor in controls is 4.27%, p_{Hist}=0.006 (Table 4). Thus, even though the responses seen in **Brammer (2001)** are in the range of the historical controls, the trend is highly significant when historical controls are used appropriately. **Greim et al. (2015)** also mentioned findings of increased toxicity at the high dose for which they provided numbers for only hepatocyte fat vacuolation and hepatitis; none of these findings were statistically significant by any test.

In conclusion, this study shows a positive result for hepatocellular adenomas in male Wistar rats and will be included in the overall evaluation of causation.

Pavkov and Wyand (1987)[75] exposed Sprague-Dawley rats to glyphosate trimesium salt (sulfosate, 56.2% pure) in feed for two years. Eighty animals/sex were tested in the control, low-dose and mid-dose groups, and 90/sex were tested in the high dose group. Doses of 0, 4.2, 21.2 and 41.8 mg/kg/day were used in males and 0, 5.4, 27, and 55.7 mg/kg/day in females. This study showed no significant findings according to EPA[61]. No details were given beyond that simple statement and no others reported on this study. The doses in this study are far below the MTD so this study would have reduced sensitivity to detect an effect if one existed. This study also used a different chemical than the other Sprague-Dawley rat studies and is not comparable on that basis.

This study is not acceptable for use in the evaluation of causality due to the lack of details about the study.

Suresh, (1996)[79] exposed Wistar rats to glyphosate (96.8% pure) in feed for two years. Fifty animals/sex were tested in four exposure groups shown in Table 5.

There were no survival differences in this study and there was no indication that the highest dose used exceeded the maximum-tolerated dose.

EPA[61] concluded there were no tumors increased due to glyphosate exposure in this study and **EFSA**[89] concluded that, "[n]one of the significant microscopic changes, increased and decreased incidences (in liver, spleen, lymph nodes, adrenals, thymus, gonads, uterus, mammary gland) observed have shown dose relationship, hence appeared to be incidental and not related to the treatment with the test compound." (page 491). **Greim et al. (2015)**[91] provided data on hepatocellular adenomas and carcinomas in both sexes but none of these showed significant trends or pairwise tests (Table 5). However, there was another study with a strong significant trend in hepatocellular adenomas in Wistar rats[69] so these are also included in Table 5 for comparison. No other tumors were mentioned by any other group and an examination of the grouped pathology tables provided by **Greim et al. (2015)** show an increase in mammary gland adenomas at the mid-dose (p_{Fisher}=0.017) but no significant trend. However, there was another study with a strong significant trend in mammary gland adenomas and adenocarcinomas combined in Wistar rats[80] so these are also included in Table 5 for comparison. Like the **Atkinson et al. (1993)**[68] study, **Suresh (1996)** did not do full pathology on all of the animals in the interim exposure groups making

interpretation of this study problematic.

This study will be included in the overall evaluation of causation.

Table 5: Tumors of interest in male and female Wistar rats from the 24-month feeding study of Suresh(1996)[79]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	6.3	59.4	595.2	
	Female	0	8.6	88.5	886	
Mammary Gland Adenoma and Carcinoma	Female	5/40	3/28	8/33	2/48	P_{Trend}=0.970
Hepatocellular Adenoma	Male	24/50	22/50	10/50	21/50	P_{Trend}=0.374
Skin Keratocanthoma	Male	0/50	0/50	0/50	0/50	P_{Trend}=1

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Enemoto (1997)[72] exposed Sprague-Dawley rats to glyphosate (95.7% pure) in feed for two years. Fifty animals/sex were tested in four exposure groups (see Table 6). In addition, 10 animals per exposure group were exposed for 1 year and another 10 for 18 months at which point they were sacrificed and examined. These interim sacrifice animals (1 year and 18 months) are included in the analysis if tumors were seen in these groups.

There were no survival differences in this study and there was no indication that the highest dose exceeded the maximum-tolerated dose.

EPA and EFSA both found no significant changes in tumors in any group. **Greim et al. (2015)** again provide tables for a number of tumors, none of which show significant effects except for the incidence of kidney adenomas in male rats (p_{Trend}=0.004, Table 6). Examining the pathology tables provided in **Greim et al. (2015)** reveals no additional tumors showing an increase in tumor incidence with dose. A different study[74] in Sprague-Dawley rats demonstrated a strong significant trend in mammary gland adenomas, thyroid C-cell carcinomas, skin Keratocanthomas and testicular interstitial cell tumors so these are also included in Table 6 for comparison.

This study showed a significant increase in kidney adenomas and will be included in the overall evaluation of causation.

Table 6: Tumors of interest in male and female Sprague-Dawley rats from the 24-month feeding study of Enemoto (1997)[72]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	104	354	1127	
	Female	0	115	393	1247	
Mammary Gland Adenoma	Female	23/50	27/50	24/50	30/50	P_{Trend}=0.106
Kidney Adenoma	Male	0/50	0/50	0/50	4/50	P_{Trend}=0.004
Thyroid C-cell Adenomas/Carcinomas	Female	4/60	7/60	8/60	4/60	P_{Trend}=0.692
Thyroid C-cell Adenomas/Carcinomas	Male	8/70	10/70	6/70	7/70	P_{Trend}=0.697
Thyroid Follicular-cell Adenomas/Carcinomas	Male	4/70	2/70	1/70	0/70	P_{Trend}=0.990
Testes Interstitial Cell Tumors	Male	3/49	2/50	0/50	2/50	P_{Trend}=0.594
Hepatocellular Adenomas	Male	1/60	0/60	2/60	1/60	P_{Trend}=0.371
Skin Keratocanthoma	Male	3/50	3/50	0/50	6/50	P_{Trend}=0.065
Pancreas Islet-Cell Adenoma	Male	4/50	1/50	2/50	1/50	P_{Trend}=0.844

*- $p_{Fisher}<0.05$, **- $p_{Fisher}<0.01$

Wood et al. (2009)[80] exposed Wistar rats to glyphosate (94.7% to 97.6% pure) in feed for two years. Fifty-one animals/sex were tested in four exposure groups at doses shown in Table 7.

No survival differences were seen in this study.

EFSA[89] found no dose-related tumor increases while **EPA**[61] noted an increase in mammary gland adenomas and adenocarcinomas combined with p_{Trend}=0.062 for adenomas, p_{Trend}=0.042 for adenocarcinomas and p_{Trend}=0.007 for the combined tumors (Table 7). EPA concluded there was no progression from adenoma to adenocarcinoma and argued the increase was not glyphosate related. This conclusion is contradicted by the fact that 6 animals in control and the lower dose groups got carcinomas with no adenomas in any of the animals in these groups. It seems likely that, in this case, mammary gland adenocarcinomas can arise without the presence of any adenomas. **Greim et al (2015)**[91] also noted an increase in skin keratoacanthoma in males (p_{Trend}=0.030). Review of the pathology tables identified no other tumors with increased tumor rates as a function of dose. There was another study with a strong significant trend in hepatocellular adenomas in Wistar rats[69] so this tumor is also included in Table 7 for comparison.

This study showed an increase in mammary tumors in females and skin keratoacanthomas in males and will be used in the evaluation of causality.

Table 7: Tumors of interest in male and female Wistar rats from the 24-month feeding study of Wood et al. (2009)[80]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	85.5	285.2	1077.4	
	Female	0	104.5	348.6	1381.9	
Mammary Gland Adenomas	Female	0/51	0/51	0/51	2/51	P_{Trend}=0.062
Mammary Gland Adenocarcinomas	Female	2/51	3/51	1/51	6/51	P_{Trend}=0.042
Mammary Gland Adenomas and Adenocarcinomas	Female	2/51	3/51	1/51	8/51*	P_{Trend}=0.007
Skin Keratocanthoma	Male	2/51	3/51	0/51	6/51	P_{Trend}=0.030
Hepatocellular Adenoma	Male	0/51	2/51	1/51	1/51	P_{Trend}=0.418

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01

Excel (1997)[73] exposed Sprague-Dawley rats to glyphosate (purity not given) in feed for two years. Fifty-one animals/sex were tested in four exposure groups at doses of 0, 150, 780 and 1290 mg/kg/day in males and 0, 210, 1060 and 1740 mg/kg/day in females. **EPA**[61], **EFSA**[89] and **Greim et al. (2015)**[91] had concerns with the quality of this study, the characterization of the chemical being used and with tumor rates in this strain of animals being too low. The Supplemental Material from **Greim et al. (2015)** on this study shows no significant increase in any tumor and virtually all animals having no tumors in controls and treated animals.

This study is inadequate for use in deciding on causality for the same reasons given by the **EPA, EFSA** and **Greim et al. (2015)**.

Chruscielska, K. (2000)[71] exposed Wistar rats to glyphosate as a 13.8% solution (purity not given) in drinking water for two years. According to **Greim et al. (2015)**[91], this appears to be the glyphosate formulation Perzocyd. Eighty-five animals/sex were tested in four exposure groups. The authors listed the doses as control, 300 mg/L, 900 mg/L and 2700 mg/L in drinking water. **Greim et al. (2015)**[91] estimated the intake of glyphosate to be 0, 1.9, 5.7 and 17 mg/kg/day for females and 0, 2.2, 6.5, and 19 mg/kg/day in males. There was a slight increase in malignant adenomas of the pituitary gland and an opposite decrease in pituitary adenomas suggesting no effect or potentially a promotional effect in which adenomas are promoted to carcinomas by glyphosate. No other increased tumor responses were reported in the manuscript. Because of the low exposures, this study is an inadequate challenge to the animals (the highest dose is far below the MTD). The reporting of this study is very limited and it the overall quality of the work cannot be evaluated.

This study is inadequate for use in deciding on causality.

Seralini, G. E., et al. (2014)[77] exposed Sprague-Dawley rats to the glyphosate formulation Roundup in drinking water for two years as part of a broader experiment on

Roundup-Ready Corn. Ten animals/sex were tested in four exposure groups at doses of 0, 0.00005, 400 and 22500 mg/L in females. The authors reported an increase in the incidence of mammary gland tumors (mainly fibroadenomas and adenocarcinomas) in female rats with incidences of 5/10 for control and 9/10, 10/10, 9/10 (p_{Fisher}=0.016) in the low-, mid- and high-doses groups respectively. It is difficult to assess the quality of this study due to limited reporting on the histopathological descriptions of the tumors and the very small sample size.

This study will not be used in the evaluation of causality.

Joint Analysis - Rats

Table 8 summarizes the significance for all tumors of interest in rats.

Brammer (2001)[69] saw a significant increase in hepatocellular adenomas in male Wistar rats with increasing dose (p_{Trend}=0.008, Table 4). The other two acceptable studies in Wistar rats (**Wood et al. (2009)**[80] and **Suresh (1996)**[79] did not see significant increases (Tables 5 and 7). On the basis of statistical significance, these studies are inconsistent. To reject these findings based upon only 1/3 being positive is the same as rejecting a coin as being fair if, in three flips of the coin, the result is one head and two tails; it simply is not possible and there is a better way to address these findings. Given different doses and different sample sizes, we need to formally test for consistency in these studies. **Suresh (1996)** saw 48% response for hepatocellular adenomas in controls whereas the other two studies saw no tumors in the control animals. Thus, although all three studies are in Wistar rats, **Suresh (1996)** has a significantly different control response from the other two. **Suresh (1996)** did not give a substrain for the Wistar rats used, but **Brammer (2001)** and **Wood et al. (2009)** used different substrains. All three studies used different diets and were conducted in different facilities. Thus, there is no obvious explanation for the dramatically different rates in **Suresh (1996).** It is known that the same strain of rats from different laboratories can have markedly different control tumor responses. Because they have similar control response, **Brammer (2001)** and **Wood et al. (2009)** can be pooled into a single study to ask the question "Does the significant trend for **Brammer (2001)** disappear when it is pooled with the negative study of **Wood et al. (2009)**?" The analysis of the pooled studies yields p_{Trend}=0.013 supporting the conclusion that glyphosate causes hepatocellular adenomas in Wistar rats with similar background responses.

Wood et al. (2009)[80] saw a significant increase in mammary gland adenomas and adenocarcinomas (p_{Trend}=0.007, Table 7) in females that was not seen in the other two studies (Tables 4 and 6). The background rates in these studies differ only slightly and a pooled analysis of all three studies yields p_{TrendA}=0.459, suggesting that combining the data eliminates the dose-response trend seen in **Wood et al. (2009)**. However, if the Wistar rats used in **Suresh (1996)** differed in their response for hepatocellular adenomas, they may differ for this tumor as well. Combining only **Wood et al. (2009)** with **Brammer (2001)** results in p_{Trend}=0.037. Given the mixed results from the pooling for this tumor I conclude there is limited support for the notion that glyphosate can cause mammary gland adenomas and adenocarcinomas in Wistar rats.

Wood et al. (2009)[80] saw a significant increase in skin keratocanthomas (p_{Trend}=0.030, Table 7) in males that was not seen in the other two studies (Tables 4 and 6). The background rates in these studies differ only slightly and a pooled analysis of all three studies yields p_{TrendA}=0.010, suggesting that combining the data does not eliminate the dose-response trend seen in **Wood et al. (2009)**. Combining only **Wood et al. (2009)** with **Brammer (2001)** results in p_{Trend}=0.053. Given the results from the pooling for this tumor I conclude there is support for the notion that glyphosate can cause skin keratocanthomas in Wistar rats.

In Sprague-Dawley rats, there were four studies that were acceptable for inclusion in the evaluation of causality with one[74] yielding strong positive responses for thyroid C-cell carcinomas in females and testicular interstitial tumors and hepatocellular adenomas in males and another[72] yielding a strong result for kidney adenomas in males. **Lankas (1981)**[74] saw a significant increase in thyroid C-cell carcinomas in female rats exposed to glyphosate (p_{Trend}=0.003, Table 1) and a marginal increase in C-cell adenomas and carcinomas combined (p_{Trend}=0.072, p_{hist}=0.072, Table 1; two of the other three studies also saw marginal results for thyroid C-cell adenomas and carcinomas in females (Tables 2 and 3). A pooled analysis using all four studies yields p_{TrendA}=0.390. This pooled analysis does not support the results seen in **Lankas (1981)**. However, the **Lankas (1981)** study was for 26 months and the other three were for 24 months; the C-cell carcinomas could be a result of the longer exposure period even though the dose is substantially lower in this study compared to the other two. From these data, I conclude that the evidence is weak that glyphosate causes thyroid C-cell tumors in female Sprague-Dawley rats.

Thyroid C-cell adenomas and carcinomas combined, in males, show marginally significant dose-response trends in **Stout and Ruecker (1990**, Table 2) but not in the remaining three studies. Pooling all four studies yields a significant trend of p_{TrendA}=0.041. From these data, I conclude that there is evidence is that glyphosate causes thyroid C-cell tumors in male Sprague-Dawley rats.

Thyroid follicular-cell adenomas and carcinomas combined, in males, show a significant dose-response trend in **Atkinson et al. (1993**, Table 3) but not in the remaining three studies;. Pooling all four studies yields no significant trend with p_{TrendA}=0.618. From these data, I conclude that there is no evidence that glyphosate causes thyroid follicular-cell tumors in male Sprague-Dawley rats.

Hepatocellular adenomas, in males, show a significant dose-response trend in **Stout and Ruecker (1990**, Table 2) but not in the remaining three studies. Pooling all four studies yields a marginally significant trend with p_{Trend}=0.073. From these data, I conclude that there is limited evidence that glyphosate causes thyroid follicular-cell tumors in male Sprague-Dawley rats.

Table 8: Summary of significance tests for 5 tumors from 7 studies in Rats

Brammer (2001)[69]	Wistar	+++[2]	-						
Wood (2009)[80]		-	+++	++					
Suresh (1996)[79]		-	-						
Pooled Wistar Rats		++[2]	++[2]	+++					
Lankas (1981)[74]	Sprague Dawley	-[3]			+	-	-	+++	-
Enemoto (1997)[72]		-			-	-	-	-	+++
Atkinson et al. (1993)[68]		-			-	-	++	-	-
Stout and Ruecker (1990)		++			-	+	-	-	-
Pooled Sprague-Dawley Rats		+			-	++	-	-	++[4]

[1]entries are p_{Trend}/p_{Hist} with values: – p>0.1, + 0.1≥p>0.05, ++ 0.05≥p>0.01, +++ p≤0.01; [2]pooling results from **Brammer (2001)** and **Wood (2009)** only; [3]liver neoplastic nodules; [4]excluding **Lankas (1981)**

Another significant trend seen in Sprague-Dawley rats is the finding of testes interstitial cell tumors from **Lankas (1981)**[74] (P_{Trend}=0.009, Table 1); the other three studies were negative for this tumor (Tables 2, 3 and 6). Combining the other three studies with that of **Lankas (1981)** for testes interstitial tumors results in a p-value for trend that is clearly non-significant (p_{TrendA}=0.608). However, as noted above, the **Lankas (1981)** study was for 26 months and the other two were for 24 months; the tumors could be a result of the longer exposure period even though the dose is substantially lower in this study compared to **Stout and Ruecker (1990)**, **Atkinson et al.(1993)** and **Enemoto (1997)**.

The final tumor in Sprague-Dawley rats showing a strong significant trend is kidney

adenomas in males from the study by **Enemoto (1997)**[72] (P_{Trend}=0.004, Table 6). The kidney tumor data is not significant for the studies by **Lankas (1981)**[74] (Table 1), **Atkinson et al. (1993)**[99] (Table 3) and **Stout and Ruecker (1990)**[78] (Table 2). Pooling the **Enemoto (1997)** study with that of **Lankas (1981)**[74], **Stout and Ruecker (1990)** and **Atkinson et al. (1993)** yields p_{TrendA}=0.201. Removing the 26-month study by **Lankas (1981)**[74] yields a p-value for the three combined 24-month studies of p_{Trend}=0.031; thus, the association between glyphosate and kidney adenomas in male Sprague-Dawley rats is supported by these data, even with the difficulty associated with interpreting the results in the low- and mid-doses in the **Atkinson et al. (1993)** study. There is evidence to support an increase in kidney tumors in male Sprague-Dawley rats exposed to glyphosate.

In summary, there is evidence that glyphosate causes hepatocellular adenomas and skin keratocanthomas in male Wistar rats, mammary gland adenomas and adenocarcinomas in female Wistar rats and kidney adenomas and thyroid C-cell adenomas and carcinomas in male Sprague-Dawley rats. There is limited evidence glyphosate causes hepatocellular adenomas in male Sprague-Dawley rats.

Mouse Studies

Reyna and Gordon (1974)[86] exposed Swiss White mice to glyphosate (>97% purity) in feed for 16 months in males and 18 months in females. Fifty animals/group/sex were tested in three exposure groups; control, 17 mg/kg and 50 mg/kg. Only 10 animals per group were examined for histopathological changes.

There was no impact on survival of administration of glyphosate and no indication that the high dose exceeded the MTD.

No significant increases were seen in any tumor from this study. However, given the small sample size for histopathological evaluation and the low doses used for this study, this study is inadequate.

This study will not be used in the evaluation of causality.

Knezevich and Hogan, (1983)[83] exposed CD-1 mice to glyphosate (99.8% pure) in feed for two years. Fifty animals/group/sex were tested in four exposure groups (see Table 9).

There were no survival differences in this study and there was no indication that the highest dose used exceeded the MTD.

EPA[100] found a significant increase in kidney tubular cell adenomas in male mice based upon the original pathology done from the study and this analysis is shown in Table 9 (p_{Trend}=0.019). Kidney tubular cell adenomas are very rare tumors in CD-1 mice so it is important to compare these results with the historical controls. No historical controls were available from the laboratory that conducted **Knezevich and Hogan, (1983)** so IARC, EPA and EFSA all used historical control databases from published studies in the

literature[101-103]. These studies have virtually identical rates for the important tumors seen in CD-1 mice; I will use the study by **Giknis and Clifford (2000)**[102] since it best covers the range of studies we have for CD-1 mice. For studies of approximately two years, the mean historical tumor response in controls is 0.27%. Applying this control response rate to the kidney adenomas yields p_{Hist}=0.005, strengthening the significance of the evaluation against the concurrent control. EPA originally used a similar analysis and reached the same conclusions. However, in 1985, the registrant had a group of pathologists review the kidney slides. Using additional kidney sections from this study, the pathologists identified an additional adenoma in the control animals and changed the classification for three adenomas to carcinomas (Table 9). With these changes, the adenomas no longer have a significant trend (P_{Trend}=0.442, P_{Hist}=0.121) but carcinomas have a marginally significant trend against concurrent controls and a clearly significant trend using historical controls (p_{Trend}=0.063, p_{Hist}=0.002, historical control rate of 0.15%). These historical control rates may not apply to this analysis because the reevaluation of the kidney tumors considered additional sections and no information is available on how additional sections affect historical control rates in this strain of mice; differences have been seen in other settings[104]. The incidence of combined carcinomas and adenomas has the same marginal significance against the concurrent control and significance against the historical controls (p_{Trend}=0.065, p_{Hist}=0.011, historical control rate of 0.44%). However, there was considerable disagreement on whether the one adenoma in the control group was correctly diagnosed[105]. Removing this one adenoma from the control group results in p_{Trend}=0.019 and p_{Hist}=0.005.

Other CD-1 mouse studies have seen increases in malignant lymphomas, hemangiosarcomas and lung adenocarcinomas (males) and hemangiomas (females). Evaluations of those tumors for this study yields results that are not significant; for malignant lymphoma, p_{Trend}=0.754, p_{Hist}=0.767, with the historical control rate equal 6.2%, for hemangiosarcomas p_{Trend}=0.503, p_{Hist}=0.591, with the historical control rate equal to 2.5%, for lung adenocarcinomas p_{Trend}=0.918, p_{Hist}=0.899, with the historical control rate equal to 9.2% and for hemangiomas p_{Trend}=0.631. No other tumors were found in this study.

The **EPA**[61] has produced many different arguments to dismiss the findings of renal tumors from this study. One argument is that the pathology working group requested by the EPA in 1986 concluded these lesions were not glyphosate related because *"1) renal tubular cell tumors are spontaneous lesions for which there is a paucity of historical control data for this mouse stock; 2) there was no statistical significance in a pairwise comparison of treated groups with the concurrent controls and there was no evidence of a statistically significant linear trend; 3) multiple renal tumors were not found in any animal; and 4) compound-related nephrotoxic lesions, including pre-neoplastic changes, were not present in male mice in this study."* Reason number one no longer exists as there are two very good historical control databases for CD-1 mice[101, 102]. The second reason, while technically correct, is not supportable since the Agency's own guidelines for evaluating carcinogenicity studies state that *"Significance in*

either kind of test [trend or pair-wise] *is sufficient to reject the hypothesis that chance accounts for the result."* The third reason is also weak since one would not expect (nor require) multiple tumors to appear when dealing with a rare tumor. For the fourth point, EPA provides data on the rate of bilateral chronic interstitial nephritis in the study which it considers to show no statistically significant results although the trend test is highly significant (p_{Trend}=0.006, Table 9). EPA then states, without reference, that *"chronic interstitial nephritis is not considered to be a precursor lesion for tubular neoplasms"*. I could find no published research to either support or refute this statement. However, chronic interstitial nephritis is an inflammation of the interstitial tissue surrounding the glomeruli and tubules in the kidney. Inflammation is well known

Table 9: Tumors of interest in male and female CD-1 mice from the 24-month feeding study of **Knezevich and Hogan (1983)**[83]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	157	814	4841	
	Female	0	190	955	5874	
Kidney Adenoma[1] (original pathology)	Male	0/49	0/49	1/50	3/50	P_{Trend}=0.019 P_{Hist}=0.005
Kidney Adenoma (EPA pathology)	Male	1/49	0/49	0/50	1/50	P_{Trend}=0.442 P_{Hist}=0.121
Kidney Carcinoma[2] (EPA pathology)u	Male	0/49	0/49	1/50	2/50	P_{Trend}=0.063 P_{Hist}=0.002
Kidney Adenoma and Carcinoma Combined[3] (EPA pathology)	Male	1/49	0/49	1/50	3/50	P_{Trend}=0.065 P_{Hist}=0.011
Malignant Lymphoma[4]	Male	2/49	5/49	4/50	2/50	P_{Trend}=0.754 P_{Hist}=0.767
Hemangiosarcoma[5]	Male	0/50	0/49	1/50	0/50	P_{Trend}=0.503 P_{Hist}=0.591
Bilateral Chronic Interstitial Nephritis	Male	5/49	1/49	7/50	11/50	P_{Trend}=0.006
Hemangiooma[6]	Female	0/49	1/49	1/50	0/50	P_{Trend}=0.631
Lung Adenocarcinoma[7]	Male	4/48	3/50	2/50	1/50	P_{Trend}=0.918 P_{Hist}=0.899

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.27%, [2]historical rate=0.15%, [3]historical rate=0.44%, [4]historical rate=6.2%, [5]historical rate=2.5%, [6]No Historical Controls, [7]Historical rate=9.2%

to play an important role in kidney cancer[106] and many other cancers so this argument also fails to support rejection of these findings.

In summary, this study shows a positive result for kidney tumors in male CD-1 mice and will be included in the overall evaluation of causation.

Atkinson, et al., (1993)[81] exposed CD-1 mice to glyphosate (>97% purity) in feed for two years. Fifty animals/group/sex were tested in four exposure groups (see Table 10).

There was no impact on survival of administration of glyphosate and no indication that the high dose exceeded the MTD.

Table 10: Tumors of interest in male and female CD-1 mice from the 24-month feeding study of **Atkinson et al. (1993)**[81]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	98	297	988	
	Female	0	102	298	1000	
Kidney Adenoma and Carcinoma Combined[1]	Male	2/50	2/50	0/50	0/50	P_{Trend}=0.981 P_{Hist}=1
Malignant Lymphoma[2]	Male	4/50	2/50	1/50	6/50	P_{Trend}=0.087 P_{Hist}=0.085
Hemangiosarcoma[3]	Male	0/50	0/50	0/50	4/50	P_{Trend}=0.004 P_{Hist}=0.001
Hemangioma[4]	Female	0/50	0/50	0/50	0/50	P_{Trend}=1
Lung Adenocarcinoma[5]	Male	10/50	7/50	8/50	9/50	P_{Trend}=0.456 P_{Hist}=0.449

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=6.2%, [3]historical rate=2.5%, [4]No historical control rate, [5]Historical rate=9.2%

Hemangiosarcomas were the only tumors showing a significant trend in this study (P_{Trend}=0.004, P_{Hist}=0.001, Table 10). Also shown in Table 10 are the results for malignant lymphomas, kidney tumors and lung adenocarcinomas (males) and hemangioma (females); there is a marginal trend for malignant lymphomas (P_{Trend}=0.087, P_{Hist}=0.085) and no trend for kidney tumors.

The **EPA**[61] concluded the findings in this study were not treatment related based upon the tumors appearing only in the high dose group, a lack of statistical significance between the response in this group and control response and that these tumors are commonly observed in mice as both spontaneous and treatment related effects. There is no scientific support for excluding positive findings in the highest dose group, a view also held by the **SAP**[54]. I have already commented on how EPA's guidelines treat trend tests and Fisher's Exact test results, although in this case, the value of the comparison of the highest exposure group to controls, p_{Fisher}=0.059, is marginally significant. The argument regarding the frequency of this tumor in controls is addressed directly by the evaluation against the historical control rates; if these rates were high enough to exclude this finding, P_{Hist} would have be above 0.05 instead of 0.001. The mean

historical control incidence of hemangiosarcomas in controls from two-year cancer bioassays in CD-1 mice is 2.5% and the response seen in the high-dose group is 8.9%. The **SAP**[54] stated very clearly that the practice, being used by the EPA, of negating a positive finding because of historical control data was not acceptable[54]. (page 63). The EPA Cancer Guidelines[33] state this very clearly *"...statistically significant increases in tumors should not be discounted simply because incidence rates in the treated groups are within the range of historical controls or because incidence rates in the concurrent controls are somewhat lower than average."*

In summary, this study shows a positive result for hemangiosarcomas in male CD-1 mice and will be included in the overall evaluation of causation.

Wood et al., (2009)[88] exposed CD-1 mice to glyphosate (95.7% pure) in feed for 80 weeks. Fifty-one animals/groups/sex were tested in four exposure groups (see Table 11).

There was no effect on survival and no information suggesting the study exceeded the MTD.

No increase in kidney tumors or hemangiosarcomas (males) or hemangiomas (females) were seen in this study. There was a monotonic increase in lung adenocarcinomas (p_{Trend}=0.028, p_{Hist}=0.031) in males and a monotonic increase in malignant lymphomas (p_{Trend}=0.007, p_{Hist}=0.007) in males. The historical control incidence for this study is different from the earlier studies because this study is only for 80 weeks instead of 104 weeks (two years); the historical control rate for malignant lymphomas in CD-1 mice after 80 weeks is 2.6% instead of 6.2%, the historical control rate at two years[102].

For lung adenocarcinomas, the **EPA**[61] again argued a lack of significance for pairwise comparisons (in violation of its guidelines) and that there was no evidence of progression from adenomas to carcinomas. Even though there was no increase in lung adenomas as a function of exposure, it is possible to have an increase in lung adenocarcinomas without an associated increase in adenomas[107]. For malignant lymphomas, EPA notes that there was a statistically significant response and that the high dose was significantly different from control (p_{Fisher}=0.028), but then uses an argument based upon the number of analyses done in this study to adjust the Fisher Exact test p-value to 0.082 (an adjustment for multiple comparisons is indeed warranted in evaluating the outcomes of these animal cancer studies, this will be addressed later in my report in the evaluation of all of the studies combined).

The **EPA**[61] uses historical control data[103, 108] to exclude the malignant lymphomas and cite a mean response of 4.5% and a range of 1.5% to 21.7%. **Son and Gopinath (2004)**[108] saw 21 animals out of 1453 examined prior to 80 weeks with lung adenocarcinomas (1.4%). **Giknis and Clifford (2005)**[103] saw a mean rate of 4.5% with a range of 0% to 21.7% in 52 studies which included mostly 78 week controls (26 studies) and 104 week controls (21 studies). Including only studies of 80 weeks or less, the rate in **Giknis and Clifford (2005)** is 37/1372=2.7% with a range of 0% to 14%. **Giknis and Clifford (2000)**[102] (the reference I have been citing) did a similar evaluation, using mostly the same data as their 2005 paper and saw an average tumor incidence before

80 weeks of 2.6% with a range of 0% to 14%. Based upon its flawed interpretation of the **Giknis and Clifford (2005)** historical controls, EPA argues that the incidence of concurrent controls in the study was low (it was 0%) and rejected the positive finding. In fact, of the 26 studies in the 18-month control groups evaluated by **Giknis and Clifford (2005),** eight (31%) had response of 0% and eight (31%) had only one tumor. The evaluation used by the EPA is incorrect. In addition, as noted earlier, the use of historical control data to negate a positive finding is not supported by **EPA's guidelines**[33, 54] or its **SAP**[54].

There was an increase in the number of animals with multiple malignant tumors (P_{Trend}=0.046)

In summary, this study shows a positive result for malignant lymphomas and lung adenocarcinomas in male CD-1 mice and will be included in the overall evaluation of causation.

Table 11: Tumors of interest in male and female CD-1 mice from the 18-month feeding study of **Wood et al. (2009)**[88]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	71.4	234.2	810	
	Female	0	97.9	299.5	1081.2	
Kidney Adenoma[1]	Male	0/51	0/51	0/51	0/51	P_{Trend}=1
Malignant Lymphoma[2]	Male	0/51	1/51	2/51	5/51*	P_{Trend}=0.007 P_{Hist}=0.007
Hemangiosarcoma	Male	0/51	0/51	0/51	0/51	P_{Trend}=1
Lung Adenocarcinoma[3]	Male	5/51	5/51	7/51	11/51	p_{Trend}=0.028 P_{Hist}=0.031
Hemangioma[4]	Female	0/51	2/51	0/51	1/51	p_{Trend}=0.438
Animals with Malignant Neoplasms	Male	14/51	20/51	17/51	20/51	P_{Trend}=0.203
Animals with Malignant Neoplasms	Female	23/51	15/51	17/51	18/51	P_{Trend}=0.628
Animals with multiple malignant tumors	Male	1/51	2/51	3/51	5/51	P_{Trend}=0.046

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=2.6%, [3]Historical rate=2.5%, [4]No Historical Control Rate

Sugimoto (1997)[87] exposed CD-1 mice to glyphosate (94.61-95.67% pure) in feed for two years. Fifty animals/group/sex were tested in four exposure groups (see Table 12).

There were no effects of treatment on survival and no indication the highest dose had exceeded the MTD.

Kidney adenomas (p_{Trend}=0.062, p_{Hist}=0.005), malignant lymphomas (p_{Trend}=0.016,

p_{Hist}=0.017) and hemangiosarcomas (p_{Trend}=0.062, p_{Hist}=0.004) in male mice and hemangiomas (p_{Trend}=0.002) in female mice all showed increased tumor incidence with increasing dose. The evaluation of lung adenocarcinomas in males showed no significant dose-related trend (p_{Trend}=0.148, p_{Hist}=0.140). This study also had an increase in animals with any malignancy in males (p_{Trend}=0.001) but not in females (p_{Trend}=0.362). Note that no hemangiosarcomas were seen in the 26 control groups evaluated by **Giknis and Clifford (2000)** so the development of an estimate of the historical control response is difficult (if the historical control rate is 0, then any observed response other than 0 has a p-value of 0). The fact that this tumor was never seen in the historical controls should strongly support any positive finding as being significant. However, to still allow for a test using historical control data, I used the historical control estimate of the mean response that would result in a 5% chance of seeing no tumors in 1149 animals. This estimated historical control response value was 0.0026. This value was used in the analysis for hemangiosarcomas in male CD-1 mice exposed for 18 months (p_{Hist} <0.001).

Table 12: Tumors of interest in male and female CD-1 mice from the 18-month feeding study of **Sugimoto (1997)**[87]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	165	838.1	4348	
	Female	0	153.2	786.8	4116	
Kidney Adenoma[1]	Male	0/50	0/50	0/50	2/50	P_{Trend}=0.062 P_{Hist}=0.005
Malignant Lymphoma[2]	Male	2/50	2/50	0/50	6/50	P_{Trend}=0.016 P_{Hist}=0.017
Hemangiosarcoma[3]	Male	0/50	0/50	0/50	2/50	P_{Trend}=0.062 P_{Hist}=0.004
Hemangioma[4]	Female	0/50	0/50	2/50	5/50*	P_{Trend}=0.002
Lung Adenocarcinoma[5]	Male	1/50	1/50	6/50	4/50	P_{Trend}=0.148 P_{Hist}=0.140
Number of animals with Malignant Neoplasms	Male	5/50	5/50	11/50	16/50**	P_{Trend}=0.001
Number of animals with Malignant Neoplasms	Female	9/50	13/50	16/50	13/50	P_{Trend}=0.362

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]historical rate=0.44%, [2]historical rate=2.6%, [3]historical rate=0/1424 (0.26% - 95% confidence limit), [4]No Historical Control Rate, [5]Historical rate=2.5%

EPA[61] only addressed the hemangiomas in the female mice and did not note any other significant effects. For the females, EPA argued that the high dose was approximately four times higher than the current recommended high dose from the **OECD guidelines**[109]. This study was correctly designed under the previous guidelines (the limit was <5% in feed) and there is no indication that this dose exceeded the MTD. The EPA also argued that when the p-value for Fisher's Exact test was adjusted for multiple comparisons, the new p-value for the high-dose group for hemangiomas was 0.055.

For the hemangiosarcomas in males, none of the 26 historical control groups examined by **Giknis and Clifford (2000)** had hemangiosarcomas, making this a very rare tumor in males prior to 80 weeks on study. The malignant lymphomas in males are statistically significant against both the concurrent controls and the historical controls. Finally, there is clearly an overall increase of malignancies in the males.

In summary, this study shows a positive result for kidney adenomas, malignant lymphomas and hemangiosarcomas in male CD-1 mice, hemangiomas in female CD-1 mice and an overall increase in malignancies as a function of exposure in male CD-1 mice. This study will be included in the overall evaluation of causation.

Kumar (2001)[84] exposed Swiss Albino mice to glyphosate (>95% purity) in feed for two years. Fifty animals/group/sex were tested in four exposure groups (see Table 13).

The survival was decreased in the highest exposure group but this was not statistically significant and there was no other data indicating the MTD was exceeded for this study.

Kidney adenomas (p_{Trend}=0.062) and malignant lymphomas (p_{Trend}=0.064, p_{Hist} =0.070) in male mice demonstrated marginal statistical significance and hemangiosarcomas (p_{Trend}=0.500) in male mice demonstrated no statistical significance. In this study, not all animals in the low- and mid- dose groups were evaluated for kidney tumors, so a second analysis was done based on only the animals examined in these two groups (p_{Trend}=0.088). No historical control data was available for hemangiosarcomas and kidney adenomas in Swiss Albino mice. For the malignant lymphomas, EFSA provided a historical control data set showing a mean response of 46/250=0.184 (18.4%) with a range of 6% to 30%. Using this historical control data, the trend is only marginally significant (p_{Hist}=0.070). I have some concern that the responses at two of the doses are outside of the historical control range and the third dose is at the upper limit of the historical control range. However, this is a small historical control dataset for a tumor with a relatively high background tumor rate, thus placing too much emphasis on this historical control population is not warranted.

In a recent memo, Martens (2017) [110] asserts that the incidence counts for malignant lymphomas and kidney adenomas appearing in Greim et al. (2015)[91] and EFSA (2013)[89] are incorrect and provides different rates (shown in Table 13). The p-values for both of these tumors are reduced using the incidence counts from the Martens memo. However, it should be noted that if the counts for malignant lymphomas in the Martens (2017) memo are correct, then all three exposure groups have responses outside of the range of the historical controls. It is unclear from Greim et al. (2015), EFSA or Martens (2017) which tumor incidence counts are correct.

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

In summary, this study shows support for an increase for malignant lymphomas and kidney adenomas as a function of exposure in male Swiss Albino mice and an increase in hemangiomas in female Swiss Albino mice. This study will be included in the overall

Table 13: Tumors of interest in male and female Swiss Albino mice from the 18-month feeding study of **Kumar (2001)**[84]

Tumor	Sex	Doses (mg/kg/day)				p-values
	Male	0	14.5	149.7	1453	
	Female	0	15	151.2	1466.8	
Kidney Adenoma (only tissues examined microscopically)	Male	0/50	0/26	1/22	2/50	P_{Trend}=0.088
Kidney Adenoma (as reported by Greim et al.)	Male	0/50	0/50	1/50	2/50	P_{Trend}=0.062
Kidney Adenoma (as reported by Martens)	Male	0/50	0/50	0/50	1/50	P_{Trend}=0.250
Malignant Lymphoma[1] (as reported by Greim et al.)	Male	10/50	15/50	16/50	19/50	P_{Trend}=0.064 P_{Hist}=0.070
Malignant Lymphoma[1] (as reported by Martens)	Male	10/50	16/50	18/50	19/50*	P_{Trend}=0.141 P_{Hist}=0.150
Hemangiosarcoma	Male	0/50	0/50	2/50	0/50	P_{Trend}=0.500
Hemangioma (any tissue)	Female	1/50	0/50	0/50	5/50	P_{Trend}=0.004

*- p_{Fisher}<0.05, **- p_{Fisher}<0.01, [1]Historical control rate=0.184 (46/250 mice)

evaluation of causation.

Pavkov and Turner (1987)[85] exposed CD-1 mice to glyphosate trimesium salt (56.2%) and 1% propylene glycol (wet weight vehicle) in feed for two years. Eighty animals/sex/group were tested in control, low- and mid-dose groups and 90 animals/sex were tested at the high dose. Exposure levels were 0, 11.7, 118 and 991 mg/kg/day in males and 0, 16, 159 and 1341 mg/kg/day in females. **EPA**[61] lists this study as completely negative for any cancer findings. No details on this study are provided by the EPA nor is it listed in the **Greim et al. (2015)**[91] manuscript. There was limited information on this study in a Data Evaluation Report from EPA (accession number 4021 40-06) that discussed findings from this study. EPA noted that body weight and food consumption were reduced in the highest exposure group, but the actual amounts of these reductions were not available. They also noted that the authors failed to make it clear that the tumors reported in the study had been histopathologically validated. Data was presented for tumors in the livers and lungs of male mice and the lungs of female mice. No other data is provided.

This study is not acceptable for inclusion in the evaluation of causation due to the lack of information on the tumor incidence in tissues other than liver and lung.

George et al. (2010)[82] exposed groups of 20 male Swiss Albino mice to a glyphosate

formulation (Roundup Original, 36g/L glyphosate) at a dose of 25 mg/kg (glyphosate equivalent dose) topically three times per week, topically once followed one week later by 12-o-tetradecanoylphorbol-13-acetate (TPA) three times per week, topically three times per week for three weeks followed one week later by TPA three times per week, or a single topical application of 7,12-dimethyl-benz[a]anthracene (DMBA) followed one week later by topical application of glyphosate three times per week for a total period of 32 weeks. Appropriate untreated, DMBA-treated, and TPA-treated controls were included. The group exposed to DMBA followed by glyphosate demonstrated a significant increase ($p<0.05$) in the number of animals with tumors (40% of the treated animals versus no tumors in the controls) indicating glyphosate has a promotional effect on carcinogenesis in the two-stage model in skin. This study addresses the question of whether glyphosate is more likely to cause skin tumors through initiation (starting the cancer process) or promotion (moving the process along after it starts). This study supports the overall concept that glyphosate can have an impact on tumor incidence.

EPA[61] discounted this study because it included only 20 animals per group, tested only males and did not conduct a histopathological analysis. It is hard to understand how EPA could reject a positive finding using 20 mice; typically one would ignore a negative study that had too few animals as not having sufficient statistical power to see an effect but never reject positive findings for this reason. Also, 20 animals per group is common for skin-painting initiation-promotion studies like the one presented here. Doing a study in only males is not a reason to ignore the positive findings in a study. Finally, in initiation-promotion studies of mouse skin, histopathological evaluation would be done if one were interested in separating papillomas from carcinomas. It is highly unlikely that the lesions seen in 40% of the DMBA/glyphosate treated mice were not papillomas or carcinomas.

Some members of the EPA SAP noted[54] that the rodent data were consistent with glyphosate acting as a tumor promoter but, because *"[t]here has been no direct test of this hypothesis (such as in a standard initiation-promotion bioassay)...,"* this *"conclusion was speculative."* (page #). Because the EPA dismissed this study without any discussion, the SAP did not recognize there was an initiation-promotion supporting a promotional effect of glyphosate.

This study is included in the evaluation of causality as support for a promotional effect of glyphosate on some tumors.

Joint Analysis - Mouse

In their evaluation of the mouse studies, **EPA**[61] and **EFSA**[89] chose to challenge the results in each study separately, dismiss the studies as showing no effect, and never compared results across the various studies. In response to the evaluation done by the **IARC**[30], **EFSA**[90] extracted the original data and did trend tests on kidney tumors, malignant lymphomas and hemangiosarcomas in male mice in five of the mouse studies, the same five studies I consider acceptable for a causation analysis. Rather than formally evaluate these cancer responses for consistency by pooling the data where appropriate, EPA and EFSA simply produced a table with the responses for each dose

group in each study and concluded (subjectively) they were inconsistent. In addition, EPA and EFSA argued that doses above 1000 mg/kg/day (there are only two of these) were outside the range of what would be tested today under OECD guidelines and should be excluded. I will now address both points.

In CD-1 mice, there are four useful animal carcinogenicity studies and one study in Swiss Albino mice. As with the rats, consistency across studies can be addressed in two ways. The first is by simply looking at the overall findings to evaluate where they agree or disagree in terms of statistical significance. Table 14 summarizes the positive and negative findings for all five cancers in which at least one study in CD-1 mice showed a significant trend. It is clear that not every tumor shows a positive trend with glyphosate exposure in every study. For hemangiosarcomas in males, there are clear positive findings in the studies by **Sugimoto (1997)** and **Atkinson et al. (1993)** and non-significant responses in **Wood et al. (2009)** and **Knezevich and Hogan (1983)**. In females, hemangiosarcomas are only present in the study by **Sugimoto (1997)**. Malignant lymphomas in males are clearly positive in two studies[87, 88] and marginally positive in a third[81] but negative in the fourth[83]. Both of the strong positive studies exposed animals for 18 months. Kidney tumors in males are positive in two studies[83, 87] and negative in the remaining two[81, 88]. Lung adenocarcinomas in males are only positive in the study by **Wood et al. (2009)**. **Sugimoto (1997)** had four clearly positive associations between tumors and glyphosate while the others had two or less.

Table 14: Summary of significance tests for 5 tumors from 4 studies in CD-1 Mice

Sugimoto 1997[87]	18	+/+++[1]	+++	++/++	+/+++	-/-
Wood 2009[88]	18	-/-	-	+++/+++	-/-	++/++
Sugimoto & Wood Pooled		++/+++	+++	+++/+++	++/+++	-/-
Atkinson 1993[81]	24	+++/+++	-	+/+	-/-	-/-
Knezevich 1983[83]	24	-/-	-	-/-	+/++	-/-
Atkinson & Knezevich Pooled		-/-	-	-/-	+/+	-/-
All CD-1 Studies Pooled		++/++	++/++	+/+	+++/+++	-/-

[1]entries are p_{Trend}/p_{Hist} with values: – p>0.1, + 0.1≥p>0.05, ++ 0.05≥p>0.01, +++ p≤0.01

As seen for the rat studies, this simple evaluation of the positive versus negative findings fails to resolve the issue of which findings are driving the overall responses in these data. To do this, I will again pool the studies. Table 14 summarizes the pooled analyses.

For kidney tumors in males, pooling the two 18-month studies yields significant increases in incidence (p_{Trend}=0.015, p_{Hist}=0.003) and pooling of the two year studies shows marginal significance (p_{Trend}=0.081, p_{Hist}=0.054). Pooling all four studies results in (p_{Trend}=0.005, p_{Hist}=0.007), thus the positive trend remains. **Knezevich and Hogan (1983)** saw a 4% response for kidney carcinomas in their highest exposure group. The largest response seen for kidney carcinomas in controls in 48 studies by **Giknis and Clifford (2000)** and in 52 studies by **Giknis and Clifford (2005)** was 2% and in the control groups from 11 two-year cancer studies, **Chandra and Frith (1992)**[101] saw only one animal out of 725 with a kidney carcinoma. In 46 control datasets, **Giknis and Clifford (2000)** saw 39 control groups with no adenomas, five with one adenoma and two with two adenomas; both 24-month studies saw two adenomas in the highest exposure group, a very rare finding. To better illustrate, there are 16 groups of animals in the four studies. For any one group, there is a 2/44 or 4.3% chance of getting a response 4% or larger. The chances of randomly getting 3 or more such responses in 16 groups is 2.9% and the chances of two of these being in any two of the four highest exposure groups is 0.01. In summary, the strong finding in two of the four studies, the positive finding when all four studies are pooled and the very low probability that this is due to chance when compared to historical controls support the conclusion that glyphosate causes kidney tumors in male mice.

For malignant lymphomas in males, pooling the two 18-month studies, **Sugimoto (1997)** and **Wood et al. (2009)**, results in a significant trend (p_{Trend}=0.005, p_{Hist}=0.006). Pooling the two 24-month studies, **Knezevich and Hogan (1983)** and **Atkinson et al. (1993)**, yields (p_{Trend}=0.653, p_{Hist}=0.649). The main differences between these two findings is in the control response; the pooled control response at 24 months is 6/99 (6%) versus 2/101 at 18 months (2%). This is expected since, in the absence of any exposure, tumor rates increase as a function of age[5]. **Giknis and Clifford (2000)** show a control response at 18 months of 4% and a control response at 24 months of 6% (matching the value for the pooled studies). Pooling all four studies results in (p_{TrendA}=0.073, p_{Hist}=0.080). However, the responses seen for malignant lymphomas in controls by **Giknis and Clifford (2000)** show only one historical control group in twenty-six 18-month groups with 10% or higher response. The responses at the high doses (10% and 12%) in the two 18-month studies are very unlikely to have arisen by chance. There are eight groups of animals in the two studies. For any one group, there is a 1/26 or 3.8% chance of getting a response of at least 10% based on the 26 control groups from **Giknis and Clifford (2000)**. The chances of getting two or more such responses in eight groups is 0.035 and the chances of these being in three of the four highest exposure groups is 0.004. For the 24-month studies, the higher background rate makes it difficult to identify a small change in incidence, thus the findings in the 24-month studies and the 18-month studies are not inconsistent. In summary, the very strong findings in the 18-month studies, the very strong positive findings when the two 18-month studies are pooled, the low probability that the responses seen in the 18-month studies are due to chance, and the

marginal increase in malignant lymphomas in the 18-month study in Swiss Albino mice[84] support the conclusion that glyphosate causes malignant lymphoma in male mice.

For hemangiosarcomas in males, pooling the two 18-month studies results in a significant trend (p_{Trend}=0.015, p_{Hist}=0.002). Pooling the two 24-month studies yields (p_{Trend}=0.490, p_{Hist}=0.429). The main difference between these two findings is the 0/50 response in animals exposed at 4841 mg/kg/day in the study by **Knezevich and Hogan (1983)**. Removing this one exposure group in the pooled 24-month analysis yields (p_{Trend}<0.001, p_{Hist}<0.001). Pooling all four studies results in (p_{Trend}=0.045, p_{Hist}=0.043). No hemangiomas were seen in controls groups from twenty-six 18-month studies by **Giknis and Clifford (2000)** so the two hemangiosarcomas seen in the high dose group in the study by **Sugimoto (1997)** are biologically very significant. For the 24-month historical controls, only two out of 20 control groups had a response greater than 8%. In summary, the very strong findings in the 18-month studies, the positive finding when all four studies are pooled and the low probability that the responses seen in the 18-month studies are due to chance support the conclusion that glyphosate causes hemangiosarcomas in male CD-1 mice.

For hemangiomas in females, pooling the two 18-month studies results in a significant trend (p_{Trend}=0.001). Pooling the two-year studies results in p_{Trend}=0.424. Pooling all four studies results in p_{Trend}=0.018. In summary, the very strong findings in one 18-month study, the positive finding when all four studies are pooled and the low probability that the responses seen in the **Sugimoto (1997)** study are due to chance, support the conclusion that glyphosate causes hemangiomas in female CD-1 mice.

For lung adenocarcinomas in male CD-1 mice, pooling the two 18-month studies results shows no significant trend (p_{Trend}=0.417, p_{Hist}0.126). Pooling the two 24 month studies yields (p_{TrendA}=0.985, p_{Hist}=0.993). Pooling all four studies results in (p_{TrendA}=0.937, p_{Hist}=0.744). In summary, the moderate findings in one 24 month study, and the negative finding when any studies are pooled suggest that the linkage between glyphosate and lung adenocarcinomas in male CD-1 mice is due to chance.

The one study in Swiss Albino mice[84] was effectively negative for all endpoints except malignant lymphomas and kidney adenomas where marginally significant tumor responses were seen. Considering the findings for kidney adenomas in CD-1 mice, glyphosate may also cause kidney adenomas in male Swiss Albino mice from the study of **Kumar (2001)**.

To summarize the findings in mice, glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice and hemangiomas in female CD-1 mice after 18 months of exposure, kidney tumors in male CD-1 mice after 24 months exposure and possibly kidney adenomas in male Swiss albino mice. When 18-month and 24-month studies are pooled, there is a significant increase in hemangiosarcomas in male mice, hemangiomas in female mice and kidney tumors in male mice.

Discussion and Summary Animal Carcinogenicity Studies

As noted earlier, there has been a suggestion that using doses substantially larger than 1000 mg/kg/day exceeds the current limit dose set by the OECD. The only place in the **OECD guidance**[67] that addresses a dose of 1000 mg/kg/day is in paragraph 23 which reads:

> *"For the chronic toxicity phase of the study, a full study using three dose levels may not be considered necessary, if it can be anticipated that a test at one dose level, equivalent to at least 1000 mg/kg body weight/day, is unlikely to produce adverse effects. This should be based on information from preliminary studies and a consideration that toxicity would not be expected, based upon data from structurally related substances. A limit of 1000 mg/kg body weight/day may apply except when human exposure indicates the need for a higher dose level to be used."*

This language does not preclude the use of a dose exceeding 1000 mg/kg/day nor does it advocate ignoring such doses when evaluating the results of an animal carcinogenicity study. In fact, the reasons for excluding a dose in an animal carcinogenicity study are clearly outlined in paragraph 90 within **OECD guidance**[59] and reads:

> *"If the main objective of the study is to identify a cancer hazard, there is broad acceptance that the top dose should ideally provide some signs of toxicity such as slight depression of body weight gain (not more than 10%), without causing e.g., tissue necrosis or metabolic saturation and without substantially altering normal life span due to effects other than tumours. Excessive toxicity at the top dose level (or any other dose level) may compromise the usefulness of the study and/or quality of data generated. Criteria that have evolved for the selection of an adequate top dose level include: (in particular) toxicokinetics; saturation of absorption; results of previous repeated dose toxicity studies; the MOA and the MTD."*

While one study has a slight decrease in body-weight gain, there are no indications in any other studies of an exceedance in dose that would support ignoring the findings from any exposure group.

EPA[33] uses a slightly different criteria to determine which dose to include or exclude based on an earlier OECD document. These are spelled out in EPA's guideline document for carcinogenicity risk assessment[33]

> *"Other signs of treatment-related toxicity associated with an excessive high dose may include (a) significant reduction of body weight gain (e.g., greater than 10%), (b) significant increases in abnormal behavioral and clinical signs, (c) significant changes in hematology or clinical chemistry, (d) saturation of absorption and detoxification mechanisms, or (e) marked changes in organ weight, morphology, and histopathology. It should be noted that practical upper limits have been established to avoid the use of excessively high doses in long-term carcinogenicity studies of environmental chemicals (e.g., 5% of the test substance in the feed for dietary studies or 1 g/kg body weight for oral gavage studies [OECD, 1981])."* As before, this applies to only one study presented in this review.

Both of these guidelines make good scientific sense. In the 12 acceptable rodent carcinogenicity studies included in this evaluation, no study had sufficient toxicity at the highest dose to justify removing the highest dose from the analysis. Hence, the analyses presented here did not drop the doses >1000 mg/kg/day. This is also supported by one member of the **EPA's SAP**[54].

Twenty chronic rodent carcinogenicity studies have been done using glyphosate as the test compound. Eight of these studies are unacceptable for use in an evaluation of causality leaving seven studies in rats and five studies in mice. Because of the large number of evaluations done in an individual animal carcinogenicity study, there is concern that the false-positive rates could be exaggerated. For example, if 20 evaluations are done and a finding is deemed significant if $p_{Trend}<0.05$, then you would expect that 20*0.05=1 evaluation would be positive simply due to chance.

Table 15: Observed versus expected tumor sites with significant trends in the 12 acceptable rodent carcinogenicity studies using glyphosate.

Species	Strain	Sex	Total Sites[1]	Exp. <0.05	Obs. <0.05	Tumors[2] p<0.05	Exp. <0.01	Obs. <0.01	Tumors p<0.01
Rat (7 studies)	Sprague-Dawley (4 studies)	M	86	4.3	4	TICT, TFAC, KA, HA	0.9	2	TICT, KA
		F	102	5.1	1	TCCC	1.0	1	TCCC
	Wistar (3 studies)	M	64.5	3.2	2	HA, SK	0.6	1	HA
		F	76.5	3.8	2	MC, MAC	0.8	1	MAC
Mouse (5 studies)	CD-1 (4 studies)	M	42	2.1	8	KA, KC, KAC, HS(2)[3], ML(2), LAC	0.4	5	KA,KC, HS(2), ML
		F	60	3	1	H	0.6	1	H
	Albino (1 study)	M	10.5	0.5	0		0.1	0	
		F	15	0.8	1	H	0.2	1	H
Rats (7 studies)	All (7 studies)	M	150.5	7.5	6	TICT, KA, HA(2), TFAC, SK	1.5	3	TICT, KA, HA
		F	178.5	8.9	3	TCCC, MC, MAC	1.8	2	TCCC, MAC
		Both	329	16.5	9	TICT, KA, HA(2), TFAC, SK, TCCC, MC, MAC	3.3	5	TICT, KA, HA, TCCC, MAC
Mice (5 studies)	All (5 studies)	M	52.5	2.6	8	KA, KC, KAC, HS(2), ML(2), LAC	0.5	5	KA,KC, HS(2), ML
		F	75	3.8	2	H(2)	0.7	2	H(2)
		Both	127.5	6.4	10	KA, KC, KAC, HS(2)[3], H(2), ML(2), LAC	1.3	7	KA,KC, HS(2), H(2), ML
All (12 studies)	All (12 studies)	M	203	10.1	14	TICT, KA(2), HA(2), TFAC, SK, KC, KAC, HS(2), ML(2), LAC	2.0	8	TICT, HA, KA(2),KC, HS(2), ML
		F	253.5	12.7	5	TCCC, MC, MAC, H(2)	2.5	4	TCCC, MAC, H(2)
		Both	456.5	22.8	19	TICT, KA(2), HA(2), TFAC, SK, KC, KAC, HS(2), H, ML(2), LAC, TCCC, MC, MAC	4.6	12	TICT, HA, KA(2), KC, HS(2), H(2), ML, TCCC, MAC

[1] Number of sites examined is based upon suggestions by Dr. J. Haseman in his written testimony to the EPA; male mice – 10.5 sites; female mice – 15 sites; male rats – 21.5 sites; female rats – 25.5 sites

[2] Tumor abbreviations are: KA – kidney adenoma; KC – kidney carcinoma; KAC – kidney adenoma or carcinoma; HS – hemangiosarcoma; H – hemangioma; HA – hepatocellular adenoma; LAC – lung adenoma or adenocarcinoma; ML – malignant lymphoma; MC – mammary gland carcinoma; MAC – mammary gland adenoma or carcinoma; TCCC – thyroid C-cell carcinoma; TFAC

– thyroid follicular cell adenoma or carcinoma; TICT – testes interstitial cell tumor; SK – skin keratocanthoma
[3](x): x studies with this result

The EPA asked the SAP to comment on its evaluation of glyphosate[61] at a meeting in Washington, DC in December 2016[54]. Many comments were received from outside experts at this meeting; one such set of comments came from Dr. J. K. **Haseman (2016)**[111]. **Haseman (2016)** directly addressed the false-positive error rate and concluded that the results seen in these studies were due to chance. He did this by deciding how many evaluations were likely for each study (broken into sex-by-species groups) and then aggregating the findings. He concluded that the effective number of analyses were 10.5 in male mice, 15 for female mice, 21.5 for male rats, and 25.5 for female rats. **Haseman (2016)** made two assumptions in his analysis that are not valid. The first was that all of the possible trend tests had been done on all of the sites he considered reasonable for such an evaluation. He identified eight positive findings. However, EPA had not evaluated all of the sites nor had they considered doing a formal analysis using historical control data. EPA identified eight sex/species groups that had at most one positive tumor finding using the trend test with $p_{Trend} \leq 0.05$. In Tables 1-14 above, I have identified 19 tumors with $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ and 12 with $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ (Table 15). Secondly, Dr. Haseman assumed one could aggregate all the studies into one large analysis of Type-1 error. However, inference in these studies is always made by sex/species/strain (e.g. glyphosate causes hemangiosarcomas in male CD-1 mice; not glyphosate causes cancer in rodents), and the analysis should have been done by grouping each separately. Table 15 shows these analyses as well as the aggregated analysis for all of the acceptable studies.

With the exception of male Sprague-Dawley rats, the observed number of tumors are at or near the expected number for the different sex/strain groups in rats (Table 15). For male Sprague-Dawley rats, 0.8 cases with $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ are expected and two were observed ($p=0.21$). In female CD-1 mice and Swiss Albino mice, the expected and observed numbers are approximately equal. However, in male CD-1 mice, there were 2.1 tumors expected for $p_{Trend} \leq 0.05$ or $p_{Hist} \leq 0.05$ and eight were observed ($p<0.001$) and there were 0.4 expected for $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ and five were observed ($p<0.001$). This clearly could not have occurred by chance alone. Even if one incorrectly groups all sexes and species together, there are 4.6 expected responses for $p_{Trend} \leq 0.01$ or $p_{Hist} \leq 0.01$ and 12 observed ($p<0.001$). Thus, chance does not explain the positive results seen in these studies.

Conclusion for Animal Carcinogenicity Studies

There are several general issues that pertain to all animal carcinogenicity studies. There is considerable genetic variability across animal strains both over time and space. It is difficult to compare experiments done in different laboratories even when using the same strain of animal. This is obvious when you examine the rates for hepatocellular adenomas in Wistar rats across the three studies using this strain. Thus, each study

should be considered separately with regard to the findings in that study before being compared across studies.

The use of a p-value of 0.05 as the cut off for increasing tumor incidence does not account for trends in the data across multiple studies. Three studies with marginal responses of 6-8% in a given tumor could, when pooled for analysis, lead to highly significant findings. This issue is well-recognized in epidemiology but not usually considered in toxicology because of a lack of replicate studies. This case is fairly unique because of the larger number of studies available for analysis and requires a more rigorous evaluation of the data such as the pooled analysis presented in this report.

Pooling of the data for the evaluation of replicate studies makes sense as it addresses the question "Does the data as a whole support a finding of increased cancer incidence in these studies?" Some toxicologists may argue that the studies are not replicates and hence cannot be pooled. But if they are not replicates, then they cannot be compared to see if there is consistency across the studies. This is because there may be some subtle change from one study to another that leads to a positive finding in one study but a negative finding in other studies. Thus, either the studies are not good replicates so you cannot compare across studies and you cannot pool them, or they are good replicates so you can compare across studies and you can pool them. There is no argument that would support a comparison across studies that is appropriate when pooling is inappropriate.

There were seven rat studies and five mouse studies that were of sufficient quality and with sufficient details available for inclusion in this evaluation.

Glyphosate has been demonstrated to cause cancer in two strains of rats and one strain of mice. Glyphosate causes hepatocellular adenomas in male Wistar rats and, to a lesser degree, in male Sprague-Dawley rats, mammary gland adenomas and adenocarcinomas in female Wistar rats, skin keratocanthomas in male Wistar rats, and kidney adenomas and thyroid C-cell adenomas and carcinomas in male Sprague-Dawley rats. Glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice and hemangiomas in female CD-1 mice and possibly causes malignant lymphomas, kidney adenomas in male Swiss albino mice and hemangiomas in female Swiss albino mice. Thus, glyphosate causes cancer in mammals.

Mechanisms Relating to Carcinogenicity

Many human carcinogens act via a variety of mechanisms causing various biological changes, taking cells through multiple stages from functioning normally to becoming invasive with little or no growth control (carcinogenic). **Hanahan and Weinberg (2011)**[112] identified morphological changes in cells as they progress though this multistage process and correlated these with genetic alterations to develop what they refer to as the "hallmarks of cancer." These hallmarks deal with the entire process of carcinogenesis and not necessarily with the reasons that cells begin this process or the early stages in the process where normal protective systems within the cells remove

potentially cancerous cells from the body. While tumors that arise from a chemical insult to the cell may be distinct from other tumors by mutational analysis, they all exhibit the hallmarks as described by **Hanahan and Weinberg (2011)**.

Systematic review of all data on the mechanisms by which a chemical causes cancer is complicated by the absence of widely accepted methods for evaluating mechanistic data to arrive at an objective conclusion on human hazards associated with carcinogenesis. Such systematic methods exist in other contexts[113], but are only now being accepted as a means of evaluating literature in toxicological evaluations[114-117].

In this portion of the report, I am focusing on the mechanisms that can cause cancer. **Smith et al. (2015)**[37] discussed the use of systematic review methods in identifying and using key information from the literature to characterize the mechanisms by which a chemical causes cancer. They identified 10 "Key Characteristics of Cancer" useful in facilitating a systematic and uniform approach to evaluating mechanistic data relevant to carcinogens. These 10 characteristics are presented in Table 16 (copied from Table 1 of **Smith et al. (2015)**[37]). While there is limited evidence on glyphosate for most of the key characteristics, genotoxicity (characteristic two) and oxidative stress (characteristic five) have sufficient evidence to warrant a full review.

Genotoxicity

Genotoxicity refers to the ability of an agent (chemical or otherwise) to damage the genetic material within a cell, thus increasing the risks for a mutation. Genotoxic substances interact with the genetic material, including DNA sequence and structure, to damage cells. DNA damage can occur in several different ways, including single- and double-strand breaks, cross-links between DNA bases and proteins, formation of micronuclei and chemical additions to the DNA.

Just because a chemical can damage DNA does not mean it will cause mutations. So, while all chemicals that cause mutations are genotoxic, all genotoxic chemicals are not necessarily mutagens. Does that mean that the genotoxicity of a chemical can be ignored if all assays used for identifying mutations in cells following exposure to a chemical are negative? The answer to that question is no and is tied to the limitations in tests for mutagenicity (the ability of a chemical to cause mutations in a cell). It is unusual to see an evaluation of the sequence of the entire genome before exposure with the same sequence after exposure to determine if the genome has been altered (mutation). There are assays that can evaluate a critical set of genes that have previously been associated with cancer outcomes (e.g. cancer oncogenes), but these are seldom applied. In general, mutagenicity tests are limited in the numbers of genes they actually screen and the manner in which these screens work.

Because screening for mutagenicity is limited in scope, any genetic damage caused by chemicals should raise concerns because of the possibility of a mutation arising from that genetic damage. In what follows, I will systematically review the scientific findings available for evaluating the genotoxic potential of glyphosate. This will be divided into six separate sources of data based on the biological source of that data: (1) data from exposed humans, (2) data from exposed human cells in a laboratory setting, (3) data

from exposed mammals (non-human), (4) data from exposed cells of mammals (non-human) in the laboratory, (5) data from non-mammalian animals and others, and (5) data from cells from non-mammalian animals and others. These six areas are based upon the priorities one would apply to the data in terms of impacts. Seeing genotoxicity in humans is more important than seeing genotoxicity in other mammals, which is more important than seeing genotoxicity in non-mammalian systems. In addition, seeing genotoxicity in whole, living organisms (*in vivo*) carries greater weight than seeing responses in cells in the laboratory (*in vitro*). Basically, the closer the findings are to real, living human beings, the more weight they should be given.

Table 16: Key characteristics of carcinogens, **Smith et al. (2016)**[37]

Characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

The data being included in this review come from the peer-reviewed scientific literature, the summaries of reports in regulatory documents that are proprietary and for which I have limited access to the original work, and reports from industry that are proprietary to which I have been given greater access. All of these studies are included in the overall evaluation of causation.

Genotoxicity in Humans *in-vivo*

Three studies have evaluated the potential genotoxicity of glyphosate formulations in exposed humans. **Paz-y-Miño et al. (2007)**[118] analyzed the blood of 24 exposed individuals (living within 3 kilometers of spraying) and 21 unexposed individuals (living 80 kilometers away from the spraying area) for DNA damage using the comet assay. All study subjects were from Ecuador and none of the controls or exposed individuals smoked, drank alcohol, took non-prescription drugs or had been exposed to pesticides during the course of their normal daily lives. Exposed and control individuals did some cultivating and harvesting but without pesticides or herbicides. Exposed individuals were analyzed within two months of spraying for the eradication of plants associated with illegal narcotics. An average of 200 cells per person were ranked between 0-400 depending on the amount of DNA in the comet's tail in order to calculate the mean amount of DNA damage. There was a significant difference between the mean total migration level of exposed individuals to controls ($p<0.001$). Data was given for each individual classified into five groups based upon the amount of DNA in the comet's tail. There was clearly a shift in the distribution of DNA in cells with the controls never seeing scores in the top two categories while all but three exposed had some scores in the top two categories. In essence, some of the DNA had been fragmented by the exposure.

In a second study by the same group, **Paz-y-Miño et al. (2011)**[119] evaluated the karyotypes (the chromosome count of the individuals and any alterations to the chromosomes as seen under a microscope) of 92 people living in 10 communities in northern Ecuador. Controls were from areas without spraying and both controls and exposed subjects had no history of exposure to smoking or other genotoxic compounds. This study saw no changes between controls and exposed subjects for 182 karyotypes evaluated.

Bolognesi et al. (2009)[120] studied women of reproductive age and their spouses in five areas of Colombia, four of which are subject to spraying for either narcotics control or sugar cane growing. There were 60 subjects from the Santa Marta area (organic coffee is grown without the use of pesticides), 52 from Boyaca (manual spraying for illicit drugs), 58 from Putumayo (aerial spraying for illicit drugs using a glyphosate formulation), 63 from Nariño (same exposure as Putumayo) and 28 from Valle del Cauca (aerial spraying of Roundup 747 (74.7% glyphosate) without additional adjuvant for sugar cane maturation). All subjects were interviewed with a standardized questionnaire designed to obtain information about current health status, health history, lifestyle and potential exposure to possible confounding factors (smoking, use of medicinal products, severe infections or viral diseases during the last six months, recent vaccinations, presence of known indoor/outdoor pollutants, exposure to diagnostic x-rays, and previous radio- or chemotherapy). In Santa Marta, blood samples were taken

once, during the initial interview. In Boyaca, blood samples were taken at the initial interview and 1 month later. In Nariño, Putumayo and Valle del Cauca, blood samples were taken at the initial interview, within five days after spraying and 4 months later. In lymphocytes, binucleated cells with micronuclei (BNMN) were lowest in Santa Marta and similar in the four exposed regions prior to exposure. Statistically significant increases in BMNM in Nariño, Putumayo and Valle del Cauca were seen between first and second sampling. The mean BNMN in Nariño and Putumayo was greater in respondents who self-reported direct contact with sprayed fields, but differences were not statistically significant. Multiple linear regression demonstrated statistically significant increases in BMNM in all four exposed regions post exposure when compared to pre-exposure and controlling for all other variables ($p<0.001$). The largest total change in mean BMNM values pre-exposure compared to immediate post exposure occurred in Valle del Cauca where spraying is done using Roundup with no additional adjuvant.

Kier (2015)[121] identified 16 additional studies of pesticide use that included some exposure to glyphosate. Eleven of the 16 studies demonstrated some degree of genotoxicity in the human populations studied but did not adequately attribute the exposure primarily to glyphosate so they are not included in this review.

In summary, two of the three studies in which genotoxicity endpoints were evaluated in humans in areas with exposure to glyphosate spraying showed statistically increased changes in DNA damage in blood. In the strongest study, in three areas where chromosomal damage (micronuclei) was examined in individuals pre- and post-spraying (<5 days) showed statistically significant increases. In one other area where post-exposure damage was measured one month after exposure, there was little change.

Genotoxicity In Human Cells (*in vitro*)

Studies have explored the *in vitro* genotoxicity of glyphosate using a variety of different cell types (lymphocytes, fibroblasts, and immortalized cells from cancers of the larynx, mouth, blood and liver) using several different assays for markers of genotoxicity with or without metabolic activation.

Mladinic et al. (2009)[122] induced DNA strand breaks (comet assay) from exposure to glyphosate (purity not given) in lymphocytes from three healthy human donors (questionnaire used to exclude genotoxic exposures) at concentrations of 3.5, 92.8 and 580 µg/ml with S9 activation and saw effects at only the highest doses for cells without S9 activation.

Alvarez-Moya et al. (2014)[123] conducted a similar study using lymphocytes from human volunteers (questionnaire used to exclude genotoxic exposures) and exposure to glyphosate (96% purity) at concentrations of 0.12, 1.2, 12 and 120 µg/ml. A significant increase in DNA strand breaks (comet assay) was seen for all exposure groups with a clear dose-response relationship without metabolic activation (metabolic activation was not tested).

Using human HEP-2 cells, **Manas et al. (2009)**[124] induced DNA damage (comet assay) by

glyphosate (96% pure) at all concentrations ranging from 676 µg/ml to 1270 µg/ml (no S9 activation tested). Cell viability at the highest concentration was below 80% and values at the other concentrations were not given.

Monroy et al. (2005)[125] induced significant DNA damage (comet assay) in fibroblast GM 38 cells at concentrations of glyphosate (technical grade, purity not given) ranging from 676 µg/ml to 1000 µg/ml with a clear dose-response pattern. Over this same concentration range, they also saw concentration-dependent decreases in cell viability at all doses making the comet assay results difficult to interpret. In a similar analysis in the same paper, using fibrosarcoma HT1080 cells, they also saw concentration-dependent DNA damage and loss of cell viability. Activation by S9 was not used in either experiment.

Lueken et al. (2004)[126] induced DNA damage (comet assay) in fibroblasts GM 5757 at a concentration of glyphosate (98.4% purity) of 12,680 µg/ml in combination with exposure to 40 or 50 mM H_2O_2. Activation by S9 was not used in this experiment. According to the authors, cell viability at this exposure level was above 80%.

Koller et al. (2012)[127] significantly induced DNA damage (comet assay) in human TR146 cells (buccal carcinoma cells) from exposure to glyphosate (>95% purity) in a dose-dependent fashion at concentrations of 20 and 40 µg/ml. Above 40 µg/ml, there was a significant increase in tail intensity relative to controls, but the actual amount increased did not change as the dose increased (plateau). Using Roundup (Ultra Max) the authors saw virtually the same level of DNA damage at 20 and 40 µg/ml, but the concentration response continued to increase above that exposure. These experiments did not use S9 activation. They also used the CBMN assay in the same system to evaluate the total number of micronuclei in binucleated cells (MNI), the number of binucleated cells with micronuclei (BN-MNI), the number of nuclear buds (NB) and the number of nucleoplasmic bridges (NPB) caused by glyphosate and Roundup exposure. Two endpoints (NB, NPB) had significant increases at concentrations of 10, 15 and 20 µg/ml and two (MNi, BN-MNi) were significantly elevated for concentrations of 15 and 20 µg/ml. Equivalent Roundup exposures resulted in significant increases in all four measures of DNA damage at 10, 15 and 20 µg/ml. The results for the Roundup were greater than for glyphosate alone.

Gasnier at al. (2009)[128] exposed cells from the hepatoma cell line HepG2 to glyphosate (purity not given) and four glyphosate formulations. Only one glyphosate formulation was tested for DNA damage (comet assay) and they saw significant effects at equivalent concentrations of 0.05 µ/ml to 4 µg/ml of glyphosate (p-values not given). No p-values are provided and presentation of the results does not provide a clear means to compare these results with other studies. This study will not be used in the evaluation.

Manas et al. (2009)[124] obtained human blood samples from three healthy, non-smoking women and three healthy men with no history of pesticide exposure. Lymphocytes were cultured with glyphosate (96% purity) at concentrations of 34, 203, and 1015 µg/ml with no statistically significant changes in chromatid breaks,

chromosome breaks, chromatid gaps, chromosome gaps, dicentrics, acentric fragments, or endoreduplication.

Mladinic et al. (2009)[129] used blood from three non-smoking, healthy volunteers to evaluate the formation of micronuclei, nuclear buds and nucleoplasmic bridges as a function of exposure to glyphosate (98% purity). Significant changes in micronuclei were seen following exposure to glyphosate at 92.8 and 580 µg/ml in S9 activated cells, but not those without metabolic activation. Changes in nuclear buds were seen at 580 µg/ml for both S9 activated and non-activated cells while significant changes in nucleoplasmic bridges were seen only at 580 µg/ml in S9 activated cells. This study contained a positive control (ethyl methanesulfonate at 200 µg/ml) which was also negative in all assays, many times showing effects below that seen for glyphosate.

Bolognesi et al. (1997)[130] obtained blood from two healthy female donors and exposed it to glyphosate (99.9% purity) or a Roundup formulation (30.4% glyphosate). At concentrations of 1000, 3000 and 6000 µg/ml of glyphosate and at 100 and 330 µg/ml of glyphosate formulation, significant changes in sister chromatid exchanges (SCEs) were seen. At 330 µg/ml, a non-significant increase in SCEs was seen for glyphosate alone that was approximately 20% below that seen for an equivalent glyphosate exposure from the Roundup formulation. This study did not consider S9 activation.

Lioi et al. (1998)[124, 131] obtained blood from three healthy donors and exposed it to glyphosate (>98% purity). At concentrations of 1.4, 2.9, and 8.7 µg/ml of glyphosate, significant changes in sister chromatid exchanges (SCEs) and chromosomal aberrations were seen. This study did not consider S9 activation.

Vigfusson and Vyse (1980)[132] exposed cultured human lymphocytes from two people to Roundup (% glyphosate unknown) at concentrations of 250, 2500 and 25000 µg/ml. Results for the highest concentration were not provided due to lack of cell growth in culture. SCEs were shown to be significantly increased for the remaining two concentrations in one donor and only for the lowest concentration in the other. While the relative SCE counts seen in this paper are similar to those from **Bolognesi et al. (1997),** the absolute counts in the controls are roughly three times higher in this study. This study did not consider S9 activation.

Genotoxicity in Non-Human Mammals (*in vivo*)

Bolognesi et al. (1997)[130] exposed groups of three Swiss CD-1 male mice by Intraperitoneal (IP) injection with a single dose of glyphosate (99.9% purity, 300 mg/kg) or Roundup (900 mg/kg, equivalent to 270 mg/kg glyphosate). Animals were sacrificed at four and 24 hours after injection and livers and kidney were removed to obtain crude nuclei from the adhering tissues. Both tissues demonstrated significant increases in DNA single-strand breaks ($p<0.05$) at four hours for both glyphosate and Roundup with no discernable difference between the responses. At 24 hours, the presence of strand breaks was reduced and no longer statistically significant from controls.

Peluso et al. (1998)[133] exposed groups of six (controls, lowest doses of glyphosate-salt and Roundup) or three Swiss CD-1 mice (males and females, specific numbers not

specified, liver and kidney tissues combined for analysis) to the isopropylammonium salt of glyphosate or Roundup (30.4% isopropylammonium salt of glyphosate) for 24 hours. DNA adducts (^{32}P-DNA post labeling) were not evident in mice exposed to the glyphosate-salt alone in either liver or kidney, but were present in liver and kidney at all tested doses of Roundup showing a dose-response pattern.

Rank et al. (1993)[134] exposed male and female NMRI mice (three to five per sex) to glyphosate isopropylamine salt (purity not specified) and Roundup (480 g glyphosate isopropylamine salt per liter) by intraperitoneal injection. After 24 or 48 hours (only 24 hours for Roundup), polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 1000 cells. No significant increases were seen for any concentration in glyphosate-exposed animals (100, 150 and 200 mg/kg) or Roundup-exposed animals (133 and 200 mg/kg glyphosate equivalent dose). The positive controls, while not statistically significant, showed an increase in micronuclei.

Bolognesi et al (1997)[130] exposed groups of three, four or six male Swiss CD-1 mice to glyphosate (99.9% purity) and Roundup (30.4% glyphosate) by intraperitoneal injection in two equal doses given 24 hours apart. After six or 24 hours following the last exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 1000 cells. Mice given two doses of 150 mg/kg of glyphosate showed a non-significant increase in micronuclei at 6 hours and a significant increase at 24 hours. In contrast, mice given two doses of 225 mg/kg glyphosate equivalent of Roundup showed a significant increase in micronuclei at both six and 24 hours. The relative differences in mean absolute increase (subtract mean response in controls) in micronucleii between glyphosate and Roundup at 24 hours was 3.6 whereas the relative difference in glyphosate equivalent dose was 1.5 indicating a greater effect of the glyphosate formulation.

Manas et al. (2009)[124] exposed groups of male and female Balb C mice (group size not given, tissues combined for analysis) to glyphosate (96% purity) by intraperitoneal injection in two equal doses given 24 hours apart. Twenty-four hours post exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 1000 cells. No significant increases were seen at doses of 50 mg/kg and 100 mg/kg in glyphosate-exposed animals but a significant increase was seen at 400 mg/kg. The positive controls showed a statistically significant increase in micronuclei (roughly three times the control rate).

Dimitrov et al. (2006)[135] exposed groups of eight male C57BL mice (tissues combined for analysis) to Roundup (41% glyphosate) via gavage at a dose of 1080 mg/kg. At 6, 24, 72, 96, or 120 hours post exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 4000 cells (500 per animal). No significant increases were seen. They also looked for chromosomal damage in these animals and saw no significant increases. The positive controls showed a statistically significant increase in micronuclei.

Prasad et al. (2009)[136] exposed groups of 15 male Swiss CD-1 mice to Roundup (30.4% glyphosate) by IP injection at doses of 25 and 50 mg/kg. At 24, 48 or 72 hours post

exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 2000 cells per animal, five animals per sacrifice. Micronucleii counts were significantly increased ($p<0.05$) at all doses at all times relative to controls. In addition, the number of cells with chromosomal aberrations was significantly increased for all doses at all times. The control rate of micronuclei was similar to that of **Bolognesi et al. (1997),** but about 50% greater response for a dose that was approximately 10 times smaller.

Grisolia et al. (2002)[137] exposed groups of Swiss mice (sex and sample size not given) to Roundup (480 g glyphosate isopropylamine salt per liter) by IP injection at doses of 50, 100 and 200 mg/kg Roundup in two doses separated by 24 hours. At 24 hours post exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 2000 cells per animal. Micronuclei counts were not increased at any dose. This exposure appears to be the same formulation of Roundup used in the study by **Rank et al. (1993)** which was also negative.

Coutinho do Nascimento and Grisolia (2000)[138] exposed groups of six male mice (strain not given) to Roundup (% glyphosate not given) by IP injection at doses of 50, 100 and 200 mg/kg in two doses separated by 24 hours. At 24 hours post exposure, polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 1000 cells per animal. A significant increase in micronuclei were seen at a dose of 85 mg/kg. No increase was seen at 42 or 170 mg/kg.

Cavusoglu et al. (2011)[139] exposed groups of six Swiss albino mice by IP injection with a single dose of glyphosate formulation (RoundupUltra Max, 450 g/l glyphosate, 50 mg/kg glyphosate equivalent dose). Animals were sacrificed at three days after injection. Micronuclei in normochromatic erythrocytes were counted from a sample of 1000 cells per animal. There was a significant increase in micronuclei in erythrocytes ($p<0.05$). *G. bilboa* eliminated these effects.

Chan and Mahler (1992)[140] exposed groups of 10 male and female $B6C3F_1$ mice to glyphosate (98.6% purity) in feed at doses of 0, 507, 1065, 2273, 4776, and 10780 mg/kg in males and 0, 753, 1411, 2707, 5846, and 11977 mg/kg in females for 13 weeks. At sacrifice, polychromatic erythrocytes from peripheral blood were extracted and micronuclei counted from a sample of 10,000 cells. No significant increases were seen at any of the tested doses.

Li and Long (1988)[141] exposed groups of 18 male and female Sprague-Dawley rats to glyphosate (98% purity) by IP injection at a dose of 1000 mg/kg. At 6, 12 and 24 hours post treatment, 6 animals of each sex were sacrificed and polychromatic erythrocytes from bone marrow were extracted and micronuclei counted from a sample of 50 cells per animal. The percentage of cells with chromosomal aberrations was not increased at any time point following exposure.

Genotoxicity in Non-Human Mammalian Cells (*in vitro*)

Li and Long (1988)[141] incubated Chinese hamster ovary cells (CHO-K1BH4) with glyphosate (98% purity) for three hours at concentrations of 5, 10, 50 and 100 mg/ml.

Cells were then plated using 200 cells per sample in triplicate and incubated for 8-12 days. Colonies were then counted and results expressed as mutant frequency. No positive results were seen in any experimental group with or without S9 activation. It is not clear why there is such a large difference in the incubation times in the various groups in this experiment, nor is it clear which groups incubated longer. In a second study in the same publication, non-induced primary rat hepatocytes (Fischer 344) were incubated with seven concentrations of glyphosate (12.5 ng/ml to 125 µg/ml) for 18-20 hours. No significant increases were seen for net grains per nucleus at any exposure concentration. There was a four-fold increase in the lowest exposure groups relative to controls and then every other treated group was below the control response. This is a very unusual finding and could be due to the way in which the data is adjusted for net grains in cytoplasm. The authors calculated net grains per nucleus by subtracting the highest cytoplasmic count from the nuclear count; if cytoplasmic count is increased by glyphosate this could bias the findings making any increase in nuclear count disappear. No data is provided to resolve this issue.

Roustan et al. (2014)[142] incubated Chinese hamster ovary cells (CHO-K1) with glyphosate (purity not provided) for three hours at concentrations of 2, 5, 10, 15, 17.5, 20, and 22.5 mg/ml. Cells were then plated using 200 cells per sample in triplicate and incubated for 24 hours. For each exposure concentration, 2000 bi-nucleated cells were examined for micronuclei. No positive results were seen in any experimental group without S9 activation but the four highest exposure groups were significant with a clear concentration-response pattern when S9 activation was present.

Lioi et al. (1998)[131] exposed lymphocytes from three unrelated healthy cows to glyphosate (>98% purity) for 72 hours to concentrations of 3, 14.4 and 28.7 µg/ml without S9 activation. Chromosomal aberrations scored from 150 cells were significantly increased ($P<0.05$) for all exposure concentrations of glyphosate with a clear concentration-response pattern. Similarly, SCEs per cell were increased at all concentrations ($p<0.05$) but no concentration response pattern was evident.

Sivikova and Dianovsky (2006)[143] exposed lymphocytes from two healthy young bovine bulls to glyphosate formulation (62% glyphosate) for 2, 24 and 48 hours using concentrations of 4.7, 9.5, 23.6, 47.3, 94.6 and 190 µg/ml without S9 activation. Chromosomal aberrations scored from 100 cells were not significantly increased ($P<0.05$) without S9 activation for any 24-hour exposure concentration of glyphosate (2- and 48-hours exposures were not done). SCEs per cell were increased at all 24-hour exposure concentrations ($p<0.05$) except the lowest concentration. At 48-hours, significant increases of SCEs per cell were seen at concentrations at or above 47.3 µg/ml (2-hour exposures were not done). Finally, after two hours of exposure with S9 activation, significant effects were seen at 5 and 10 µg/ml but not at 15 µg/ml (24- and 48-hour exposures were not done for S9 activation).

Holeckova (2006)[144] exposed lymphocytes from two healthy young bovine bulls to glyphosate formulation (62% glyphosate) for 24 hours to concentrations ranging from 28 to 1120 µmol/L without S9 activation. A significant increase in polyploidy was observed at 56 µmol/L, all other comparisons were without significance. However, this

one finding cannot be easily dismissed because all exposure groups above this concentration had too few cells for evaluation. This study did not consider S9 activation.

Genotoxicity in Non-Human Systems (*in vivo* and *in vitro*)

Four studies[123, 145-147] in fish have seen positive results for genotoxicity (DNA strand breaks, different assays) following exposure to glyphosate. In addition, one study[148] in oyster sperm and embryos exposed to glyphosate saw no increase in DNA damage (comet assay) and one study[149] in two strains of Drosophila melanogaster showed an increase in mutations (wing spot test) at the higher doses of exposure.

Fourteen studies[137, 145, 147, 150-160] in multiple fish species evaluated the relationship between various glyphosate formulations and genotoxicity with all studies showing positive results for various endpoints (DNA strand breaks, micronucleus formation, and chromosomal aberrations). Two of the studies[150, 152] were negative for micronucleus formation after exposure to glyphosate formulations and one of these[150] was also negative for chromosomal aberrations but both were positive in other markers of genotoxicity. Two studies[161, 162] demonstrated genotoxicity (DNA strand breaks, micronuclei) in caiman from *in-vivo* exposure to a glyphosate formulation. Three studies[163-165] demonstrated genotoxicity (DNA strand breaks, micronucleus formation) in frogs or tadpoles from exposure to glyphosate formulations. One study[148] in oyster sperm and embryos, one study[166] in clams and one study[167] in mussels exposed to a glyphosate formulation saw no increase in DNA damage (comet assay). One study[168] in snails saw increased DNA damage (comet assay) following exposure to a glyphosate formulation. Two studies[169, 170] in worms saw mixed results for DNA damage (comet assay) with one of these studies[169] showing a positive result for micronucleus formation. One study[171] in Drosophila melanogaster showed an increase in sex-linked recessive lethal mutations.

In the published literature, five studies evaluated the impact of glyphosate in *in vitro* systems. Two of these studies[172, 173] looked at genotoxicity of glyphosate in combination with UVB radiation and saw significant increases in DNA strand breaks (FADU assay) in bacteria without metabolic activation. One study[174] in eukaryote fish saw a significant increase in DNA strand breaks (comet assay) without S9 activation. Another study[141] showed no increase in reverse mutations in two strains of bacteria with and without S9 activation.

Williams et al. (2000)[175] summarized the literature regarding the use of reverse mutation assays in *S. typhimurium* (Ames Test). Four studies using glyphosate and five studies of glyphosate formulations were all negative. They cited one study[134] of a glyphosate formulation that was positive with S9 activation and negative without S9 activation. However, this study was positive with S9 activation in TA100 cells, negative with S9 activation in TA98 cells, negative without S9 activation for TA100 cells and positive without activation for TA98 cells. They also summarized two studies of glyphosate in *e. coli* that were negative with and without activation.

Two additional studies[141, 176] of glyphosate using reverse mutation assays are available

from the scientific literature, both of which are negative.

Regulatory Studies

EFSA[89] cited 14 reverse mutation assays in *S. typhimurium* (Ames Test), most of which were tested in strains TA 98, 100, 1535, 1537 (Table B.6.4-1). All 14 studies are listed as negative by EFSA. Actual data is provided for only one of the 14 studies and this study is clearly negative. **EPA**[61] cited 27 reverse mutation assays in *S. typhimurium* (Ames Test), most of which were tested in strains TA 98, 100, 1535, 1537 (EPA Table 5.1). All 27 studies are listed as negative. No data is provided for any of the studies. **Kier and Kirkland (2013)**[177] cited results from 18 bacterial reverse mutation assays of glyphosate and 16 of glyphosate formulations. Tabulated results and background information were provided for all 34 studies. Six studies of glyphosate alone demonstrated positive findings in one or more groups.

EFSA[89] cites three studies of gene mutations in mammalian cells, all of which are listed as negative (EFSA Table B.6.4-5), two use the mouse lymphoma assay, and one uses the Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl transferase (CHO/HGPRT) mutation assay. **EPA**[61] cites four studies, three of which appear to be the same as those cited by EFSA (EPA Table 5.2) and the fourth is another mouse lymphoma assay. All four are listed as negative. **Kier and Kirkland (2013)**[177] cite two of the mouse lymphoma studies and provide tabulated data. Neither study shows any indication of a statistically significant increase in mutation frequency at the thymidine kinase locus of L5178 mouse lymphoma tk(+/-) cells.

EFSA[89] cites one *in vitro* study of DNA damage and repair in mammalian cells which is listed as negative (EFSA Table B.6.4-6). This study is of unscheduled DNA synthesis (UDS assay) in primary rat lymphocytes. They also list five studies of chromosome aberrations (EFSA Table B.6.4-8), which are characterized as negative. Two studies are in human lymphocytes and two are in Chinese hamster lung (CHL) cells. Data for one of the studies in CHL is provided in tabular form and is clearly negative. **EPA**[61] cites eight *in vitro* studies of chromosome aberrations in mammalian cells (EPA Table 5.3); two of these studies match studies in the EFSA report. Four of the studies are from the literature[124, 131, 143, 178] and are reviewed above. Surprisingly, EPA refers to the study by **Manas et al. (2009)**[124] as negative although it was clearly positive in the comet assay., Additionally, EPA refers to the study by **Sivikova and Dainovsky (2006)**[143] as negative even though they saw clear effects of glyphosate on SCEs. Basically, all four of the literature studies cited by EPA are positive yet EPA lists only two of the four as positive. The remaining four studies are noted as negative; however, no data is supplied for these studies. **Kier and Kirkland (2013)**[177] cites eight literature studies (all reviewed above) and three regulatory studies with glyphosate exposure. The three regulatory studies are listed as negative, and the data are available as a table in the supplement material to **Kier and Kirkland (2013)**; these studies are negative at all tested concentrations in CHL cells; one matches the study data provided by EFSA[89].

EFSA[89] cites nine micronucleus assays, three in Swiss Albino mice, two in NMRI mice, two in CD-1 mice, one in Sprague-Dawley rats, and one in CD rats (EFSA Table B.6.4-12). They list one study in Swiss Albino mice as weakly positive in males, one study in CD-1 mice as positive at the highest dose (data for this study is provided) and all other studies as negative. They discard one study with low doses in male Swiss mice, but the tables provided for this study show a clearly significant result at the highest dose used (30 mg/kg) and clear dose-response. They provide data for two of the negative studies which indicate these studies were indeed negative. **EPA**[61] (EPA Table 5.5) cites 20 micronucleus assays, four are available in the scientific literature and three are reviewed above (the fourth reference[179] was unavailable to me at the time of preparation of this report). The remaining 16 studies include six studies in Swiss Albino mice, four studies in CD-1 mice, three studies in NMRI mice, two studies in Sprague-Dawley rats and one study in Wistar rats. Since EFSA does not provide names associated with their micronucleus studies, I cannot determine if any of the studies cited by the EPA are the same as those cited by EFSA. EPA lists two of the literature studies as positive and two as negative (matching my reviews for the three studies I have access to) and all but one of the regulatory studies as negative (the one positive study was in Swiss-Albino mice). **Kier and Kirkland (2013)**[177] cite 12 regulatory micronucleus assays of glyphosate and provide data tables for all 12. All 12 of these studies are cited by EPA. **Kier and Kirkland (2013)** list 11 studies as negative and one as inconclusive. However, four of the studies show positive effects in at least one sex-by-treatment group. One of these four studies they list as inconclusive and the remaining three studies are determined to be negative because the response is within the range of the historical controls. As was discussed for the animal carcinogenicity studies, the correct group to use is the concurrent control. **Kier and Kirkland (2013)**[177] also cite 12 regulatory studies and three literature studies where animals are exposed to a glyphosate formulation. Two of the literature studies are reviewed above and the remaining study[179] was unavailable. Data for the 12 regulatory studies are all provided in tables by **Kier and Kirkland (2013)** and show two positive studies in CD-1 mice and negative studies for the remaining 10.

Summary for Genotoxicity

This is a complicated area from which to draw a conclusion due to the diversity of the studies available (there are multiple species, multiple strains within a species, multiple cell types from multiple species, differing lengths of exposure, differing times of evaluation after exposure, differing exposures, numerous markers of genotoxicity, and finally both glyphosate and multiple different glyphosate formulations). There are three studies that evaluate the genotoxicity of glyphosate in humans directly, 36 experiments in eight strains of mice, three studies in rats, nine studies in human lymphocytes and four studies in other human cells, 12 studies in non-human mammalian cell lines (two using mouse cells, five using hamster cells, two using rat cells and three using cells from cows), a large number of studies in a wide variety of non-mammalian species, and a plethora of studies, mostly identical, in bacteria.

Some conclusions are straightforward"; glyphosate does not appear to cause reverse mutations for histidine synthesis in *Salmonella typhimurium*, regardless of whether

these reverse mutations are due to frameshift mutations or point mutations. I am cautious in this determination because there were several studies with positive results, but no clear pattern is evident. There is ample evidence supporting the conclusion that glyphosate formulations and glyphosate can cause genotoxicity in non-mammalian animal species. This clearly indicates that both glyphosate and the formulations are able to cause injury to DNA. So while findings of genotoxicity in these species do not speak directly to the hazard potential in humans, they do support a cause for concern.

The more important studies are those that have been done using mammalian systems, human cells and direct human contact. Table 16 summarizes these studies in a simple framework that allows all of the experimental data to be seen in one glance. This table does not address the subtlety needed to interpret any one study, but simply demonstrates when a study produced positive versus negative results.

Clearly, for *in vitro* evaluations in human cells, the majority of the studies have produced positive results. There was only one regulatory study evaluating glyphosate genotoxicity in human lymphocytes from healthy volunteers and that study was negative. The study was not significantly different from the other six studies in this category, five of which produced positive results. The majority of these studies used either the comet assay (a simple way for measuring any type of DNA strand break) or methods that counted specific types of strand breaks in the cells (e.g. SCEs, micronuclei, nuclear buds and nucleoplasmic bridges). From these assays, we can conclude there is DNA damage. For glyphosate formulations, there are only three studies in humans *in vivo*, two of which were positive.

The magnitude of the concentrations used in these studies could potentially lead to false positives if the glyphosate is causing cytotoxicity in the cells. All six studies using the comet assay were positive with no study showing a negative response below 10 µg/ml and mixed results below that with positive results at 0.12 and 3.5 µg/ml and negative results at 2.91 and 10 µg/ml. In general, the comet assays provide strong support for genotoxicity.

The four studies that directly addressed specific types of strand breaks in cells following exposure to glyphosate showed markedly different responses across the various concentrations used. **Manas et al. (2009)** saw no changes in chromatid breaks, chromosome breaks, chromatid gaps, chromosome gaps, dicentrics, acentric fragments or endoreduplication over the range of concentrations 3.4-1015 µg/ml. In contrast, **Lioi et al. (1998)** saw changes in SCEs over concentrations ranging from 1.4 to 8.7 µg/ml. Both studies were done in lymphocytes from volunteers. **Mladinic et al. (2009)** saw significant changes in micronuclei above 92.8 µg/ml and **Bolognesi et al. (1997)** saw positive changes in SCEs above 1000 µg/ml but not at 330 µg/ml. While changes have been seen in three of the four studies, the actual concentrations in which the changes are seen is not consistent across studies. I conclude that glyphosate causes DNA strand breaks, which is indicative of genotoxicity.

The micronucleus assays in rodents examining glyphosate genotoxicity are either all positive in one strain or all negative in one strain with the exception of the three studies

in CD-1 mice and four studies in Swiss Albino mice. For the positive studies, we can ask the question of whether, in this strain, the actual number of micronuclei are consistent.

Table 17: Summary of *in vivo* and *in vitro* genotoxicity studies of glyphosate and glyphosate formulations in mammals[1]

In vivo or *in vitro*	Species	Cell type or tissue	Glyphosate[2]		Glyphosate Formulations	
			Number Positive	Number Negative	Number Positive	Number Negative
In vivo	Humans	Peripheral blood			2	1
in vitro	Humans	lymphocytes	5	2(1)	2	
		Hep 2	1			
		GM 38 HT1080	1			
		GM 5757	1			
		TR146	1		1	
In vivo	Swiss CD-1 Mouse	Liver/Kidney	1	1	2	
In vivo (micro-nucleus assay)	NMRI mouse	Erythrocytes		4(3)		2(1)
	Swiss CD-1 mouse		1		2	
	Balb C mouse		1			
	B6C3F$_1$ mouse			1		
	Swiss mouse		1(1)			3(2)
	CD-1 mouse		2(2)	1(1)	2 (2)	6 (6)
	Swiss albino mouse		1(1)	3(3)	1	
	C57BL mouse					1
	Mouse (not specified)				1	
	Rats (all)			2(1)		1(1)
In vitro	Mouse	L5178 lymphoma		2(2)		
	Chinese hamster	Lung		3(3)		
	Chinese hamster	ovary	1	1		
	Fischer rat	liver		1		

	Rat	Lymphocytes		1(1)		
	Bovine	Lymphocytes	1		2	

[1]each entry in the table corresponds to a single study where a study is positive if at least one valid positive finding emerged from the study $p<0.05$; entries in the table are only for studies where data was available to review including data from EFSA[89] and Kier and Kirkland (2000)[177]; [2]numbers are the total number of studies in this category, numbers in parentheses are the subset of studies that are regulatory studies

In Swiss Albino mice, all four studies were done with males and females. Exposures were by oral gavage for the positive study (in female mice) and IP injection by the negative studies. The positive study was at 5000 mg/kg and the highest dose in any of the negative studies was 3024 mg/kg. Finally, the control response in the positive study was 6.7 micronucleated PCE per 1000 PCE whereas the controls in the three negative studies were between 0 and 0.6 micronucleated PCE per 1000 PCE. Any of these differences could easily explain the differences in response so the positive result in Swiss Albino mice should be accepted.

For CD-1 mice, the one negative micronucleus study was by oral gavage in males and females at a single dose of 5000 mg/kg. One of the positive studies was also by oral gavage in males at a single dose of 2000 mg/kg. Because of the nature of statistical noise, these two studies could both occur whether there is a true effect or not. For the other positive study, the dose was by IP injection in male mice with a positive response at 600 mg/kg that was more than double the response of the controls. These data support the finding that glyphosate can cause micronuclei in male CD-1 mice, which is indicative of genotoxicity.

The remaining *in vitro* assays in mammalian cells exposed to glyphosate show mixed results. The mouse lymphoma assay and the Chinese hamster ovary assays are looking for specific mutations that will allow these cells to grow in culture. The Chinese hamster lung, the two rat assays and the assay in bovine lymphocytes are measuring DNA damage and provide mixed results. In general, these responses appear to be negative with the exception of those seen in bovine lymphocytes that appear to show a positive increase in SCEs following exposure to glyphosate.

For glyphosate formulations, the main difference between the findings for glyphosate and those for the glyphosate formulations is the direct evidence for genotoxicity in humans and the micronucleus assays in Swiss mice. The observation of genotoxicity in humans following exposure to glyphosate formulations must carry the greatest weight in the overall analysis and two of the three studies were positive with the strongest study by **Bolognesi et al. (2009)**[120] showing the strongest response.

For the Swiss mouse studies of micronuclei, the fact that all three studies are negative for glyphosate formulations while one study is positive for glyphosate creates a clear disagreement. The positive study is an oral gavage study with an effect seen in male mice at 30 mg/kg/day. The two negative regulatory studies for glyphosate formulations were done at 2000 mg/kg (about 500 mg/kg glyphosate equivalent), were also oral

gavage studies and were replicates done in the same laboratory at different times. The remaining negative study used glyphosate formulation doses of 50-200 mg/kg (25-100 mg/kg glyphosate equivalent) but was done by intraperitoneal injection. With the exception of the different routes of exposure, the differences between these studies cannot be resolved.

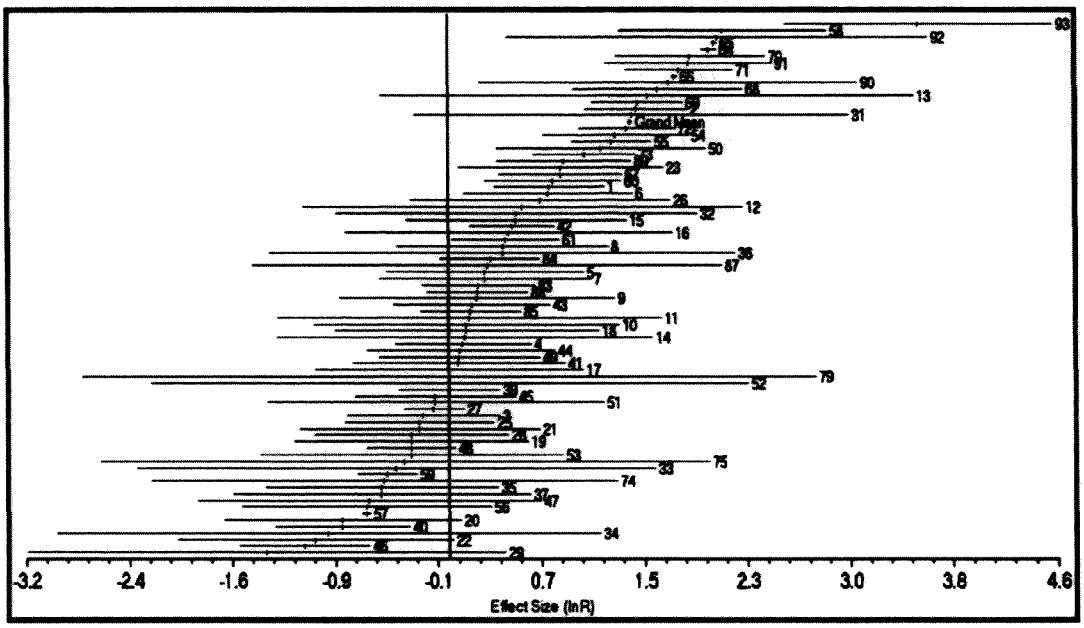
In this case, a pooled analysis of the data is not possible because in almost every case, no one study is a clear replicate of another. Instead, the appropriate approach would be to do a meta-analysis and evaluate which aspects of the experimental designs are important to producing positive findings of genotoxicity. The studies with the most data for this type of analysis are the various *in vivo* assays of micronucleus formation. **Ghisi et al. (2016)**[180] did a systematic search to identify all published studies evaluating the ability of glyphosate or glyphosate formulations to induce micronuclei *in vivo*. The authors also used the data from **Kier and Kirkland (2013)**[177] summarized above. An experiment, in their evaluation, was defined by sex/species/route/form of glyphosate so that some studies doing both sexes using glyphosate and a glyphosate formulation will enter multiple times into the analysis. They identified 93 experiments from which it was possible to do a meta-analysis. Data were extracted for each study and the log ratio of the mean of each experimental group to the mean control response (E+) was used to evaluate effect sizes in the meta-analysis. For this meta-analytic mean, a value below zero suggests no genotoxicity while a value above zero suggests increased genotoxicity. A test of heterogeneity (Cochran's Q statistic discussed earlier for the epidemiological data) was also evaluated.

Figure 2 is a reprint of Figure 1 from the study by **Ghisi et al. (2016)**[180] and is a forest plot from all studies they evaluated for glyphosate and glyphosate formulations. It is clear from this plot that the predominant response is positive in these data with an overall grand mean response across all studies of E+=1.37 and a 95% confidence interval of (1.356-1.381) (this is highly statistically significant with a $p<0.0001$). The Qt value for the grand mean was also statistically significant suggesting there are other explanatory variables in the data that would help to explain the overall variance.

Categorical variables were then used to make comparisons across the various strata in the data to identify which experimental conditions show the largest impacts on the mean response. Mammalian species presented a higher mean effect (E+=1.379; 1.366-1.391) than non-mammalian species (E+=0.740; 0.641-0.840). Glyphosate formulations showed a greater mean response (E+=1.388; 1.375-1.400) than did glyphosate (E+=0.121; 0.021-0.221), but both were significantly greater than zero. The mean response in studies using only male animals (E+=1.833; 1.819-1.847) was significantly different from zero as were studies using both males and females (E+=0.674;0.523-0.825) whereas the mean response in studies using only females (E+0.088; -0.153-0.328) was not. Peer-reviewed studies had higher mean response (E+=1.394; 1.381-1.407) compared to regulatory studies (E+=0.114; 0.027-0.202), but both means were significantly greater than zero, indicating an overall genotoxic effect. Other variables were examined such as length of exposure and magnitude of exposure that had very little impact on the overall findings.

The meta-analysis by **Ghisi et al. (2016)**[180] provides strong support for the hypothesis that exposure to glyphosate and glyphosate formulations increases the formation of micronuclei *in vivo*. This means that glyphosate and glyphosate formulations are damaging DNA in living, functioning organisms with intact DNA repair capacity strengthening the finding that glyphosate is genotoxic to humans.

Figure 2: Forest plot of studies evaluating micronucleus frequency in glyphosate exposure, arranged by effects size. The plot shows the estimate of the response ratio and 95% confidence interval (CI) of each experiment included in the meta-analysis. The number beside the bars represents the reference number of each experiment as in Table 1 of Ghisi et al. (2016)[180]. Grand Mean is the overall mean effects size of all studies. [Reprinted from Ghisi et al. (2016)[180]]



From a simply statistical perspective, there is another way in which one can decide if the positive findings in the micronucleus assays in the mice are due to chance. For the glyphosate studies, if one adds up all of the individual experimental groups, there are 79 total groups which correspond to 79 statistical tests. Assuming the critical testing level is 0.05 for all of the tests, one would expect to see just under four positive findings, yet six are observed. For the glyphosate formulations, there were 70 experimental groups so one expects 3.5 positive findings yet 12 are observed ($p<0.01$). Overall, there were a total of 149 experimental groups examined in mice for micronucleus formation and we observed 18 (7.5 expected, $p<0.01$). Repeating this analysis on the basis of studies instead of experimental groups, there were 15 studies for glyphosate (expected number is 0.75 positive) yet six positive were observed ($p<0.01$). For the glyphosate formulations, there were 18 studies (expected number is 0.9 positive) yet six positive

are observed ($p<0.01$). Now expanding to all 69 studies presented in Table 17, there were 33 positive studies, but the expectation is a mere 3.5 ($p<0.01$).

It is clear that both glyphosate and glyphosate formulations have genotoxic potential. But which is worse? Of the 69 experiments in Table 17, there were eight experiments from five research publications that addressed both glyphosate and a glyphosate formulation in the same laboratory. Of these, two were negative for both glyphosate and the formulation and do not contribute to a discussion of relative potency. The remaining six can provide some guidance on the relative potency of glyphosate to glyphosate formulations. In **Koller et al. (2007)**[127], tail intensity for the comet assay were virtually identical when the amount of glyphosate in the formulation was compared to the results using glyphosate alone. In the same paper, micronuclei and related biomarkers were consistently higher in the glyphosate formulation by 10-20%. In **Bolognesi et al. (1997),** DNA strand breaks in liver and kidney in Swiss CD-1 mice were virtually identical under equivalent doses of glyphosate and glyphosate formulations. In their micronucleus assay, the glyphosate formulation was approximately 50% more potent. Finally, **Bolognesi et al. (1997),** in their analysis of SCEs in human lymphocytes, the glyphosate formulation was approximately twice as effective as glyphosate alone. In **Peluso et al. (1988)**[133], DNA adducts in livers and kidneys were only seen in mice treated with the glyphosate formulation, so these findings are not likely to be due to glyphosate. The data suggest a small increase in the potential for genotoxicity for glyphosate formulations relative to the genotoxicity one would see with glyphosate alone.

In summary, the data support a conclusion that both glyphosate and glyphosate formulations are genotoxic. Thus, there is a reasonable mechanism supporting the increases in tumors caused by glyphosate and glyphosate formulations in humans and animals.

Oxidative Stress

Oxidative stress refers to an imbalance between the production of reactive oxygen species (free radicals) in a cell and the antioxidant defenses the cell has in place to prevent this. Oxidative stress has been linked to both the causes and consequences of several diseases[181-186] including cancer[37, 187-191]. Multiple biomarkers exist for oxidative stress; the most common being the increased antioxidant enzyme activity, depletion of glutathione or increases in lipid peroxidation. In addition, many studies evaluating oxidative stress used antioxidants following exposure to glyphosate to demonstrate that the effect of the oxidative stress can be diminished.

Oxidative Stress in Human Cells (*in vitro*)

Mladinic et al. (2009)[122] examined the induction of oxidative stress from exposure to glyphosate (98% purity) in lymphocytes from three healthy human donors (questionnaires were used to exclude other genotoxic exposures) at concentrations of 0.5, 2.91, 3.5, 92.8 and 580 µg/ml. Cells with and without S9 activation saw increases in total antioxidant capacity at only the highest dose for cells without S9 activation although a clear concentration response pattern was seen with S9 activation.

Kwiatkowska et al. (2014)[192] examined the induction of oxidative stress from exposure to glyphosate (purity not given) in erythrocytes obtained from healthy donors in the Blood Bank of Lodz, Poland. Erythrocytes were exposed to concentrations of 1.7, 8.4, 17, 42.3, 85 and 845 µg/ml and incubated for 1 hour. Oxidative stress (oxidation of dihydrorhodamine 123) was significantly increased at 42.3, 85 and 845 µg/l with a clear concentration-response pattern.

Chaufan et al. (2014)[193] examined the induction of oxidative stress from exposure to glyphosate (95% purity) and Roundup UltraMax (74.7% glyphosate) in HepG2 cells (human hepatoma cell line). Exposure concentrations were 900 µg/ml for glyphosate and 40 µg/ml for the glyphosate formulation. After incubation for 24 hours, oxidative stress (expressed as the activity of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and glutathione-S-transferase (GST)) was significantly increased ($p<0.0\text{-}5$) for the glyphosate formulation (increased SOD activity) but not for glyphosate alone.

Coalova et al. (2014)[194] examined the induction of oxidative stress from exposure to a glyphosate formulation (Atanor, 48% glyphosate) or with a surfactant (Impacto) in Hep-2 cells (human epithelial cell line). Exposure concentrations were 376.4 µg/ml for Atanor, 12.1 µg/ml for Impacto and 180.2 µg/ml for a mixture of the two. After incubation for 24 hours, oxidative stress (measured as activity of SOD, CAT, GSH, and GST) was significantly increased for Impacto, Atanor and the mixture (CAT and GSH only, $p<0.05$ or $p<0.01$).

Gehin et al. (2005)[195] examined the induction of oxidative stress from exposure to glyphosate (purity unknown) and a glyphosate formulation (Roundup 3 plus, 21% glyphosate) in HaCaT cells (human keratinocyte cell line). Glyphosate induced cytotoxicity in the cells which was reduced or eliminated by antioxidants. The authors attributed the cytotoxicity to oxidative stress.

Elie-Caille et al. (2010)[196] examined the induction of oxidative stress from exposure to glyphosate (purity unknown) in HaCaT cells (human keratinocyte cell line). Exposure concentrations ranged from 1700 µg/l to almost 12,000 µg/ml. Glyphosate induced cytotoxicity in the cells and increased hydrogen peroxide H_2O_2 (dichlorodihydrofluorescein diacetate assay). This study used exceptionally high concentrations that may be inducing cytotoxicity by means that are independent of the oxidative stress observed. Measuring oxidative stress using the dichlorodihydrofluorescein diacetate assay has limitations[197, 198].

George and Shukla (2013)[199] examined the induction of oxidative stress from exposure to a glyphosate formulation (Roundup Original, 41% glyphosate) in HaCaT cells (human keratinocyte cell line). Exposure concentration ranged from 1.7 µg/ml to 17,000 µg/ml and exposure was for 24 hours. Glyphosate significantly induced the formation of reactive oxygen species (dichlorodihydrofluorescein diacetate assay) at all exposures in a concentration-dependent fashion. Prior treatment of the cells with N-Acetylcysteine reduced the impact of glyphosate, but did not eliminate it. Measuring oxidative stress using dichlorodihydrofluorescein diacetate has limitations[197, 198] that affect the clear

interpretation of these results.

Oxidative Stress in Non-Human Mammals (*in vivo*)

Bolognesi et al. (1997)[130] exposed groups of three Swiss CD-1 male mice by IP injection with a single dose of glyphosate (99.9% purity, 300 mg/kg) or Roundup (900 mg/kg, equivalent to 270 mg/kg glyphosate). Animals were sacrificed at eight and 24 hours after injection and livers and kidney were removed to obtain crude nuclei from the adhering tissues. Samples of liver and kidneys from these mice were evaluated for levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG) which is a biomarker of oxidative stress[200]. There was a significant increase in the liver of 8-OHdG at 24 hours following glyphosate exposure, but not at eight hours and not in the kidney. At both eight hours and 24 hours, Roundup increased 8-OHdG in the kidneys, but the mild increase seen in the liver at 24 hours was not significant.

Cavusoglu et al. (2011)[139] exposed groups of six Swiss albino mice by IP injection of a glyphosate formulation (RoundupUltra Max, 450 g/l glyphosate, 50 mg/kg formulation). At the end of dosing, animals were fasted overnight then sacrificed. There was a significant increase in malondialdehyde in both liver and kidney and a significant decrease in GSH in liver and kidney from exposure to the glyphosate formulation. *G. bilboa* eliminated these effects.

Jasper et al. (2012)[201] exposed groups of 10 male and 10 female Swiss albino mice via oral gavage for 15 days to a glyphosate formulation (Roundup Original, 41% glyphosate, 50 mg/kg glyphosate equivalent dose). Animals were sacrificed at three days after injection. There was a significant increase in thiobarbituric acid-reactive substances (TBARS) in the liver for both male and female mice at both doses ($p<0.05$). The concentration of non-protein thiols was elevated in both dose groups for males and for the high dose only in females (no dose-response was seen for this endpoint).

Astiz et al. (2009)[202] exposed groups of four male Wistar rats by IP injection to a single dose of glyphosate (purity unknown, 10 mg/kg). Animals were injected three times per week for five weeks and then sacrificed. Thiobarbituric acid-reactive substances (TBARS assay), protein carbonyls (PCOSs), total glutathione levels, individual glutathione levels, SOD and CAT were all measured as biomarkers for oxidative stress in plasma, brain, liver and kidney. Glyphosate significantly increased TBARS in all tissues ($p<0.01$), total glutathione in brain ($p<0.01$), SOD in liver and brain ($p<0.01$) and CAT in brain. In a follow-up report[203], they demonstrate that lipoic acid eliminates or severely reduces the impacts of glyphosate on the brain.

Cattani et al. (2014)[204] exposed groups of four pregnant Wistar rats to glyphosate formulation (Roundup Original, 360 g/L glyphosate) in drinking water from gestational days 5-15 at a dose of 71.4mg/kg. Fifteen day-old pups (2 per dam) were examined for oxidative stress markers in the hippocampus. Pups had a significant increase in TBARS ($p<0.05$) and a significant decrease in GSH ($p<0.01$).

George et al. (2010)[82] exposed groups of four Swiss albino mice to a glyphosate formulation (Roundup Original, 36g/L glyphosate) at a dose of 50 mg/kg (glyphosate

equivalent dose) via a single topical application. Proteomic analysis of skin from the treated animals saw alterations in SOD1, CA III and PRX II, proteins known to play a role in the management of oxidative stress.

Oxidative Stress in Non-Mammalian Systems

As for genotoxicity, oxidative stress from exposure to glyphosate and glyphosate formulations have been studied in various aquatic organisms; reviewed in **Slaninova et al. (2009)**[205]. Many of the studies reviewed by **Slaninova et al. (2009)** showed associations with glyphosate and oxidative stress in various organs. Since that review, additional studies have been completed that also demonstrate a positive association between glyphosate and oxidative stress[147, 156-159, 206-217].

Summary for Oxidative Stress

Seven studies addressed oxidative stress in human cells and another six studies addressed it in mammalian systems. In lymphocytes and erythrocytes from healthy donors, oxidative stress was detected as low as 580 µg/ml in lymphocytes and at 42.3 µg/ml in erythrocytes. In Hep-G2 cells, no increased oxidative stress was seen for a single concentration of 900 µg/l. In two studies in HaCat cells, glyphosate induced oxidative stress in a continuous model fit to the results in one study and at the lowest concentration (1700 µg/ml) in the other. The most convincing studies in human cells for oxidative stress are the two studies in human blood.

In Swiss CD-1 male mice, increased oxidative stress was seen in the liver at 24 hours, but not at four hours after injection of 300 mg/kg glyphosate. No increase was seen in the kidney. In Wistar rats, repeated IP dosing with glyphosate lead to increased oxidative stress in multiple organs using multiple biomarkers. Thus, all of the laboratory studies demonstrated oxidative stress with a significant finding in the rat study.

In Hep-G2 cells, a glyphosate formulation demonstrated a robust increase in oxidative stress at 40 µg/ml. Given the negative response in this cell line for glyphosate alone, it must be concluded that this response is not due to glyphosate. In HEP-2 cells, a glyphosate formulation demonstrated a robust increase in oxidative stress via multiple biomarkers at 376 µg/ml and when a surfactant is added, at 180.2 µg/ml. In HaCaT cells, a glyphosate formulation demonstrated significant increases in oxidative stress from doses starting as low as 1.7 µg/ml in a concentration-dependent fashion. No studies were available in human lymphocytes.

In Swiss CD-1 mice, a glyphosate formulation significantly increased oxidative stress in the kidney but only demonstrated a mild (non-significant) increase in the liver. This study evaluated oxidative stress at two different time points following exposure and saw responses that differed over time. The strong increase in the liver for glyphosate but not glyphosate formulation, suggests a complicated response pattern for pure glyphosate versus the formulation that could be linked to the time since exposure. In Swiss Albino mice, a glyphosate formulation demonstrated increased oxidative stress by two separate biomarkers in both the liver and the kidney. In a second study in Swiss albino mice using a different biomarker but a similar dose, increased oxidative stress

was seen in both the liver and the kidney. In Wistar rat pups exposed in utero, an increase in oxidative stress was seen in the hippocampus. In Swiss albino mice, topical application of a glyphosate formulation to the skin resulted in a proteomic fingerprint suggesting oxidative stress was increased.

Though there are fewer studies for oxidative stress than there are for genotoxicity, the robust response seen here in human cells and in rodent studies clearly supports a role for both glyphosate and glyphosate formulations in inducing oxidative stress. Thus, there is a second reasonable mechanism through which the tumors seen in humans and those seen in animals can be caused by glyphosate and glyphosate formulations.

Summary for Biological Plausibility

In the evaluation of causality, the evidence for biological plausibility is overwhelming. Glyphosate clearly causes multiple cancers in mice, two cancers in the hematopoietic system similar to what is seen in humans, causes cancer in rats, is genotoxic and induces oxidative stress. The findings are clear for both glyphosate alone and for glyphosate formulations. **There is strong support for biological plausibility in support of a causal association of glyphosate and glyphosate formulations with NHL.**

Biological Gradient

Only three of the epidemiological studies provided information on biological gradients in their publications.

Eriksson et al. (2008)[46] divided their cases and controls into those with ≤10 days per year of exposure and those with >10 days per year of exposure. The ORs were calculated using a multivariate analysis that included agents with statistically significant increased OR, or with an OR > 1.50 and at least 10 exposed subjects. ORs for glyphosate were 1.69 (0.70-4.07) for ≤10 days per year and 2.36 (1.04-5.37) for >10 days per year. In their multivariate analysis, latency periods of 1-10 years showed an OR of 1.11 (0.24-5.08) and >10 years had an OR of 2.26 (1.16-4.40). Thus, they show an increase with intensity of exposure and with latency.

McDuffie et al. (2001)[50], using a conditional logistic regression analysis controlling for major chemical classes of pesticides and all other covariates with $p<0.05$, the OR for ≤2 days per year of exposure was 1.0 (0.63-1.57) and for >2 days per year, the OR was 2.12 (1.20-3.73). Thus, they show an increase with intensity of exposure.

De Roos et al. (2005)[45] used three exposure metrics in their analyses: a) ever personally mixed or applied pesticides containing glyphosate; b) cumulative exposure days of use of glyphosate (years of use times days per year); and c) intensity weighted cumulative exposure days (years of use times days per year times intensity of use). For exposure measurements b and c, they divided the respondents into tertiles chosen *a priori* to avoid having sparse data when dealing with rare tumors. For cumulative exposure days and using the lowest exposed tertile as the reference group, the RRs drop with values of 0.7 (0.4-1.4) and 0.9 (0.5-1.6) for tertiles 2 and 3 respectively adjusted for demographic and lifestyle factors and other pesticides (30,699 subjects). When

intensity-weighted exposure days are examined, the RRs drop with values of 0.6 (0.3-1.1) and 0.8 (0.5-1.4) for tertiles 2 and 3, respectively adjusted for demographic and lifestyle factors and other pesticides (30,699 subjects). Thus, they do not see a biological gradient in their responses. However, the high frequency of exposure to many pesticides (e.g. 73.8% were exposed to 2,4-D) means subjects with low exposure to glyphosate were likely to be exposed to other agents that may also induce NHL; this could reduce the RRs in the higher exposure classes because it would inflate the RR in the low-exposure referent group.

Eriksson et al. (2008)[46] and **McDuffie et al. (2001)**[50] had consistent results for intensity of exposure per year (≤2 days per year, OR=1.0; ≤10 days per year, OR=1.69; >2 days per year, OR=2.12; >10 days per year, OR=2.26). It is not possible to resolve the remaining differences between these three studies nor is it easy to argue that one study has more weight on this question than any other. The studies use different measures of exposure or time since exposure, are done on different populations and have different statistical power to detect a trend.

In rodent carcinogenicity studies, there is clear evidence of a biological gradient.

In general, there is support that a biological gradient exists for the epidemiological data and thus support from this aspect of the Bradford-Hill evaluation.

Temporal Relationship

Exposure must come before the cancers occur otherwise the epidemiology studies are useless. In this case, it is clear that exposure came before the onset of NHL. **The need for a temporal relationship in the data supporting a causal association between glyphosate and NHL is satisfied.**

Specificity

There are other causes of NHL[218-221] so this group of cancers is not specific to glyphosate. **There is little support for specificity**.

Coherence

Humans, coming into contact with glyphosate, can absorb the compound into their bodies where it has been measured in blood and in urine[56, 222-226]. In laboratory animals, absorption, distribution and elimination of glyphosate and glyphosate compounds have been studied[140, 227] and show that glyphosate gets into the animal's bodies, distributes to numerous organs and is eliminated in urine. The animal cancer studies clearly demonstrate that glyphosate in mammals can have toxic effects.

Mouse models have long served as surrogates for humans in understanding and developing treatments for many diseases. The same holds true for lymphoid tumors seen in humans. For over 30 years, mouse models have been studied and evaluated as surrogates for NHL[228-232]. These publications and the associated classification systems for humans and mice indicate a close linkage between the diseases in humans and mice.

Thus, coherence is supported by the increased risk of malignant lymphomas in CD-1 mice, the marginal increase in these tumors in Swiss mice and the strong similarity between malignant lymphomas in mice and NHL in humans.

There is strong support for coherence in the data supporting a causal association of glyphosate and glyphosate formulations with NHL.

Experimental Evidence in Humans

There is no experimental evidence in humans since purposely exposing humans to a pesticide, especially one that is probably carcinogenic, is not ethical and would never pass review by a human subject's advisory board.

Analogy

I am unaware of any analogous compounds from the scientific literature. This, however, is not an area where I have sufficient background to express an opinion.

Summary

Table 18 summarizes the information for each of Hill's aspects of causality. For these data, causality is strengthened because the available epidemiological studies show a consistent positive association between cancer and the exposure. The studies do not show different responses with some studies being positive and others negative, nor do they show any heterogeneity when analyzed together. And, in answer to Hill's question, the relationship between NHL and glyphosate exposure has been observed by different persons, in different places, circumstances, and times.

Causality is strengthened for these data because the strength of the observed associations, when evaluated simultaneously, are statistically significant, the findings are uni-directional and the results are unlikely to be due to chance. Even though none of the individual studies provide relative risks or odds ratios that are large and precise, the meta-analysis has objectively shown that the observed association across these studies is significant and supports a positive association between NHL and glyphosate.

Biological plausibility is strongly supported by the animal carcinogenicity data and the mechanistic data on genotoxicity and oxidative stress. When addressing biological plausibility, the first question generally asked is "Can you show that glyphosate causes cancers in experimental animals?" In this case, the answer to that question is clearly yes. Glyphosate has been demonstrated to cause cancer in two strains of rats and one strain of mice. Glyphosate has been demonstrated to cause cancer in two strains of rats and one strain of mice. Glyphosate causes hepatocellular adenomas in male Wistar rats and, to a lesser degree, in male Sprague-Dawley rats, mammary gland adenomas and adenocarcinomas in female Wistar rats, skin keratocanthomas in male Wistar rats, and kidney adenomas and thyroid C-cell adenomas and carcinomas in male Sprague-Dawley rats. Glyphosate causes hemangiosarcomas, kidney tumors and malignant lymphomas in male CD-1 mice and hemangiomas in female CD-1 mice and possibly

causes malignant lymphomas, kidney adenomas in male Swiss albino mice and hemangiomas in female Swiss albino mice. Thus, glyphosate causes cancer in mammals. Thus, it is biologically plausible that glyphosate alone can cause cancer in mammals.

The next question generally asked is "Does the mechanism by which glyphosate causes cancer in experimental animals also work in humans?" The best understood mechanism by which chemicals cause cancer in both humans and animals is through damaging DNA that leads to mutations in cells that then leads to uncontrolled cellular replication and eventually cancer. It is absolutely clear from the available scientific data that both glyphosate and glyphosate formulations are genotoxic. This has been amply demonstrated in humans that were exposed to glyphosate, in human cells *in vitro*, in experimental animal models and their cells *in vitro* and *in vivo*, and in wildlife. One way in which DNA can be damaged is through the presence of free oxygen radicals that overwhelm a cell's antioxidant defenses. Glyphosate induces this type of oxidative stress, providing additional support for a biological mechanism that works in humans.

Table 18: Summary conclusions for Hill's nine aspects of epidemiological data and related science

Aspect	Conclusion	Reason
Consistency of the observed association	Strong	Multiple studies, all are positive, meta-analysis shows little heterogeneity, different research teams, different continents, different questionnaires, no obvious bias or confounding
Strength of the observed association	Strong	Six core epidemiology studies all show the same modest increase, significant meta-analyses
Biological plausibility	Very Strong	Multiple cancers in multiple species, not due to chance, increased risk of rare tumors, convincing evidence for genotoxicity and oxidative stress
Biological gradient	Moderate	Clearly seen in the two case-control studies that evaluated it, not seen in the cohort study
Temporal relationship of the observed association	Satisfied	Exposure clearly came before cancers
Specificity of the observed association	Not needed	NHL has other causes, this does not subtract from the causal argument
Coherence	Strong	Glyphosate is absorbed, distributed and excreted from the body, cancers seen in the mice have strong similarity to human NHL
Evidence from human experimentation	No data	No studies are available
Analogy	No data	No studies available in the literature

In general, there is support that a biological gradient exists for the epidemiological data and thus support from this aspect of the Bradford-Hill evaluation. Glyphosate ORs increased with time since first exposure and with intensity of use per year in the two case-control studies that evaluated at least one of these issues.

There is clearly the proper temporal relationship with the exposure coming before the cancers.

The human evidence is coherent. The basic findings in humans agree with the animal evidence for absorption, distribution and elimination of glyphosate. Also, one of the tumors seen in mice has almost the same etiology as NHL.

NHL is not specific to glyphosate exposure. There is no experimental evidence in humans and I did not find any references where researchers looked for analogous compounds with similar toxicity.

Hill (1965)[36] asks *"is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"* There is no better way of explaining the scientific evidence relating glyphosate to an increase in NHL in humans than cause and effect.

In my opinion, glyphosate probably causes NHL and, given the human, animal and experimental evidence, I assert that, to a reasonable degree of scientific certainty, the probability that glyphosate causes NHL is high.

The IARC Assessment of Glyphosate

In March 2015, the International Agency for Research on Cancer (an agency of the World Health Organization) brought together seventeen scientists (the Working Group) to evaluate the scientific evidence on whether glyphosate can cause cancer in humans. This group also contained one invited specialist (myself) to aid the Working Group (WG) in going through the science but who was not allowed to join discussions on the final conclusion or write any part of the document. The Working Group concluded that glyphosate falls in the category *"probably carcinogenic to humans (Group 2A)"*[56].

The IARC preamble[30] guides Working Groups on how to evaluate scientific literature to determine if something is a hazard. All Working Groups follow these guidelines and this process is accepted worldwide as a proper way to evaluate the literature for a hazard (e.g., the European Chemical Agency cites the IARC review process as guidance and then uses the exact same wording as IARC does to guide their own hazard evaluation process[34]).

The WG examined the epidemiological data and classified it as *"limited evidence of carcinogenicity,"* which is defined to mean *"a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with*

reasonable confidence." This is a precise and clear description of the strength of the evidence from the epidemiological studies.

The WG examined the evidence from animal carcinogenicity studies and classified it as "*sufficient evidence of carcinogenicity,*" which IARC defines as: "*a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.*" Based on the data available to IARC at the time of their review and the restrictions placed on the studies they can review by the Preamble, this conclusion is justified and correct.

One of the major criticisms of the WG review was that the WG did not review all of the animal carcinogenicity data that was available to the regulatory bodies and thus came to the wrong conclusions on the animal cancer data. In this review, I evaluated all 19 animal carcinogenicity experiments that have been collectively mentioned by any agency that reviews glyphosate. Where possible, I have analyzed the original data and used sound statistical methods to test for significant increases in cancer incidence in animals exposed to glyphosate. My conclusion is that the WG would have called this data "*sufficient evidence*" to support their findings despite not reviewing the additional studies analyzed herein. Despite the fact the industry kept these studies confidential, nothing contained in the withheld studies would have changed the WG conclusion.

On the mechanistic data, the IARC Working Group reviewed the same data that I reviewed, but I also evaluated, where possible, the proprietary data supporting the regulatory decisions. Where possible, I reanalyzed that data to be certain the results being presented were accurate. The IARC Working Group, using the guidelines set forth in their Preamble, declared strong support for the biological mechanisms of genotoxicity and oxidative stress. As I have shown here, there is strong support for these two mechanisms, even with the proprietary evidence from the industry studies. Thus, the IARC Working Group reached the correct conclusion.

To decide on a final classification for a compound, the IARC Preamble provides guidance on how the classification of the three areas are to be used. If the data in humans is "*limited*" and the data from animal carcinogenicity studies is "*sufficient*," the discussions should begin with Class 2A, "*the agent is probably carcinogenic to humans.*" Then, given the overall quality of the data set, the strength of the evidence from the mechanistic studies and any additional scientific issues that need to be considered, the Working Group will determine whether the data justifies a different category. In this case, the Working Group concluded 2A was the right category and I still believe the evidence supports that finding.

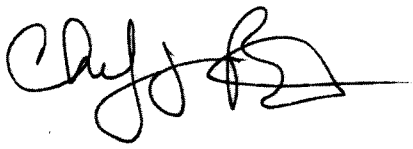
The EPA Assessment of Glyphosate

Like IARC, the EPA has guidelines that are to be followed when evaluating scientific literature and making a determination about the carcinogenic potential of a chemical. Those guidelines have been developed over many years and are based on sound scientific guidance that myself and many other scientists have provided to the Agency. For their evaluation of glyphosate, the Agency did not follow their own guidelines, nor did they follow sound scientific practice. This opinion is consistent with the review done by the **EPA FIFRA Scientific Advisory Panel**[54]. In addition, the Agency failed to find all of the relevant animal cancer studies and misinterpreted several of them. The major problems with the Agency evaluation are:

- Misinterpretation of the epidemiological evidence, confusing the potential for bias and potential for confounding with real bias and real confounding, allowing them to give almost no weight to the case-control studies in favor of the one cohort study;
- Misinterpretation of the findings in the meta-analysis;
- Failure to properly use historical controls in the analysis of the animal carcinogenicity studies; declaring a significant finding as not due to the compound if it is in the range of the historical controls;
- Failure to analyze all tumors in all studies relying upon the industry submissions to have done this correctly;
- Failure to follow their guidelines on what constitutes a positive finding, disregarding significant trend tests when no corresponding pairwise comparisons are also significant;
- Disregarding positive findings in doses that are clearly not above the maximum dose the animals could be given with compromising the integrity of the study;
- Using unreasonable arguments about the overall false positive rates in the study without actually doing an analysis of this issue;
- Failing to recognize the similar findings in similar studies and to do a pooled analysis to determine if the negative effects in one study cancel out the positive effects in another;
- Giving very little weight to studies from the literature and relying almost entirely on studies provided by industry that have not undergone peer review for both quality and, more importantly in some cases, interpretation of the findings; and
- Comparing results across different species and strains for the animal cancer studies and the mechanistic studies with little regard for unique findings in any one study and consistent findings across multiple studies.

Similar comments apply to the evaluation done by the **European Food Safety Authority**[89] and the **European Chemical Agency**[233]. My detailed comments to these

agencies on their risk assessments are attached. There were comments to my comments to EPA by other scientists and I also responded to those comments in the EPA docket for glyphosate. These are also included in the attached Appendices.



Dr. Christopher J. Portier

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EXHIBIT 95 Part 4

Spontaneous Neoplastic Lesions in the Crl:CD-1®(ICR)BR Mouse

March, 2000

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CHARLES RIVER
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INTRODUCTION

The data presented in these tables was gathered from 51 toxicology studies of at least 78 weeks duration. All studies were performed in the United States or Europe by contract laboratories or industrial toxicology facilities.

PURPOSE

The purpose of this compilation is to offer the study director, reviewing toxicologist and/or study pathologist some reported incidences of neoplasms in Crl:CD-1 (ICR)BR mice, maintained as control animals, in studies of 78-104 weeks duration. Diagnoses in this compilation are intentionally grouped in a manner to provide the user with a range of reported incidences of similar types of lesions. This compilation is not intended in any way to propose a system of standardized nomenclature nor does it separately include each and every variant of the lesion.

COMMON STUDY PARAMETERS

The 51 studies included in this publication were initiated between January 1987 and December of 1996 in seven different laboratories. All studies used male and/or female Crl:CD-1® (ICR)BR mice from three different Charles River Laboratories production sites: Raleigh, North Carolina; Kingston, New York and Portage Michigan.

The mice in these studies were from control groups of dietary or gavage studies and were approximately 4-7 weeks of age at study initiation. Some groups were untreated while others received the study vehicle, all served as control groups.

The mice included in this publication were generally singly housed in hanging wire mesh cages, fed a diet of Purina 5002 Certified Rodent Chow and had free access to water. The animal rooms were generally maintained at average temperatures of 72 +/- 5° Fahrenheit with an average relative humidity of 30-70%. A 12hr/12hr light/dark cycle was employed in all studies. Since these studies were conducted in different facilities over a period of several years, there was some variation in environmental conditions. The overall environmental conditions were not considered by those performing the studies to have had any effect on the quality or integrity of the studies. Information on the health monitoring, other than that associated with pathological examination conducted in accordance with scheduled or moribund sacrifices, was not available.

DATA SETS PRESENTED

Survival data are presented by study as the actual number surviving to terminal sacrifice and as a percent survival at terminal sacrifice, Tables1 and 2. The survival data are also presented in graphic form, Graphs 1 and 2. Survival data were not available for all studies at the time of publication. Only those studies for which data were available are represented on the graphs.

The overall incidences of all neoplastic lesions observed in any organ are reported and summarized by sex, Tables 3 and 4. These data also include neoplastic lesions from mice that died or were found moribund and killed prior to terminal sacrifice. It does not include information from mice that were killed at any interim sacrifice. Due to the apparent diversity in terminology and the variability among studies in the incidence of

particular lesions, the individual study incidences of lesions in selected organs/systems are also presented, Tables 5 and 6. These organs/systems include liver, lung and whole body/multiple organ.

SUMMARY TABLE CALCULATIONS

The following is a description of how each of the parameters in the tables was calculated.

Number of Studies (# Studies)

This is the number of studies in which a particular tissue/organ was examined. In this publication, the number of studies is usually 46 for males and 48 for females. It is important for the reader to realize that some of the studies reported in this document were performed in only males or females and occasionally a specific tissue/organ was not examined in a particular study.

Total Number of Organs (Total # Organs)

This number represents the sum of the total number of tissues or organs examined in all of the control groups from all studies combined. Widespread tumors which showed involvement of multiple organs were listed on the basis of the total number of animals examined. Occasionally a tumor would be noticed in a tissue not designated for histological examination by the study protocol. In these instances, the tumor incidence was based on the total number of animals examined as any such tumor or lesion would have been noticed on gross examination of the animal. Autolysis did not routinely exclude tissues from diagnosis. Tissue numbers were adjusted only if the individual study table indicated that some tissues were missing or inadequate for examination. Some laboratories presented data separately for different regions within a organ (i.e., duodenum, jejunum, and ileum) while most presented data by the organ (i.e., small intestine). When data were presented separately by organ region, they were grouped under the organ and calculations were based on the number of organs examined.

Total Number of lesions (# Lesions)

This represents the total number of occurrences of this lesion in a specific organ in all studies examined.

Percent of Total

These values represent the particular incidence of a particular lesion/diagnosis in the total number (all studies combined) of a particular organ examined. These values were calculated by dividing the total number of lesions by the total number of organs/animals examined and multiplying by 100 to express the value as a percent. Values are expressed to the second decimal place. Some caution is indicated in using this number, since not all pathologists or institutions will include all diagnoses in their lexicon.

Number of Studies Using This Diagnosis

This is the number of studies in which a particular diagnosis was reported. This number may be useful in interpreting the overall incidence (percent of total) of a particular diagnosis, see above.

Minimum and Maximum Percent Found (Minimum and Maximum % Found)

The range reported is the lowest and highest percent incidence for each lesion from the studies where the diagnosis was made. Therefore, if a study did not include a particular diagnosis, it was excluded from these calculations. The minimum and maximum percent found values should be considered in conjunction with the Number of Studies Using the Diagnosis.

The individual study percentages, Minimum % Found and Maximum % Found, were calculated by dividing the number of times each diagnosis was made by the total number of organs examined in each study and then multiplying the resultant value by 100 to express it as a percent. Values are expressed to the second decimal place.

ADDITIONAL INFORMATION

If additional information is desired regarding the conduct of these studies or the incidence of a particular neoplasm please contact Mary Giknis through Charles River Laboratories, or via e-mail at MLAGIKNIS@att.net.

SYNONYMS

Synonymous terms or diagnoses were frequently encountered in different studies and were combined under a single, often broad diagnosis, which was considered to be the primary diagnosis. Although some effort was made to use currently acceptable terms, it is beyond the scope of this publication to propose a system of preferred diagnoses. The synonyms which were included in the various diagnoses are presented in the synonym list which follows. Where possible, terminology is consistent with the classification system proposed by the Society of Toxicologic Pathologists.

Skin:
Nerve Sheath Tumor = Schwannoma

Testis:
Sertoli Cell Tumor, Benign = Sertoliform Adenoma

Uterus:
Endometrium, Adenocarcinoma = Endometrial Carcimoma
Endometrial Stromal Sarcoma = Endometrial Sarcoma

Whole Body/Multiple Organ:
Lymphoma, Malignant = Lymphosarcoma
Mast Cell Tumor = Mastocytoma

ABBREVIATIONS

NR = Not Recorded or not available at the time of publication.

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REQUEST FOR DATA

The purpose of these publications is to assist you, our clients, in evaluating your data. Our aim is to provide you with the data that you need to do your job well. We welcome any suggestions that you may have to improve this document as well as suggested topics for future documents. However, please realize that the publication is only as good as the data. To this end we invite you to participate in and support this worthwhile project by sending us your control data. If you or someone at your laboratory is willing to participate, please contact Mary Giknis through Charles River Laboratories, 251 Ballardvale Street, Wilmington, MA 01887 or at MLAGIKNIS@att.net.

Table 1: Summary of Individual Study Information and Survival/Males

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study Initiation Date	1987	1988	1988	1988	1988	1988	1989	1989	1989	1990	1990	1990	1990	1991	1991	1991
Total Number on Study	53	47	50	49	50	59	50	60	50	48	50	50	69	50	59	60
Number Surviving to Termination	NR	40	NR	NR	31	NR	NR	45	NR	NR	NR	47	NR	31	38	NR
% Survival		85.11			62.00			75.00				94.0		62.0	64.4	
Study Duration in Weeks	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78

Study Identification	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Study Initiation Date	1992	1992	1992	1992	1993	1993	1993	1993	1994	1995	1989	1992	1990	1991	1991	1993
Total Number on Study	50	50	50	50	50	50	60	50	50	70	50	49	60	70	65	60
Number Surviving to Termination	35	39	NR	NR	NR	NR	NR	NR	NR	NR	30	39	11	40	NR	22
% Survival	70.0	78.0									60.0	79.6	18.3	57.1		36.7
Study Duration in Weeks	78	78	78	78	78	78	78	78	78	78	97	100	104	104	104	104

Study Identification	33	34	35	36	37	38	39	40	41	42	43	44	45	46
Study Initiation Date	1993	1993	1993	1993	1994	1994	1994	1995	1995	1995	1995	1996	1996	1996
Total Number on Study	70	50	65	50	50	65	65	60	60	60	80	50	50	116
Number Surviving to Termination	17	18	24	NR	22	43	28	26	29	NR	NR	27	22	NR
% Survival	24.3	36.0	36.9		44.0	66.2	43.1	43.3	48.3			54.0	44.0	
Study Duration in Weeks	104	104	104	104	104	104	104	104	104	104	104	104	104	104

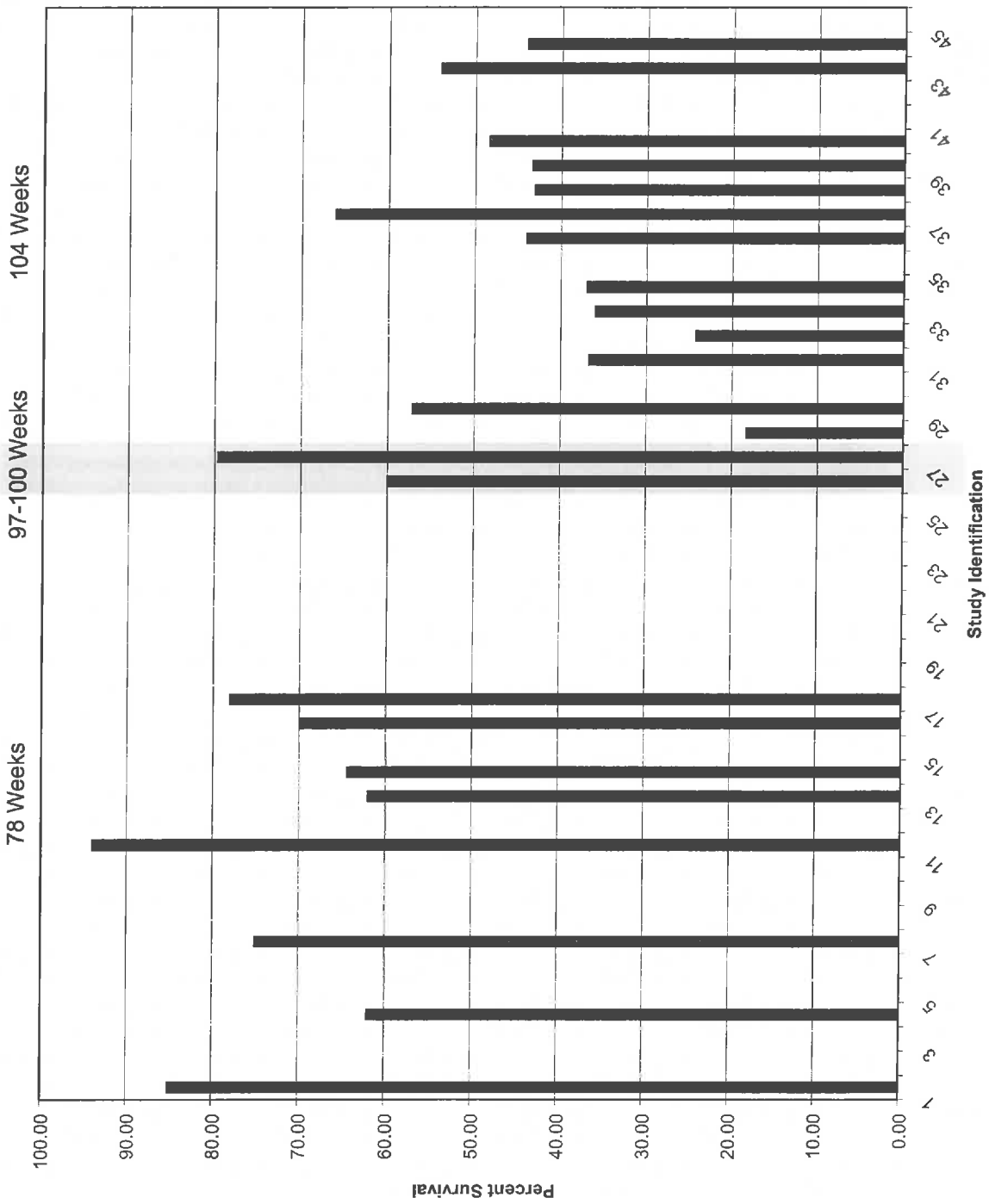
Table 2: Summary of Individual Study Information and Survival/Females

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Study Initiation Date	1987	1988	1988	1988	1988	1988	1989	1989	1989	1990	1990	1990	1990	1991	1991	1991
Total Number on Study	52	49	50	48	49	60	50	60	50	48	50	49	70	49	59	60
Number Surviving to Termination	NR	40	NR	NR	33	NR	NR	45	NR	NR	NR	36	NR	31	38	NR
% Survival		81.6			67.3			75.0				73.5		63.3	64.4	
Study Duration in Weeks	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78	78

Study Identification	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32
Study Initiation Date	1992	1992	1992	1993	1993	1993	1993	1994	1995	1996	1995	1995	1989	1992	1990	1991
Total Number on Study	50	50	50	50	50	59	50	50	70	116	60	75	50	50	60	70
Number Surviving to Termination	39	NR	NR	NR	NR	NR	NR	NR	NR	NR	36	47	37	39	13	31
% Survival	78.0										60.0	62.7	74.0	78.0	21.7	44.3
Study Duration in Weeks	78	78	78	78	78	78	78	78	78	91	94	94	97	100	104	104

Study Identification	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
Study Initiation Date	1991	1992	1993	1993	1993	1993	1993	1994	1994	1994	1995	1995	1995	1995	1996	1996
Total Number on Study	65	150	60	70	50	65	59	50	65	65	60	60	60	80	50	50
Number Surviving to Termination	NR	NR	21	13	16	20		22	36	28	27	23	NR	NR	21	21
% Survival			35.0	18.6	32.0	30.8		44.0	55.4	43.1	45.0	38.3			42.0	42.0
Study Duration in Weeks	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104	104

Graph 1: Male Survival



Graph 2: Female Survival

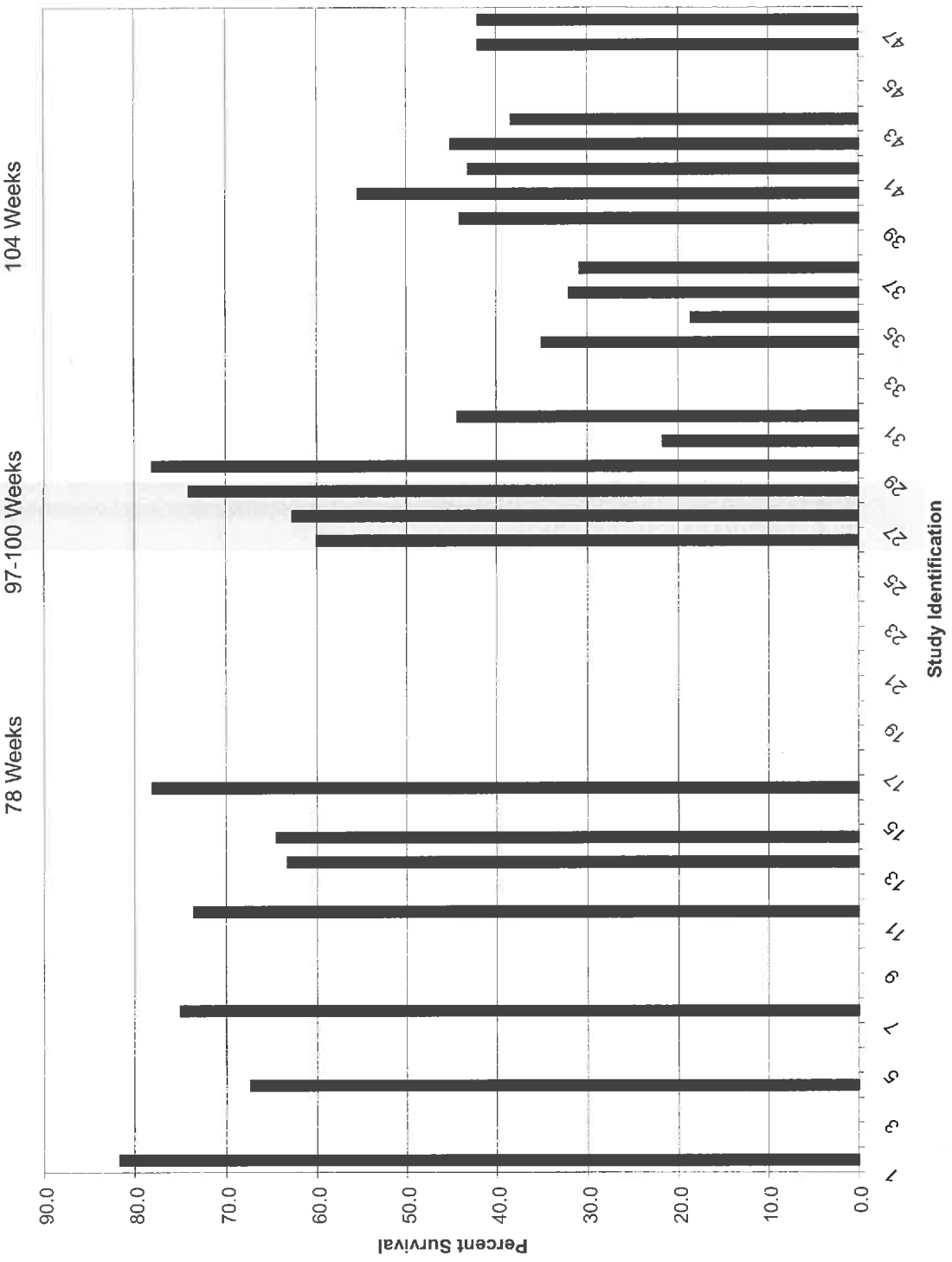


Table 3: Neoplasms/Males

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
DIGESTIVE SYSTEM						
ORAL CAVITY	46	2577				
SALIVARY GLAND	46	2577				
STOMACH	46	2546				
Nonglandular Mucosa/Squamous Cell Papilloma		3	0.12	3	1.67	1.72
Adenocarcinoma		1	0.04	1	1.79	1.79
SMALL INTESTINE	46	2455				
Adenoma		1	0.04	1	1.72	1.72
Adenocarcinoma		5	0.20	4	1.67	2.90
LARGE INTESTINE/CECUM/ANUS	46	2482				
Adenocarcinoma		3	0.12	2	1.43	4.08
LIVER	46	2571				
Hepatocellular Adenoma		269	10.46	44	2.86	28.00
Hepatocellular Carcinoma		136	5.29	39	1.54	16.00
Hemangioma		9	0.35	7	1.54	4.00
Hemangiosarcoma		29	1.13	15	1.11	5.00
GALL BLADDER	46	2257				
Adenoma		3	0.13	3	1.69	2.00
Papilloma		6	0.27	3	2.08	5.00
PERITONEUM	46	2577				
Fibrosarcoma		1	0.04	1	1.69	1.69
Lipoma		2	0.08	2	1.43	2.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
RESPIRATORY SYSTEM						
NASAL CAVITY	46	2577				
Nasal Adenocarcinoma		1	0.04	1	2.00	2.00
LUNG	46	2575				
Adenoma, Alveolar/Bronchiolar		368	14.29	43	2.00	42.00
Adenocarcinoma, Alveolar/Bronchiolar		177	6.87	37	1.43	26.00
UROGENITAL SYSTEM						
KIDNEY	46	2569				
Adenoma/Tubular Adenoma		7	0.27	5	2.00	4.00
Adenocarcinoma/Tubular Adenocarcinoma		4	0.16	4	1.43	2.00
URINARY BLADDER	46	2535				
Leiomyoma		1	0.04	1	1.67	1.67
Leiomyoblastoma, Malignant		2	0.08	2	1.45	1.67
Leiomyosarcoma		5	0.20	3	2.00	4.00
TESTIS	46	2576				
Interstitial Cell Tumor, Benign		19	0.74	15	1.43	4.00
Interstitial Cell Tumor, Malignant		2	0.08	2	1.67	2.00
Hemangioma		2	0.08	2	1.67	2.00
Hemangiosarcoma		2	0.08	2	1.43	1.67
Sertoli Cell Tumor, Benign		3	0.12	3	1.43	1.69
SEMINAL VESICLE	46	2542				
Adenocarcinoma		1	0.04	1	2.00	2.00
Leiomyosarcoma		1	0.04	1	1.67	1.67
PROSTATE	46	2565				
Adenoma		1	0.04	1	1.67	1.67
EPIDIDYMIS	46	2515				
Adenoma		1	0.04	1	2.00	2.00
Fibrosarcoma/Stromal Sarcoma		2	0.08	2	1.43	1.54
Leiomyoma		1	0.04	1	1.67	1.67

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
SKIN						
SKIN	46	2552				
Papilloma/Squamous Cell Papilloma		4	0.16	4	1.47	2.00
Trichoepithelioma, Benign		1	0.04	1	2.63	2.63
SKIN, cont'd						
Chondroma		1	0.04	1	1.67	1.67
Fibroma		2	0.08	2	2.00	2.08
Fibrosarcoma		2	0.08	2	1.54	2.00
Hemangioma		1	0.04	1	1.54	1.54
Hemangiosarcoma		4	0.16	4	1.43	1.67
Leiomyosarcoma		1	0.04	1	1.43	1.43
Mast Cell Tumor		1	0.04	1	1.54	1.54
Nerve Sheath Tumor, Benign		1	0.04	1	1.67	1.67
Nerve Sheath Tumor, Malignant		3	0.12	3	1.43	2.00
Sarcoma		1	0.04	1	2.00	2.00
Neurofibroma		1	0.04	1	2.00	2.00
ENDOCRINE SYSTEM						
ADRENAL	46	2526				
Cortex, Adenoma		30	1.19	17	1.56	7.14
Cortex, Carcinoma		1	0.04	1	2.00	2.00
Pheochromocytoma, Benign		11	0.44	7	1.11	5.00
Spindle Cell Tumor, Benign		6	0.24	4	1.56	4.00
PANCREAS	46	2559				
Islet Cell, Adenoma		4	0.16	3	1.54	2.00
Hemangiosarcoma		1	0.04	1	1.69	1.69
PITUITARY	46	2504				
Adenoma		6	0.24	5	1.45	3.23
Carcinoma		1	0.04	1	2.04	2.04
Pars Intermedia, Adenoma		1	0.04	1	2.00	2.00
THYROID	46	2524				
C-Cell, Adenoma		1	0.04	1	2.00	2.00
Follicular Cell, Adenoma		12	0.48	12	1.11	2.00
Follicular Cell, Carcinoma		1	0.04	1	2.00	2.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	**# STUDIES**	**# LESIONS**	**OF TOTAL**	**DIAGNOSIS**	**% FOUND**	**%FOUND**
PARATHYROID	46	2200				
ENDOCRINE SYSTEM						
BRAIN	46	2576				
Oligodendroglioma		1	0.04	1	2.04	2.04
BRAIN, cont'd.						
Meningioma		1	0.04	1	1.43	1.43
SPINAL CORD	46	2575				
PERIPHERAL NERVE	46	2509				
MUSCULOSKELETAL SYSTEM						
SKELETAL MUSCLE	46	2412				
BONE	46	2570				
Osteoma, Benign		1	0.04	1	1.43	1.43
Osteosarcoma		1	0.04	1	1.54	1.54
Sarcoma		1	0.04	1	1.43	1.43
CIRCULATORY SYSTEM						
HEART	46	2578				
BLOOD VESSEL	46	2554				
HEMATOPOIETIC/LYMPHOID SYSTEM						
BONE MARROW	46	2498				
Lymphoma, Malignant		1	0.04	1	2.00	2.00
SPLEEN	46	2543				
Hemangioma		8	0.31	7	1.67	4.00
Hemangiosarcoma		28	1.10	15	1.67	8.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
LOCATION AND TUMOR	**# STUDIES**	**# LESIONS**	**OF TOTAL**	**DIAGNOSIS**	**% FOUND**	**%FOUND**
Lymphoma, Malignant		4	0.16	1	8.00	8.00
THYMUS	46	2037				
Lymphoma, Malignant		7	0.34	1	14.89	14.89
LYMPH NODES	46	2504				
Hemangioma		3	0.12	3	1.43	2.04
Hemangiosarcoma		2	0.08	2	2.00	2.00
Lymphoma, Malignant		3	0.12	1	6.00	6.00
WHOLE BODY/MULTIPLE ORGAN	46	2565				
Lymphoma, Malignant		105	4.09	33	1.45	21.67
Lymphoma, Lymphocytic		11	0.43	8	1.69	4.08
Leukemia, Granulocytic		6	0.23	6	1.43	2.04
Leukemia, Lymphocytic		3	0.12	2	2.00	3.33
Hemangiosarcoma		29	1.13	8	1.67	12.00
Histiocytic Sarcoma		35	1.36	19	1.11	8.00
Mast Cell Tumor, Malignant		4	0.16	3	1.43	2.00
SPECIAL SENSES						
EYE	46	2539				
Harderian Gland, Adenoma		120	4.73	31	1.67	14.00
Harderian Gland, Adenocarcinoma		11	0.43	7	1.43	8.33
EAR	46	2575				
Pinna, Hemangioma		1	0.04	1	1.67	1.67
Pinna, Papilloma		1	0.04	1	1.67	1.67

Table 4: Neoplasms/Females

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
DIGESTIVE SYSTEM						
ORAL CAVITY	48	2695				
Tongue, Papilloma		1	0.04	1	1.67	1.67
STOMACH	48	2772				
Polypoid Adenoma		2	0.07	2	1.47	2.00
Squamous Papilloma		4	0.14	4	0.79	2.04
Squamous Cell Carcinoma		1	0.04	1	2.00	2.00
Undifferentiated Carcinoma		2	0.07	2	1.56	2.00
SMALL INTESTINE	48	2667				
Adenoma		1	0.04	1	1.18	1.18
Adenocarcinoma		3	0.11	3	1.49	2.00
LARGE INTESTINE/CECUM/ANUS	48	2645				
Leiomyoma		1	0.04	1	1.72	1.72
LIVER	48	2740				
Hepatocellular Adenoma		27	0.99	20	0.85	7.84
Hepatocellular Carcinoma		18	0.66	13	1.43	4.29
Undifferentiated Carcinoma		1	0.04	1	1.54	1.54
Hemangioma		6	0.22	6	1.54	2.00
Hemangiosarcoma		17	0.62	12	1.43	4.29
GALL BLADDER	48	2513				
Papilloma		2	0.08	2	2.00	3.03
Adenoma		1	0.04	1	3.03	3.03
PERITONEUM	48	2841				

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
RESPIRATORY SYSTEM						
NASAL CAVITY	48	2781				
LUNG	48	2773				
Adenoma, Alveolar/Bronchiolar		236	8.51	43	1.67	26.67
Adenocarcinoma, Alveolar/Bronchiolar		113	4.08	35	0.77	18.37
Mesothelioma, Benign		1	0.04	1	1.67	1.67
UROGENITAL SYSTEM						
KIDNEY	48	2857				
Adenoma/Tubular Adenoma		1	0.04	1	2.00	2.00
Adenocarcinoma/Tubular Adenocarcinoma		1	0.04	1	2.00	2.00
Transitional Cell Carcinoma		1	0.04	1	2.00	2.00
URINARY BLADDER	48	2718				
Transitional Cell Carcinoma		1	0.04	1	2.17	2.17
Leiomyosarcoma		4	0.15	4	1.75	2.44
Undifferentiated Sarcoma, Malignant		1	0.04	1	2.00	2.00
OVARY	48	2735				
Cystadenoma		18	0.66	12	1.54	6.00
Granulosa Cell Tumor, Benign		6	0.22	6	1.47	2.08
Tubular Adenoma		22	0.80	13	1.43	8.16
Luteal Cell Tumor, Benign		6	0.22	5	1.47	4.00
Luteal Cell Tumor, Malignant		1	0.04	1	1.11	1.11
Sertoliform Adenoma		2	0.07	2	2.00	2.04
Theca Cell Tumor, Benign		6	0.22	6	0.77	2.04
Theca Cell Tumor, Malignant		1	0.04	1	2.04	2.04
Hemangioma		8	0.29	7	1.11	2.90
Hemangiosarcoma		2	0.07	2	1.75	2.00
Leiomyoma		4	0.15	4	1.69	2.13
Oviduct, Fibroma		2	0.07	2	0.77	2.04
UTERUS	48	2812				
Endometrium, Adenoma		3	0.11	3	1.54	2.00
Endometrium, Adenocarcinoma		11	0.39	7	0.86	4.00
Endometrial Stromal Polyp		146	5.19	35	1.67	17.14

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
Endometrial Stromal Sarcoma		33	1.17	19	1.43	8.00
Fibroma		2	0.07	2	1.67	2.00
Fibrosarcoma		2	0.07	2	1.54	1.69
Granular Cell Tumor		1	0.04	1	2.04	2.04
Hemangioma		15	0.53	11	1.25	4.62
UTERUS, cont'd.						
Hemangiosarcoma		14	0.50	12	0.77	4.08
Leiomyoma		40	1.42	20	1.43	7.50
Leiomyosarcoma		36	1.28	21	0.86	6.00
Nerve Sheath Tumor, Malignant		6	0.21	5	1.43	3.08
Neurofibrosarcoma		1	0.04	1	2.00	2.00
Osteosarcoma		8	0.28	4	1.54	8.00
Deciduoma		1	0.04	1	1.75	1.75
CERVIX	48	2724				
Squamous Cell Carcinoma		5	0.18	5	1.15	2.00
Endometrial Stromal Polyp		7	0.26	6	1.15	3.33
Endometrial Stromal Sarcoma		6	0.22	6	0.80	2.04
Fibrosarcoma		3	0.11	3	0.80	1.69
Hemangiopericytoma		1	0.04	1	1.75	1.75
Leiomyoma		12	0.44	10	0.80	4.17
Leiomyosarcoma		16	0.59	11	1.45	4.17
Lymphangioma		1	0.04	1	2.04	2.04
Myxoma		1	0.04	1	2.00	2.00
Nerve Sheath Tumor, Benign		1	0.04	1	2.00	2.00
VAGINA	48	2744				
Papilloma		1	0.04	1	2.04	2.04
Polyp		4	0.15	3	0.78	2.86
Adenocarcinoma		1	0.04	1	2.04	2.04
Fibrosarcoma		1	0.04	1	1.43	1.43
Leiomyoma		7	0.26	6	1.47	3.33
Leiomyosarcoma		3	0.11	2	2.08	3.33
CLITORAL GLAND	48	2771				

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
SKIN						
SKIN	48	2803				
Basal Cell Tumor, Benign		1	0.04	1	1.67	1.67
Basal Cell Carcinoma		1	0.04	1	2.00	2.00
Squamous Cell Papilloma		4	0.14	4	1.43	2.00
Squamous Cell Carcinoma		8	0.29	7	1.43	3.33
Fibrosarcoma		10	0.36	8	1.54	4.29
Leiomyosarcoma		1	0.04	1	2.00	2.00
SKIN, cont'd.						
Liposarcoma		2	0.07	1	4.00	4.00
Rhabdomyosarcoma		1	0.04	1	1.54	1.54
Sarcoma		3	0.11	3	1.43	1.67
Nerve Sheath Tumor, Malignant		14	0.50	3	1.67	14.00
MAMMARY GLAND	48	2573				
Adenoma		2	0.08	2	2.04	2.63
Adenocarcinoma		42	1.63	22	0.78	8.33
Adenoacanthoma		1	0.04	1	1.79	1.79
Adenoacanthoma, Malignant		5	0.19	3	2.08	3.85
Fibrosarcoma		3	0.12	2	2.04	2.35
ENDOCRINE SYSTEM						
ADRENAL	48	2797				
Cortex, Adenoma		7	0.25	5	0.78	3.08
Cortex, Adenocarcinoma		1	0.04	1	2.00	2.00
Pheochromocytoma, Benign		8	0.29	5	0.78	5.00
Pheochromocytoma, Malignant		1	0.04	1	1.96	1.96
Spindle Cell Tumor, Benign		7	0.25	5	1.54	4.00
PANCREAS	48	2774				
Acinar Cell Adenoma		2	0.07	2	1.54	2.00
Islet Cell, Adenoma		6	0.22	6	1.54	2.08
PITUITARY	48	2697				
Adenoma		55	2.04	27	0.78	14.29
Carcinoma		1	0.04	1	1.69	1.69
Pars Intermedia, Adenoma		1	0.04	1	1.45	1.45

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
THYROID	48	2733				
C-Cell, Carcinoma		2	0.07	2	2.00	2.00
Follicular Cell, Adenoma		8	0.29	8	0.77	2.08
Follicular Cell, Carcinoma		1	0.04	1	1.56	1.56
PARATHYROID	48	2340				
Adenoma		4	0.17	4	1.64	3.23
NERVOUS SYSTEM						
BRAIN	48	2784				
Ependymoma		1	0.04	1	1.43	1.43
Meningeal Sarcoma		1	0.04	1	2.04	2.04
SPINAL CORD	48	1913				
PERIPHERAL NERVE	48	2837				
MUSCULOSKELETAL SYSTEM						
SKELETAL MUSCLE	48	2630				
Rhabdomyosarcoma		5	0.19	5	1.67	2.00
Carcinoma, Squamous Cell		1	0.04	1	0.78	0.78
Sarcoma		1	0.04	1	2.00	2.00
BONE	48	2814				
Osteoma		8	0.28	6	1.43	3.08
Osteosarcoma		4	0.14	4	1.43	2.00
Fibrosarcoma		1	0.04	1	1.56	1.56
CIRCULATORY SYSTEM						
HEART	48	2789				
Hemangiosarcoma		1	0.04	1	2.00	2.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
BLOOD VESSEL	48	2533				
HEMATOPOIETIC/LYMPHOID SYSTEM						
BONE MARROW	48	2817				
Fibrosarcoma		1	0.04	1	1.54	1.54
Plasmacytoma		1	0.04	1	2.04	2.04
Hemangiosarcoma		2	0.07	2	1.67	1.69
SPLEEN	48	2772				
Hemangioma		2	0.07	2	1.69	2.00
SPLEEN, cont'd.						
Hemangiosarcoma		12	0.43	11	1.43	3.85
Leiomyosarcoma		1	0.04	1	2.00	2.00
THYMUS	48	2404				
Thymoma, Malignant		2	0.08	2	1.49	2.00
Lymphoma, Thymic		1	0.04	1	1.89	1.89
LYMPH NODES	48	2742				
Hemangioma		5	0.18	4	1.43	4.17
WHOLE BODY/MULTIPLE ORGAN	48	2822				
Lymphoma, Malignant		274	9.71	41	1.67	50.00
Lymphoma, Lymphocytic		30	1.06	4	2.00	27.45
Fibrous Histiocytoma		1	0.04	1	2.00	2.00
Histiocytic Sarcoma		111	3.93	31	1.67	18.33
Lymphoma, Histiocytic		10	0.35	4	2.08	6.38
Leukemia, Lymphocytic		6	0.21	2	1.54	8.62
Leukemia, Granulocytic		7	0.25	5	0.77	4.08
Mast Cell Tumor, Malignant		1	0.04	1	2.00	2.00
Hemangioma		4	0.14	3	1.43	2.67
Hemangiosarcoma		25	0.89	9	1.67	12.00

		TOTAL		# STUDIES		
		# ORGANS	PERCENT	USING THIS	MINIMUM	MAXIMUM
	# STUDIES	# LESIONS	OF TOTAL	DIAGNOSIS	% FOUND	%FOUND
SPECIAL SENSES						
EYE	48	2733				
Harderian Gland, Adenoma		62	2.27	30	1.35	8.33
Harderian Gland, Adenocarcinoma		5	0.18	5	1.43	2.38
EAR	48	2544				
Squamous Cell Carcinoma		1	0.04	1	2.00	2.00

Table 5: Incidence of Neoplasms by Study for Selected Organs/Males

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
LIVER	53	47	50	49	50	59	50	60	50	47	50	50	68	50	59	60	50	50	50	49	50	50	60
Hepatocellular Adenoma	4	7	5	7	3	7	3	3	2	2	5	2	11	3	9	3	12	6	5	2	3	3	3
Hepatocellular Carcinoma	4	6	1	1	2		1	4	1	2	1	1	6	2	2	2	3	4		4	2	2	1
Hemangioma										1							1						
Hemangiosarcoma	2						2				2			1		1	2		2				
LUNG	53	47	50	49	50	58	50	60	50	48	50	50	69	50	59	60	50	50	50	49	50	50	60
Adenoma, Alveolar/Bronchiolar	6	9	9	10	1	5	6	6		10	3	8	15	6	8	3	13	7	1	2	2	2	4
Adenocarcinoma, Alveolar/Bronchiolar	1	1	3	1	4	2	5	3		3			16		1		3	5	6	3	3	3	4
Hemangiosarcoma																							
WHOLE BODY/MULTIPLE ORGAN	53	47	50	49	50	59	50	60	50	46	50	50	69	50	59	60	50	50	50	50	50	50	50
Lymphoma, Malignant	2	2	1	4	1	3	1	2	2	2		1	1	1	2		7		1		1		
Lymphoma, Lymphocytic												2	2	1	1							1	
Leukemia, Granulocytic																							1
Leukemia, Lymphocytic								2															1
Hemangiosarcoma																							
Histiocytic Sarcoma							1	1					2		1					1			
Mast Cell Tumor, Malignant	1						1																

Table 5: Incidence of Neoplasms by Study for Selected Organs/Males (cont'd.)

Study Identification	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46
LIVER	50	50	60	50	49	60	67	60	59	70	50	65	50	50	65	65	60	60	60	70	50	50	90
Hepatocellular Adenoma	6	6	8	7	3	3	4	15	4	3	8	13	8	7	3	8	8	11	5	2	14	6	7
Hepatocellular Carcinoma		1	2	3	5	4	10	2	8	4	3	1	8	2		5		2	4	6	4	5	5
Hemangioma											2	1					1	1		2			
Hemangiosarcoma				2		3	1	1	2	3			1							3			1
LUNG	50	50	60	50	49	60	69	60	60	70	50	65	50	50	65	65	60	60	60	70	50	50	90
Adenoma, Alveolar/Bronchiolar	8	9	7	14	12	5	11	2	6	8	4	6	6	13	14	17	10	11	14	15	13	21	6
Adenocarcinoma, Alveolar/Bronchiolar	3	1		13	6		6	3	6	12	7	8	6	3	7	2	4	1	4	1	3	4	10
Hemangiosarcoma																							
WHOLE BODY/MULTIPLE ORGAN	50	50	60	49	49	60	70	60	60	70	50	65	50	50	65	65	60	60	60	70	50	50	90
Lymphoma, Malignant			3	3		4	2	6	13	5		1		2	4	5	3	5	3	2	4	1	5
Lymphoma, Lymphocytic				1	2								1										
Leukemia, Granulocytic				1		1				1								1	1				
Leukemia, Lymphocytic																							
Hemangiosarcoma												3		1	5	3	4	1			6	6	
Histiocytic Sarcoma			1	2			2			2	2		1	4	1	4	2	2	1	4			1
Mast Cell Tumor, Malignant														1						1			

Table 6: Incidence of Neoplasms by Study for Selected Organs/Females

Study Identification	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
LIVER	52	49	50	47	49	60	50	57	49	47	50	49	70	48	59	60	50	49	49	50	50	59	50	50
Hepatocellular Adenoma					1	1	1											1	1	1				
Hepatocellular Carcinoma			1										1			2		1	1		1			
Undifferentiated Carcinoma																								
Hemangioma																							1	
Hemangiosarcoma	2					1					1	1					1						1	
LUNG	52	49	50	48	49	60	50	57	50	48	50	49	70	49	59	60	50	50	50	50	50	59	50	50
Adenoma, Alveolar/Bronchiolar	3	6	6	5	2	2	5	6		3	5	5	11	3	6	5	8	3	2	2	2	2	6	2
Adenocarcinoma, Alveolar/Bronchiolar		3	4	1	3	2	4	2	4	5		1	7		2		3	6	1	2		5	1	1
Mesothelioma, Benign																								
WHOLE BODY/MULTIPLE ORGAN	52	49	50	48	50	60	50	58	50	47	50	49	70	49	59	60	50	50	50	50	50	59	50	50
Lymphoma, Malignant	2	2	7	6	1	5	7	10	2	5	4	2		3		6	4	3	1	3	3	9		5
Lymphoma, Lymphocytic													9										1	
Fibrous Histiocytoma											1													
Histiocytic Sarcoma		1						1					2	2	1	2	2		2	1	1	3	1	
Lymphoma, Histiocytic			3	1						3														
Leukemia, Lymphocytic								5																
Leukemia, Granulocytic														2									2	
Mast Cell Tumor, Malignant																								
Hemangioma													1											
Hemangiosarcoma													2											

Table 6: Incidence of Neoplasms by Study for Selected Organs/Females (cont'd.)

Study Identification	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48
LIVER	58	85	59	75	50	50	60	70	58	117	59	70	50	65	51	50	65	65	60	41	59	70	50	50
Hepatocellular Adenoma				1	1				1	1		1			4	1	1	1	1	3	2		2	1
Hepatocellular Carcinoma			1				2	1	2		1	3						1						
Undifferentiated Carcinoma														1										
Hemangioma					1		1							1					1					1
Hemangiosarcoma							2	1	1	2	1	3												
LUNG	60	89	59	75	49	50	60	70	60	130	60	70	50	65	51	50	65	65	60	46	60	70	50	50
Adenoma, Alveolar/Bronchiolar	1	2	3	9	6	7			2	9			5	4	2	8	8	10	16	9	7	7	9	12
Adenocarcinoma, Alveolar/Bronchiolar		3			9	3			5	1			4	6		3	3	2	5	3	3	2	1	3
Mesothelioma, Benign																			1					
WHOLE BODY/MULTIPLE ORGAN	60	116	60	75	50	50	60	70	60	130	60	70	50	65	51	50	65	65	60	60	60	75	50	50
Lymphoma, Malignant			1	6	2	3	12	35	10	11	17	13	7	3		5	8	10	5	8	6		16	6
Lymphoma, Lymphocytic						6									14									
Fibrous Histiocytoma																								
Histiocytic Sarcoma	9		2	3			5	5	1	9	11	2	3	8	2	4	5	7	4	3			3	6
Lymphoma, Histiocytic						3																		
Leukemia, Lymphocytic																	1							
Leukemia, Granulocytic									1	1							1							
Mast Cell Tumor, Malignant																1								
Hemangioma			1	2																				
Hemangiosarcoma			1										4	2		1			2	4			3	6

Spontaneous Neoplastic Lesions in the Crl:CD-1®BR Mouse

March, 1995

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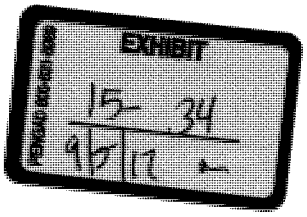

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SPONTANEOUS NEOPLASTIC LESIONS IN THE Crl:CD-1 ®13R MOUSE

These mouse data were obtained from clients who routinely use mice from Charles River Laboratories in product safety evaluation. Only control groups are presented here. These data were taken from studies run in thirteen different labs, including six contract toxicology labs and seven industrial labs. Starting dates ranged from November, 1981 to March, 1991, but most were begun in the late 1980s. This publication complements an earlier reference paper published by Charles River in February, 1987 with the same title. The study groups presented in the current publication are different from those in the previous publication.

The information presented here includes primary neoplastic lesion incidence from toxicology studies which ran for up to 24 months. It is divided into three groups because chronic mouse studies are terminated at times varying from 18 months to 24 months after initiation. The majority of the studies ran either 18 months or 24 months, but there were 7 groups which could not justifiably be added to either of these time points. They are presented in the 21 month group of studies. Study CV is presented under 21 months for males and 24 months for females because the sexes were sacrificed at different times.

COMMON STUDY PARAMETERS

Some of the important parameters for each study group are listed in Table 1. These include the date the in-life portion of the study was initiated, the diet fed, the cage type used (either shoebox or metal with wire mesh floor), the route of dosing, and the number of animals housed per cage. The CRL animal breeding site is also presented.

Data presented in the summary tables are grouped by organ system. Included in this summary are data from mice which died or were sacrificed moribund during the course of the study and those sacrificed at study termination. No data from animals that were part of a scheduled interim sacrifice (i.e., at 12 or 18 months of study) are included in this compilation.

All studies from which these data were obtained were run under U. S. Good Laboratory Practice Regulations promulgated by either the EPA or FDA or both. Therefore a quality assurance unit oversaw the performance of the study and reviewed the final report from which the data were taken.

SECTIONS OF REPORT

The report is divided into three sections. Section A includes several tables describing incidence of neoplastic lesions in 18 month study groups; Section B presents 21 month study groups; Section C presents 24 month study groups.

TABLES

Within each section two summary tables are presented; #1 is males and #2 is females. Also within each section three expanded tables are presented; one for liver (#3), lung (#4), lymphoreticular tissues (#5). The latter present data for both males and females in the same table by study group. This allows the reader to see the distribution of diagnoses across groups.

SUMMARY TABLE CALCULATIONS

The first column in the summary tables defines the organ and tumor evaluated. The second presents the total number of tissues which were examined for each organ. The third column shows the number of study groups in which this organ was examined. Some organs, such as the nasal turbinates, were examined routinely only in a few study groups. The fourth column shows the total number of specific tumors reported in these study groups. The fifth column reports the overall incidence of each tumor. This is obtained by dividing the total number of tumors (column 4) by the total number of organs examined (column 2) and multiplying by 100 to convert it to a percent. The sixth column shows the minimum and maximum percent in which each individual tumor was diagnosed in any of the groups in which the organ was examined. For example, in the testes of males in the 18 month studies (Table A1), the interstitial cell tumor was reported at the following incidences in the 12 study groups: none in 10 groups, 1.25% in one and 4.08% in another. Therefore the minimum presented in column 5 is 0.00% and the maximum is 4.08%. In another example, female groups from the 24 month interval show incidences of bronchiolar/alveolar adenoma of 14.0%, 18.37%, 10.00%, 9.62%, 8.00%, 9.80%, 4.00%, 8.00%, 8.16%, 12.00% and 7.04%. In Table C2 column 6 the range therefore is reported as 4.00% to 18.37%

LIVER LESIONS

The liver lesions listed in these tables are not necessarily neoplastic lesions. The altered foci and nodular proliferation are thought to possibly be pre-neoplastic lesions and are presented here because their incidence is frequently requested. The expanded tables presenting all liver lesions allow the reader to interpret the data according to need.

SURVIVAL GRAPHS

Survival data for each group of animals reported above are shown in Figures 1-6 by study code. This information is shown here for two reasons. First, the actual range of survival values for groups of mice at these three time points can be used to compare to other datasets either in-house or from the literature. Second, the distribution of animals sacrificed at study termination vs. those which died (or were sacrificed moribund) during the course of each study can be compared between groups. Also, the tumor incidence in the lungs, liver and lymphoreticular tissues in which there was good survival can be compared to that in groups with poor survival.

When fate tables were available, the data were transformed using the Kaplan-Meier procedure (Kaplan, E. and P. Meier, "Non-parametric Estimation from Incomplete Observations", Journal of the American Statistical Association, 23:1958 p. 457). This procedure handles the mice that were killed accidentally (from gavage error, bleeding procedure, etc.) during the course of the study differently than those that died or were sacrificed moribund. When individual fate tables were not available, the total number of mice surviving at study termination was reported as a percent of the total at initiation. Animals that were sacrificed prior to study termination for the purpose of evaluating health at that interval (interim sacrifice group) were not included in this calculation.

SYNONYMS

In compiling the summary tables for neoplastic lesions, it became clear that pathologists gave different names to the same tumor. In general, it was felt that the information would be more useful to the reader if identical, or similar, tumors were combined under one heading. For example, all tumors of granulosa cell origin, including tumors of luteinized cells, were combined in the category "granulosa/theca cell tumor". Recent texts used in developing lists of synonyms included "Mouse Histopathology", by J.M. Faccini, D.P. Abbott, and G.J.J. Paulus, Elsevier, 1990, and "Pathology of Laboratory Rodents and Rabbits", by D.H. Percy and S.W. Barthold, Iowa State University Press, 1993.

The synonyms which were included in the various diagnoses are presented in the synonym list which follows. Synonymous terms or diagnoses were frequently encountered in different study groups, and for utilitarian purposes were combined under a single, often broad, diagnosis, which was termed the primary diagnosis. Although some effort was made to use currently acceptable terms, it is beyond the scope of this publication to propose a system of "preferred" diagnoses. The number of lesions reported in each table include all those listed by either the primary diagnoses or the synonymous diagnoses.

SYNONYMS

Ovary:

CYSTADENOMA: tubular adenoma; papillary adenoma; papilloma; papillary cystadenoma; adenoma

GRANULOSA/ THECA CELL TUMOR: luteoma; granulosa cell tumor, luteinized

Uterus:

ENDOMETRIAL STROMAL SARCOMA: sarcoma, endometrial sarcoma, stromal sarcoma

ENDOMETRIAL STROMAL POLYP: glandular polyp, endometrial polyp, polyp (B)

ADENOCARCINOMA: endometrial adenocarcinoma

LEIOMYOSARCOMA: leiomyoma/ leiomyosarcoma

Pituitary Gland:

ADENOMA: adenoma, pars distalis; adenoma, anterior lobe

CARCINOMA: carcinoma, pars distalis

Bone:

OSTEOSARCOMA: osteogenic sarcoma

Lymphoreticular Tumors:

MALIGNANT LYMPHOMA (NOS): lymphosarcoma; malignant lymphoma undifferentiated

HISTIOCYTIC SARCOMA: malignant lymphoma histiocytic; reticulum cell sarcoma

Mammary Gland:

CARCINOMA: adenocarcinoma; adenocarcinoma, Type A (acinar pattern); adenocarcinoma, Type B (multiform)

Lung:

BRONCHIOLAR/ ALVEOLAR ADENOMA: adenoma; pulmonary adenoma

BRONCHIOLAR/ ALVEOLAR CARCINOMA: carcinoma; pulmonary carcinoma; adenocarcinoma; pulmonary adenocarcinoma

Liver:

NODULAR HEPATOCELLULAR PROLIFERATION: nodular hyperplasia

HEPATOCELLULAR ADENOMA: benign liver cell tumor

HEPATOCELLULAR CARCINOMA: malignant liver cell tumor

ACIDOPHILIC FOCUS: eosinophilic focus; hepatocellular alteration, eosinophilic

BASOPHILIC FOCUS: basophilic hepatocytes; hepatocellular alteration, basophilic

Adrenal:

CORTICAL ADENOCARCINOMA: carcinoma

Kidney:

RENAL CELL ADENOMA: tubular adenoma

RENAL CELL CARCINOMA: tubular carcinoma

Table 1
STUDY GROUP INFORMATION
18 MONTH STUDIES

Study Code	DJ	DI	DH	DL	BU	DK	AB	M	I	DF	DY	DG
Study Start Date	Mar-91	Oct-90	Jun-90	Nov-90	Dec-84	Oct-90	Sep-85	Mar-85	Oct-85	May-85	Jun-90	Feb-91
Diet	LAD # 2	LAD # 2	LAD # 1	LAD# 2	Purina	LAD # 2	Purina	Purina	Purina	Purina	LAD # 2	LAD # 2
CRL Source	UK	UK	UK	UK	Portage	UK	Kingston	Kingston	Kingston	Wilmington	UK	UK
Cage Type	box w/ bed	box w/ bed	box w/ bed	box w/ bed	wire mesh	box w/ bed	wire mesh	wire mesh	wire mesh	wire mesh	box w/ bed	box w/ bed
Route of Dosing	diet	diet	gavage[1]	diet	diet	diet	diet	diet	diet	dermal+	diet	diet
Diet Form	ground	ground	extruded	ground	ground	ground	ground	ground*	ground	pellets	ground	ground
No. per Cage	1	4	4	4	1	4	1	1	1	1	4	4

* with 0.5% corn oil
vehicle control received 5% gum arabic
\+ vehicle patched with purified water

21 MONTH STUDIES

Study Code	CT	DE	DD	CI	CJ	EF	CV
Study Start Date	Aug 85	Mar-86	Feb-85	Jun-86	Jun-86	Oct-90	Jul-83
Diet	Purina	Purina	Labsure RM M(S)	Altromin	Altromin	R/M 1	Purina
CRL Source	Kingston	Kingston	UK	Germany	Germany	UK	Kingston
Cage Type	wire mesh	wire mesh	wire mesh	box w/ bed	box w/ bed	box w/ bed	wire mesh
Route of Dosing	diet	diet	gavage	diet	diet	diet	diet
Diet Form	ground	ground	extruded	ground	ground	ground	ground
No. per Cage	1	1	4	M1, F2-4	M1, F2-4	1	1

24 MONTH STUDIES

Study Code	CX	CQ	CR	DN	DU	DZ	CP	BX	EG	CV
Study Start Date	Sep-83	Apr-85	Apr-85	Jan-88	Sep-89	Oct-90	Jul-85	Nov-81	Aug-89	Jul-83
Diet	LAD # 2	Purina	Purina	RM-1	RM-1	RM-1	RM-1	LAD # 2	RM-1	Purina
CRL Source	UK	Q	Q	UK	UK	UK	UK	UK	UK	Kingston
Cage Type	wire mesh	wire mesh	wire mesh	box/ bed	box/ bed	box/ bed	wire mesh	box/ bed	box/ bed	wire mesh
Route of Dosing	diet	diet	diet	diet	diet	diet	diet	diet	diet	diet
Diet Form	ground	ground	ground	ground	ground	ground	ground	ground	ground	ground
No. per Cage	4	1	1	1	1	1	3	4	1	1

Table A 1
NEOPLASMS
18 MONTH STUDIES
MALE CD-1® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	718	12			
THYMUS	648	12			
SPLEEN	767	12			
hemangiosarcoma			4	0.52	0-2.53
BONE MARROW	640	10			
LYMPHORETICULAR TUMORS	770^^	12			
malignant lymphoma, (NOS)			14	1.82	0-5.77
malignant lymphoma, lymphocytic			2	0.26	0-1.25
malignant lymphoma, mixed cell			2	0.26	0-1.25
histiocytic sarcoma			5	0.65	0-5.00
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	741	12			
lipoma			5	0.67	0-4.00
neurofibroma			1	0.13	0-1.03
basal cell tumor			1	0.13	0-3.70
fibroma			1	0.13	0-3.70
sarcoma			3	0.40	0-3.85
adenocarcinoma			1	0.13	0-1.92
squamous cell carcinoma, footpad			1	0.13	0-1.25
MAMMARY GLAND	279	7			
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	476	7			
sarcoma, musculoskeletal sys.			3*		
osteosarcoma			1	0.21	0-1.25
BONE	697	12			
sarcoma			1	0.14	0-1.92
RESPIRATORY SYSTEM					
NASAL TURBINATES	236	3			
hemangiosarcoma			1	0.42	0-1.32
TRACHEA	409	6			
LUNG	770	12			
bronchiolar/alveolar adenoma			58	7.53	1.92-12.00
bronchiolar/alveolar carcinoma			45	5.84	0-21.15
CIRCULATORY SYSTEM					
HEART	770	12			
AORTA	413	6			

Table AI (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
ORAL CAVITY	+				
squamous cell papilloma			1		
squamous cell papilloma, tongue			1		
SALIVARY GLAND	720	11			
fibrosarcoma			1	0.14	0-1.92
ESOPHAGUS	509	7			
STOMACH	743	12			
adenoma			1	0.13	0-1.18
SMALL INTESTINE	716	12			
adenoma			1	0.14	0-1.89
polypoid adenoma			1	0.14	0-1.28
adenocarcinoma			1	0.14	0-1.18
COLON/ CECUM	678	11			
carcinoma, cecum			1	0.15	0-1.92
LIVER	770	12			
focus/ area of cellular alteration			3	0.39	0-2.50
acidophilic focus/ area			1	0.13	0-1.92
clear cell focus/ area			3	0.39	0-2.00
basophilic focus/ area			7	0.91	0-5.00
nodular hepatocellular proliferation			15	1.95	0-15.38
hepatocellular adenoma			83	10.78	0-19.23
hepatocellular carcinoma			38	4.94	1.25-11.54
hemangioma			3	0.39	0-2.50
hemangiosarcoma			8	1.04	0-3.85
GALL BLADDER	659	11			
papilloma (B)			1	0.15	0-2.27
PANCREAS (EXOCRINE)	763	12			
URINARY SYSTEM					
KIDNEY	770	12			
URINARY BLADDER	758	12			
leiomyoma			2	0.26	0-2.53
leiomyosarcoma			1	0.13	0-1.27
undifferentiated sarcoma			1	0.13	0-1.27
REPRODUCTIVE SYSTEM					
TESTIS	768	12			
interstitial cell tumor (B)			3	0.39	0-4.08
granular cell tumor (M)			1	0.13	0-1.92
germ cell tumor (M)			1	0.13	0-1.92
hemangioma			1	0.13	0-1.25
fibrosarcoma, epididymides			1	0.13	0-1.92
PROSTATE	660	11			
SEMINAL VESICLES	766	12			
PREPUTIAL/ CLITORAL GLAND**	91	1			
adenoma			1		1.10

Table AI (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	763	12			
islet cell adenoma			1	0.13	0-1.69
PITUITARY GLAND	607	11			
THYROID GLAND	757	12			
follicular cell adenoma			4	0.53	0-2.53
PARATHYROID GLAND	499	11			
adenoma (B)			5++	1.00	0-10.42
ADRENAL GLAND	759	12			
nodular hyperplasia			17++	2.24	0-17.17
cortical adenoma			15	1.98	0-11.67
cortical adenocarcinoma			1	0.13	0-1.01
pheochromocytoma(B)			2	0.26	0-1.92
NERVOUS SYSTEM					
SPINAL CORD	716	12			
BRAIN	637	11			
astrocytoma(B)			1	0.16	0-1.18
oligodendroglioma			1	0.16	0-1.25
PERIPHERAL NERVES	489	8			
SPECIAL SENSES					
EYE AND ADNEXA	751	12			
LACRIMAL GLAND	331	4			
adenoma			5-H-	1.51	0-5.43
HARDERIAN GLAND	239	3			
adenoma			6++	2.51	0-7.59^
papillary cystadenoma			2++	0.84	0-2.5
BODY CAVITIES					
ABDOMINAL CAVITY	+				
mesothelioma (M), mesentery			1		

* 2 found in one group, one in another: muscle tissue was not on tissue list to be examined in either study
** examined in one study only
^ 1 additional adenoma found in group in which Harderian gland not on tissue list to be examined
^^ number animals examined
+ gross lesions not reported elsewhere
++ all found in one study group

Table A2
NEOPLASMS
18 MONTH STUDIES
FEMALE CD-1 ® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	732	12			
hemangiosarcoma			1	0.14	0-1.14
myeloid sarcoma (M)			1	0.14	0-1.14
THYMUS	693	12			
thymoma			1	0.14	0-1.41
SPLEEN	768	12			
hemangioma			1	0.13	0-1.92
hemangiosarcoma			2	0.26	0-1.92
BONE MARROW	667	10			
LYMPHORETICULAR TUMORS	770^^	12			
malignant lymphoma, (NOS)			49	6.36	0-23.08
malignant lymphoma, lymphocytic			6	0.78	0-5.00
lymphosarcoma (thymus)			16++	2.08	0-26.67
malignant lymphoma, mixed cell			1	0.13	0-1.25
histiocytic sarcoma			17	2.21	0-10.00
large granular lymphocyte leukemia			1	0.13	0-1.92
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	730	12			
hair matrix tumor (B)			1	0.14	0-1.04
basal cell carcinoma			1	0.14	0-1.27
adenocarcinoma			1	0.14	0-1.67
sarcoma			2	0.27	0-3.33
MAMMARY GLAND	610	10			
fibroadenoma			1	0.16	0-1.69
carcinoma (M)			13*	2.13	0-5.77
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	463	7			
rhabdomyosarcoma			1**		
BONE	769	12			
osteoma			1	0.13	0-1.27
osteosarcoma			1	0.13	0-1.67
RESPIRATORY SYSTEM					
NASAL TURBINATES	239	3			
TRACHEA	454	6			
LUNG	770	12			
bronchiolar/alveolar adenoma			50	6.49	0-15.38
bronchiolar/alveolar carcinoma			31	4.03	0-9.62
leiomyosarcoma			1	0.13	0-1.00
CIRCULATORY SYSTEM					
HEART	774	12			
AORTA	402	6			

Table A2 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
SALIVARY GLAND	718	11			
carcinoma			1	0.14	0-1.92
ESOPHAGUS	504	7			
STOMACH	747	12			
squamous cell carcinoma			1	0.13	0-1.67
SMALL INTESTINE	731	12			
COLON/CECUM	649	11			
leiomyoma, cecum			1	0.15	0-1.25
LIVER	769	12			
acidophilic focus/area			2	0.26	0-1.92
basophilic focus/area			3	0.39	0-3.85
nodular hepatocellular proliferation			1	0.13	0-1.67
hepatocellularadenoma			5	0.65	0-2.00
hepatocellular carcinoma			3	0.39	0-2.00
hemangioma			3	0.39	0-2.50
hemangiosarcoma			6	0.78	0-2.50
GALL BLADDER	686	11			
PANCREAS (EXOCRINE)	769	12			
URINARY SYSTEM					
KIDNEY	770	12			
URINARY BLADDER	726	12			
transitional cell carcinoma			2	0.28	0-1.72
REPRODUCTIVE SYSTEM					
OVARY	761	12			
cystadenoma			9	1.18	0-3.85
granulosa/theca cell tumor			6	0.79	0-2.53
fibroma			1	0.13	0-1.69
hemangioma			3	0.39	0-1.96
hemangiosarcoma			1	0.13	0-1.67
UTERUS/CERVIX	766	12			
adenocarcinoma(M)			1	0.13	0-1.92
endometrial stromal polyp			24	3.13	0-13.92
endometrial stromal sarcoma			4	0.52	0-6.00
leiomyoma			13	1.70	0-3.85
leiomyoma, cervical			1	0.13	0-2.00
leiomyosarcoma			8	1.04	0-8.00
hemangioma (B)			2	0.26	0-1.92

Table A2 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	769	12			
PITUITARY GLAND	651	11			
adenoma			5	0.77	0-2.08
THYROID GLAND	757	12			
adenoma			1	0.52	0-1.92
C-cell adenoma			1	0.13	0-1.67
PARATHYROID GLAND	489	11			
adenoma(B)			2	0.41	0-3.08
ADRENAL GLAND	762	12			
nodular hyperplasia			2++	0.26	0-2.02
cortical adenocarcinoma			1	0.13	0-1.25
pheochromocytoma(B)			1	0.13	0-1.01
pheochromocytoma (M)			1	0.13	0-1.01
NERVOUS SYSTEM					
SPINAL CORD	732	12			
BRAIN	631	11			
PERIPHERAL NERVES	514	8			
SPECIAL SENSES					
EYE AND ADNEXA	757	12			
LACRIMAL GLAND	323	4			
adenoma			3++	0.93	0-3.33
HARDERIAN GLAND	239	3			
adenoma			10	4.18	0-8.75[A]
carcinoma			1**		
OTHER	+				
hemangioma, tail (M)			1		

* 2 additional carcinomas found in study group in which mammary not on tissue list to be examined
** found in group in which tissue was not on list to be examined
[A] 1 additional adenoma found in group in which Harderian gland not on tissue list to be examined
[AA] number animals examined
+ gross lesions not reported elsewhere
++ all found in one study group

Table A3
LIVER NEOPLASMS BY STUDY GROUP
18 MONTH STUDIES
MALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. tissues examined	50	52	60	100	52	52	80	52	80	80	52	60
focus/area of cellular alteration									1	2		
%									1.25	2.50		
acidophilic focus/area											1	
%											1.92	
clear cell focus/area	1				1						1	
%	2.00				1.92						1.92	
basophilic focus/area		1	1		2							3
%		1.92	1.67		3.85							5.00
nodular hepatocellular proliferation	2		4			8					1	
%	4.00		6.67			15.38					1.92	
hepatocellular adenoma	4	10		16	10	2	9	3	4	11	8	6
%	8.00	19.23		16.00	19.23	3.85	11.25	5.77	5.00	13.75	15.38	10.00
hepatocellular carcinoma	1	1	2	6	4	6	3	6	4	1	2	2
%	2.00	1.92	3.33	6.00	7.69	11.54	3.75	11.54	5.00	1.25	3.85	3.33
hemangioma				1					2			
%				1.00					2.50			
hemangiosarcoma	1				1	2	1			3		
%	2.00				1.92	3.85	1.25			3.75		

FEMALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. tissues examined	50	52	60	100	52	52	80	52	80	80	51	60
acidophilic focus/area		1		1								
%		1.92		1.00								
basophilic focus/area				1	2							
%				1.00	3.85							
nodular hepatocellular proliferation			1									
%			1.67									
hepatocellular adenoma	1			2			1			1		
%	2.00			2.00			1.25			1.25		
hepatocellular carcinoma	1					1				1		
%	2.00					1.92				1.25		
hemangioma		1							2			
%		1.92							2.50			
hemangiosarcoma	1		1				2			1	1	
%	2.00		1.67				2.50			1.25	1.96	

Table A4
LUNG NEOPLASMS BY STUDY GROUP
18 MONTH STUDIES
MALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. tissues examined	50	52	60	100	52	52	80	52	80	80	52	60
bronchiolar/ alveolar adenoma	6	4	5	12	5	4	3	5	5	4	1	4
%	12.00	7.69	8.33	12.00	9.62	7.69	3.75	9.62	6.25	5.00	1.92	6.67
bronchiolar/ alveolar carcinoma	4	4	9	2	3	6		5		1	11	
%	8.00	7.69	15.00	2.00	5.77	11.54		9.62		1.25	21.15	

FEMALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. tissues examined	50	52	60	100	52	52	80	52	80	80	52	60
bronchiolar/ alveolar adenoma		3		14	1	8	8	3	3	4	3	3
%		5.77		14.00	1.92	15.38	10.00	5.77	3.75	5.00	5.77	5.00
bronchiolar/ alveolar carcinoma	3	5	2	6	5	2		1	1	2	3	1
%	6.00	9.62	3.33	6.00	9.62	3.85		1.92	1.25	2.50	5.77	1.67
leiomyosarcoma				1								
%				1.00								

Table AS
LYMPHORETICULAR NEOPLASMS BY STUDY GROUP
18 MONTH STUDIES
MALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. animals examined	50	52	60	100	52	52	80	52	80	80	52	60
malignant lymphoma, (NOS)	2	2		1		3	1	1	1		1	2
%	4.00	3.85		1.00		5.77	1.25	1.92	1.25		1.92	3.33
malignant lymphoma, lymphocytic									1	1		
%									1.25	1.25		
malignant lymphoma, mixed cell									1	1		
%									1.25	1.25		
histiocytic sarcoma		1	3								1	
%		1.92	5.00								1.92	

FEMALE

Study Code	DJ	DI	DH	ED	DL	DK	AB	DY	I	M	DG	DF
No. animals examined	50	52	60	100	52	52	80	52	80	80	52	60
malignant lymphoma, (NOS)	1	3	5	9	5	12	6	5	2		1	
%	2.00	5.77	8.33	9.00	9.62	23.08	7.50	9.62	2.50		1.92	
malignant lymphoma, lymphocytic									4	2		
%									5.00	2.50		
lymphosarcoma (thymus)												16
%												26.67
malignant lymphoma, mixed cell										1		
%										1.25		
histiocytic sarcoma	5		1		1	1	1	1	2	4	1	
%	10.00		1.67		1.92	1.92	1.25	1.92	2.50	5.00	1.92	
large granular lymphocyte,leukemia											1	
%											1.92	

Table B 1
NEOPLASMS
21 MONTH STUDIES
MALE CD-1® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	358	7			
hemangioma			1	0.28	0-1.89
THYMUS	287	7			
SPLEEN	369	7			
hemangiosarcoma			3	0.81	0-2.00
BONE MARROW	368	7			
hemangiosarcoma			1	0.27	0-2.00
LYMPHORETICULAR TUMORS	160^^	3			
malignant lymphoma (NOS)			2	1.25	0-2.00
malignant lymphoma, lymphocytic			3++	1.88	0-6.00
malignant lymphoma, mixed			1	0.63	0-2.00
histiocytic sarcoma			2	1.25	0-2.00
INTEGUMENTARY SYSTEM					
SKIN/ SUBCUTIS	368	7			
sarcoma			1	0.27	0-2.00
lipoma			1	0.27	0-2.00
hemangioma			1	0.27	0-1.72
MAMMARY GLAND	167	4			
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	310	6			
BONE	318	6			
RESPIRATORY SYSTEM					
TRACHEA	270	5			
NASAL TURBINATES	51	1			
LUNG	370	7			
bronchiolar/ alveolar adenoma			43	11.62	0-26.00
bronchiolar/ alveolar carcinoma			18	4.86	0-16.67
CIRCULATORY SYSTEM					
VASCULAR SYSTEM	+				
hemangiosarcoma			2		
HEART	370	7			
AORTA	156	3			

Table B 1 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
ESOPHAGUS	270	5			
GALL BLADDER	339	7			
STOMACH	368	7			
SALIVARY GLAND	369	7			
mixed tumor, (M)			1	0.27	0-2.00
SMALL INTESTINE	365	7			
LIVER	370	7			
basophilic focus/area			3	0.81	0-5.00
nodular hepatocellular proliferation			1	0.27	0-2.00
hepatocellular adenoma			28	7.57	0-12.00
hepatocellular carcinoma			20	5.41	0-12.00
hemangioma			3	0.81	0-3.33
hemangiosarcoma			10	2.70	0-6.00
COLON/CECUM	363	7			
PANCREAS (EXOCRINE)	369	7			
URINARY SYSTEM					
KIDNEY	370	7			
URINARY BLADDER	370	7			
REPRODUCTIVE SYSTEM					
TESTIS	369	7			
interstitial cell tumor (NOS)			2	0.54	0-2.00
interstitial cell adenoma			1	0.27	0-2.00
sarcoma, epididymides, (NOS)			1	0.27	0-1.69
sarcoma, undifferentiated			1	0.27	0-1.67
PROSTATE	367	7			
SEMINAL VESICLES	309	7			
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	369	7			
PITUITARY GLAND	325	7			
THYROID GLAND	369	7			
follicular cell adenoma			2++	0.54	0-3.33
PARATHYROID GLAND	307	7			
ADRENAL GLAND	368	7			
cortical adenoma			5	1.36	0-6.00
pheochromocytoma(B)			1	0.27	0-1.67

Table B 1 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
NERVOUS SYSTEM					
SPINAL CORD	310	6			
BRAIN	369	7			
PERIPHERAL NERVES	272	6			
SPECIAL SENSES					
EYE AND ADNEXA	260	5			
HARDERIAN GLAND	151	3			
adenoma			3	1.99	0-3.45
LACRIMAL GLAND	127	3			
BODY CAVITIES					
ABDOMINAL CAVITY	+				
sarcoma (M)			1		

^ 1 additional adenoma was found in a group in which Harderian gland not on the tissue list to be examined
+ gross lesions not reported elsewhere
++ all found in one study group
^^ number animals examined

Table B2
NEOPLASMS
21 MONTH STUDIES
FEMALE CD-1® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	312	6			
leiomyosarcoma			1	0.32	0-1.85
THYMUS	278	6			
carcinoma			1	0.36	0-3.33
BONE MARROW	319	6			
SPLEEN	317	6			
hemangiosarcoma			2++	0.63	0-4.00
LYMPHORETICULAR TUMORS	180**	3			
malignant lymphoma (NOS)			12	7.50	0-14.00
malignant lymphoma, lymphocytic			9++	5.63	0-18.00
malignant lymphoma, mixed			2++	1.25	0-4.00
histiocytic sarcoma			6	3.75	0-6.00
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	320	6			
myxoma			1	0.31	0-2.00
MAMMARY GLAND	303	6			
carcinoma (M)			7	2.31	0-4.08
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	266	5			
BONE	249	5			
osteogenic sarcoma			1	0.37	0-1.69
RESPIRATORY SYSTEM					
NASAL TURBINATES	56	1			
TRACHEA	220	4			
LUNG	320	6			
bronchiolar/alveolar adenoma			20	6.25	0-10.00
bronchiolar/alveolar carcinoma			10	3.13	0-10.00
CIRCULATORY SYSTEM					
VASCULAR SYSTEM	+				
hemangioma			1		
hemangiosarcoma			4++		
HEART	320	6			
AORTA	149	3			

Table B2 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
SALIVARY GLAND	319	6			
ESOPHAGUS	214	4			
STOMACH	315	6			
sarcoma			1	0.32	0-2.00
SMALL INTESTINE	310	6			
COLON/CECUM	309	6			
LIVER	318	6			
focus/area of cellular alteration			1	0.31	0-2.00
hepatocellularadenoma			4	1.26	0-2.00
hepatocellular carcinoma			1	0.31	0-1.72
hemangiosarcoma			4	1.26	0-2.00
GALL BLADDER	280	6			
PANCREAS (EXOCRINE)	318	6			
leiomyosarcoma			1	0.31	0-1.72
URINARY SYSTEM					
KIDNEY	318	6			
leiomyosarcoma			1	0.31	0-1.72
URINARY BLADDER	314	6			
carcinosarcoma			1	0.32	0-2.00
carcinoma			1	0.32	0-2.00
REPRODUCTIVE SYSTEM					
OVARY	317	6			
cystadenoma			3	0.95	0-4.00
granulosa/theca cell tumor			7	2.21	0-6.67
fibroma			1	0.32	0-2.00
leiomyosarcoma			1	0.32	0-1.75
UTERUS/CERVIX	318	6			
adenocarcinoma			1	0.31	0-2.00
endometrial stromal polyp			17	5.35	1.67-10.00
endometrial stromal sarcoma			6	1.89	0-4.02
fibroma			2++	0.63	0-4.00
leiomyoma			3	0.94	0-4.01
leiomyosarcoma			5	1.57	0-4.03
hemangiosarcoma			1	0.31	0-2.00

Table B2 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Lesions	Mean Percent	Range Percent
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	318	6			
islet cell adenoma			1	0.31	0-2.00
PITUITARY GLAND	316	6			
adenoma			3	0.95	0-3.57
carcinoma			1	0.32	0-2.00
meningioma			1	0.32	0-1.79
THYROID GLAND	319	6			
PARATHYROID GLAND	282	6			
adenoma			1	0.35	0-3.13
ADRENAL GLAND	317	6			
cortical adenoma			11++	3.47	0-22.45
leiomyosarcoma			1	0.32	0-1.72
NERVOUS SYSTEM					
SPINAL CORD	260	5			
BRAIN	319	6			
PERIPHERAL NERVES	260	5			
SPECIAL SENSES					
EYE AND ADNEXA	210	4			
LACRIMAL GLAND	126	3			
HARDERIAN GLAND	108	2			
adenoma			2	1.85	0-2.08
BODY CAVITIES					
ABDOMINAL CAVITY	+				
hemangiosarcoma			1		
sarcoma			1		

+ gross lesions not reported elsewhere
AA number animals examined
++ all found in one study group

Table B3
LIVER NEOPLASMS BY STUDY GROUP
21 MONTH STUDIES
MALE

Study Code	CT	DE	DD	CI	CJ	EF	CV*
No. tissues examined	50	60	60	50	50	50	50
basophilic focus/area		3					
%		5.00					
nodular hepatocellular proliferation				1			
%				2.00			
hepatocellular adenoma	4	7		3	3	6	5
%	8.00	11.67		6.00	6.00	12.00	10.00
hepatocellular carcinoma	2	2	6		2	2	6
%	4.00	3.33	10.00		4.00	4.00	12.00
hemangioma		2					1
%		3.33					2.00
hemangiosarcoma	1	1	1	1	3		3
%	2.00	1.67	1.67	2.00	6.00		6.00

FEMALE

Study Code	CT	DE	DD	CI	CJ	EF
No. tissues examined	50	58	60	50	50	50
focus !area of cellular alteration				1		
%				2.00		
hepatocellular adenoma	1	1			1	1
%	2.00	1.72			2.00	2.00
hepatocellular carcinoma		1				
%		1.72				
hemangiosarcoma	1	1		1	1	
%	2.00	1.72		2.00	2.00	

* Data on females are found in 24 month study tables.

Table B4
LUNG NEOPLASMS BY STUDY GROUP
18 MONTH STUDIES
MALE

Study Code	CT	DE	DD	CI	CJ	EF	CV*
No. tissues examined	50	60	60	50	50	50	50
bronchiolar/ alveolar adenoma	8	13		2	3	13	4
%	16.00	21.67		4.00	6.00	26.00	8.00
bronchiolar/ alveolar carcinoma	2	3	10		1	2	
%	4.00	5.00	16.67		2.00	4.00	

FEMALE

Study Code	CT	DE	DD	CI	CJ	EF
No. tissues examined	50	60	60	50	50	50
bronchiolar/ alveolar adenoma	5	3		3	4	5
%	10.00	5.00		6.00	8.00	10.00
bronchiolar/ alveolar carcinoma	1	1	6			2
%	2.00	1.67	10.00			4.00

* Data on females found in 24 month study tables.

Table B5
LYMPHORETICULAR NEOPLASMS BY STUDY GROUP
21 MONTH STUDIES
MALE

Study Code	CT	DE	DD	CI	CJ	EF	CV*
No. animals examined	50	60		---		50	
malignant lymphoma (NOS)		1				1	
%		1.67				2.00	
malignant lymphoma,							
lymphocytic	3						
%	6.00						
malignant lymphoma, mixed	1						
%	2.00						
histiocytic sarcoma	1					1	
%	2.00					2.00	

FEMALE

Study Code	CT	DE	DD	CI	CJ	EF
No. animals examined	50	60				50
malignant lymphoma (NOS)		5				7
%		8.33				14.00
malignant lymphoma,						
lymphocytic	9					
%	18.00					
malignant lymphoma, mixed	2					
%	4.00					
histiocytic sarcoma	3	1				2
%	6.00	1.67				4.00

* Data on females are found in 24 month study tables.

Table C1
NEOPLASMS
24 MONTH STUDIES
MALE CD-1® MICE

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
HEMATOPOIETIC SYSTEM					
LYMPH NODES	488	10			
hemangiosarcoma			1	0.20	0-2.04
THYMUS	406	10			
thymic lymphoma			1	0.25	0-1.64
SPLEEN	519	10			
hemangiosarcoma			3	0.58	0-2.08
BONE MARROW	259	6			
LYMPHORETICULAR TUMORS	423**	8			
malignant lymphoma (NOS)			25	5.91	0-12.00
malignant lymphoma, lymphocytic			2++	0.47	0-4.00
malignant lymphoma, mixed			1	0.24	0-2.00
histiocytic sarcoma			8	1.89	0-7.69
mast cell tumor			1	0.24	0-2.04
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	523	10			
squamous cell carcinoma			2	0.38	0-2.00
sarcoma			4	0.76	0-4.23
hemangiosarcoma			1	0.19	0-2.04
subcutaneous fibrosarcoma (M)			2	0.38	0-3.85
MAMMARY GLAND	364	9			
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	417	9			
BONE	324	6			
RESPIRATORY SYSTEM					
TRACHEA	519	8			
LUNG	524	10			
bronchiolar/alveolar adenoma			94	17.94	9.72-28.00
bronchiolar/alveolar carcinoma			58	11.07	1.92-20.00
sarcoma (unknown origin)			1	0.19	0-1.39
pleural mesothelioma			1	0.19	0-1.92
CIRCULATORY SYSTEM					
HEART	522	10			
AORTA	416	8			
hemangiosarcoma			1	0.24	0-2.00

Table C 1 (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
DIGESTIVE SYSTEM					
SALIVARY GLAND	523	10			
ESOPHAGUS	518	10			
STOMACH	515	10			
squamous cell carcinoma			1	0.19	0-2.00
SMALL INTESTINE	386	8			
polyp (B)			1	0.26	0-2.17
COLON/ CECUM	501	10			
intestinal carcinoma			1	0.20	0-1.41
LIVER	521	10			
acidophilic focus/ area			7	1.34	0-4.08
basophilic focus/ area			21	4.03	0-10.00
focus of alteration, mixed cell			1	0.19	0-2.00
clear cell focus/ area			5	0.96	0-6.00
bile duct proliferation			1	0.19	0-1.39
nodular hepatocellular proliferation			6	1.15	0-6.00
hepatocellular adenoma			97	18.62	4.08-37.5
hepatocellular carcinoma			68	13.05	0-28.00
carcinoma/ adenoma			3++	0.58	0-6.00
hemangioma			5	0.96	0-4.00
hemangiosarcoma			11	2.11	0-8.0
cholangioma			8++	1.54	0-16.00
GALL BLADDER	421	9			
papilloma (B)			1	0.24	0-2.13
PANCREAS (EXOCRINE)	517	10			
URINARY SYSTEM					
KIDNEY	521	10			
renal cell adenoma			7	1.34	0-4.26
renal cell carcinoma			5	0.96	0-2.13
URINARY BLADDER	514	10			
REPRODUCTIVE SYSTEM					
TESTIS	524	10			
Rete Testis papilloma			2++	0.38	0-4.00
interstitial cell tumor (B)			10	1.91	0-6.12
interstitial cell tumor (NOS)			3++	0.57	0-5.77
papillary adenoma (B)			2++	0.38	0-4.08
mesothelioma (NOS)			1	0.19	0-1.92
PROSTATE	505	10			
SEMINAL VESICLES	431	10			
sarcoma			1	0.23	0-2.08
fibrosarcoma			1	0.23	0-2.00

Table CI (Cont.)

LOCATION & TUMOR	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	517	10			
islet cell adenoma			2	0.39	0-2.08
pancreatic duct adenocarcinoma			1	0.19	0-2.00
PITUITARY GLAND	479	10			
adenoma			4	0.84	0-4.55
carcinoma			1	0.21	0-2.27
THYROID GLAND	511	10			
follicular cell adenoma			3	0.59	0-4.08
PARATHYROID GLAND	353	10			0-6.00
ADRENAL GLAND	509	10			
cortical adenoma			8	1.57	0-4.00
pheochromocytoma (NOS)			1	0.20	0-1.92
pheochromocytoma (B)			1	0.20	0-2.22
subcapsular cell adenoma			1	0.20	0-2.22
spindle cell fibroma			1	0.20	0-2.13
NERVOUS SYSTEM					
SPINAL CORD	350	7			
oligodendroglioma			1	0.29	0-2.00
ganglioneuroma			1	0.29	0-2.00
schwannoma (M)			1	0.29	0-2.04
BRAIN	518	10			
ependymoma (M)			1	0.21	0-2.00
PERIPHERAL NERVES	516	10			
SPECIAL SENSES					
EYE AND ADNEXA*	409	8			
adenoma, accessory			5	1.22	0-8.16
HARDERIAN GLAND	172	3			
adenoma			22	12.79	0-18.06^
BODY CAVITIES					
THORACIC CAVITY	+				
mesothesioma (M)			1		

* accessory gland could be Harderian or lacrimal; all found in groups in which gland was not on tissue list to be examined

^ 5 additional adenomas were found in study groups in which Harderian gland not on tissue list to be examined

^^ number animals examined

+ gross lesions not reported elsewhere

++ all found in one study group

Table C2
NEOPLASMS
24 MONTH STUDIES
FEMALE CD-1® MICE

Location & Tumor	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
LOCATION & TUMOR					
HEMATOPOIETIC SYSTEM					
LYMPH NODES	553	11			
hemangiosarcoma			1	0.18	0-1.92
THYMUS	505	11			
thymic lymphoma			2++	0.40	0-2.99
hemangiosarcoma			6	1.19	0-6.82
BONE MARROW	338	7			
SPLEEN	573	11			
hemangioma			2	0.35	0-1.96
hemangiosarcoma			8	1.40	0-6.00
LYMPHORETICULAR TUMORS	425^^	8			
malignant lymphoma (NOS)			57	13.41	0-28.00
malignant lymphoma, lymphocytic			10++	2.35	0-19.61
malignant lymphoma, mixed			2++	0.47	0-3.92
myeloid leukemia			1	0.24	0-1.92
histiocytic sarcoma			16	3.76	0-10.00
INTEGUMENTARY SYSTEM					
SKIN/SUBCUTIS	575	11			
papilloma			1	0.17	0-2.00
sarcoma			7	1.22	0-3.92
hemangioma			1	0.17	0-1.96
hemangiosarcoma			4	0.70	0-4.00
chondrosarcoma			1	0.17	0-1.39
myxoma (B)			1	0.17	0-2.00
subcutaneous osteosarcoma			1	0.17	0-2.00
MAMMARY GLAND	549	11			
adenoacanthoma			3++	0.55	0-4.23
adenoma			1	0.18	0-2.00
carcinoma			25	4.55	0-12.20
MUSCULOSKELETAL SYSTEM					
SKELETAL MUSCLE	496	10			
BONE	374	7			
osteoma			2	0.45	0-2.00
osteosarcoma			3	0.60	0-4.00
RESPIRATORY SYSTEM					
TRACHEA	464	9			
LUNG	572	11			
bronchiolar/alveolar adenoma			56	9.79	4.00-18.37
bronchiolar/alveolar carcinoma			38	6.64	0-13.46
hemangiosarcoma			1	0.17	0-2.00

Table C2 (Cont.)

Location & Tumor	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
CIRCULATORY SYSTEM					
VASCULAR SYSTEM	7				
hemangiosarcoma			1		
hemangioma			1		
intercostal hemangiosarcoma			1		
HEART	574	11			
hemangiosarcoma			1	0.17	0-1.92
AORTA	415	8			
hemangioma			1	0.29	0-2.04
hemangiosarcoma			2	0.58	0-4.08
DIGESTIVE SYSTEM					
SALIVARY GLAND	572	11			
ESOPHAGUS	570	11			
STOMACH	568	11			
squamous cell papilloma			1	0.18	0-2.00
SMALL INTESTINE	456	9			
adenomatous polyp			1	0.22	0-2.08
adenocarcinoma			2	0.44	0-2.08
hemangiosarcoma			1	0.22	0-2.13
COLON/CECTUM	484	11			
leiomyoma, cecum			1	0.21	0-2.08
LIVER	573	11			
acidophilic focus/area			4	0.70	0-2.00
focus of alteration-mixed cell			1	0.18	0-2.00
basophilic focus/area			2	0.35	0-2.04
hepatocellular adenoma			18	3.15	0-11.27
hepatocellular carcinoma			9	1.58	0-4.00
hemangioma			4	0.70	0-2.04
hemangiosarcoma			3	0.53	0-2.00
GALL BLADDER	488	10			
PANCREAS (EXOCRINE)	523	11			
URINARY SYSTEM					
KIDNEY	582	11			
renal cell adenoma			3	0.52	0-4.00
renal cell carcinoma			1	0.17	0-2.00
URINARY BLADDER	560	11			
REPRODUCTIVE SYSTEM					
OVARY	568	11			
cystadenoma			11	1.94	0-6.12
granulosa/theca cell tumor			11	1.94	0-6.00
granulosa cell tumor (M)			2	0.35	0-2.00
adenoma, fallopian tube (69 exam.)			2	0.35	0-2.00
interstitial cell tumor (B)			1	0.18	0-2.08
hemangiosarcoma			2	0.35	0-2.04
Sertoli cell tumor (B)			1	0.18	0-2.04
mesothelioma			1	0.18	0-1.92
stromal cell tumor			1	0.18	0-0.44

Table C2 (Cont.)

Location & Tumor	No. Tissues Examined	No. Study Groups	Total No. Tumors	Mean Percent	Range Percent
REPRODUCTIVE SYSTEM (Cont.)					
UTERUS/CERVIX	572	11			
endometrial adenoma			1	0.17	0-1.41
adenocarcinoma			7	1.22	0-6.00
endometrial stromal polyp			35	6.12	0-22.00
endometrial stromal sarcoma			14	2.45	0-14.00
fibroma			2	0.35	0-2.00
leiomyoma			13	2.27	0-8.00
leiomyosarcoma			12	2.10	0-9.80
hemangioma			2	0.35	0-2.00
hemangiosarcoma			9	1.57	0-6.00
ENDOCRINE SYSTEM					
PANCREAS (ENDOCRINE)	573	11			
islet cell adenoma			2	0.35	0-2.00
PITUITARY GLAND	544	11			
adenoma			21	3.86	0-8.00
craniopharyngeal cyst carcinoma			1	0.18	0-2.04
THYROID GLAND	565	11			
follicular cell adenoma			2	0.35	0-2.00
follicular cell carcinoma			2	0.35	0-2.08
PARATHYROID GLAND	359	11			
ADRENAL GLAND	569	11			
cortical adenoma			3	0.53	0-2.00
pheochromocytoma (B)			2	0.35	0-2.08
NERVOUS SYSTEM					
SPINAL CORD	431	8			
BRAIN	575	11			
PERIPHERAL NERVES	517	10			
schwannoma			1	0.19	0-2.08
SPECIAL SENSES					
EYE AND ADNEXA	468	9			
cataract			25	5.34	0-28.00
adenoma, accessory gland			6*		
HARDERIAN GLAND	222	4			
adenoma			11	4.95	0-6.94[A]
adenocarcinoma			1	0.45	0-2.04

* accessory gland could be Harderian or lacrimal If Harderian, they were found in groups in which gland was not on tissue list to be examined
\+ gross lesions not reported elsewhere
++ all found in one study group
[A] 2 additional found in group in which Harderian gland not on tissue list to be examined not on tissue list to be examined
[AA] number animals examined

Table C3
LIVER NEOPLASMS BY STUDY GROUP
24 MONTH STUDIES
MALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG
No. tissues examined	50	50	49	50	52	48	50	72	50	50
acidophilic focus/area		2	2		1				2	
%		4.00	4.08		1.92				4.00	
focus of alteration, mixed cell									1	
%									2.00	
clear cell focus/area							3	2		
%							6.00	2.78		
basophilic focus/area	2	3	1		3	2	3	1	5	1
%	4.00	6.00	2.04		5.77	4.17	6.00	1.39	10.00	2.00
nodular hepatocellular proliferation	3	2		1						
%	6.00	4.00		2.00						
hepatocellular adenoma	9	7	2	9	6	10	9	27	9	9
%	18.00	14.00	4.08	18.00	11.54	20.83	18.00	37.50	18.00	18.00
hepatocellular carcinoma	14		8	1	9	4	8	12	7	5
%	28.00		16.33	2.00	17.31	8.33	16.00	16.67	14.00	10.00
carcinoma/adenoma				3						
%				6.00						
hemangioma	2			1	1				1	
%	4.00			2.00	1.92				2.00	
hemangiosarcoma	2	4				3			2	
%	4.00	8.00				6.25			4.00	
cholangioma		8								
%		16.00								

FEMALE

Study Code	**CQ**	**CR**	DZ	CP	BX	DN	DX	CX	DU	EG	CV
No. tissues examined	50	50	49	51	52	49	50	71	50	49	50
eosinophilic focus	1	1		1	1						
%	2.00	2.00		1.96	1.92						
focus of alteration-mixed cell									1		
%									2.00		
basophilic focus					1	1					
%					1.92	2.04					
hepatocellular adenoma	1	1			2	1	1	8		3	1
%	2.00	2.00			3.85	2.04	2.00	11.27		6.12	2.00
hepatocellular carcinoma	1	2		1	1		1		2	1	
%	2.00	4.00		1.96	1.92		2.00		4.00	2.04	
hemangioma					1	1			1		1
%					1.92	2.04			2.00		2.00
hemangiosarcoma	1							1			1
%	2.00							1.41			2.00

Table C4
LUNG NEOPLASMS BY STUDY GROUP
24 MONTH STUDIES
MALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG
No. tissues examined	50	50	50	51	52	49	50	72	50	50
bronchiolar/alveolar adenoma	8	8	9	7	12	9	9	7	11	14
%	16.00	16.00	18.00	13.73	23.08	18.37	18.00	9.72	22.00	28.00
bronchiolar/alveolar carcinoma	5	4	8	1	1	6	10	10	8	5
%	10.00	8.00	16.00	1.96	1.92	12.24	20.00	13.89	16.00	10.00
sarcoma (unknown origin)								1		
%								1.39		
pleural mesothelioma					1					
%					1.92					

FEMALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG	CV
No. tissues examined	50	49	50	51	52	49	50	71	50	50	50
bronchiolar/alveolar adenoma	6	4	2	5	5	9	7	5	4	5	4
%	12.00	8.16	4.00	9.80	9.62	18.37	14.00	7.04	8.00	10.00	8.00
bronchiolar/alveolar carcinoma		2	5	3	7	2	3	7	5	1	3
%		4.08	10.00	5.88	13.46	4.08	6.00	9.86	10.00	2.00	6.00
hemangiosarcoma	1										
%	2.00										

Table C5
LYMPHORETICULAR NEOPLASMS BY STUDY GROUP
24 MONTH STUDIES
MALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG
No. animals examined	---		50	50	52	49	50	72	50	50
malignant lymphoma (NOS)			6	1	2	3	4	6	3	
%			12.00	2.00	3.85	6.12	8.00	8.33	6.00	
malignant lymphoma, lymphocytic				2						
%				4.00						
malignant lymphoma, mixed				1						
%				2.00						
histiocytic sarcoma				3	4	1				
%				6.00	7.69	2.04				
mast cell tumor						1				
%						2.04				

FEMALE

Study Code	CQ	CR	DZ	CP	BX	DN	DX	CX	DU	EG	CV
No. tissues examined	---	---	50	51	52	50	50	72	50	50	---
malignant lymphoma			6	1	4	12	14	12	5	3	
%			12.00	1.96	7.69	24.00	28.00	16.67	10.00	6.00	
malignant lymphoma, lymphocytic				10							
%				19.61							
malignant lymphoma, mixed				2							
%				3.92							
myeloid leukemia					1						
%					1.92						
histiocytic sarcoma				2	2	3			5	4	
%				3.92	3.85	6.00			10.00	8.00	

FIGURE A1
MALE - SURVIVAL AT 18 MONTHS

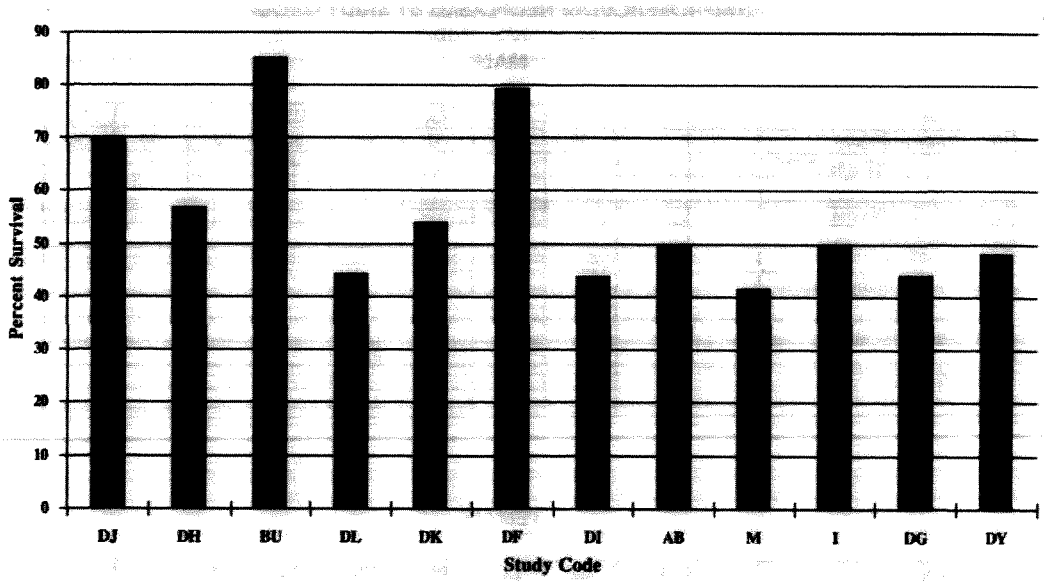


FIGURE A2
FEMALE - SURVIVAL AT 18 MONTHS

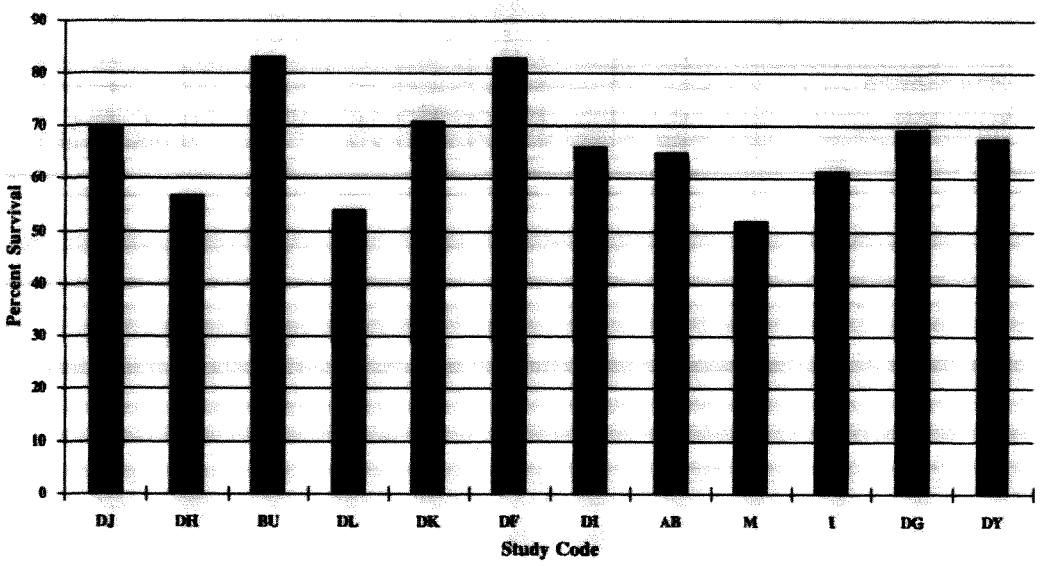


FIGURE B1
MALE - SURVIVAL AT 21 MONTHS

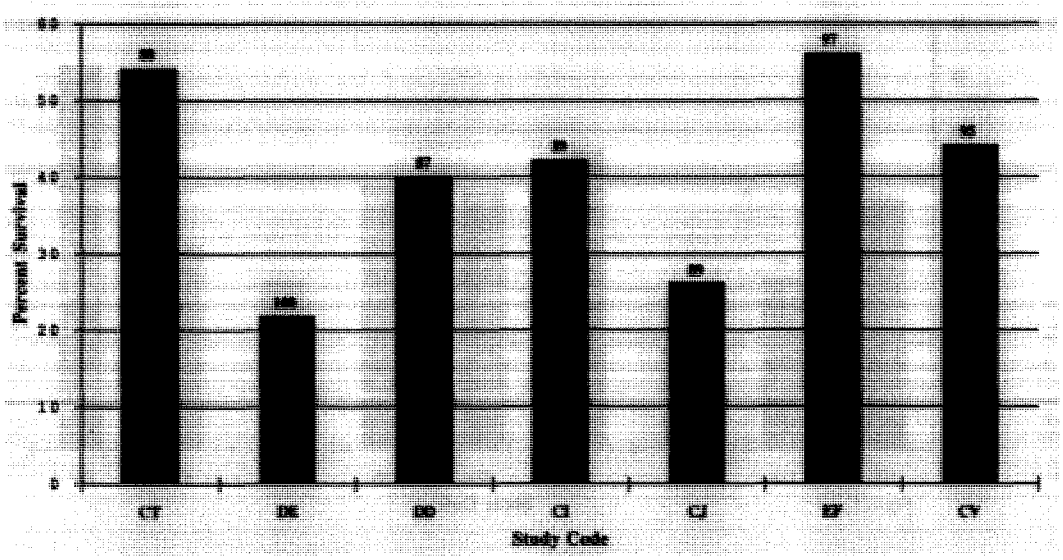
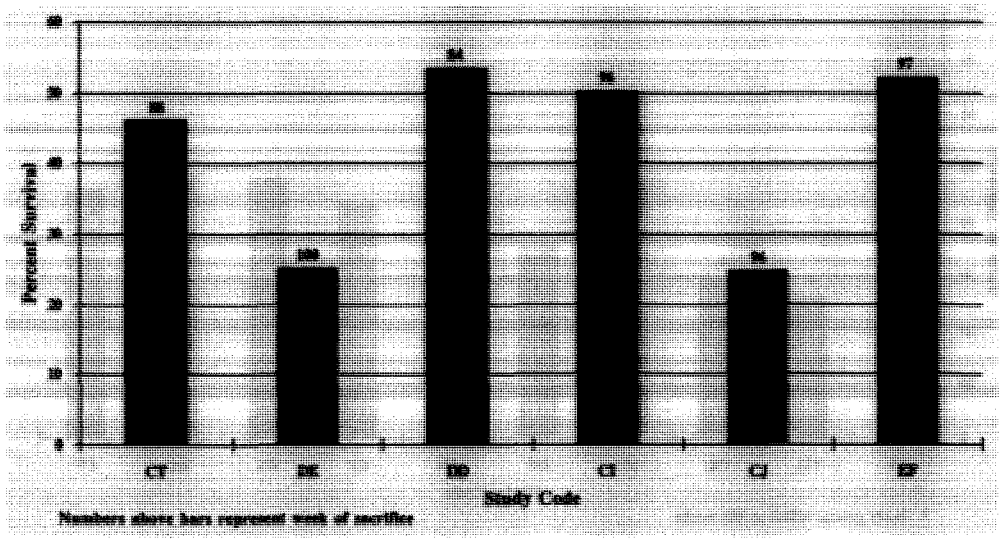


FIGURE B2
FEMALE - SURVIVAL AT 21 MONTHS



C1 FIGURE
MALE - SURVIVAL AT 24 MONTHS

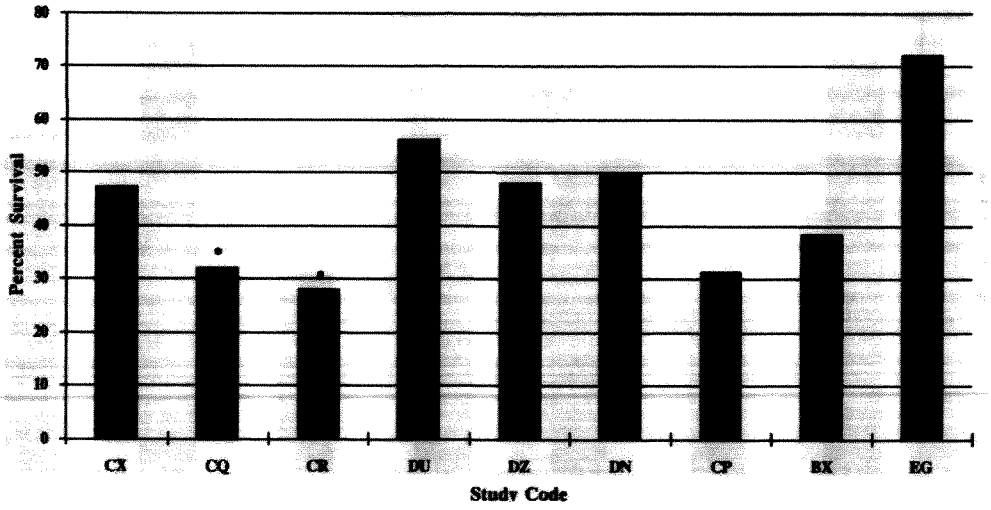
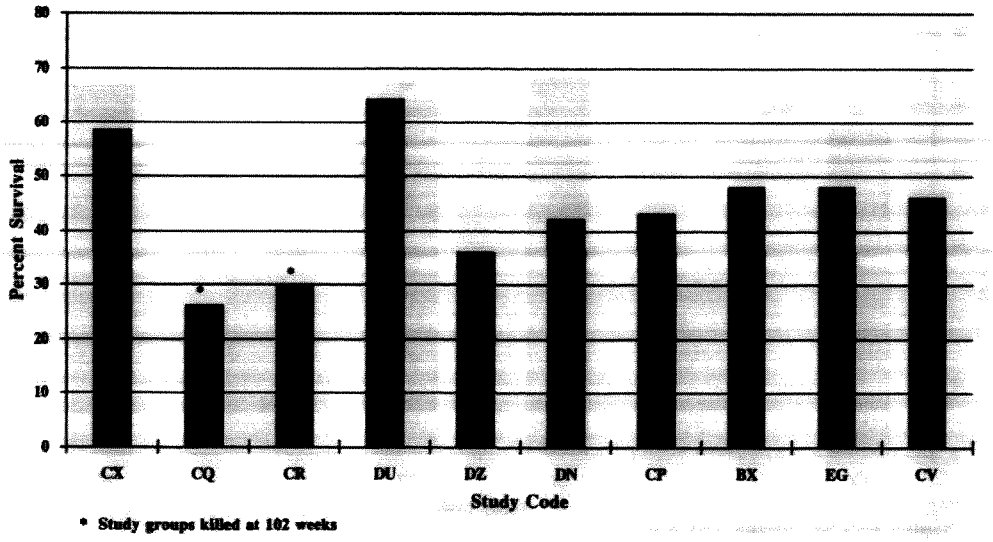


FIGURE C2
FEMALE - SURVIVAL AT 24 MONTHS



From: Carey Gillam <careygillamnewsnow@gmail.com>
Subject: Re: CD-1 mouse study
Date: June 7, 2017 at 6:11:14 PM GMT+2
To: Chris Portier <[redacted]>

One quick quote perhaps? I'm writing about Monsanto's manipulation of the kidney study results, or their efforts to convince regulators of their industry-friendly "interpretation." I see dog studies, rats, mice, rabbits, etc..that show tumors, reduced pregnancy rates, other negative impacts, and yet the data all eventually are discounted by regulators as not statistically significant. Can you offer a reader-friendly quote addressing this?
Carey

On Mon, Jun 5, 2017 at 9:32 PM, Chris Portier <[redacted]> wrote:
The kidney tumors in the 1983 study are definitely important. When the two 24 month mouse studies are combined, the kidney tumors are statistically significant. Individually, when historical controls are used against the rates seen in the 1983 study, the finiding is highly statistically significant. The argument used by the regulatory agencies that these tumors fall within the range of historical controls is an incorrect statistical comparison and a mor rigorous approach needs to be used - this leads to significance as noted by IARC. In general, all four mouse studies in CD-1 mice showed some positive trend in kidney tumors that, when combined, is highly significant. The same is true for hemangiosarcomas in male mice and malignant lymphoma in male mice in the 18-month studies. They are all important.

C.

On Jun 6, 2017, at 4:37 AM, Carey Gillam <careygillamnewsnow@gmail.com> wrote:

Hello again - I'm writing up a piece about the twisted path of the 1983 CD-1 mouse study that has appeared fairly pivotal when it comes to glyphosate carcinogenicity classifications. You know the saga of the non-existent tumor in the control group that then appeared after Monsanto enlisted an outside pathologist to review tissue slides.
I'm wondering how you view this study and how much weight it carries, or

does not carry, in your evaluations of the research surrounding glyphosate and cancer.
You are aware, I believe, that the plaintiffs' attorneys in the Roundup cancer litigation in San Francisco received court approval to review the tissue slides. I'd be most interested in your view on that study. This is the one prepared by BioDynamics for Monsanto's submission to EPA.

--
Best regards,
Carey Gillam
913-526-6190
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--
Best regards,
Carey Gillam
913-526-6190
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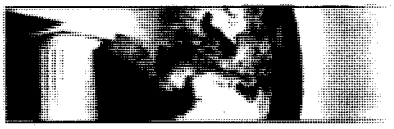
www.careygillam.com
https://twitter.com/careygillam



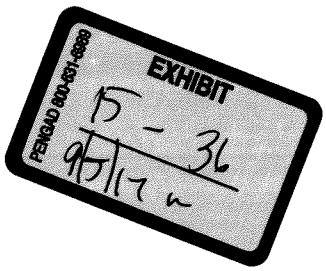
National Toxicology Program
Department of Health and Human Services

NTP Historical Controls Report

All Routes and Vehicles

Wistar-Han RATS

August 2016



REPORT DESCRIPTION

This report shows the tumor rates of control group animals from selected studies. The studies used are shown on the Study Summary page.

The report combines all the data from all of the historical control studies into one section. To see this data broken up by route and vehicle you must run the "By Route And Vehicle" report.

The individual tumor rates shown on the data pages of the report relate to the Study Summary page as follows: the tumor rates are shown in the same order as the Study Summary page, except that they are grouped horizontally in sets of three, with the males in the first set of three and the females in the second set. For example if the study summary showed the studies like this:

Male
M1
M2
M3
M4
M5
Female
F1
F2
F3
F4
F5

the data would be shown as:

Male			Female		
M1	M2	M3	F1	F2	F3
M4	M5		F4	F5	

Directly beneath the individual tumor rates on the data pages are the overall totals for that tumor/site combination. This includes the total tumors/animals, the overall mean (in parentheses), the mean of the study means, and the standard deviation of the study means.

Studies with no control animals of a particular gender are listed on the summary page with the Number of Animals shown as zero and the Start Date and Length of Study shown as "N/A". On the data pages there are blank spaces where tumor rates for these studies would normally be found, so that the male and female rates for the remaining studies can be easily compared.

Study Summary

Laboratory Name	Study Number	Study Start Date	Length of Study in Days	Number of Animals Total and (#/Cage)	Number Surviving and (Mean Life Span)	Maximum Mean Weekly Body Weight	Chemical
				Male			
Battelle Northwest	052060103	09/22/08	729	50(5)	30(672)	606.7	Antimony trioxide
Battelle Northwest	052072503	08/17/09	729	50(5)	36(692)	615.2	2,3-Butanedione
Battelle Columbus Laboratory	052020303	07/18/07	727	50(3)	35(687)	632.7	Green Tea Extract
Battelle Northwest	052051503	04/14/08	729	50(5)	33(688)	602.8	Metal Working Fluids: CIMSTAR 3800
Battelle Northwest	052052303	07/20/09	729	50(5)	36(696)	622.2	Metal Working Fluids: TRIM VX
Southern Research Institute	052020903	08/26/08	729	49(3)	36(671)	673.4	Pentabromodiphenyl Ether Mixture [DE-71 (Technical Grade)]
Battelle Columbus Laboratory	052032003	07/25/07	727	50(3)	33(642)	662.9	Tetrabromobisphenol A
				Female			
Battelle Northwest	052060103	09/22/08	730	50(5)	39(704)	395.6	Antimony trioxide
Battelle Northwest	052072503	08/17/09	731	50(5)	34(688)	400.0	2,3-Butanedione
Battelle Columbus Laboratory	052020303	07/19/07	729	50(5)	26(671)	369.7	Green Tea Extract
Battelle Northwest	052051503	04/14/08	731	50(5)	35(700)	384.9	Metal Working Fluids: CIMSTAR 3800
Battelle Northwest	052052303	07/20/09	731	50(5)	30(681)	391.1	Metal Working Fluids: TRIM VX
Southern Research Institute	052020903	08/26/08	732	50(5)	37(678)	389.6	Pentabromodiphenyl Ether Mixture [DE-71 (Technical Grade)]
Battelle Columbus Laboratory	052032003	07/26/07	728	50(5)	34(678)	375.2	Tetrabromobisphenol A

NOTE: The text on page 2 ("Report Description") describes how the studies listed here are displayed on the data pages that follow.

		Male				Female		
#All Organs:								
Benign Tumors								
		34/50 (68%)	27/50 (54%)	26/50 (52%)		33/50 (66%)	39/50 (78%)	38/50 (76%)
		32/50 (64%)	24/50 (48%)	33/49 (67%)		42/50 (84%)	42/50 (84%)	37/50 (74%)
		30/50 (60%)				38/50 (76%)		
Overall Incidence	Total	206/349 (59.03%)	Mean 59.05%	SD 7.87%	Total	269/350 (76.86%)	Mean 76.86%	SD 6.2%
#All Organs:								
Malignant Tumors								
		6/50 (12%)	13/50 (26%)	12/50 (24%)		17/50 (34%)	12/50 (24%)	16/50 (32%)
		13/50 (26%)	4/50 (8%)	13/49 (27%)		11/50 (22%)	13/50 (26%)	10/50 (20%)
		8/50 (16%)				10/50 (20%)		
Overall Incidence	Total	69/349 (19.77%)	Mean 19.79%	SD 7.68%	Total	89/350 (25.43%)	Mean 25.43%	SD 5.62%
#All Organs:								
Malignant and Benign Tumors								
		36/50 (72%)	35/50 (70%)	36/50 (72%)		40/50 (80%)	40/50 (80%)	43/50 (86%)
		37/50 (74%)	26/50 (52%)	36/49 (73%)		43/50 (86%)	47/50 (94%)	40/50 (80%)
		34/50 (68%)				40/50 (80%)		
Overall Incidence	Total	240/349 (68.77%)	Mean 68.78%	SD 7.68%	Total	293/350 (83.71%)	Mean 83.71%	SD 5.35%
#All Organs:								
Hemangioma								
		1/50 (2%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	0/50 (0%)
		0/50 (0%)	1/50 (2%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 0.98%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
#All Organs:								
Hemangiosarcoma								
		3/50 (6%)	3/50 (6%)	0/50 (0%)		1/50 (2%)	2/50 (4%)	2/50 (4%)
		3/50 (6%)	0/50 (0%)	8/49 (16%)		1/50 (2%)	0/50 (0%)	2/50 (4%)
		3/50 (6%)				2/50 (4%)		
Overall Incidence	Total	20/349 (5.73%)	Mean 5.76%	SD 5.45%	Total	10/350 (2.86%)	Mean 2.86%	SD 1.57%
#All Organs:								
Hemangiosarcoma or Hemangioma								
		4/50 (8%)	4/50 (8%)	0/50 (0%)		1/50 (2%)	3/50 (6%)	2/50 (4%)
		3/50 (6%)	1/50 (2%)	9/49 (18%)		1/50 (2%)	0/50 (0%)	2/50 (4%)
		4/50 (8%)				2/50 (4%)		
Overall Incidence	Total	25/349 (7.16%)	Mean 7.2%	SD 5.87%	Total	11/350 (3.14%)	Mean 3.14%	SD 1.95%
#All Organs:								
Histiocytic Sarcoma								
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	2/50 (4%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%
#All Organs:								
Leukemia: Lymphocytic, Monocytic, Mononuclear, or Undifferentiated								
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.08%	Total	0/350 (0%)	Mean 0%	SD 0%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#All Organs:									
Malignant Lymphoma: Histiocytic, Lymphocytic, Mixed, NOS, or Undifferentiated Cell Type									
		0/50 (0%)	3/50 (6%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	1/50 (2%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		2/50 (4%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 2.27%	Total	5/350 (1.43%)	Mean 1.43%	SD 1.51%	
#All Organs:									
Mesothelioma: Benign, Malignant, NOS									
		0/50 (0%)	1/50 (2%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	2/50 (4%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	6/349 (1.72%)	Mean 1.71%	SD 1.8%	Total	0/350 (0%)	Mean 0%	SD 0%	
#All Organs:									
Mesothelioma: Malignant									
		0/50 (0%)	1/50 (2%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 1.51%	Total	0/350 (0%)	Mean 0%	SD 0%	
#All Organs:									
Osteoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#All Organs:									
Osteosarcoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#All Organs:									
Osteosarcoma or Osteoma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.57%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Adrenal Cortex:**									
Adenoma									
		3/50 (6%)	2/50 (4%)	1/50 (2%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		2/50 (4%)	1/50 (2%)	0/49 (0%)		2/50 (4%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	9/349 (2.58%)	Mean 2.57%	SD 2.23%	Total	5/350 (1.43%)	Mean 1.43%	SD 1.51%	
***Adrenal Cortex:**									
Carcinoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.58%	SD 0.99%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Adrenal Medulla:**									
Pheochromocytoma Benign									
		1/49 (2%)	1/50 (2%)	1/50 (2%)		0/49 (0%)	3/50 (6%)	1/50 (2%)	
		4/50 (8%)	0/50 (0%)	0/49 (0%)		1/49 (2%)	0/50 (0%)	1/50 (2%)	
		0/49 (0%)				2/49 (4%)			
Overall Incidence	Total	7/347 (2.02%)	Mean 2.01%	SD 2.83%	Total	8/347 (2.31%)	Mean 2.3%	SD 2.15%	
***Adrenal Medulla:**									
Pheochromocytoma Complex									
		1/49 (2%)	0/50 (0%)	0/50 (0%)		0/49 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/49 (0%)	0/50 (0%)	1/50 (2%)	
		0/49 (0%)				0/49 (0%)			
Overall Incidence	Total	1/347 (0.29%)	Mean 0.29%	SD 0.77%	Total	1/347 (0.29%)	Mean 0.29%	SD 0.76%	
***Adrenal Medulla:**									
Pheochromocytoma Malignant									
		0/49 (0%)	0/50 (0%)	0/50 (0%)		0/49 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		1/49 (2%)	0/50 (0%)	0/50 (0%)	
		0/49 (0%)				0/49 (0%)			
Overall Incidence	Total	1/347 (0.29%)	Mean 0.29%	SD 0.77%	Total	1/347 (0.29%)	Mean 0.29%	SD 0.77%	
***Adrenal Medulla:**									
Pheochromocytoma: Benign, Complex, Malignant, NOS									
		2/49 (4%)	1/50 (2%)	1/50 (2%)		0/49 (0%)	3/50 (6%)	1/50 (2%)	
		4/50 (8%)	0/50 (0%)	1/49 (2%)		2/49 (4%)	0/50 (0%)	2/50 (4%)	
		0/49 (0%)				2/49 (4%)			
Overall Incidence	Total	9/347 (2.59%)	Mean 2.59%	SD 2.77%	Total	10/347 (2.88%)	Mean 2.88%	SD 2.28%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Blood Vessel:									
Hemangiosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Bone Marrow:**									
Hemangiosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Bone:									
Osteoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Bone:									
Osteosarcoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Bone:									
Osteosarcoma or Osteoma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.57%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Bone:									
Sarcoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%		Total 0/350 (0%)	Mean 0%	SD 0%	
***Brain:**									
Glioma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 1.51%		Total 0/350 (0%)	Mean 0%	SD 0%	
***Brain:**									
Glioma Malignant									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.08%		Total 0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Brain:**									
Granular Cell Tumor Benign									
		1/50 (2%)	3/50 (6%)	2/50 (4%)		1/50 (2%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		2/50 (4%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	8/349 (2.29%)	Mean 2.29%	SD 2.14%	Total	4/350 (1.14%)	Mean 1.14%	SD 1.57%	
***Brain:**									
Granular Cell Tumor Malignant									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Brain:**									
Meningioma Malignant									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Brain:**									
Meningioma: Benign, Malignant, NOS									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Brain:**									
Oligodendroglioma Benign									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Brain:**									
Oligodendroglioma, Glioma, or Astrocytoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.08%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Clitoral/Preputial Gland:**									
Carcinoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/49 (0%)	0/49 (0%)	
		0/50 (0%)	0/49 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/348 (0.57%)	Mean 0.58%	SD 0.99%		Total 0/347 (0%)	Mean 0%	SD 0%	
***Clitoral/Preputial Gland:**									
Carcinoma or Adenoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/49 (0%)	0/49 (0%)	
		0/50 (0%)	0/49 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/348 (0.57%)	Mean 0.58%	SD 0.99%		Total 0/347 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Heart:**									
Schwannoma Benign									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Heart:**									
Schwannoma NOS									
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Intestine Small: Duodenum:									
Fibroma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Intestine Small: Duodenum:									
Leiomyosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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#: Denominator is number of animals necropsied

		Male				Female			
#Intestine Small: Jejunum: Leiomyoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Intestine Small: Jejunum: Leiomyosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Intestine Small: Site Unspecified: Fibroma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Intestine Small: Site Unspecified: Leiomyoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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#: Denominator is number of animals necropsied

		Male				Female		
#Intestine Small: Site Unspecified:								
Leiomyosarcoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				1/50 (2%)		
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%
***Islets, Pancreatic:**								
Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	5/50 (10%)	4/49 (8%)		1/49 (2%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	10/349 (2.87%)	Mean 2.88%	SD 4.33%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%
***Islets, Pancreatic:**								
Carcinoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	0/50 (0%)	2/49 (4%)		0/49 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	2/349 (0.57%)	Mean 0.58%	SD 1.54%	Total	0/349 (0%)	Mean 0%	SD 0%
***Islets, Pancreatic:**								
Carcinoma or Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	5/50 (10%)	6/49 (12%)		1/49 (2%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	12/349 (3.44%)	Mean 3.46%	SD 5.32%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%

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		Male				Female			
***Kidney: Pelvis and Transitional Epithelium:**									
Papilloma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Kidney: Renal Tubule:**									
Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Kidney: Renal Tubule:**									
Carcinoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Kidney: Renal Tubule:**									
Carcinoma or Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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#: Denominator is number of animals necropsied

		Male				Female			
***Kidney: Renal Tubule: Lipoma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Kidney: Renal Tubule: Liposarcoma**									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%		Total 0/350 (0%)	Mean 0%	SD 0%	
***Liver: Cholangioma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	3/50 (6%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%		Total 3/350 (0.86%)	Mean 0.86%	SD 2.27%	
***Liver: Hemangioma**									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%		Total 0/350 (0%)	Mean 0%	SD 0%	

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		Male				Female			
***Liver:**									
Hepatocellular Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	1/50 (2%)	3/49 (6%)		0/50 (0%)	0/50 (0%)	3/50 (6%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.16%	SD 2.31%	Total	6/350 (1.71%)	Mean 1.71%	SD 2.14%	
***Liver:**									
Hepatocellular Carcinoma or Hepatocellular Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	1/50 (2%)	3/49 (6%)		0/50 (0%)	0/50 (0%)	3/50 (6%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.16%	SD 2.31%	Total	6/350 (1.71%)	Mean 1.71%	SD 2.14%	
***Liver:**									
Hepatocellular Carcinoma, Hepatocellular Adenoma, or Hepatoblastoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	1/50 (2%)	3/49 (6%)		0/50 (0%)	0/50 (0%)	3/50 (6%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.16%	SD 2.31%	Total	6/350 (1.71%)	Mean 1.71%	SD 2.14%	
***Lung:**									
Alveolar/Bronchiolar Adenoma									
		3/50 (6%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 2.23%	Total	0/350 (0%)	Mean 0%	SD 0%	

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		Male				Female			
***Lung:**									
Alveolar/Bronchiolar Carcinoma or Alveolar/Bronchiolar Adenoma									
		3/50 (6%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 2.23%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Lymph Node:									
Hemangioma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Lymph Node, Mandibular:									
Hemangioma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Lymph Node, Mesenteric:									
Hemangioma									
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.08%	Total	0/350 (0%)	Mean 0%	SD 0%	

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		Male				Female		
#Lymph Node, Mesenteric:								
Hemangiosarcoma								
		2/50 (4%)	2/50 (4%)	0/50 (0%)		0/50 (0%)	2/50 (4%)	1/50 (2%)
		3/50 (6%)	0/50 (0%)	7/49 (14%)		1/50 (2%)	0/50 (0%)	2/50 (4%)
		1/50 (2%)				1/50 (2%)		
Overall Incidence	Total	15/349 (4.3%)	Mean 4.33%	SD 4.92%	Total	7/350 (2%)	Mean 2%	SD 1.63%
#Mammary Gland:								
Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	5/50 (10%)	2/50 (4%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		2/50 (4%)	4/50 (8%)	0/50 (0%)
		0/50 (0%)				4/50 (8%)		
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	17/350 (4.86%)	Mean 4.86%	SD 3.98%
#Mammary Gland:								
Carcinoma								
		0/50 (0%)	1/50 (2%)	0/50 (0%)		5/50 (10%)	4/50 (8%)	6/50 (12%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		4/50 (8%)	4/50 (8%)	1/50 (2%)
		0/50 (0%)				1/50 (2%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	25/350 (7.14%)	Mean 7.14%	SD 3.8%
#Mammary Gland:								
Carcinoma or Adenoma								
		0/50 (0%)	1/50 (2%)	0/50 (0%)		5/50 (10%)	8/50 (16%)	8/50 (16%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		6/50 (12%)	8/50 (16%)	1/50 (2%)
		0/50 (0%)				4/50 (8%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	40/350 (11.43%)	Mean 11.43%	SD 5.26%

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		Male				Female		
#Mammary Gland:								
Fibroadenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		7/50 (14%)	13/50 (26%)	11/50 (22%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		9/50 (18%)	2/50 (4%)	9/50 (18%)
		1/50 (2%)				8/50 (16%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	59/350 (16.86%)	Mean 16.86%	SD 6.91%
#Mammary Gland:								
Fibroma, Fibroadenoma or Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		7/50 (14%)	15/50 (30%)	11/50 (22%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		11/50 (22%)	6/50 (12%)	9/50 (18%)
		1/50 (2%)				12/50 (24%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	71/350 (20.29%)	Mean 20.29%	SD 6.16%
#Mammary Gland:								
Fibroma, Fibroadenoma, Carcinoma, or Adenoma								
		0/50 (0%)	1/50 (2%)	0/50 (0%)		10/50 (20%)	15/50 (30%)	15/50 (30%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		13/50 (26%)	9/50 (18%)	10/50 (20%)
		1/50 (2%)				12/50 (24%)		
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	84/350 (24%)	Mean 24%	SD 4.9%
#Mesentery:								
Hemangiosarcoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%

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#: Denominator is number of animals necropsied

		Male				Female			
#Mesentery:									
Lipoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Mesentery:									
Schwannoma Malignant									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Nose:**									
Adenoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/349 (0%)	Mean 0%	SD 0%	
***Nose:**									
Chondroma									
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	

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#: Denominator is number of animals necropsied

		Male				Female			
***Nose:**									
Olfactory Neuroblastoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%		Total 1/349 (0.29%)	Mean 0.29%	SD 0.76%	
#Oral Cavity (Oral Mucosa, Tongue, Pharynx, Tooth, Gingiva):									
Squamous Cell Carcinoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Oral Cavity (Oral Mucosa, Tongue, Pharynx, Tooth, Gingiva):									
Squamous Cell Carcinoma, Papilloma Squamous, or Papilloma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Oral Mucosa:									
Squamous Cell Carcinoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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#: Denominator is number of animals necropsied

		Male		Female	
***Ovary:**					
Adenoma					
		2/50 (4%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%	
***Ovary:**					
Cystadenoma					
		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
***Ovary:**					
Granulosa Cell Tumor Benign					
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)			
Overall Incidence	Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%	
***Ovary:**					
Granulosa Cell Tumor Malignant					
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	1/50 (2%)	
		1/50 (2%)			
Overall Incidence	Total	3/350 (0.86%)	Mean 0.86%	SD 1.07%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male		Female	
***Ovary:**					
Granulosa Cell Tumor: Benign, Malignant, NOS					
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		1/50 (2%)		1/50 (2%)	2/50 (4%)
		1/50 (2%)			
Overall Incidence	Total	5/350 (1.43%)		Mean 1.43%	SD 1.51%
***Ovary:**					
Granulosa-Theca Tumor Malignant					
		0/50 (0%)		1/50 (2%)	0/50 (0%)
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)		Mean 0.29%	SD 0.76%
***Ovary:**					
Sex Cord Stromal Tumor, Benign					
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		2/50 (4%)			
Overall Incidence	Total	2/350 (0.57%)		Mean 0.57%	SD 1.51%
***Ovary:**					
Tubulostromal Adenoma					
		2/50 (4%)		1/50 (2%)	0/50 (0%)
		0/50 (0%)		0/50 (0%)	0/50 (0%)
		0/50 (0%)			
Overall Incidence	Total	3/350 (0.86%)		Mean 0.86%	SD 1.57%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
***Pancreas:**								
Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)	1/50 (2%)	1/46 (2%)		0/49 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	4/346 (1.16%)	Mean 1.17%	SD 1.09%	Total	0/349 (0%)	Mean 0%	SD 0%
***Pancreas:**								
Carcinoma or Adenoma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)	1/50 (2%)	1/46 (2%)		0/49 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				0/50 (0%)		
Overall Incidence	Total	4/346 (1.16%)	Mean 1.17%	SD 1.09%	Total	0/349 (0%)	Mean 0%	SD 0%
***Parathyroid Gland:**								
Adenoma								
		0/44 (0%)	1/49 (2%)	0/47 (0%)		0/39 (0%)	0/46 (0%)	0/47 (0%)
		0/43 (0%)	0/39 (0%)	2/47 (4%)		0/47 (0%)	1/42 (2%)	1/49 (2%)
		0/45 (0%)				0/48 (0%)		
Overall Incidence	Total	3/314 (0.96%)	Mean 0.9%	SD 1.66%	Total	2/318 (0.63%)	Mean 0.63%	SD 1.08%
***Pituitary Gland: Pars Distalis or Unspecified Site:**								
Adenoma								
		14/50 (28%)	9/50 (18%)	17/50 (34%)		19/50 (38%)	26/50 (52%)	32/50 (64%)
		16/49 (33%)	14/50 (28%)	19/49 (39%)		35/50 (70%)	34/50 (68%)	23/50 (46%)
		21/50 (42%)				21/50 (42%)		
Overall Incidence	Total	110/348 (31.61%)	Mean 31.63%	SD 7.93%	Total	190/350 (54.29%)	Mean 54.29%	SD 13.03%

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#: Denominator is number of animals necropsied

		Male				Female		
***Pituitary Gland: Pars Distalis or Unspecified Site: Carcinoma**								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)
		0/49 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	0/348 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%
***Pituitary Gland: Pars Distalis or Unspecified Site: Carcinoma or Adenoma**								
		14/50 (28%)	9/50 (18%)	17/50 (34%)		20/50 (40%)	26/50 (52%)	32/50 (64%)
		16/49 (33%)	14/50 (28%)	19/49 (39%)		35/50 (70%)	34/50 (68%)	23/50 (46%)
		21/50 (42%)				21/50 (42%)		
Overall Incidence	Total	110/348 (31.61%)	Mean 31.63%	SD 7.93%	Total	191/350 (54.57%)	Mean 54.57%	SD 12.63%
***Pituitary Gland: Pars Intermedia: Adenoma**								
		1/50 (2%)	2/50 (4%)	1/50 (2%)		0/50 (0%)	1/50 (2%)	2/50 (4%)
		2/49 (4%)	1/50 (2%)	0/49 (0%)		1/50 (2%)	1/50 (2%)	1/50 (2%)
		2/50 (4%)				4/50 (8%)		
Overall Incidence	Total	9/348 (2.59%)	Mean 2.58%	SD 1.52%	Total	10/350 (2.86%)	Mean 2.86%	SD 2.54%
***Pituitary Gland: Pars Intermedia: Carcinoma or Adenoma**								
		1/50 (2%)	2/50 (4%)	1/50 (2%)		0/50 (0%)	1/50 (2%)	2/50 (4%)
		2/49 (4%)	1/50 (2%)	0/49 (0%)		1/50 (2%)	1/50 (2%)	1/50 (2%)
		2/50 (4%)				4/50 (8%)		
Overall Incidence	Total	9/348 (2.59%)	Mean 2.58%	SD 1.52%	Total	10/350 (2.86%)	Mean 2.86%	SD 2.54%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male			Female		
***Prostate:**							
Adenoma							
		1/50 (2%)	0/50 (0%)	0/50 (0%)			
		1/50 (2%)	0/50 (0%)	0/49 (0%)			
		0/50 (0%)					
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%			
***Prostate:**							
Carcinoma							
		0/50 (0%)	1/50 (2%)	0/50 (0%)			
		0/50 (0%)	0/50 (0%)	0/49 (0%)			
		0/50 (0%)					
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%			
***Prostate:**							
Carcinoma or Adenoma							
		1/50 (2%)	1/50 (2%)	0/50 (0%)			
		1/50 (2%)	0/50 (0%)	0/49 (0%)			
		0/50 (0%)					
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.07%			
***Salivary Glands:**							
Adenoma							
		0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/50 (0%)	0/49 (0%)
		0/50 (0%)	0/50 (0%)	1/46 (2%)	0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)			0/50 (0%)		
Overall Incidence	Total	1/346 (0.29%)	Mean 0.31%	SD 0.82%	Total 0/349 (0%)	Mean 0%	SD 0%

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#: Denominator is number of animals necropsied

		Male				Female			
***Salivary Glands: Carcinoma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/46 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/346 (0%)	Mean 0%	SD 0%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	
***Salivary Glands: Carcinoma or Adenoma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	1/46 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/346 (0.29%)	Mean 0.31%	SD 0.82%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	
***Salivary Glands: Myoepithelioma**									
		1/50 (2%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/46 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	2/346 (0.58%)	Mean 0.57%	SD 0.98%	Total	0/349 (0%)	Mean 0%	SD 0%	
***Salivary Glands: Schwannoma Malignant**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		1/50 (2%)	0/50 (0%)	0/46 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/346 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/349 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Seminal Vesicle:									
Adenoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)					
		1/50 (2%)	0/50 (0%)	0/49 (0%)					
		0/50 (0%)							
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%					
#Skeletal Muscle:									
Hemangiosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skeletal Muscle:									
Sarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Basal Cell Adenoma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 1.9%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

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#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Basal Cell Adenoma or Basosquamous Tumor Benign									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 1.9%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Basal Cell Adenoma, Basosquemous Tumor Benign, or Trichoepithelioma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	5/349 (1.43%)	Mean 1.43%	SD 1.9%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Basal Cell Carcinoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Basal Cell Carcinoma or Basosquamous Tumor (malignant or NOS)									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total 0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Basal Cell Carcinoma, Basal Cell Adenoma, Basosquamous Tumor (benign, malignant or NOS), or Trichoepithelioma									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	6/349 (1.72%)	Mean 1.72%	SD 1.8%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Basal or Sq. Cell Carcinoma, Carcinoma, Basosq. Tumor (M or B), Basal Cell Adenoma, Adenoma, Papilloma, Sq Papilloma, Keratoacanthoma, Trichoepithelioma									
		1/50 (2%)	3/50 (6%)	6/50 (12%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)	1/50 (2%)	3/49 (6%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		7/50 (14%)				0/50 (0%)			
Overall Incidence	Total	23/349 (6.59%)	Mean 6.59%	SD 4.72%		Total 1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Fibroma									
		2/50 (4%)	0/50 (0%)	1/50 (2%)		2/50 (4%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	6/349 (1.72%)	Mean 1.72%	SD 1.38%		Total 2/350 (0.57%)	Mean 0.57%	SD 1.51%	
#Skin:									
Fibroma, Fibrosarcoma, Sarcoma, Myxoma, Myxosarcoma, or Fibrous Histiocytoma									
		2/50 (4%)	2/50 (4%)	1/50 (2%)		2/50 (4%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)	1/50 (2%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	9/349 (2.58%)	Mean 2.58%	SD 1.51%		Total 2/350 (0.57%)	Mean 0.57%	SD 1.51%	

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#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Fibrosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Fibrosarcoma, Sarcoma, Myxosarcoma, or Fibrous Histiocytoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Fibrous Histiocytoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Hamartoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	

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#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Hemangiosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Skin:									
Keratoacanthoma									
		1/50 (2%)	3/50 (6%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	2/49 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		4/50 (8%)				0/50 (0%)			
Overall Incidence	Total	14/349 (4.01%)	Mean 4.01%	SD 2.31%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Lipoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Liposarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Myxoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Neurofibrosarcoma or Schwannoma (malignant or NOS)									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	2/50 (4%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.95%	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%	
#Skin:									
Neurofibrosarcoma, Neurofibroma, or Schwannoma (benign, malignant or NOS)									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	2/50 (4%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.95%	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%	
#Skin:									
Schwannoma Malignant									
		0/50 (0%)	0/50 (0%)	2/50 (4%)		0/50 (0%)	0/50 (0%)	2/50 (4%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.95%	Total	2/350 (0.57%)	Mean 0.57%	SD 1.51%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male					Female				
#Skin:											
Squamous Cell Carcinoma											
		0/50 (0%)	0/50 (0%)	1/50 (2%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		0/50 (0%)	0/50 (0%)	0/49 (0%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		0/50 (0%)					0/50 (0%)				
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%		Total	0/350 (0%)	Mean 0%	SD 0%		
#Skin:											
Squamous Cell Carcinoma, Basal Cell Carcinoma, Basosquamous Tumor (malignant or NOS), or Carcinoma											
		0/50 (0%)	0/50 (0%)	1/50 (2%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		1/50 (2%)	0/50 (0%)	0/49 (0%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		1/50 (2%)					0/50 (0%)				
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.07%		Total	0/350 (0%)	Mean 0%	SD 0%		
#Skin:											
Squamous Cell Papilloma											
		0/50 (0%)	0/50 (0%)	1/50 (2%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		0/50 (0%)	0/50 (0%)	0/49 (0%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		1/50 (2%)					0/50 (0%)				
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total	0/350 (0%)	Mean 0%	SD 0%		
#Skin:											
Squamous Cell Papilloma or Papilloma											
		0/50 (0%)	0/50 (0%)	1/50 (2%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		0/50 (0%)	0/50 (0%)	0/49 (0%)			0/50 (0%)	0/50 (0%)	0/50 (0%)		
		1/50 (2%)					0/50 (0%)				
Overall Incidence	Total	2/349 (0.57%)	Mean 0.57%	SD 0.98%		Total	0/350 (0%)	Mean 0%	SD 0%		

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Skin:									
Squamous Cell Papilloma, Papilloma, Squamous Cell Carcinoma or Keratoacanthoma									
		1/50 (2%)	3/50 (6%)	4/50 (8%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	2/49 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		5/50 (10%)				0/50 (0%)			
Overall Incidence	Total	17/349 (4.87%)	Mean 4.87%	SD 3.23%		Total 0/350 (0%)	Mean 0%	SD 0%	
#Skin:									
Squamous Cell Papilloma, Papilloma, or Keratoacanthoma									
		1/50 (2%)	3/50 (6%)	3/50 (6%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	1/50 (2%)	2/49 (4%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		5/50 (10%)				0/50 (0%)			
Overall Incidence	Total	16/349 (4.58%)	Mean 4.58%	SD 2.99%		Total 0/350 (0%)	Mean 0%	SD 0%	
#Skin: Sebaceous Gland:									
Adenoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.07%		Total 0/350 (0%)	Mean 0%	SD 0%	
#Skin: Sebaceous Gland:									
Carcinoma or Adenoma									
		0/50 (0%)	1/50 (2%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	3/349 (0.86%)	Mean 0.86%	SD 1.07%		Total 0/350 (0%)	Mean 0%	SD 0%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Spleen:**									
Hemangiosarcoma									
		0/50 (0%)	1/50 (2%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/47 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				0/50 (0%)			
Overall Incidence	Total	3/347 (0.86%)	Mean 0.88%	SD 1.09%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Stomach, Forestomach:									
Fibrosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Stomach, Forestomach:									
Leiomyoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Stomach, Forestomach:									
Leiomyosarcoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Stomach, Forestomach:									
Sarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Stomach, Forestomach:									
Squamous Cell Carcinoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Stomach, Forestomach:									
Squamous Cell Carcinoma or Papilloma Squamous									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	1/50 (2%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%	
#Stomach, Forestomach:									
Squamous Cell Papilloma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Stomach, Glandular:									
Fibrosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/49 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.77%	Total	0/350 (0%)	Mean 0%	SD 0%	
#Stomach, Glandular:									
Leiomyosarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				1/50 (2%)			
Overall Incidence	Total	0/349 (0%)	Mean 0%	SD 0%	Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%	
#Stomach, Glandular:									
Sarcoma									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	0/350 (0%)	Mean 0%	SD 0%	
***Testes:**									
Adenoma									
		6/50 (12%)	3/50 (6%)	2/50 (4%)					
		2/50 (4%)	0/50 (0%)	2/49 (4%)					
		0/50 (0%)							
Overall Incidence	Total	15/349 (4.3%)	Mean 4.3%	SD 4.07%					

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#: Denominator is number of animals necropsied

		Male			Female		
***Testes:**							
Hemangiosarcoma							
		1/50 (2%)	0/50 (0%)	0/50 (0%)			
		0/50 (0%)	0/50 (0%)	0/49 (0%)			
		0/50 (0%)					
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%			
***Thymus:**							
Sarcoma							
		0/41 (0%)	0/47 (0%)	0/49 (0%)	0/46 (0%)	0/49 (0%)	0/49 (0%)
		0/40 (0%)	0/48 (0%)	0/45 (0%)	0/48 (0%)	0/48 (0%)	0/50 (0%)
		0/49 (0%)			1/50 (2%)		
Overall Incidence	Total	0/319 (0%)	Mean 0%	SD 0%	Total 1/340 (0.29%)	Mean 0.29%	SD 0.76%
***Thymus:**							
Thymoma Benign							
		3/41 (7%)	1/47 (2%)	2/49 (4%)	6/46 (13%)	0/49 (0%)	3/49 (6%)
		1/40 (3%)	3/48 (6%)	0/45 (0%)	5/48 (10%)	8/48 (17%)	0/50 (0%)
		1/49 (2%)			1/50 (2%)		
Overall Incidence	Total	11/319 (3.45%)	Mean 3.47%	SD 2.57%	Total 23/340 (6.76%)	Mean 6.89%	SD 6.65%
***Thymus:**							
Thymoma: Benign, Malignant, NOS							
		3/41 (7%)	1/47 (2%)	2/49 (4%)	6/46 (13%)	0/49 (0%)	3/49 (6%)
		1/40 (3%)	3/48 (6%)	0/45 (0%)	5/48 (10%)	8/48 (17%)	0/50 (0%)
		1/49 (2%)			1/50 (2%)		
Overall Incidence	Total	11/319 (3.45%)	Mean 3.47%	SD 2.57%	Total 23/340 (6.76%)	Mean 6.89%	SD 6.65%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
***Thyroid Gland: Carcinoma**								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)	0/50 (0%)	0/45 (0%)		0/50 (0%)	0/49 (0%)	0/45 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	0/345 (0%)	Mean 0%	SD 0%	Total	1/344 (0.29%)	Mean 0.29%	SD 0.76%
***Thyroid Gland: C-Cell: Adenoma**								
		5/50 (10%)	6/50 (12%)	4/50 (8%)		4/50 (8%)	2/50 (4%)	3/50 (6%)
		7/50 (14%)	3/50 (6%)	11/45 (24%)		3/50 (6%)	7/49 (14%)	7/45 (16%)
		5/50 (10%)				7/50 (14%)		
Overall Incidence	Total	41/345 (11.88%)	Mean 12.06%	SD 6.04%	Total	33/344 (9.59%)	Mean 9.69%	SD 4.77%
***Thyroid Gland: C-Cell: Carcinoma**								
		1/50 (2%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	1/50 (2%)	1/50 (2%)
		0/50 (0%)	0/50 (0%)	0/45 (0%)		0/50 (0%)	0/49 (0%)	0/45 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	1/345 (0.29%)	Mean 0.29%	SD 0.76%	Total	3/344 (0.87%)	Mean 0.86%	SD 1.07%
***Thyroid Gland: C-Cell: Carcinoma or Adenoma**								
		6/50 (12%)	6/50 (12%)	4/50 (8%)		5/50 (10%)	3/50 (6%)	4/50 (8%)
		7/50 (14%)	3/50 (6%)	11/45 (24%)		3/50 (6%)	7/49 (14%)	7/45 (16%)
		5/50 (10%)				7/50 (14%)		
Overall Incidence	Total	42/345 (12.17%)	Mean 12.35%	SD 5.97%	Total	36/344 (10.47%)	Mean 10.55%	SD 4.06%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
***Thyroid Gland: Follicular Cell: Adenoma**									
		0/50 (0%)	2/50 (4%)	0/50 (0%)		1/50 (2%)	2/50 (4%)	1/50 (2%)	
		1/50 (2%)	0/50 (0%)	1/45 (2%)		1/50 (2%)	0/49 (0%)	1/45 (2%)	
		3/50 (6%)				3/50 (6%)			
Overall Incidence	Total	7/345 (2.03%)	Mean 2.03%	SD 2.31%	Total	9/344 (2.62%)	Mean 2.6%	SD 1.89%	
***Thyroid Gland: Follicular Cell: Carcinoma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/45 (0%)		1/50 (2%)	1/49 (2%)	0/45 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	0/345 (0%)	Mean 0%	SD 0%	Total	3/344 (0.87%)	Mean 0.86%	SD 1.08%	
***Thyroid Gland: Follicular Cell: Carcinoma or Adenoma**									
		0/50 (0%)	2/50 (4%)	0/50 (0%)		2/50 (4%)	2/50 (4%)	1/50 (2%)	
		1/50 (2%)	0/50 (0%)	1/45 (2%)		2/50 (4%)	1/49 (2%)	1/45 (2%)	
		3/50 (6%)				3/50 (6%)			
Overall Incidence	Total	7/345 (2.03%)	Mean 2.03%	SD 2.31%	Total	12/344 (3.49%)	Mean 3.47%	SD 1.47%	
***Urinary Bladder: Carcinoma or Papilloma**									
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)	
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)				1/50 (2%)			
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
***Urinary Bladder:**								
Papilloma								
		0/50 (0%)	0/50 (0%)	0/50 (0%)		0/50 (0%)	0/50 (0%)	0/49 (0%)
		0/50 (0%)	0/50 (0%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		1/50 (2%)				1/50 (2%)		
Overall Incidence	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%	Total	1/349 (0.29%)	Mean 0.29%	SD 0.76%
#Uterus:								
Adenoma								
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)	1/50 (2%)	1/50 (2%)
						0/50 (0%)		
Overall Incidence					Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%
#Uterus:								
Carcinoma								
						3/50 (6%)	2/50 (4%)	3/50 (6%)
						1/50 (2%)	1/50 (2%)	1/50 (2%)
						3/50 (6%)		
Overall Incidence					Total	14/350 (4%)	Mean 4%	SD 2%
#Uterus:								
Granular Cell Tumor Benign								
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)	1/50 (2%)	1/50 (2%)
						0/50 (0%)		
Overall Incidence					Total	2/350 (0.57%)	Mean 0.57%	SD 0.98%

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#: Denominator is number of animals necropsied

		Male		Female	
#Uterus:					
Hemangiosarcoma					
		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Uterus:					
Leiomyosarcoma					
		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Uterus:					
Malignant Mixed Mullerian Tumor					
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)	0/50 (0%)	1/50 (2%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	
#Uterus:					
Polyp Stromal					
		2/50 (4%)	9/50 (18%)	3/50 (6%)	
		5/50 (10%)	6/50 (12%)	3/50 (6%)	
		2/50 (4%)			
Overall Incidence	Total	30/350 (8.57%)	Mean 8.57%	SD 5.13%	

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#: Denominator is number of animals necropsied

		Male		Female	
#Uterus:					
Sarcoma Stromal					
		1/50 (2%)	1/50 (2%)	1/50 (2%)	
		2/50 (4%)	1/50 (2%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	6/350 (1.71%)	Mean 1.71%	SD 1.38%	
#Uterus:					
Sarcoma Stromal or Polyp Stromal					
		3/50 (6%)	10/50 (20%)	4/50 (8%)	
		6/50 (12%)	7/50 (14%)	3/50 (6%)	
		2/50 (4%)			
Overall Incidence	Total	35/350 (10%)	Mean 10%	SD 5.66%	
#Uterus:					
Schwannoma Malignant					
		0/50 (0%)	1/50 (2%)	1/50 (2%)	
		0/50 (0%)	2/50 (4%)	1/50 (2%)	
		0/50 (0%)			
Overall Incidence	Total	5/350 (1.43%)	Mean 1.43%	SD 1.51%	
#Uterus:					
Squamous Cell Papilloma					
		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		1/50 (2%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)			
Overall Incidence	Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%	

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female		
#Vagina:								
Fibrosarcoma								
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)	1/50 (2%)	0/50 (0%)
						0/50 (0%)		
Overall Incidence					Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%
#Vagina:								
Leiomyoma								
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						1/50 (2%)		
Overall Incidence					Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%
#Vagina:								
Polyp								
						0/50 (0%)	0/50 (0%)	1/50 (2%)
						0/50 (0%)	0/50 (0%)	0/50 (0%)
						0/50 (0%)		
Overall Incidence					Total	1/350 (0.29%)	Mean 0.29%	SD 0.76%
#Zymbal's Gland:								
Carcinoma								
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		2/50 (4%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)
		0/50 (0%)				0/50 (0%)		
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.57%	Total	0/350 (0%)	Mean 0%	SD 0%

*: Denominator is number of animals with tissues examined microscopically
#: Denominator is number of animals necropsied

		Male				Female			
#Zymbal's Gland:									
Carcinoma or Adenoma									
		0/50 (0%)	0/50 (0%)	1/50 (2%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		2/50 (4%)	1/50 (2%)	0/49 (0%)		0/50 (0%)	0/50 (0%)	0/50 (0%)	
		0/50 (0%)				0/50 (0%)			
Overall Incidence	Total	4/349 (1.15%)	Mean 1.14%	SD 1.57%	Total	0/350 (0%)	Mean 0%	SD 0%	

*: Denominetor is number of animals with tissues examined microscopically
#: Denominetor is number of animals necropsied

Glyphosat – Auf Kosten der Menschen

19/07/2017 NPR

Glyphosat: EU-Bewertung hat gravierende Mängel – US-Experte Christopher Portier rügt EU-Behörden: Bei der Risikobewertung von Glyphosat wurde schlampig und fehlerhaft gearbeitet.

Die zur Weltgesundheitsorganisation WHO gehörende Agentur für Krebsforschung IARC hat den Unkrautvernichter Glyphosat im Jahr 2015 als «wahrscheinlich krebserregend» eingestuft. Vor Kurzem hat sich die kalifornische Behörde für Gesundheit und Umwelt dieser Beurteilung angeschlossen. Seit dem 7. Juli 2017 gilt der Unkrautvernichter in Kalifornien als «krebserregende Substanz». Monsanto ficht den Entscheid an.

Die Europäische Behörde für Lebensmittelsicherheit EFSA und das deutsche Bundesinstitut für Risikobewertung (BfR) hingegen stuften Glyphosat 2016 als «ungefährlich» ein. Es gebe keine Hinweise auf eine krebserzeugende oder erbgutschädigende Wirkung durch Glyphosat, so ihre Bewertung. Auch die Europäische Chemikalienagentur (ECHA) gab Mitte März Entwarnung: Glyphosat sei nicht krebserregend, heisst es im Gutachten der ECHA. Gestützt auf die Bewertung der europäischen Behörden will die EU-Kommission Glyphosat für weitere zehn Jahre zulassen. Erfahrungsgemäss wird sich die Schweiz stark an die Massnahmen der EU anlehnen.

Widerspruch gegen die Risikobewertung der EU-Behörden kommt von Christopher Portier, Experte für Chemikaliensicherheit in den USA. Er hat die Krebsrisiken von Glyphosat im Auftrag der IARC untersucht und bewertet. Portier und weitere 93 WissenschaftlerInnen kritisieren die europäischen Zulassungsbehörden scharf: Die EU-Bewertung weise schwere wissenschaftliche Mängel auf1, die «eine ernsthafte Gefährdung der öffentlichen Gesundheit bedeuten können».

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Das Interview mit Christopher Portier ist in der Fachzeitschrift «Oekoskop» 2/17 der Ärztinnen und Ärzte für Umweltschutz erschienen.

«Oekoskop»: Christopher Portier, Sie tragen den Entscheid der IARC mit, Glyphosat sei als «wahrscheinlich krebsfördernd» einzustufen, und kritisieren die gegenteilige Einschätzung durch die EFSA und die ECHA scharf. Weshalb sollten wir der IARC mehr vertrauen als den europäischen Behörden?

Christopher Portier: Es gibt ein paar grundsätzliche Unterschiede, wie die IARC bzw. die EFSA und die ECHA zu ihren Einschätzungen kommen. Die IARC verwendet ausschliesslich öffentlich verfügbare Studiendaten. Denn sie überprüft auch die Rohdaten der Studien, um sicher zu gehen, dass alle Angaben und Zahlen richtig sind. Viele der Studien zu Tierkrebs und Genotoxizität[2] sind jedoch im Besitz der Industrie. Sie sind weder für die IARC noch für sonst jemanden öffentlich einsehbar.

Es scheint, dass die EFSA und die ECHA die Rohdaten nicht überprüfen. Wenn sie nur die Berichte überprüfen, die ihnen die Industrie einreicht, so kann es sein, dass die Behörden wichtige Studienresultate übersehen.

Woraus schliessen Sie, dass die Behörden das nicht tun?

Die EFSA hat in ihrem Bericht zur Glyphosat-Einschätzung acht positive Tumorbefunde in Tierstudien übersehen. Das BfR lieferte die Grundlage für diesen EFSA-Bericht. Die entsprechende Kritik von zahlreichen Wissenschaftlern haben BfR-Mitarbeitende bestätigt. Wäre ich Chef des BfR, würde ich mich unter diesen Umständen sofort fragen: Haben wir noch andere Tumore übersehen? An diesem Punkt liesse ich das gesamte Datenmaterial durch meine Mitarbeitenden nochmals evaluieren und jeden Tumor-Typ auf seine statistische Signifikanz hin neu bewerten. Das ist die einfachste und offensichtlichste Sache, die sie in einer Krebs-Evaluation tun können. Trotzdem hat dies das BfR nicht getan.

Warum überprüfen EFSA und ECHA nicht genauer?
Ich kann nicht für sie sprechen, aber ich kann von meiner Funktion innerhalb einer Regulierungsbehörde berichten. Nicht nur beim BfR, der EFSA und der ECHA sind alle mit Arbeit überlastet. Zudem stehen die Behörden unter Druck, sehr schnell Resultate zu liefern. Denn wird Glyphosat über längere Zeit nicht genehmigt oder verliert Monsanto gar die Zulassung in Europa, entgeht dem Konzern viel Geld. Die Behörden stehen also unter starkem Druck und haben keine Zeit.

Zulassungsprozess muss unabhängig und transparent seinNach Ansicht von Christopher Portier gibt es bei der Zulassung von chemischen Substanzen einiges zu verbessern. Seine Forderungen:

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- Sie beweist Charakter
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- Unternehmen sollen ihre Unterlagen elektronisch einreichen, damit die Daten nicht mehr mühsam digitalisiert werden müssen, um sie zu prüfen.
- Die Industrie muss die Rohdaten ihrer Studien öffentlich zugänglich machen, damit alle die gleichen Überprüfungsmöglichkeiten haben. Alle positiven und negativen Befunde sollten aufgelistet werden, damit eine schnelle Reevaluation möglich ist.
- Der Zulassungsprozess muss unabhängig sein. Heute bestimmt die Regierung, wer in der ECHA sitzt und wer den EFSA-Bericht evaluiert. Eine unabhängige Institution sollte Wissenschaftler nominieren, die dafür qualifiziert sind und aus Universitäten und Institutionen stammen, die weder mit der Industrie noch mit Behörden verbandelt sind. Eine hohes Mass an Unabhängigkeit könnte so gewährleistet werden, auch wenn die Regierung am Ende aus den Nominierten auswählt.
- Es braucht strenge Gesetze über mögliche Interessenkonflikte. Die fehlen z B. in der EU weitgehend. Es müsste unter anderem auch definiert sein, was ein Interessenkonflikt ist.

Welche weiteren Unterschiede sehen Sie zwischen IARC und EFSA/ECHA?

Die Regeln, nach welchen sowohl IARC wie auch EFSA und ECHA arbeiten, um die wissenschaftliche Evidenz für Krebs zu evaluieren, sind identisch. Also sollte man meinen, dass auch die Schlüsse, die gezogen werden, identisch sind. Dem ist aber nicht so. Die IARC fand bei der Überprüfung einer epidemiologischen Studie einen plausiblen Zusammenhang zwischen der Glyphosat-Exposition und Non-Hodgkin-Lymphom-Erkrankungen. Deshalb kam die IARC zum Schluss, dass eine limitierte Evidenz für Krebserkrankungen beim Menschen besteht. EFSA und ECHA hingegen wiesen dem Befund eine «sehr limitierte Evidenz» zu. Das ist eine Kategorie, die es offiziell gar nicht gibt. Es ist nicht nachvollziehbar, was sie damit meinen.

Die Gegenseite wirft der IARC genauso vor, sie würde unwissenschaftlich arbeiten: Nicht nur EFSA und ECHA. Auch die US-amerikanische Umweltbehörde EPA und andere Behörden sagen, bei Glyphosat liege die IARC falsch.

Wenn zwei positive Tierstudien vorliegen muss die Evidenz als ausreichend kategorisiert werden. Beim Glyphosat fand die IARC vier Tierstudien mit positivem Krebsbefund. Es gab keinen Grund, sie anzuzweifeln. Die Befunde waren plausibel und statistisch signifikant gegenüber den Kontrollgruppen. Die Behörden hingegen gaben immer wieder andere Gründe an, weshalb die Befunde dennoch nicht taugen würden.

Bundesrat Josef Schneider-Amman schrieb uns kürzlich: «Die Schlussfolgerungen der IARC basieren nicht auf neuen Studien, sondern auf einer anderen Beurteilungsmethode, welche die Exposition, d.h. die Menge und Dosis, der ein Anwender und/oder Konsument ausgesetzt ist, nicht berücksichtigt».[3] Was sagen Sie dazu?

Das ist richtig. Ich kenne das Schweizer Gesetz nicht, aber in der EU ist es sehr klar: Das Dosis-Wirkung-Prinzip wird bei nicht genotoxischen Substanzen angewandt. Ist eine Substanz aber genotoxisch, dann spielt die Dosis der Exposition keine Rolle und die Substanz muss gemäss EU-Recht verboten werden. Deshalb ist die Aussage des Bundesrates zumindest bezüglich EU-Recht für Glyphosat kein statthaftes Argument.

Die meisten Behörden auf der Welt haben festgelegt: Ist eine Substanz genotoxisch und handelt es sich um ein Karzinogen, dann wird sie verboten.

Ist Glyphosat genotoxisch?

Wir wissen es nicht genau: Die Daten von 50 Prozent der Studien sprechen für eine Genotoxizität, 50 Prozent dagegen. Im Interesse der öffentlichen Gesundheit sollten wir Glyphosat deshalb meiner Meinung nach als genotoxisch klassieren.

Die Zulassungsbehörden wurden in den 1970er-Jahren aufgebaut, um einen zweiten «Fall DDT» zu verhindern. Mit Blick auf die Pestizide Glyphosat, Triclosan oder die Neonicotinoide: Wurde dieses Ziel erreicht?

Das ist schwer zu beantworten. Seitdem chemische Substanzen verboten wurden, wissen wir nicht, ob wir damit tatsächlich präventiv Krebsfälle verhindert haben. Aber ganz klar, seit DDT haben wir Fehler gemacht. Viele Substanzen haben wir falsch angegangen; z. B. Blei im Benzin, es dauerte lange, bis es verboten wurde. Es hiess zwar, Blei ist ein Problem, aber nur ein kleines. Dann zeigten Studien, dass das Problem doch grösser sein könnte...

...ist das nicht immer so?

Es ist oft so, dass die Behörden bei einer Substanz einen Grenzwert festlegen, um später festzustellen, dass dieser zu hoch war. Sie senken ihn, um danach erneut zu bemerken, dass er noch immer zu hoch ist. So wiederholte es sich bei zahlreichen Substanzen, etwa bei den Dioxinen, den Dibenzofuranen, den PCBs und auch bei den bromierten Brandschutzchemikalien.

Anders aber scheint es bei den klassischen Pestiziden abzulaufen. Sind sie einmal zugelassen, so verfolgt kaum jemand mehr ihre gesundheitlichen Konsequenzen. Wer geht der Frage nach, ob zugelassene Pestizide Krebs auslösen oder nicht? Beim Glyphosat stammen einige der Studien, die wir überprüft haben, aus dem Jahre 1981. Darin tauchen Tumore auf, obwohl meist nur rund 200 Menschen berücksichtigt wurden. Während 36 Jahren will weltweit keine Zulassungsbehörde diese Tumor-Befunde erkannt haben, obwohl die Literatur nur neun Studien zum Krebsrisiko durch Glyphosat beim Menschen umfasst. Stellen Sie sich vor, schon 1981 hätte jemand dieses Versehen entdeckt und es korrigiert. Das hätte wohl zu einer geringeren Akzeptanz von Glyphosat geführt.

Nehmen wir die grosse US-Umweltbehörde EPA: Warum hat sie diese Tumore nicht erkannt?

Das überraschte mich auch. Die EPA betont, sie würde Pestizide ständig reevaluieren. Dasselbe sagt die EFSA. Offensichtlich tun sie es nicht richtig. Bei richtigem Vorgehen sind diese Tumor-Befunde schwerlich zu übersehen.

Heute stehen wir auch vor dem Problem der neuartigen Neonicotinoide, also Insektiziden, die systemisch in die Pflanzen eindringen. Waren sich die Behörden der neuen Dimension bewusst, als sie diese neue Art von Pestiziden zuliessen?

Früher wurde das sehr giftige Nikotin als Insektizid verwendet. Die Neonicotinoide sind viel weniger giftig, bestanden die Tests und wurden zugelassen. Der Zulassungsprozess war aber nicht speziell an die neuen Substanzen angepasst worden. Inzwischen wissen wir, dass Neonicotinoide ökotoxikologisch ein Problem sind. Ich bin überzeugt, dass die Evidenz gegeben ist, dass sie Bienen töten. Ich denke, sie werden verboten und durch ein neues Produkt ersetzt, welches dann möglicherweise wiederum problematisch ist.

Die Bienen starben schon in den 1940er-Jahren durch DDT und danach bei allen neuen Insektiziden, die auf den Markt kamen. Die Bienenverträglichkeit müsste doch zumindest heute getestet werden...

...das gehört in den USA auch heute nicht zum Zulassungsprozedere.

Warum nicht?

Das ist eine sehr gute Frage, die Sie den Zulassungsbehörden stellen sollten. In den USA werden Insektizide an Schmetterlingen getestet, nicht aber an Bienen, obwohl deren Biologie verschieden ist. Auch bei den Schmetterlingen ist die Beurteilung mehr als fragwürdig: Sterben 20 Prozent auf Grund eines Insektizids, gilt das als okay. Sterben über 20 Prozent, schauen sie genauer hin. Sind es mehr als 50 Prozent, wird die Substanz verboten.

Wie sehen Sie die Zukunft von Glyphosat?

Ich war lange Zeit in Zulassungsbehörden tätig und hatte die Möglichkeit, Substanzen zu verbieten. Darum antworte ich als Wissenschaftler und ehemaliger Funktionär: Die EFSA und die ECHA haben ihren Job nicht gemacht. Die Informationen, die sie den gesetzgebenden Politikern geliefert haben, sind wissenschaftlich nicht haltbar und qualitativ schlecht. Mir geht es nicht vordringlich darum, dass Glyphosat verboten wird. Mir geht es grundsätzlich um die wissenschaftliche Beurteilung des Krebspotenzials von Substanzen. Dafür bestehen Regeln, welche die Behörden streng befolgen müssen. Das ist bei Glyphosat momentan nicht der Fall. Folgen die Politiker der Empfehlung ihrer Behörden, wird beim Glyphosat der öffentliche Gesundheitsschutz scheitern. Deshalb habe ich den EU-Kommissionspräsidenten Jean-Claude Juncker in einem Brief auf die fehlerhaften Grundlagen aufmerksam gemacht, die er von seinen Behörden erhalten hat.

1. Christopher Portier et al.: Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA), J Epidemiol Community Health Month, JECH Online First, published on March 3, 2016 as 10.1136/jech-2015-207005.

2. Chemische Stoffe werden als genotoxisch bezeichnet, wenn sie das genetische Material von Zellen verändern.

3. E-Mail von Bundesrat Schneider-Ammann vom 22.05.2017 als Antwort auf ein Schreiben von Bernadette Scherrer (Genkritisches Forum GenAu) und Dr. med. Peter Kälin (AefU) betreffend «Unzulässige Öko-Fördergelder für Glyphosat».

Quelle: Glyphosat: EU-Bewertung hat gravierende Mängel

Video, Wirtschaft Christopher Portier, EFSA, Glyphosat, IARC, Krebs, WHO

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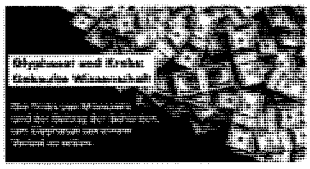

27/03/2017 NPR 0

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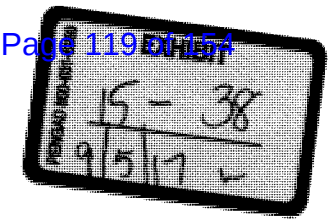

Glyphosate: EU assessment has serious flaws

Martin Forter/Stephanie Fuchs / July 18, 2017 - **US expert Christopher Portier reprimanded the EU authorities: During the risk assessment of glyphosate work had been performed sloppy and flawed.**

Red. * The agency for research on cancer IARC, which belongs to the World Health Organization WHO, has classified the herbicide glyphosate as "probably carcinogenic" in 2015. The California authority for health and environment has recently joint this assessment. Since July 7, 2017 the herbicide is classified as a "carcinogenic substance" in California. Monsanto contests the decision.

On the other hand the European Food Safety Authority EFSA and the German Federal Institute for Risk Assessment (BfR) classified glyphosate as "harmless" in 2016. There is no evidence for a carcinogenic or mutagenic effect of glyphosate, they assessed. The European Chemicals Agency (ECHA) also gave an all-clear in mid-March: According to the expert opinion of ECHA glyphosate is not carcinogenic. Supported by the assessment of the European authorities the EU commission wants to approve glyphosate for another ten years. Experience has shown that Switzerland will strongly follow the measures of the EU.

Objection against the risk assessment of the EU authorities is voiced by Christopher Portier, an expert for chemical security in the US. He has investigated and assessed cancer risks of glyphosate on behalf of the IARC. Portier and other 93 researchers excoriate the European regulatory authority: The assessments of the EU show severe scientific flaws[1], which could mean a "serious danger to public health".

The Interview with Christopher Portier appeared in the professional journal "Oeskop" 2/17 of Ärztinnen und Ärzte für Umweltschutz.

Encountering hostility by the glyphosate lobby

Christopher Portier (PhD) is a mathematician and biostatistician. He was director of the US National Center for Environmental Health, Centers for Disease Control and Prevention, and the US Agency for Toxic Substances and Disease Registry from 2010 - 2013.

Portier has been involved as an external advisor of the assessment of glyphosate at the agency for research on cancer (IARC) of the WHO among others. At that time he worked already for the US environmental fund. To exclude conflicts of interest he was allowed to contribute his expertise but had no voting right. Portier neither wrote assessments nor was he admitted to final assessments. His analysis has, however, contributed to WHO's classification of glyphosate as

* Translators note: Red. Most likely refers to "Redaktion/Redakteur" (English: editorial office/editor)

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Susanna Weerth

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NOTARY PUBLIC OF MARYLAND
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2/17/21

"probably carcinogenic". After the vote of IARC Portier encountered hostility on the internet and also partially in the media by the glyphosate lobby. To protect the work of researchers from such attacks Portier does no longer perform any function at IARC. Today Portier is, among others, an independent advisor of government authorities for several countries.

"Oekoskop": Christopher Portier, you supported the decision of the IARC that glyphosate is to be classified as "probably carcinogenic" and excoriate the contrary assessment by EFSA and ECHA. Why should we trust IARC more than the European authorities?

Christopher Portier: There are a few fundamental differences how IARC or rather EFSA and ECHA arrive at their assessments. The IARC uses solely publicly available study data. It also reviews the raw data of the studies to make sure that all data and numbers are correct. Many studies regarding animal cancer and genotoxicity[2] are, however, property of the industry. They are neither for IARC nor for anyone else publicly available.

It seems that EFSA and ECHA don't review the raw data. If they only review the reports, which the industry submits, it could be that the authorities miss important study results.

From what do you conclude that the authorities don't do this?

The EFSA has missed in their report of the glyphosate assessment eight positive tumor findings in animal studies. The BfR provided the background for this EFSA report. BfR employees confirmed the appropriate critic of numerous researchers. If I would be the head of BfR I would immediately ask myself under these circumstances: Have we missed still other tumors? At this point I would let my employees re-assess the entire data and newly assess the statistical significance of each tumor type. This is the simplest and most obvious thing you can do at a cancer assessment. Nevertheless the BfR did not do this

Why aren't EFSA and ECHA reviewing more accurately?

I cannot speak for them but I can report about my function at a regulatory authority. Everyone is overburdened with work not only at BfR, EFSA and ECHA. In addition the authorities are more and more under pressure to deliver fast results. If glyphosate is not approved for a longer period or even Monsanto looses its approval in Europe, the corporate group looses a lot of money. Thus the authorities are under severe pressure and don't have time.

The approval process has to be independent and transparent

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From Christopher Portier's point of view there is some room for improvement for approval of chemical substances. His requests:

- Companies should submit their documents electronically so that the data need no longer be tediously digitized to review them.
- The industry has to make the raw data of their studies publicly available that everyone has the same possibilities to review. All positive and negative findings should be listed that a faster re-assessment is possible.
- The approval process has to be independent. Today the government decides, who is sitting in the ECHA and who assesses the EFSA report. An independent institution should nominate researchers, who are qualified and come from universities and institutions, which have neither a relationship with the industry nor the authorities. A high degree of independence could so be guaranteed even if the government chooses the nominees in the end.
- Stronger laws about possible conflicts of interests are needed. They are for instance largely absent in the EU. It should also be defined, among others, what a conflict of interest is.
- **Which other differences do you see between IARC and EFSA/ECHA?**
- The regulations by which the IARC as well as the EFSA and ECHA work to assess the scientific evidence for cancer are identical. Therefore you would think that also the conclusions that are drawn are identical. This is not the case. The IARC has found a probable association between glyphosate exposure and non-Hodkin's disease at a review of an epidemiological study. Thus the IARC came to the conclusion that there is limited evidence for cancer diseases in humans. EFSA and ECHA, however, allotted the finding "very limited evidence". This is a category, which does not exist officially. It is not comprehensible what they mean by this.
- **The opposite site accuses IARC just as well that they would work nonscientific: Not only EFSA and ECHA. Also the US environmental protection agency EPA and other authorities say that IARC is wrong concerning glyphosate.**
- If two positive animal studies are on hand the evidence has to be sufficiently categorized. The IARC found with glyphosate four animal studies with positive cancer findings. There was no reason to question them. The findings were feasible and statistically significant compared to control groups. The authorities, however, stated consistently other reasons why the findings would be

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2/17/21

nonetheless no good.

- **The Swiss Federal Councilor Josef Schneider-Amman wrote to us recently: "The conclusions of IARC are not based on new studies but on another assessment method, which does not consider the exposure, i.e. the amount and doses, which an operator and/or user is exposed."[3] What is your position on this?**

- This is right. I don't know the Swiss law but in the EU it is very clear: The dose-response principle is applied to non-genotoxic substances. However if a substance is genotoxic than the dose of the exposure does not play a role and the substance has to be banned according to EU law. Therefore the statement of the Swiss Federal Councilor is no permissible argument at least with regard to EU law for glyphosate.

- Most authorities in the world have determined: If a substance is genotoxic and if it concerns a carcinogen than it is banned.

- **Is glyphosate genotoxic?**

- We don't know for sure: The data of 50 percent of the studies argue for genotixicity, 50 percent against it. In the interest of public health we should therefore classify glyphosate as genotoxic, in my opinion.

- **The regulatory authorities were established in the 1970s to prevent a second "DDT case". In view of the pesticides glyphosate, triclosan or the neonicotinoids: Has this goal been achieved?**

- This is difficult to answer. Since chemical substances were banned we don't know if we actually prevented cancer cases in a preventive manner with this. But it is quiet clear that we have made mistakes since DDT. We have wrongly approached many substances: for instance lead in gas, it has taken long until it was banned. Although it was said lead is a problem, however, only a small one. Then studies showed that the problem could be bigger after all...

- **... is this not always the case?**

- It often happens that the authorities determine a threshold limit value of a substance to realize later that it was too high. They lower it to notice again thereafter that it is still too high. This repeatedly happened with many substances, for example dioxins, dibenzofurans, PCBs and also with the brominated fire-control chemicals.

- It seems, however, to proceed differently with the classical pesticides. Once they are approved, hardly anybody tracks anymore their health consequences. Who explores the question if approved pesticides trigger cancer or not? Some studies with glyphosate, which we reviewed, dated back to the year 1981. Therein tumors emerged even though only about 200 people were considered in most

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cases. During 36 years no regulatory authority worldwide supposedly identified these tumor findings even though the literature includes only nine studies for cancer risk in humans with glyphosate. Imagine already 1981 someone would have discovered this accidental slip and corrected it. This would have resulted in a lower acceptance of glyphosate

- **Take the big US environmental protection agency EPA: Why didn't it detect these tumors?**
- This also surprises me. The EPA stresses that it would re-assess pesticides constantly. EFSA states the same. Obviously they don't do it right. At the right approach these tumor findings are hard to miss.
- **Today we are also facing the problem of novel neonicotinoids, thus insecticides, which are systematically invading our plants. Where the authorities aware of the new dimensions when they approved this new type of pesticides?**
- In former times the very toxic nicotine was used as an insecticide. The neonicotinoids are a lot less toxic, passed the tests and were approved. The approval process had not been specifically adjusted to the new substances. In the meantime we know that neonicotinoide are ecotoxicologically a problem. I am convinced that the evidence exists that they kill bees. I think they are banned and replaced by a new product, which is probably again problematic after that.
- **Bees died already in the 1940s through DDT and then thereafter by all new insecticides that came on the market. The bee tolerance needed to be tested at least today…**
- …this also does not belong to the approval procedure in the US today.
- **Why not?**
- This is an excellent question you should ask the regulatory authorities. In the US insecticides are tested on butterflies but not on bees even though their biology is different. The assessment with butterflies is also very questionable: If 20 percent die due to an insecticide this is deemed to be okay. If more than 20 percent die they look closer. If these are more than 50 percent the substance is banned.
- **How do you see the future of glyphosate?**
- I worked for a long time at regulatory authorities and had the possibility to ban substances. Therefore I answer as a scientist and former official: The EFSA and ECHA have not done their jobs. The information that they delivered to the legislative politicians is not scientifically tenable and qualitatively poor. My priority is not to ban glyphosate. I am basically concerned about the scientific assessment of cancer-causing potentials of substances. For this regulations, with which the authorities have to strictly comply with, exist. This is currently not the

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MY COMMISSION EXPIRES FEBRUARY 17, 2021

I, Susanna Weerth, hereby declare that I am fluent in English and German. I hereby certify that I have translated the attached document and, to the best of my knowledge, it is a true, accurate and complete translation of the original text.

Susanna Weerth

case with glyphosate. If the politicians follow the advise of their authorities the public health protection will fail with glyphosate. Therefore I have pointed out in a letter to the president of the European Commission, Jean-Claude Juncker, the faulty principles he had received from his authorities.

I, Susanna Weerth, hereby declare that I am fluent in English and German. I hereby certify that I have translated the attached document and, to the best of my knowledge, it is a true, accurate and complete translation of the original text.

Susanna Weerth

August 14, 2017

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Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis

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Background: A recent review by the International Agency for Research on Cancer (IARC) updated the assessments of the > 100 agents classified as Group 1, carcinogenic to humans (IARC Monographs Volume 100, parts A–F). This exercise was complicated by the absence of a broadly accepted, systematic method for evaluating mechanistic data to support conclusions regarding human hazard from exposure to carcinogens.

Objectives and Methods: IARC therefore convened two workshops in which an international Working Group of experts identified 10 key characteristics, one or more of which are commonly exhibited by established human carcinogens.

Discussion: These characteristics provide the basis for an objective approach to identifying and organizing results from pertinent mechanistic studies. The 10 characteristics are the abilities of an agent to *1*) act as an electrophile either directly or after metabolic activation; *2*) be genotoxic; *3*) alter DNA repair or cause genomic instability; *4*) induce epigenetic alterations; *5*) induce oxidative stress; *6*) induce chronic inflammation; *7*) be immunosuppressive; *8*) modulate receptor-mediated effects; *9*) cause immortalization; and *10*) alter cell proliferation, cell death, or nutrient supply.

Conclusion: We describe the use of the 10 key characteristics to conduct a systematic literature search focused on relevant end points and construct a graphical representation of the identified mechanistic information. Next, we use benzene and polychlorinated biphenyls as examples to illustrate how this approach may work in practice. The approach described is similar in many respects to those currently being implemented by the U.S. EPA's Integrated Risk Information System Program and the U.S. National Toxicology Program.

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Introduction

Recently, the International Agency for Research on Cancer (IARC) completed a review of all its Group 1 human carcinogens and updated information on tumor sites and mechanisms of carcinogenesis (IARC Monograph Volume 100A–F) (http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php). About half of the agents classified in Group 1 had been last reviewed > 25 years ago, before mechanistic studies became prominent in evaluations of carcinogenicity. In addition, more recent studies have demonstrated that many cancer hazards reported in earlier studies were later observed to also cause cancer in other organs or through different exposure scenarios (Cogliano et al. 2011).

In compiling and updating the information for Volume 100A–F, two overarching issues became apparent. First, no broadly accepted systematic method for identifying, organizing, and summarizing mechanistic data for the purpose of decision making in cancer hazard identification was readily available. Second, the agents documented and listed as human carcinogens showed a number of characteristics that are shared among many carcinogenic agents. Many human carcinogens act via multiple mechanisms causing various biological changes in the multistage process of carcinogenesis. Indeed, cancer was once described by reference to causative agents, with multistage development of tumors being characterized through the impact of particular chemicals described as initiators and promoters of cancer. Subsequently, multistage development of cancer was identified with morphological change being correlated with genetic alterations. The more recent description by Hanahan and Weinberg of hallmarks of cancer is predicated not on morphology or the impact of carcinogens, but on changes in gene expression and cell signaling (Hanahan and Weinberg 2011). These hallmarks are the properties of cancer cells and neoplasms, and are not characteristic of the agents that cause cancer. Tumors attributable to chemical carcinogens may be distinct by mutational analysis (Westcott et al. 2015), but all neoplasms exhibit the hallmarks. A recent computational toxicology study has shown that chemicals that alter the targets or pathways among the hallmarks of cancer are likely to be carcinogenic (Kleinstreuer et al. 2013). In addition, a series of reviews

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in *Carcinogenesis* by members of the Halifax Project Task Force used the hallmarks framework to identify the carcinogenic potential of low doses and mixtures of chemicals (Harris 2015).

In 2012, participants at two workshops convened by the IARC in Lyon, France, extensively debated the mechanisms by which agents identified as human carcinogens (Group 1) produce cancer. The participants concluded that these carcinogens frequently exhibit ≥ 1 of 10 key characteristics (Table 1). Herein we describe these 10 key characteristics and discuss their importance in carcinogenesis. These characteristics are properties that human carcinogens commonly show and can encompass many different types of mechanistic end points. They are not mechanisms in and of themselves nor are they adverse outcome pathways.

Further, we describe how the 10 key characteristics can provide a basis for systematically identifying, organizing, and summarizing mechanistic information as part of the carcinogen evaluation process. The U.S. Environmental Protection Agency (EPA) and the National Toxicology Program (NTP) in the United States, as well as the IARC internationally, have recognized a need for such an approach (Rooney et al. 2014). The U.S. National Research Council (NRC) emphasized the need for consistent, transparent, systematic approaches for the identification, evaluation, and integration of data in the U.S. EPA's Integrated Risk Information System (IRIS) assessments of carcinogens and elsewhere in human health hazard assessments (NRC 2014).

Progress in the systematic evaluation of published evidence on the adverse health effects of environmental agents has been made through application of methods developed by evidence-based medicine (Koustas et al. 2014). However, mechanistic study databases present a challenge to systematic reviews in that the studies are typically both numerous and diverse, reporting on a multitude of end points and toxicity pathways. One recent example of a systematic approach searched for studies on end points relevant to nine cancer-related mechanistic categories in identifying and presenting mechanistic evidence on di(2-ethylhexyl) phthalate, a chemical with a complex database of > 3,000 research papers (Kushman et al. 2013). In this publication, the categories of mechanistic evidence were identified from a compendium of published reviews. This approach may be difficult to translate to agents with controversial or limited mechanistic evidence. It also would not permit comparisons across agents, including attempts to understand similarities or differences with human carcinogens. Further, it may be biased against the most recent mechanistic and molecular epidemiology studies that have not been the subject of a prior expert review.

To facilitate a systematic and uniform approach to organizing mechanistic data relevant to carcinogens, we propose use of the 10 key characteristics of human carcinogens as a basis for identifying and categorizing scientific findings relevant to cancer mechanisms when assessing whether an agent is a potential human carcinogen. A significant advantage of this approach is that it would encompass a wide range of end points of known relevance to carcinogenesis as identified through examination of the IARC Monographs on Group 1 carcinogens. Mechanistic topics can be included regardless of whether they have been the subject of prior expert reviews of any particular chemical. This should introduce objectivity that could reduce reliance on expert opinion, as well as facilitate comparisons across agents. Moreover, at its essence, the approach may afford a broad consideration of the mechanistic evidence rather than focusing narrowly on independent mechanistic hypotheses or pathways in isolation.

Herein, we demonstrate the applicability of this proposed systematic strategy for searching and organizing the literature using benzene and polychlorinated biphenyls (PCBs) as examples. The mechanistic study database for both of these chemicals is large, comprising > 1,800 studies for benzene and almost 3,900 for PCBs, many with multiple mechanistic end points. We conducted systematic literature searches for end points pertinent to the 10 key characteristics of human carcinogens, using literature trees to indicate the human and experimental animal studies that reported end points relevant to each characteristic. To further indicate their potential contribution to benzene and PCB carcinogenesis, we organized the characteristics into a graphical network representative of an overall mechanistic pathway.

Several recent IARC Monographs (e.g., Guyton et al. 2015; Loomis et al. 2015) have applied the 10 key characteristics described here for a variety of agents and organized the literature search results into flow diagrams. Overall, this categorization facilitated objective consideration of the relevant mechanistic information, thereby advancing analyses of hypothesized mechanisms and toxicity pathways. Because mechanistic data may provide evidence of carcinogenicity, and can play a role in up- or downgrading an evaluation based on cancer findings in animals, we suggest that this systematic approach to organizing the available data will assist future IARC Working Groups and other agencies in evaluating agents as potential human carcinogens, especially in the absence of convincing epidemiological data on cancer in humans.

Description of the Key Characteristics of Carcinogens

The number of ways by which agents contribute to carcinogenesis can be extensive if all biochemical or molecular end points are considered. However, these mechanisms can be grouped into a limited number of categories (e.g., genotoxicity, immunosuppression). Guyton et al. (2009) described 15 types of "key events" associated with human carcinogens that collectively represented many carcinogenic mechanisms. The experts present at the first of the IARC meetings in 2012 originally identified 24 mechanistic end points with several subcategories in each. This number of end points was considered too impractical as a guide for categorizing the literature, and the Working Group merged

Table 1. Key characteristics of carcinogens.

Characteristic	Examples of relevant evidence
1. Is electrophilic or can be metabolically activated	Parent compound or metabolite with an electrophilic structure (e.g., epoxide, quinone), formation of DNA and protein adducts
2. Is genotoxic	DNA damage (DNA strand breaks, DNA–protein cross-links, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g., chromosome aberrations, micronuclei)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g., topoisomerase II, base-excision or double-strand break repair)
4. Induces epigenetic alterations	DNA methylation, histone modification, microRNA expression
5. Induces oxidative stress	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g., DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Is immunosuppressive	Decreased immunosurveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g., ER, PPAR, AhR) or modulation of endogenous ligands (including hormones)
9. Causes immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell cycle control, angiogenesis

Abbreviations: AhR, aryl hydrocarbon receptor; ER, estrogen receptor; PPAR, peroxisome proliferator–activated receptor. Any of the 10 characteristics in this table could interact with any other (e.g., oxidative stress, DNA damage, and chronic inflammation), which when combined provides stronger evidence for a cancer mechanism than would oxidative stress alone.

these categories into 10 at the second meeting in 2012, concluding that human carcinogens commonly show ≥ 1 of the 10 key characteristic properties listed in Table 1. These represent the majority of established properties of human carcinogens as described below.

Characteristic 1: Is Electrophilic or Can Be Metabolically Activated to Electrophiles

Electrophiles are electron-seeking molecules that commonly form addition products, commonly referred to as adducts, with cellular macromolecules including DNA, RNA, lipids, and proteins. Some chemical carcinogens are direct-acting electrophiles, whereas others require chemical conversion within the body (Salnikow and Zhitkovich 2008) or biotransformation by enzymes in a process termed metabolic activation (Miller 1970). Examples of direct-acting electrophilic carcinogens include sulfur mustards and ethylene oxide (Batal et al. 2014; Grosse et al. 2007; IARC 2008; Rusyn et al. 2005). The classic examples of chemical agents that require metabolic activation to become carcinogenic include polycyclic aromatic hydrocarbons, aromatic amines, *N*-nitrosamines, aflatoxins, and benzene, which by themselves are relatively inert (Slaga et al. 1980; Smith 1996). A number of enzymes, including cytochrome P450s, flavin monooxygenase, prostaglandin synthase, and various peroxidases, can biotransform relatively inert chemical compounds to potent toxic and carcinogenic metabolites or reactive intermediates (Hecht 2012; O'Brien 2000). The ability to form adducts on nucleic acids and proteins is a common property of these inherently electrophilic and/or metabolically activated human carcinogens (Ehrenberg 1984).

Characteristic 2: Is Genotoxic

The term "genotoxic" (Ehrenberg et al. 1973) refers to an agent that induces DNA damage, mutation, or both. DNA damage can be spontaneous in origin through errors of nucleic acid metabolism or can be induced by endogenous or exogenous agents. In some cases the exogenous agents may also be generated endogenously, such as formaldehyde and acetaldehyde, producing a background level of DNA damage. Examples of DNA damage include DNA adducts (a molecule bound covalently to DNA), DNA strand breaks (breaks in the phosphodiester bonds), DNA crosslinks, and DNA alkylation. DNA damage by itself is not a mutation and generally does not alter the linear sequence of nucleotides (or bases) in the DNA, whereas a mutation is a change in the DNA sequence and usually arises as the cell attempts to repair the DNA damage (Shaughnessy and DeMarini 2009).

Mutations can be classified into three groups based on their location or involvement in the genome. Gene or point mutations are changes in nucleotide sequence within a gene (e.g., base substitutions, frameshifts, and small deletions/duplications). Chromosomal mutations are changes in nucleotide sequence that extend over multiple genes (e.g., chromosome aberrations, translocations, large deletions, duplications, insertions, inversions, or micronuclei due to chromosome breakage). Genomic mutations involve the duplication or deletion of nucleotide sequences of an entire chromosome, an example of which is aneuploidy or formation of micronuclei that contain a centromere. A large proportion of Group 1 carcinogens are genotoxic, as documented in IARC Monographs Volume 100 A–F.

Characteristic 3: Alters DNA Repair or Causes Genomic Instability

Normal cells avoid deleterious mutations by replicating their genomes with high accuracy. However, the fidelity of DNA replication can vary widely depending on the DNA polymerase involved, introducing the possibility of error. Indeed, most spontaneous mutations are caused by polymerase error (Preston et al. 2010). The nature of the error, the flanking sequence, the presence of DNA damage, and the ability to correct errors all affect the outcome of this process (Arana and Kunkel 2010). As a consequence, defects in processes that determine DNA-replication fidelity can confer strong mutator phenotypes that result in genomic instability. Thus, carcinogens may act not only by producing DNA damage directly, but also by altering the processes that control normal DNA replication or repair of DNA damage. Examples include the inhibition of DNA repair by cadmium (Candéias et al. 2010) and formaldehyde (Luch et al. 2014).

Genomic instabiliry is a well-recognized feature of many cancers (Bielas et al. 2006) and is considered to be one of the enabling characteristics of cancer (Hanahan and Weinberg 2011). Cells exposed to ionizing radiation have genetic instability that is a relatively late-occurring event that appears several cell generations after irradiation and results in a reduced ability to replicate the genotype faithfully (Kadhim et al. 2013). The events indicating genomic instability include chromosome aberrations, gene mutations, microsatellite instability, and apoptosis. These events are observed after exposure to arsenic (Bhattacharjee et al. 2013) and cadmium (Filipic 2012).

Characteristic 4: Induces Epigenetic Alterations

The term "epigenetic" refers to stable changes in gene expression and chromatin organization that are not caused by changes in the DNA sequence itself and can be inherited over cell divisions (Herceg et al. 2013). Epigenetic phenomena, including changes to the DNA methylome and chromatin compaction states, along with histone modification can impact the carcinogenic process by affecting gene expression and DNA repair dynamics (Herceg et al. 2013). A wide range of carcinogens have been shown to deregulate the epigenome, and it has been suggested that their mechanism may involve disruption of epigenetic mechanisms (Pogribny and Rusyn 2013). However, evidence for a causal role of epigenetic changes in cancer caused by Group 1 agents was considered to be limited in Volume 100, and the impact of many agents on the epigenome was considered to be a secondary mechanism of carcinogenesis (Herceg et al. 2013). Herceg et al. (2013) have described a wealth of studies demonstrating the impact of carcinogens on epigenetic mechanisms. Most carcinogens (even those reviewed for Volume 100) were evaluated by IARC Working Groups before new data on their epigenetic effects became available (Chappell et al. 2016). This evolving area will generate new mechanistic data in the years to come.

Characteristic 5: Induces Oxidative Stress

Many carcinogens are capable of influencing redox balance within target cells. If an imbalance occurs, favoring formation of reactive oxygen and/or nitrogen species at the expense of their detoxification, this is referred to as oxidative stress. Reactive oxygen species and other free radicals arising from tissue inflammation, xenobiotic metabolism, interruption of mitochondrial oxidative phosphorylation (Figueira et al. 2013), or reduced turnover of oxidized cellular components may play key roles in many of the processes necessary for the conversion of normal cells to cancer cells. However, oxidative stress is not unique to cancer induction and is associated with a number of chronic diseases and pathological conditions—for example, cardiovascular disease (Kayama et al. 2015), neurodegenerative disease (Chen et al. 2016), and chronic inflammation (Suman et al. 2015). Oxidative stress is also a common occurrence in neoplastic tissue and can be part of the tumor environment (Suman et al. 2015).

Oxidative damage is considered a major factor in the generation of mutations in DNA, and > 100 different types of oxidative DNA damage have been identified (Klaunig et al. 2011). At least 24 base modifications are produced by reactive oxygen species, as well as DNA–protein crosslinks and other lesions (Berquist and Wilson 2012), all potentially leading to genomic instability. Oxidative damage to DNA can lead to point mutations, deletions, insertions, or

chromosomal translocations, which may cause oncogene activation and tumor suppressor gene inactivation, and potentially initiate or promote carcinogenesis (Berquist and Wilson 2012; Klaunig et al. 2011). Thus, the induction of oxygen radical–induced cellular injury is a characteristic of a set of diverse carcinogens, including radiation, asbestos, and carcinogenic infectious agents.

Characteristic 6: Induces Chronic Inflammation

Chronic inflammation from persistent infections, such as that caused by *Helicobacter pylori*, as well as that produced by chemical agents including silica or asbestos fibers, has been associated with several forms of cancer (Grivennikov et al. 2010). Indeed, inflammation has been hypothesized to contribute to multiple aspects of cancer development and progression (Trinchieri 2012) and is an enabling hallmark of cancer (Hanahan and Weinberg 2011). Inflammation acts by both intrinsic and extrinsic pathways. Persistent infection and chronic inflammation disrupt local tissue homeostasis and alter cell signaling, leading to the recruitment and activation of inflammatory cells. These constitute extrinsic pathways linking inflammation to cancer (Multhoff and Radons 2012). On the other hand, intrinsic pathways driven by activation of proto-oncogenes in pre-neoplastic and neoplastic cells recruit host-derived inflammatory cells that accelerate tumor promotion and progression (Grivennikov et al. 2010). Because strong links exist between inflammation and the induction of oxidative stress and genomic instability, it may be difficult to separate out the importance of each of these mechanisms.

Characteristic 7: Is Immunosuppressive

Immunosuppression is a reduction in the capacity of the immune system to respond effectively to foreign antigens, including antigens on tumor cells. Persistent immunosuppression presents a risk of cancer, especially excess risk for lymphoma. For example, immunosuppression poses a significant risk when it is accompanied by continuing exposure to foreign antigens, such as in people with organ transplants, or when it occurs in individuals who are latently infected with a carcinogenic virus (Hartge and Smith 2007; Smith et al. 2004). Immune suppression differs from other mechanisms of carcinogenesis in that agents that cause immunosuppression may not directly transform normal cells into potential tumor cells. Potentially neoplastic cells that arise naturally, or that have been transformed by other carcinogens acting by a mechanism such as genotoxicity or by the various mechanisms of action associated with carcinogenic viruses, escape immune surveillance in immunosuppressed individuals. As a result, survival of these cells and their replication to form tumors is greatly facilitated by immune suppression. Several carcinogens act entirely or largely by immunosuppression, often in concert with other Group 1 agents, especially oncogenic infectious agents. The Group 1 agents that act by immunosuppression include human immunodeficiency virus (HIV-1) and the immunosuppressive drug cyclosporin (Rafferty et al. 2012).

Characteristic 8: Modulates Receptor-Mediated Effects

Numerous carcinogens act as ligands to receptor proteins, including menopausal hormone therapy, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and PCBs (Wallace and Redinbo 2013). Receptor-mediated activation broadly falls into two categories: *a*) intracellular activation, mediated by nuclear receptors that translocate into the nucleus and act on DNA as transcription factors (Aranda and Pascual 2001); and *b*) activation of cell surface receptors that induce signal-transduction pathways resulting in biological responses that involve a variety of protein kinases (Griner and Kazanietz 2007). Most exogenous agents act as agonists by competing for binding with an endogenous ligand; however, there are also receptors for which few or no endogenous ligands have been identified, such as the aryl hydrocarbon (Ah) receptor (Baek and Kim 2014; Ma 2011). Receptor-mediated activation most often results in changes in gene transcription. Molecular pathways that are regulated through ligand-receptor interaction and are most relevant to carcinogenesis include cell proliferation (e.g., stimulation of the normal proliferative pathways, as is the case for estrogen-dependent tissues and hormone therapy), xenobiotic metabolism, apoptosis, as well as modulation of the bioavailability of endogenous ligands by affecting biosynthesis, bioactivation, and degradation (Rushmore and Kong 2002).

Characteristic 9: Causes Immortalization

Several human DNA and RNA viruses, including various human papillomaviruses, Epstein-Barr virus, Kaposi sarcoma–associated herpes virus, hepatitis B virus, hepatitis C virus, HIV, Merkel cell polyomavirus (MCPyV), and human T-lymphotropic virus type 1 (HTLV-1) are carcinogenic to humans (Bouvard et al. 2009). These viruses have evolved multiple molecular mechanisms to disrupt specific cellular pathways to facilitate aberrant replication. Although oncogenic viruses belong to different families, their strategies in human cancer development show many similarities and involve viral-encoded oncoproteins targeting the key cellular proteins that regulate cell growth (Saha et al. 2010). Recent studies show that virus and host interactions also occur at the epigenetic level (Allday 2013). The result of these viral effects is to immortalize the target tissue cells such that they are not subject to the Hayflick limit, the point at which cells can no longer divide due to DNA damage or shortened telomeres (Klingelhutz 1999). For example, the human papilloma virus type 16 (HPV-16) *E6* and *E7* oncogenes are selectively retained and expressed in cervical carcinomas, and expression of *E6* and *E7* is sufficient to immortalize human cervical epithelial cells (Yugawa and Kiyono 2009).

Characteristic 10: Alters Cell Proliferation, Cell Death, or Nutrient Supply

There are at least three scenarios related to carcinogenesis in which alterations in cellular replication and/or cell-cycle control have been described. One invokes the predisposition for unrepaired DNA damage leading to cancer-causing mutations in replicating cells; another has attempted to identify sustained replication as a key mechanistic event; and a third describes the ability of a transformed cell to escape normal cell-cycle control and to continue replication. A component common to all three scenarios is the evasion of apoptosis or other terminal programming, including autophagy, in at least a proportion of the cell population (Ryter et al. 2014).

Necrotic cell death releases pro-inflammatory signals into the surrounding tissue microenvironment, recruiting inflammatory immune cells to the site of trauma, which can enhance cancer-cell proliferation and promote cancer metastasis (Coussens and Pollard 2011; Coussens et al. 2013; Pollard 2008). In contrast, various forms of apoptosis and autophagy (Galluzzi et al. 2015) have the opposite effect by removing potentially cancerous cells from a population before they acquire the changes permitting malignancy. Many agents affect necrosis, apoptosis, and/or autophagy and can have profoundly divergent effects on cancer induction in different tissues.

In addition to cell death caused directly by agent toxicity, cells may die within a tumor as a result of an impaired nutrient supply. Neoplastic cell numbers can increase exponentially, quickly outstripping the supply capabilities of the existing tissue vasculature. Neoangiogenesis, in which new blood vessels grow into a tumor, is key to providing this supply of nutrients. Thus, agents that promote or inhibit angiogenesis will promote or delay tumor growth (Hu et al. 2015).

Cancer cells also usually show quite different cellular energetics, relying on glycolysis for energy even under aerobic conditions (Rajendran et al. 2004). Although a likely

consequence of mutation and altered gene expression rather than a cancer-inducing mechanism, any modification of cellular energetics may reflect an important cancer-relevant switch in the cell's or tissue's metabolic state.

Using the Key Characteristics to Systematically Identify, Organize, and Summarize Mechanistic Information

Step 1: Identifying the Relevant Information

The starting point for systematic evaluation is to conduct comprehensive searches of the peer-reviewed literature aimed at identifying mechanistic data (Kushman et al. 2013). The searches can be constructed to address a series of study questions in the PECO (population, exposure, comparator, and outcomes) framework (Higgins and Green 2011) wherein end points associated with the key characteristics are identified. Specifically, the question to be answered by the searches is "Does exposure to the agent induce end points associated with one or more specific key characteristic properties of carcinogens?" The population (humans and any relevant experimental systems), exposure (the agent and relevant metabolites), and comparator (the unexposed comparison group or condition) should be sufficiently broad to identify a range of available mechanistic data informative of the overall evaluation of carcinogenic hazard. This approach thus entails comprehensive, targeted literature searches using appropriate medical search heading (MeSH) terms and key words to identify evidence on the 10 key characteristics for the agent(s) or exposure(s) under evaluation.

Additional complementary literature searches may incorporate terms for the agent and its metabolites, alone or in combination with broad terms for carcinogenicity or related effects. For instance, because U.S. EPA IRIS toxicological reviews also encompass a range of non-cancer toxicities, "top-down" broad literature searches aimed at comprehensively identifying studies on all potential toxic effects of an agent are employed (NRC 2014; U.S. EPA 2014). These comprehensive searches of peer-reviewed literature are supplemented by examining past IARC Monographs or other authoritative reviews, databases (e.g., PubChem), and peer-reviewed government reports can also be systematically searched. The search terms used and literature retrieved

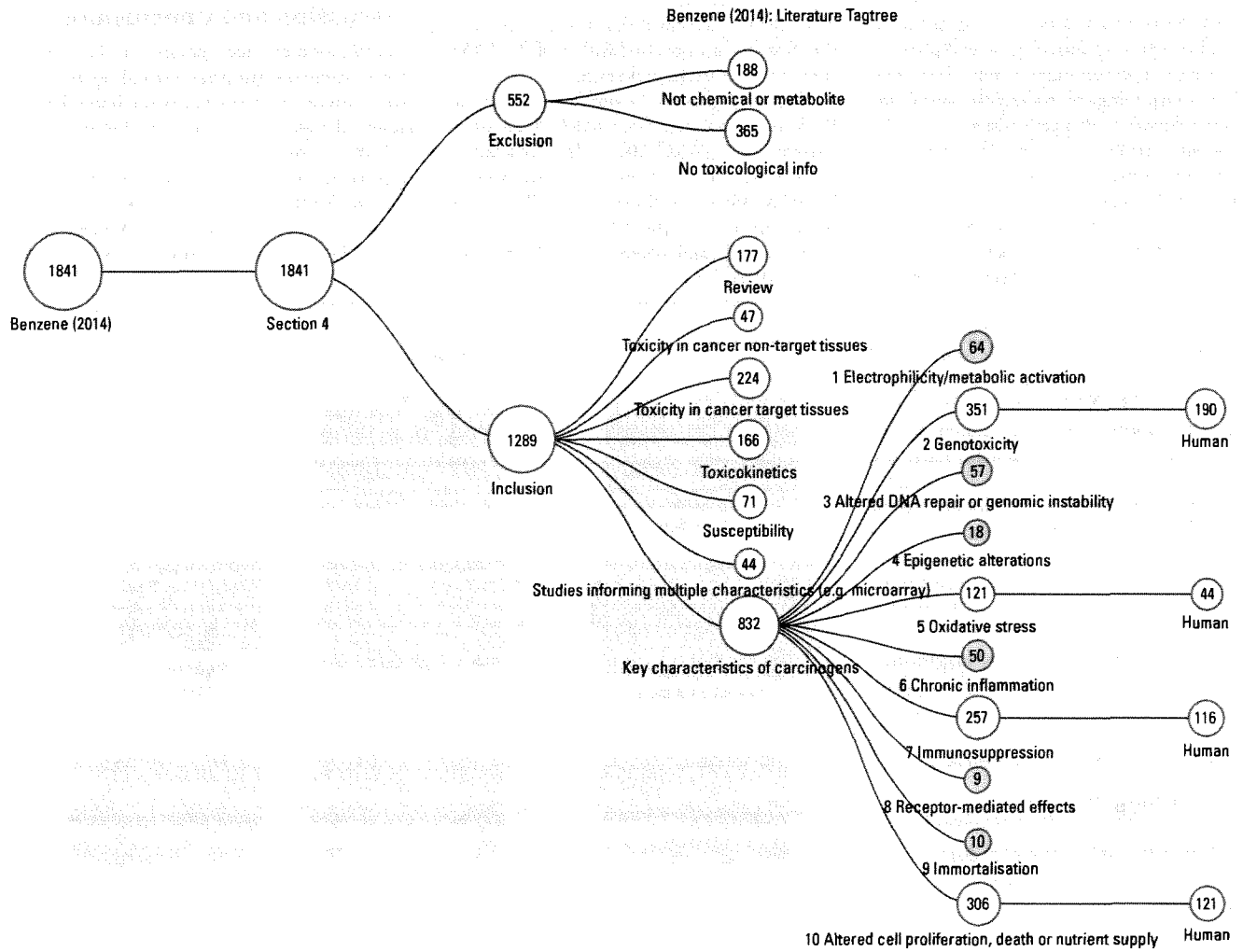

Figure 1. Literature flow diagram, illustrating the systematic identification and categorization process for benzene mechanistic studies. Using appropriate MeSH terms and key words, targeted literature searches were conducted for the 10 key characteristics using online tools available from the HAWC Project (https://hawcproject.org/). Section 4 refers to the location of the discussion of mechanistic data within the IARC Monograph structure (http://monographs.iarc.fr/ENG/Preamble/currentb4studiesother0706.php). All inclusion categories were expanded to document the number of studies attributed to each, down to the individual key characteristic level, which were expanded to illustrate human information when > 100 total studies were identified. Less frequently encountered key characteristic categories (blue-shaded circles) were left unexpanded for clarity. "Human" refers to both humans exposed *in vivo* and human cells exposed *in vitro*.

can be documented (e.g., using MyNCBI, which saves searches of the National Center for Biotechnology database, or https://hawcproject.org/).

Step 2: Screening and Organizing the Results

Based on title and abstract review, studies identified initially are excluded if no data on the chemical or a metabolite are reported, or if no data on toxicological or other cancer-related effects of the chemical are provided. For example, a study on levels of a chemical, but not effects of the chemical, would be excluded. Included studies are then organized by the population (human or experimental systems) and by the end points associated with the 10 key characteristics (Table 1). Studies relevant to toxicokinetics (covering absorption, distribution, metabolism, and excretion) are also identified. Additionally, authoritative, comprehensive review articles are identified, as are studies reporting toxicological end points in cancer target and non-target tissues. These may include morphological evaluations pertaining to the dysfunction of organs, tissues, and cells. Importantly, studies reporting end points that are relevant to multiple characteristics may fall under several categories.

To illustrate these two steps, targeted literature searches were conducted to identify end points for the effects of benzene pertinent to the 10 key characteristics, in populations comprising humans or experimental systems. The literature searches were conducted using the Health Assessment Workplace Collaborative (HAWC) Literature Search tool (https://hawcproject.org/), documenting the search terms, sources, and articles retrieved. Following title and abstract review, studies were excluded if they were not about benzene or its metabolites, or if they reported no data on toxicological end points. Included studies were further sorted into categories representing the 10 key characteristics based on the mechanistic end points and species evaluated (i.e., human *in vivo*, human *in vitro*, mammalian *in vivo*, mammalian *in vitro*, nonmammalian; Figure 1). The figure also identifies reviews, gene expression studies, and articles relevant to toxicokinetics, toxicity, or susceptibility.

Step 3: Using the Key Characteristics to Synthesize Mechanistic Information and to Develop Adverse-Outcome Networks

It is increasingly evident that multiple biological alterations or sets of different perturbations are necessary to convert a normal cell to a transformed cell and ultimately a tumor (Hanahan and Weinberg 2011). Carcinogens appear to affect this complex process in various ways and can act through multiple mechanisms to induce cancer and other adverse health outcomes (Goodson et al. 2015; Guyton et al. 2009). Using the 10 key characteristics as a basis, the collected information can be organized to form hypotheses and evaluate the evidentiary support for mechanistic events as a function of relevant aspects (e.g., dose, species, temporality) (Guyton et al. 2009). The diverse and complex mechanistic end points elicited by benzene can then be organized into an overview inclusive of multiple alterations and any linkages thereof (Figure 2). The resulting overview can provide guidance for further assessments of the literature, including dose relevance, species relevance, and temporality of events. This additional detailed information can then be used to produce proposed mechanisms or adverse outcome pathway networks as described by McHale et al. (2012) and the EPA's NexGen Risk Assessment Report (U.S. EPA 2014). We note that there is evidence that benzene is associated with 8 of the 10 key characteristics we have described.

Figure 3 presents a similar overview for PCBs based on data from IARC Monograph Volume 107 (IARC 2015). In summarizing the mechanistic evidence, this Monograph Working Group indicated that PCBs may induce up to 7 of the 10 key characteristics in producing carcinogenicity (Lauby-Secretan et al. 2013). The less chlorinated PCBs are associated with key characteristics similar to benzene (metabolic activation, DNA damage, cellular proliferation), whereas the dioxin-like PCBs are associated primarily with receptor-mediated activities.

Recently, using this same approach, the Working Groups of IARC Monograph Volume 112 and Volume 113 (in progress) concluded that strong mechanistic evidence exists for five key characteristics being involved in malathion carcinogenicity (i.e., genotoxicity, oxidative stress, inflammation, receptor-mediated effects, and cell proliferation or death), three in DDT carcinogenicity (i.e., immunosuppression, receptor-mediated effects and oxidative stress), and two each for diazinon and glyphosate (i.e., genotoxicity and oxidative stress), providing evidence to support their classification as probable human carcinogens in Group 2A (Guyton et al. 2015; Loomis et al. 2015).

Discussion and Conclusions

Identification and incorporation of important, novel scientific findings providing insights into cancer mechanisms is an increasingly essential aspect of carcinogen hazard identification and risk assessment. Systematic approaches are needed to organize the available mechanistic data relevant to the overall evaluation of the carcinogenic hazard of an agent. Information to support the identification of 10 key characteristics of human carcinogens was obtained during the Volume

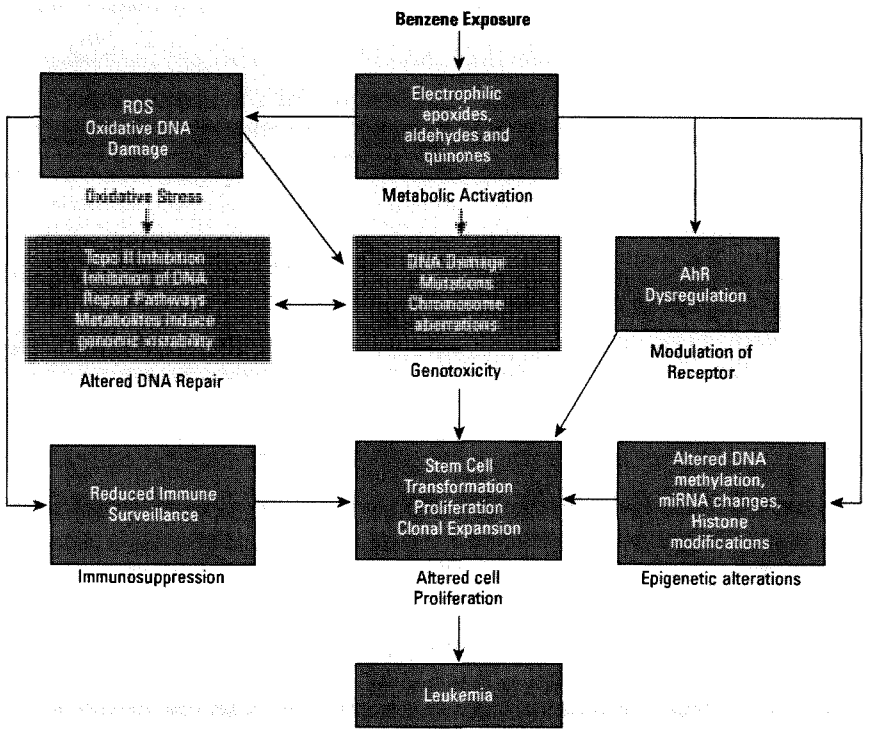

Figure 2. An overview of how benzene induces eight of the key characteristics in a probable mechanism of carcinogenicity. A full review of these mechanistic data is given by McHale et al. (2012), from which this figure was adapted.

100 Monographs and two subsequent expert workshops. These characteristics, although not necessarily representing mechanisms themselves, provide the rationale for an objective approach to identifying and organizing relevant mechanistic data. Using literature collected previously by others as well as by us, we have categorized the literature data according to the 10 characteristics for benzene and PCBs. This approach identified pertinent positive literature for 8 of the 10 key characteristics on benzene and 7 for PCBs, thereby providing a practical, objective method for organizing the large mechanistic literature associated with these chemicals.

This approach also lays the groundwork for a structured evaluation of the strength of the mechanistic evidence base, and therefore its utility in supporting hazard classifications. In the IARC Monographs the strength of the evidence that any carcinogenic effect observed is attributable to a particular mechanism is evaluated using the terms "weak," "moderate," or "strong" (http://monographs.iarc.fr/ENG/Preamble/index.php). In general, the strongest indications that a particular mechanism operates in humans derive from data obtained in exposed humans or in human cells *in vitro*. Data from experimental animals can support a mechanism by findings of consistent results and from studies that challenge the hypothesized mechanism experimentally. Other considerations include whether multiple mechanisms might contribute to tumor development, whether different mechanisms might operate in different dose ranges, whether separate mechanisms might operate in humans and experimental animals, and whether a unique mechanism might operate in a susceptible group. The possible contribution of alternative mechanisms must be considered before concluding that tumors observed in experimental animals are not relevant to humans. An uneven level of experimental support for different mechanisms may reflect that disproportionate resources have been focused on investigating a favored mechanism. All of these factors make assignment of descriptors such as "strong" to the mechanistic evidence challenging; but recent experience with two IARC Monograph meetings suggest that the weighing of the evidence on the basis of the 10 key characteristics focuses the group discussion on the available science and allows rapid consensus to be reached regardless of the strength of the evidence base (Guyton et al. 2015; Loomis et al. 2015).

Because the literature search and categorization approach described herein is comprehensive, it may aid consideration of the overall strength of the mechanistic database according to these principles. In particular, it is inclusive of diverse mechanistic evidence, enabling support for divergent or related mechanisms from human and experimental systems to be identified. Moreover, the literature support for end points relevant to specific mechanisms can be evaluated in an integrated manner when the mechanism is complex. Additionally, comparisons across agents will be facilitated, including evaluation of any similarities or differences in the pattern of key characteristics with agents that are currently classified.

As this approach is carried forward, we hope it will facilitate the objective identification of mechanistic data for consideration in the context of epidemiology, animal bioassay, or other types of evidence (e.g., studies in model organisms or *in vitro* assays) when classifying agents with regard to carcinogenic hazard. Equally important is to consider whether key characteristics of carcinogens are apparent upon exposures that are relevant to human health (Thomas et al. 2013). Overall, these developments will aid advancement of future evaluations of newly introduced agents, including those for which mechanistic data provide the primary evidence of carcinogenicity.

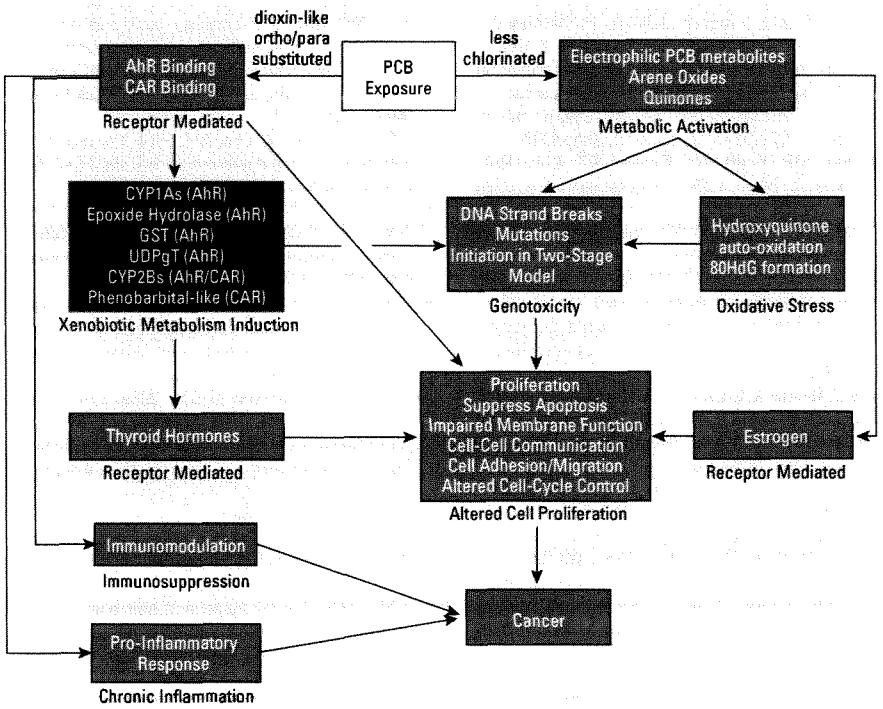

Figure 3. An overview of how polychlorinated biphenyls (PCBs) may induce seven key characteristics in their carcinogenicity (Lauby-Secretan et al. 2013). Highly chlorinated PCBs act as ligands for the aryl hydrocarbon receptor (AhR) and other receptors activating a large number of genes in a tissue- and cell-specific manner that can lead to cell proliferation, apoptosis, and other effects that influence cancer risk. Less chlorinated PCBs can be activated to electrophilic metabolites, such as arene oxides and quinones, which can cause genotoxic effects and induce oxidative stress. Receptor binding to CAR (constitutive androstane receptor) and AhR (a key characteristic) leads to xenobiotic metabolism induction (not a key characteristic; brown box) that in turn leads to genotoxicity and other key characteristics.

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Biomonitoring of Genotoxic Risk in Agricultural Workers from Five Colombian Regions: Association to Occupational Exposure to Glyphosate

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In order to assess possible human effects associated with glyphosate formulations used in the Colombian aerial spray program for control of illicit crops, a cytogenetic biomonitoring study was carried out in subjects from five Colombian regions, characterized by different exposure to glyphosate and other pesticides. Women of reproductive age (137 persons 15–49 yr old) and their spouses (137 persons) were interviewed to obtain data on current health status, history, lifestyle, including past and current occupational exposure to pesticides, and factors including those known to be associated with increased frequency of micronuclei (MN). In regions where glyphosate was being sprayed, blood samples were taken prior to spraying (indicative of baseline exposure), 5 d after spraying, and 4 mo after spraying. Lymphocytes were cultured and a cytokinesis-block micronucleus cytome assay was applied to evaluate chromosomal damage and cytotoxicity. Compared with Santa Marta, where organic coffee is grown without pesticides, the baseline frequency of binucleated cells with micronuclei (BNMN) was significantly greater in subjects from the other four regions. The highest frequency of BNMN was in Boyacá, where no aerial eradication spraying of glyphosate was conducted, and in Valle del Cauca, where glyphosate was used for maturation of sugar cane. Region, gender, and older age (≥35 yr) were the only variables associated with the frequency of BNMN measured before spraying. A significant increase in frequency of BNMN between first and second sampling was observed in Nariño, Putumayo, and Valle immediately (<5 d) after spraying. In the post-spray sample, those who reported direct contact with the eradication spray showed a higher quantitative frequency of BNMN compared to those without glyphosate exposure. The increase in frequency of BNMN observed immediately after the glyphosate spraying was not consistent with the rates of application used in the regions and there was no association between self-reported direct contact with eradication sprays and frequency of BNMN. Four months after spraying, a statistically significant decrease in the mean frequency of BNMN compared with the second sampling was observed in Nariño, but not in Putumayo and Valle del Cauca. Overall, data suggest that genotoxic damage associated with glyphosate spraying for control of illicit crops as evidenced by MN test is small and appears to be transient. Evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for coca and poppy eradication is low.

Glyphosate (*N*-phosphonomethyl glycine), a nonselective herbicide, is the active ingredient of a number of herbicide formulations and one of the most widely used pesticides on a global basis (Baylis, 2000; Woodburn, 2000; Duke & Powles, 2008). It is a postemergence herbicide, effective for the control of annual, biennial, and perennial species of grasses, sedges, and broadleaf weeds. The relatively high water solubility and the ionic nature of glyphosate retard penetration through plant hydrophobic cuticular waxes. For this reason, glyphosate is commonly formulated with surfactants that decrease the surface tension of the solution and increase penetration into the tissues of plants (World Health Organization International Program on Chemical Safety, 1994; Giesy et al., 2000).

A large number of glyphosate-based formulations are registered in more than 100 countries and are available under different brand names. One of the most commonly applied glyphosate-based products is Roundup, containing glyphosate as the active ingredient (AI) and polyethoxylated tallowamine

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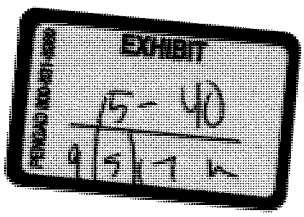

(POEA) as a surfactant. Glyphosate and its formulations have been extensively investigated for potential adverse effects in humans (Williams et al., 2000). This pesticide was reported to exert a low acute toxicity to different animal species. Experimental evidence showed that glyphosate did not bioaccumulate in any animal tissues (Williams et al., 2000). Chronic feeding studies in rodents did not find evidence of carcinogenic activity or any other relevant chronic effects (U.S. EPA, 1993; World Health Organization International Program on Chemical Safety, 1994).

With in vitro studies with tissue cultures or aquatic organisms, several of the formulated products are more toxic than glyphosate AI (Giesy et al., 2000; Williams et al., 2000). Differences in the response of test organisms to the AI and the commercial formulation, e.g., Roundup, are likely due to the toxicity of different formulants and surfactants contained in commercial products. There is a general agreement that adjuvants may be more toxic for animals than glyphosate itself (Giesy et al., 2000; Williams et al., 2000; Richard et al., 2005). Cytotoxicity of the commercial formulation Roundup to human peripheral mononuclear cells was 30-fold higher (LC_{50} = 56 mg/L) than for the AI (LC_{50} = 1640 mg/L) (Martinez et al., 2007). Several in vitro and in vivo studies with parallel testing of glyphosate AI and Roundup showed that only the commercial formulation was genotoxic (Rank et al., 1993; Bolognesi et al., 1997b; Gebel et al., 1997; Grisolia 2002). Cytotoxic and genotoxic effects were observed with Roundup and other formulations of glyphosate, but not with glyphosate AI alone in comparative studies involving different experimental systems (Peluso et al., 1998; Richard et al., 2005; Dimitrov et al., 2006). The observed differences were attributed to some ingredients of Roundup, mainly surfactants, and/or to a synergic effect of glyphosate and components of the formulation (Sirisattha et al., 2004; Peixoto 2005).

Epidemiological studies generally showed no consistent or strong relationships between human exposure to glyphosate or glyphosate-containing products and health outcomes in human populations. No statistically significant association in humans was found with spontaneous abortion, fetal deaths, preterm birth, neural tube defects (Rull et al., 2006), and cancer incidence overall, although a suggested association between cumulative exposure to glyphosate and the risk of multiple myeloma was reported (De Roos et al., 2005).The epidemiologic evidence is insufficient to verify a cause–effect relationship for childhood cancer (Wigle et al., 2008). Four case-control studies suggested an association between reported glyphosate use and the risk of non-Hodgkin's lymphoma (NHL) in age groups from 20 to 70 yr (Hardell & Eriksson, 1999; McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003; Eriksson et al., 2008).

Glyphosate AI and Roundup were extensively tested for genotoxicity in a wide range of in vitro and in vivo systems evaluating different genetic endpoints (gene mutation, chromosome mutation, DNA damage and repair) using bacteria and mammalian somatic cells (Williams et al., 2000). The active ingredient did not induce any relevant genotoxic effects such as gene mutations in a variety of in vitro bacterial assays including the *Salmonella typhimurium* reversion assay, with and without metabolic activation (Wildeman & Nazar 1982; Moriya et al., 1983; Li & Long, 1988) and *Escherichia coli* WP-2 (Moriya et al., 1983; Li & Long, 1988). The active ingredient was also negative in the Chinese hamster ovary cell HGPRT gene mutation assay and in primary hepatocyte DNA repair assay (Li & Long, 1988). The genotoxic potential of the formulation Roundup was investigated in a number of studies evaluating various genetic endpoints in different biological systems and was (1) negative in the *S. typhimurium* reversion assay (Kier et al., 1997), (2) negative in the sex-linked recessive lethal assay with *Drosophila melanogaster* (Gopalan & Njagi, 1981), and (3) negative for in vivo micronucleus (MN) induction in mouse bone marrow (Rank et al., 1993; Kier et al., 1997; Dimitrov et al., 2006). The Roundup formulation was reported in a number of studies to exert weak genotoxic effects in short-term assays.

Differences in the response of test organisms to the active ingredient glyphosate and the commercial formulation Roundup might be due to the toxicity of different co-formulants and surfactants contained in commercial products. Several studies with parallel testing of glyphosate and Roundup showed that only the commercial formulation was genotoxic (Rank et al., 1993; Bolognesi et al., 1997b; Gebel et al., 1997; Grisolia 2002). A recent study on the genotoxic potential of glyphosate formulations found that in some cases the genotoxic effects were obtained under exposure conditions that are not relevant for humans (Heydens et al., 2008).

An in vitro study described a concentration-dependent increase of DNA single-strand breaks (SSB), evaluated by comet assay, in two different human cell lines treated with glyphosate at sublethal concentrations (Monroy et al., 2005). Roundup formulations were shown to affect the cell cycle by inhibiting the G2/M transition and DNA synthesis leading to a genomic instability (Marc et al., 2004a, 2004b). Evidence of DNA damage in peripheral lymphocytes from a small group of subjects potentially exposed to glyphosate was reported in a recent paper (Paz-y-Miño et al., 2007). The number of subjects (21 control and 24 exposed) was small and there were 23 females and only 1 male in the exposed group, making interpretation of the results difficult.

Frequency of MN in human lymphocytes has been widely used for biomonitoring exposure to pesticides (Bolognesi, 2003; Costa et al., 2006; Montero et al., 2006). The MN test, an index of chromosomal damage, is one of the most appropriate biomarkers for monitoring a cumulative exposure to genotoxic agents. Chromosomal damage, as a result of inefficient or incorrect DNA repair, is expressed during the cell

division and represents an index of accumulated genotoxic effects. The cytokinesis-block micronucleus (CBMN) methodology (Fenech & Morley, 1985) allows a distinction to be made between a mononucleated cell that did not divide and a binucleated cell that has divided once, expressing any genomic damage associated to recent exposure. The test in its comprehensive application, as was proposed by Fenech (2007) including a set of markers of gene amplification, cellular necrosis, and apoptosis, allows evaluation of genotoxic and cytotoxic effects induced by exposure to a genotoxic agent.

Colombia's anti-drugs strategy includes a number of measures ranging from aerial spraying of a mixture of a commercial formulation of glyphosate (Glyphos) and an adjuvant, Cosmo-Flux (Solomon et al., 2007b), to manual eradication, including alternative development and crop substitution programs (UNODC, 2007). In order to assess the potential genotoxic risk associated with the aerial spraying program with the glyphosate mixture, a cytogenetic biomonitoring study was carried out in subjects from five Colombian regions, characterized by different exposure to glyphosate formulations and other pesticides.

MATERIALS AND METHODS

The study was carried out in five regions of Colombia, with different potential exposure to glyphosate as reported by Sanin et al. (2009). Briefly, the characteristics of the study areas are described here:

Sierra Nevada de Santa Marta—where organic coffee is grown without use of pesticides.

Boyacá—an area of illicit crops, where manual eradication is performed and the use of pesticides and other chemical agents is common.

Putumayo and Nariño—where aerial spraying of glyphosate is performed for coca and poppy eradication. The aerial application rate for eradication of coca is 3.69 kg glyphosate a.e. (acid equivalents)/ha (Solomon et al., 2007b). In order to maximize penetration and effectiveness of the spray formulation, Glyphos is tank-mixed with an adjuvant (Cosmo-Flux® 411F; Cosmoagro, Bogotá).

Valle del Cauca—where glyphosate is applied through aerial spraying for sugar cane maturation. Roundup 747 is the most commonly used product and is applied at a rate of 1 kg a.e./ha, and has no additional adjuvant (personal communication, ASOCAÑA, the Colombian Association for Sugar Growers, December 2008).

Study Population

Two hundred and seventy-four individuals were included in the study. The objective was to sample 30 couples of reproductive age in each area and, where possible, the same couples in the study conducted by Sanin et al. (2009) were sampled. In Putumayo, Nariño, and Valle del Cauca, the population was selected based on the scheduled aerial spraying of glyphosate. This schedule was confidential and provided exclusively for the purpose of the study by the Antinarcotics Police (Putumayo and Nariño) or ASOCAÑA (Valle del Cauca). In Valle del Cauca, a sample size of 30 couples could not be achieved because spraying was not carried out in populated areas of the study region. Most spraying during the study period was carried out on sugar cane crops where no inhabitants were found. All reported areas to be sprayed in Valle del Cauca were visited to search for couples; however, only 14 could be included.

In Sierra Nevada de Santa Marta and Boyacá, the same areas investigated in a previous study (Sanin et al., 2009) were identified, although, due to the instability of the population and high migration, most couples from the previous study were not located. In all regions, the same strategy as described before (Sanin et al., 2009) was followed, visiting household by household until completing 30 couples who fulfilled the inclusion criteria, women of reproductive age (15–49 yr of age) and their spouses, who voluntarily accepted to participate in the study.

Field Data Collection

Field data collection was carried out between October 2006 and December 2007. Epidemiologists and interviewers in the five regions who participated in the Sanin et al. (2009) study were informed about the objectives of the study and trained for data collection. The Ethical Committee of Fundacion Santa Fe de Bogotá approved the study protocol and the informed consent forms used for the study. All the subjects were informed about the aims of the study. All of them gave their informed consent and volunteered to donate blood for sampling. They did not self-report illness at the time of blood sampling and interviews. Every volunteer was interviewed with a standardized questionnaire, designed to obtain relevant details about the current health status, history, and lifestyle. This included information about possible confounding factors for chromosomal damage: smoking, use of medicinal products, severe infections or viral diseases during the last 6 mo, recent vaccinations, presence of known indoor/outdoor pollutants, exposure to diagnostic x-rays, and previous radio- or chemotherapy. A simplified food frequency questionnaire that had already been used in other regions of Colombia was also applied, in order to evaluate dietary folic acid intake. Folic acid intake was characterized because of the role of folic acid deficiency in baseline genetic damage in human lymphocytes (Fenech & Rinaldi, 1994). Specific information about exposure at the time of aerial spraying in Putumayo, Nariño, and Valle del Cauca was addressed in the questionnaire.

Blood Sampling and Cell Culture

Blood samples were collected twice in Boyacá, at the beginning of the study and 1 mo after the first survey, and at 3 different times in Nariño, Putumayo, and Valle del Cauca: immediately before spraying, within 5 d after spraying, and 4 mo later. A sample of 10 ml whole blood was collected from each subject, by venipuncture, using heparinized Vacutainer tubes kept at room temperature and sent within 24 h for the establishment of the lymphocyte cultures. The samples were coded before culturing. The modified cytokinesis-blocked method of Fenech and Morley (1985) was used to determine frequency of MN in lymphocytes. Whole blood cultures were set up for cytogenetic analysis in Bogotá (Colombia) by personnel specifically trained by cytogeneticists from Environmental Carcinogenesis Unit of the National Cancer Research Institute (Genoa, Italy).

Three sterile cultures of lymphocytes were prepared. A 0.4-ml aliquot of whole blood was incubated at 37°C in duplicate in 4.6 ml RPMI 1640 (Life Technologies, Milano, Italy) supplemented with 10% fetal bovine serum (Gibco BRL, Life Technologies SrL, Milano, Italy), 1.5% phytohemoagglutinin (Murex Biotech, Dartford, UK), 100 units/ml penicillin, and 100 µg/ml streptomycin. After 44 h, cytochalasin B (Sigma, Milano, Italy) was added at a concentration of 6 µg/ml. At the end of incubation at 37°C for 72 h, cells were centrifuged (800 × g, 10 min), then treated with 5 ml of 0.075 m*M* KCl for 3 min at room temperature to lyse erythrocytes. The samples were then treated with pre-fixative (methanol:acetic acid 3:1) and centrifuged . The cellular pellets were resuspended in 1 ml methanol. At this step the samples were sent to the Environmental Carcinogenesis Unit (National Cancer Research Institute, Genoa, Italy). All the samples were centrifuged in methanol. Treatment with fixative (methanol:acetic acid, 5:1) followed by centrifugation was repeated twice for 20 min. Lymphocytes in fresh fixative were dropped onto clean iced slides, air-dried, and stained in 2% Giemsa (Sigma, Milano, Italy). MN analysis was performed blind only on lymphocytes with preserved cytoplasm. On average, 2000 cells were analyzed for each subject. Cells were scored cytologically using the cytome approach to evaluate viability status (necrosis, apoptosis), mitotic status (mononucleated, binucleated, multinucleated) and chromosomal damage or instability status (presence of micronuclei, nucleoplasmic bridges, nucleoplasmic buds) (Fenech 2007). The proliferation index (PI) was calculated as follows:

$$\begin{aligned} PI = &(\text{number of mononucleated cells} + 2 \\ &\times \text{number of binucleated cells} + 3 \\ &\times \text{number of polynucleated cells})/ \text{total number of cells.} \end{aligned}$$

Statistical Analysis

Continuous variables were characterized using mean and standard deviation, while categorical variables were expressed as proportions. Dependent variables, micronuclei per binucleated cell (BNMN), and differences in MN between sampling were square-root transformed where required to comply with the required assumptions of normal distribution and equal variances. Comparison of MN between areas was made by one-way analysis of variance (ANOVA). A significance level at 5% was used to assess differences among areas. For multiple comparisons, the Bonferroni test was applied ($\alpha = .05$). Significance of differences in frequency of BNMN between first and second, and second and third sampling were tested by the unpaired *t*-test with equal variances. Difference and 95% confidence interval were used to compare between samplings.

Bivariate analysis between dependent variables and putative risk factors was performed by one-way ANOVA, comparing exposed and nonexposed subjects. In cases where risk factor was continuous, such as age, folic acid intake, alcohol consumption, and coffee consumption, the correlation coefficient was used.

A multiple linear regression was conducted to assess association with BNMN at the first sampling with different variables: region, age (as continuous variable as well as categorical age), ethnicity as a dichotomous variable, exposure to genotoxic products as defined earlier, gender (female vs. male), and intake of folic acid (categorized in quartiles). Regression analysis was conducted with transformed variables, with square root transformation of BNMN and natural logarithm of age, to obtain a normal distribution.

RESULTS

Demographic characteristics and habits of the study groups are described in Table 1. The study population comprised 274 subjects (137 female and 137 male; average age 30.4 ± 7.8 yr). The mean age of the subjects was similar in the different regions. A large part of the studied population was mestizo, with the exception of the Nariño area consisting of individuals of African origin. In the total population, 38% of interviewees had not completed primary education. Putumayo had the largest proportion with education and Valle del Cauca the lowest as shown in Table 1. Only 10% of all subjects were smokers, (20% in Putumayo); a large majority of subjects were drinkers of beer or liquor with a consistent consumption of guarapo (traditional alcoholic beverage prepared by fermentation of maize) in Santa Marta and Boyacá. No statistically significant differences of folic acid intake were observed between different regions (the mean values ranged from 750 and 1189 µg/wk).

One hundred and nine (39.8%) of 274 participants reported current use of pesticides in their occupation or other activities. Nariño (76.6%) and Putumayo (61.7%) were the two regions where prevalence of use of genotoxic pesticides was higher; Boyacá (24.2%) and Valle del Cauca (28.6%) reported lower use. None of the study subjects in Santa Marta reported use of pesticides. No data regarding quantity of pesticide used were available. Fifty (18.3%) out of 273 who gave information

TABLE 1
Demographic Characteristics and Possible Confounding Exposures in the Study Populations

Area	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca
Number of subjects	60	62	60	64	28
Age (mean (SD))	27.0 (5.6)	29.1 (8.8)	31.4 (7.2)	32.5 (7.4)	33.4 (8.7)
Ethnicity (%)					
Mestizo	100	100	88.3	3.1	60.7
African			6.7	96.9	39.3
Indian			5.0		
Education (%)					
None		4.8	1.7		
Primary incomplete	26.7	38.7	53.3	42.2	21.4
Primary complete	21.7	29.0	20.0	23.4	32.1
High school incomplete	25.0	8.1	20.0	25.0	28.6
High school complete	26.7	19.4	3.3	9.4	17.9
Technical			1.7		
Occupation (%)					
Agriculture	10.0	41.9	60.0	62.5	7.1
Housewife	40.0	50.0	38.3	34.4	50.0
Other	50.0	8.1	1.7	3.1	42.9
Health insurance (%)					
Uninsured	50.0	9.7	36.7	71.9	7.1
Subsidized	38.3	83.9	60.0	18.7	50.0
Insured	11.7	6.4	3.3	9.4	42.9
Coffee consumption (cups/day)					
Mean (SD)	1.8 (2.3)	1.7 (0.8)	2.3 (4.1)	1.3 (0.4)	1.7 (1.2)
Percent of population	80.0	67.7	88.3	76.6	82.1
Smoking (%)					
Nonsmokers	91.7	95.2	80.0	87.5	92.9
Alcohol (%)					
Liquor	28.3	25.8	53.3	78.1	78.6
Beer	51.6	67.7	63.1	82.8	64.3
Guarapo	6.7	59.7	1.7	3.2	10.7
Users of illicit drugs (%)	6.7	0	5.0	7.8	0
Diet					
Folic acid intake (μg/wk)	1189	873	750	1160	812

about x-ray examination reported to having been exposed at some time; however, only 21 out of 46 who gave information on dates of x-ray reported exposure in the last 6 mo before the interview and first blood sample. Sixty-one percent of population reported viral infections, the highest prevalence in Nariño (89.5%) and the lowest in Putumayo (49.2%). However, 89.3% of viral infections were the common cold and 6.1% dengue fever. Hepatitis was reported by six interviewees without any specification of the type of the infection.

The means and standard deviations of frequency of MN and related parameters according to regions are shown in Table 2 and presented graphically in Figure 1. Compared with Santa Marta, where people grow organic coffee without the use of pesticides and which is considered as a reference area, the baseline frequency of BNMN was significantly greater in subjects from the other four regions. The highest frequency of BNMN was in Boyacá, where no aerial eradication spraying of glyphosate was carried out, and Valle del Cauca, where aerial spraying was for maturation of sugar cane. There was no significant difference between mean frequency of BNMN in Boyacá and Valle del Cauca. There was no significant difference in frequency of BNMN between Putumayo and Nariño,

TABLE 2

Mean (SD) Frequency of Binucleated Cells with Micronuclei (BNMN), Total Micronuclei (MNL) per 1000 Binucleated Peripheral Lymphocytes, Frequency of Mononucleated Cells per 1000 Lymphocytes (MNMO), and Proliferation Index (PI) by Region before the Exposure (Phase 1), 5 d after Spraying (Phase 2) and 4 mo Later (Phase 3)

Region	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca
Phase 1					
Number of subjects	60	62	58	63	28
BNMN	1.83 (0.97)	5.64 (1.72)	3.61 (1.51)	4.12 (1.65)	5.75 (2.48)
MNL	1.97 (1.05)	6.16 (1.91)	3.90 (1.66)	4.36 (1.85)	6.02 (2.50)
MNMO	0.41 (0.44)	0.99 (0.64)	0.47 (0.51)	0.51 (0.39)	1.12 (0.88)
PI	1.54 (0.14)	1.45 (0.14)	1.68 (0.15)	1.47 (0.12)	1.51 (0.15)
Phase 2					
Number of subjects	ND	55	53	55	27
BNMN		4.96 (2.00)	4.64 (2.45)	5.98 (2.03)	8.64 (2.81)
MNL		5.41 (2.25)	5.02 (2.95)	6.35 (2.18)	8.98 (2.93)
MNMO		0.87 (0.65)	0.44 (0.46)	0.70 (0.45)	1.65 (0.62)
PI		1.72 (0.14)	1.66 (0.20)	1.40 (0.18)	1.51 (0.14)
Phase 3					
Number of subjects	ND	ND	50	56	26
BNMN			5.61(3.08)	3.91 (1.99)	7.38 (2.41)
MNL			5.96 (3.23)	4.13 (2.20)	8.17 (2.72)
MNMO			0.82 (0.54)	0.55 (0.42)	0.98 (0.60)
PI			1.43 (0.17)	1.41 (0.14)	1.45 (0.20)

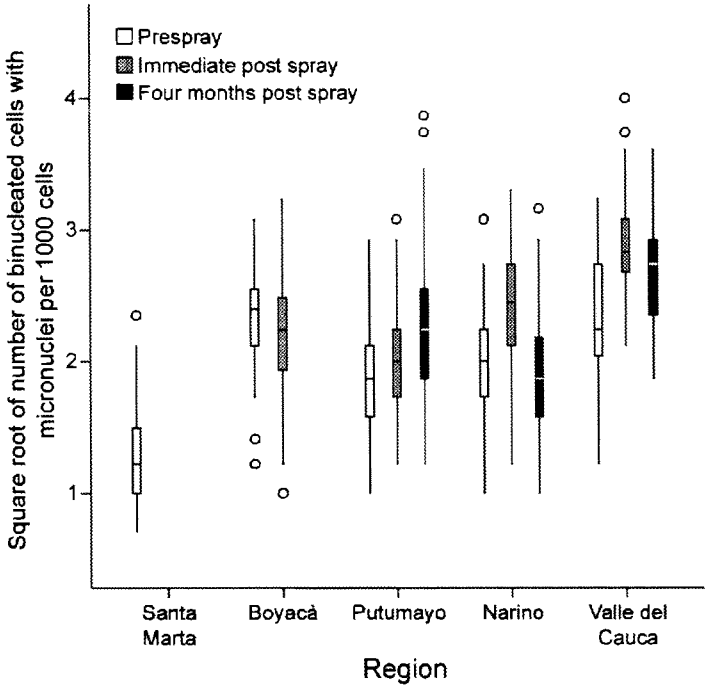

FIG. 1. Box plot of frequency of BNMN in the five study regions with samples taken prespray, 4–5 d post-spray, and 4 mo post-spray. Box plots: The center horizontal line marks the median of the sample. The length of each box shows the range within which the central 50% of the values fall, with the top and bottom of the box at the first and third quartiles. The vertical T-lines represent intervals in which 90% of the values fall. The O symbols show outliers. See text for description of statistically significant differences.

although Boyacá and Valle del Cauca showed a significantly higher frequency than Nariño and Putumayo. A higher frequency of BNMN in Boyacá was also observed in a second sampling 1 mo later.

There were differences in frequency of BNMN between sampling periods. A statistically significant difference in frequency of BNMN between first and second sampling was observed in Valle, Putumayo, and Nariño immediately (<5 d) after spraying. Four months after spraying in Nariño, there was a statistically significant decrease in the mean frequency of BNMN compared with the second sampling, but in Valle del Cauca the decrease was not significant nor was the increase observed in Putumayo significant (Figure 1 and Table 2).

The frequency of mononucleated cells with micronuclei (MOMN) was used as an index of background level of chromosomal damage accumulated in vivo (Table 2). The lowest frequency of MOMN for the first sampling was observed in Santa Marta; however, there was no marked difference in frequency of MOMN in Santa Marta, Putumayo, and Nariño and no statistically significant difference between Valle and Boyacá. However, Valle and Boyacá had a significantly higher frequency of MOMN than Putumayo, Nariño, and Santa Marta at first sampling. Immediately after spraying, Valle showed a significantly higher frequency of MOMN compared to Putumayo and Nariño, and Nariño was also higher than Putumayo. Between first and second sampling, the increase in frequency of MOMN in Nariño and Valle was statistically significant, but there was no difference in Putumayo nor in Boyacá 4 mo after the first sampling. Data suggest greater exposure to genotoxic agents in these populations is independent of the exposure to glyphosate products.

The proliferation index (PI) in all the studied groups was in the range of normal values described in the literature. No significant reduction of PI was observed in association with environmental exposures in groups of subjects from the different regions. A statistically significant correlation coefficient (0.288) between PI values from the first and the second samplings was observed, confirming the association with individual characteristics and not with any toxicity related to the exposure or to the culture techniques. Due to the low frequency observed, data with respect to other nuclear alterations, including in cytome analysis (Fenech, 2007), are not described in Table 2: the mean frequency of nucleoplasmic bridges (NPB) for all subjects was 0.010 per 1000 cells, that of nuclear buds was 0.022 per 1000 cells, and only rare necrotic and apoptotic cells were found in some samples.

Gender was the most important demographic variable affecting the BNMN index. Frequencies of BNMN in females were greater than those in males (mean 4.43 ± 2.36 vs. 3.61 ± 1.82, respectively, in total population) (Table 3). The groups of subjects were evenly matched for gender by including only couples in the study. No association was found between frequency of MN and age as a categorical variable, nor was there an association with smoking, but prevalence of smoking was low (~10% in the total population). A higher baseline frequency of MN was observed in subjects of African origin, suggesting greater susceptibility. Other lifestyle factors such as alcohol, coffee consumption, or illicit drug intake were not associated with initial measures of BNMN and MOMN.

One hundred and thirty-four of the 152 subjects in Nariño, Putumayo, and Valle reported information on contact with Glyphos and Cosmo-Flux after eradication spraying. The other 18 did not provide information in the second survey or blood samples were inadequate for testing micronuclei. Sixty-six (49.2.0%) reported no contact with the spray and 68 (50.8%) reported coming into contact with the spray because they entered sprayed fields or reported contact with the spray droplets. The mean BNMN in Nariño and Putumayo was greater in respondents who self-reported exposure, but differences were not statistically significant (Table 4). In Valle, only one respondent reported contact with glyphosate.

Region, gender, and older age (≥35 yr) were the only variables associated with the frequency of BNMN before spraying (Table 5). In fact, using Santa Martha, where no use of pesticides was reported, as reference, Boyacá, Valle del Cauca, Putumayo, and Nariño showed a statistically significant higher mean frequency of BNMN. There were also significant differences between Boyacá and Valle and Putumayo and Nariño. Females had a statistically higher mean frequency of BNMN than males after adjusting for all other variables. Greater age was also associated with greater frequency of BNMN. Neither exposure to genotoxic products, nor ethnicity, nor intake of folic acid was associated with frequency of BMMN at the first sampling. The multiple linear regression analysis of difference between second and first sampling only demonstrated statistically significant association with region after adjusting for all other variables, indicating that Putumayo, Nariño, and Valle had significantly greater differences between second and first sampling than Boyacá.

DISCUSSION

The main objective of this study was to test whether there was an association between aerial spraying of glyphosate and cytogenetic alterations, evaluated as frequency of MN in peripheral leukocytes. Biomonitoring was carried out in three regions of Colombia in populations exposed to aerial spraying of glyphosate: Putumayo and Nariño, where the application was performed for eradication of coca and poppy, and Valle del Cauca where the herbicide was used for maturation of sugar cane. Two control populations not exposed to aerial spraying of glyphosate were also selected: the first one from Sierra Nevada de Santa Marta, where organic coffee is grown without the use of any pesticides, and the other from Boyacá, with a region of illicit crops, where manual eradication is performed and subjects were potentially exposed to several pesticides but not glyphosate for aerial eradication. The ex vivo analysis of leukocytes in the presence of cytochalasin B, added 44 h after the

TABLE 3
Association of Mean (SD) Frequency of Binucleated Cells (First Sampling) with Micronuclei (BNMN/1000 Binucleated Lymphocytes) and Demographic Variables

Variable	Santa Marta	Boyacá	Putumayo	Nariño	Valle del Cauca	Total
Sex						
Females	1.98 (1.03)	6.22 (1.79)	3.91 (1.71)	4.57(1.77)	6.45 (2.82)	4.43 (2.36)
Males	1.68 (0.90)	5.06 (1.46)	3.31 (1.25)	3.66 (1.39)	5.05 (1.94)	3.61 (1.82)
p	.236	.007	.131	.028	.138	.002
Age						
18–24 yr	2.00 (1.14)	5.50 (1.96)	3.32 (1.25)	3.64 (1.72)	6.19 (2.15)	3.67 (2.16)
25–34 yr	1.66 (0.87)	5.70 (1.66)	3.53 (1.17)	4.20 (1.77)	4.20 (0.76)	3.97 (2.08)
35 yr and older	1.93 (0.67)	5.62 (1.73)	3.84 (1.86)	4.25 (1.52)	6.04 (2.84)	4.41 (2.19)
p	.438	.929	.574	.564	.313	.093
Ethnicity						
Mestizo	1.83 (0.97)	5.64 (1.72)	3.72 (1.52)	4.75 (1.06)	5.82 (2.44)	3.94(2.24)
Africa and Indian	0	0	2.86 (1.31)	4.10 (1.66)	5.64 (2.65)	4.20(1.90)
p			.162	.588	.850	.368
Smoking						
Yes	2.00 (1.06)	5.33 (0.76)	3.31 (1.00)	4.77 (1.51)	4.50 (1.41)	3.83 (1.60)
No	1.82 (0.97)	5.65 (1.76)	3.80 (1.56)	4.03 (1.66)	5.90 (2.57)	4.07 (2.20)
p	.693	.756	.395	.233	.459	.592
Folic acid intake (quartiles)						
1	1.92 (0.99)	6.11 (1.95)	3.23 (1.12)	4.50 (1.75)	5.86 (2.34)	3.89 (2.23)
2	1.64 (0.66)	5.70 (1.75)	3.47 (1.49)	3.80 (1.47)	5.86 (2.74)	3.97 (2.21)
3	1.69 (0.92)	5.69 (1.82)	4.00 (1.37)	3.85 (2.04)	6.58 (2.84)	4.47 (2.22)
4	1.94 (1.20)	4.94 (1.13)	3.69 (2.429)	4.28 (1.51)	4.63 (2.05)	3.75 (1.89)
p	.779	.399	.515	.645	.612	.220

TABLE 4
Mean Frequency of Binucleated Cells with Micronuclei (BNMN) at the Second Sampling per 1000 Binucleated Lymphocytes and Self-Reported Exposures to the Glyphosate Spray in Three Areas Where Aerial Application Had Occurred

	Nariño (*n* = 55)		Putumayo (*n* = 53)		Valle del Cauca (*n* = 26)	
Route of exposure	*n*	Mean BNMN (SD)	*n*	Mean BNMN (SD)	*n*	Mean BNMN (SD)
No exposure	28	5.81 (1.85)	13	3.84 (1.30)	25	8.56 (2.90)
Spray in air	5	7.30 (0.57)	1	5.50 (0)		
Spray on skin	8	5.62 (1.60)	15	4.90 (1.87)	1	9.50 (0)
Entered sprayed field	14	6.06 (2.77)	24	4.87 (3.18)		
p Value (ANOVA)		0.472		0.612		0.760
Any exposure	27	6.16 (2.22)	40	4.90 (2.69)	1	9.50 (0)
p Value (no exposure vs. any exposure)		0.525		0.181		0.760

Note. The data comprise respondents in the second survey from which blood samples were obtained.

TABLE 5
Multiple Linear Regression Analysis Adjusted for Region, Age, Gender, Ethnicity, and Folic Acid Intake

Variable	Coefficient	*p*	95% CI
Region			
Boyacá	3.75	≤.0001	3.19, 4.31
Putumayo	1.58	≤.0001	1.00, 2.16
Nariño	2.06	≤.0001	1.49, 2.64
Valle del Cauca	3.65	≤.0001	2.92, 4.39
Age (yr)			
25–34	0.28	.250	–0.20, 0.76
35 and older	0.75	.008	0.20, 1.31
Gender			
Females	1.00	≤.0001	0.60, 1.40

start of cultivation, made it possible to distinguish between non-dividing mononucleated cells—as an index of accumulated chromosomal damage—and binucleated cells, which had completed one nuclear division during in vitro culture and expressed MN associated with recent exposure to genotoxic agents.

The baseline level of chromosomal damage, evaluated as frequency of BNMN, was associated with the different regions considered in our study. The frequency of BNMN before spraying was also associated with region, gender, and age. Gender difference in the background incidence of MN in peripheral leukocytes, with the frequency being consistently higher in females, and a strong correlation between MN frequency and increasing age are well documented (Bonassi et al., 1995, 2001; Bolognesi et al., 1997a).

Data demonstrated no significant effect of smoking, confirming findings from the literature (Bonassi et al., 2003) although prevalence of smoking in our study population was small (7–20%, Table 1). No association with alcohol consumption was observed. A higher susceptibility of people of African origin compared to the mestizo group was suggested by a greater baseline frequency of BNMN and increased frequency at the second sampling period.

There was some indication of an association between BNMN and exposure to pesticides in general. The lowest frequency of BNMN was observed in Sierra Nevada de Santa Marta, where people self-reported that they did not use pesticides. The mean frequency of BNMN in this group of subjects (1.83 ± 0.97) was similar to that observed in healthy unexposed subjects for the same range of age (Bolognesi et al., personal communication). The higher mean frequency of BNMN observed in Boyacá and Valle del Cauca (5.64 ± 1.72 and 5.75 ± 2.48, respectively) and that in Nariño and Putumayo (4.12 ± 1.65 and 3.65 ± 1.51, respectively), compared to Santa Marta, are in agreement with similar biomonitoring studies carried out in subjects exposed to pesticides using the MN test or other genetic endpoints (Bolognesi, 2003; Bull et al., 2006).

There was no clear relationship between BNMN and the reported use of pesticides classified as genotoxic. Participants in Boyacá and Valle del Cauca showed higher frequency of BNMN than those in Putumayo and Nariño. However, a greater proportion of participants in the latter regions self-reported the use genotoxic pesticides (76.6% in Nariño and 61.7% in Putumayo). There is no information available on other relevant factors such as frequency of use, rate applied, time of exposure, and protective measures used, and we could therefore not characterize exposures to explain the differences. There were further inconsistencies; for example, in Boyacá, where more frequent use of pesticides was expected, only 24.2% of participants self-reported use, compared with the greater values in Nariño and Putumayo. However, it is possible that in areas such as Boyacá, individuals might be potentially exposed to persistent pesticides applied in the past and still present in the environment.

There was no evidence of an association between BNMN and folic acid deficiency. An assessment of folic acid intake from the semiquantitative food frequency questionnaire showed that, according to accepted recommendations (Herbert, 1987), the diet of the study populations was not deficient in folic acid and there were only small differences between regions. Consistent with these data, no association was found between MN and folic acid intake, either as a continuous variable or by quartiles.

The frequency of BNMN increased after spraying with glyphosate but not consistently. The results obtained with a second sampling, carried out immediately after the glyphosate spraying, showed a statistically significant increase in frequency of BNMN in the three regions where glyphosate was sprayed. However, this was not consistent with the rates of application use in the regions. The increase in frequency of BNMN in Valle (application rate = 1 kg a.e. glyphosate/ha) was greater than that in Nariño and Putumayo (3.69 kg a.e. glyphosate/ha).

There was no significant association between self-reported direct contact with eradication sprays and frequency of BNMN. The frequency of BNMN in participants who self-reported that they were exposed to glyphosate because they entered the field immediately after spraying (to pick the coca leaves), felt spray drops in their skin, or they thought they were exposed because they had contact with the chemical in the air, was not significantly greater than in subjects living in the same areas but who were not present during spraying. Decreases in frequency of BNMN in the recovery period after glyphosate spraying were not consistent. The third sampling, 4 mo after spraying, demonstrated a statistically significant decrease in frequency of BNMN only in Nariño.

Overall, these results suggest that genotoxic damage associated with glyphosate spraying, as evidenced by the MN test, is small and appears to be transient. The frequencies of BNMN in Nariño and Putumayo during the second and the third sampling fell within the range of values observed in Boyacá, an area

where people were exposed to a complex mixture of different pesticides (including glyphosate). A greater increase in frequency of BNMN was observed in Valle del Cauca, but it cannot be attributed only to the glyphosate exposure, because the application rate of the herbicide in this area was one-third compared with that in Nariño and Putumayo. This conclusion is further supported by the frequency of MN in mononucleated cells (MOMN), which provides an indication of the background level of chromosome/genome mutations accumulated in vivo (Manteuca et al., 2006). A statistically significant increase of MOMN was observed in Boyacá and Valle del Cauca before and after the aerial spraying, suggesting exposure to other genotoxic compounds in these populations was independent of the exposure to glyphosate. Evidence indicates that the genotoxic risk potentially associated with exposure to glyphosate in the areas where the herbicide is applied for eradication of coca and poppy is of low biological relevance. One of the strengths of our study was the detection of a transient chromosomal damage, evaluated as MN frequency in peripheral blood of the exposed subjects, since it was possible to compare the baseline before spraying with the effects detected immediately after spraying. Glyphosate persists in the environment for only a short time (half-life for biological availability in soil and sediments is hours, and 1-3 d in water; Giesy et al., 2000), is rapidly excreted by mammals and other vertebrates (Williams et al., 2000; Acquavella et al., 2004) and chronic effects, if any, would not be expected.

One of the major drawbacks of environmental epidemiology studies is the characterization of exposures to the agents being investigated. In this study two approaches were used to characterize exposures to glyphosate: ecological and self-reported. In the ecological study design, frequency of BNMN in participants was compared from regions with different patterns of pesticide use. As previously discussed (Sanin et al., 2009), this ecological design may result in misclassification of exposures (Arbuckle et al., 2004), but as an exploratory assessment of exposure it is useful (Ritter et al., 2006).

Others have attempted to improve assessment of exposure to pesticides in epidemiological studies. One study used a self-administered questionnaire for the assessment of exposure to glyphosate, which was defined as (a) ever personally mixed or applied products containing glyphosate; (b) cumulative lifetime days of use, or "cumulative exposure days" (years of use times days/year); and (c) intensity-weighted cumulative exposure days (years of use times days/year times estimated intensity level) (De Roos et al., 2005). A pesticide exposure score based on self-reported work practices was recently developed to estimate annual exposure level (Firth et al., 2007). Based on an algorithm to estimate lifetime exposure to glyphosate from questionnaire information, a moderate correlation was found with concentrations of glyphosate in urine and no significant correlation with self-reported exposure (Acquavella et al., 2004).

In our study, questions related to whether there was direct contact with the spray were used but this did not consider area of skin exposed, region of skin exposed, differences in rates of penetration, or personal hygiene.

Given the situation, the best approach possible, a prospective cohort, was used but the need to use better procedures to estimate the exposure is acknowledged. Based on the applicable Bradford–Hill guidelines (Hill, 1965), it is not possible to assign causality to the increases in frequency of BNMN observed in our study. There was a smaller frequency of BNMN and MOMN in the region of no pesticide use compared with the regions where pesticides (including glyphosate) were used, which is consistent with other reports in the literature. Although temporality was satisfied in the increase in frequency of BNMN after spraying, this response did not show strength as it was not consistently correlated with the rate of application. Recovery was also inconsistent with decreases in frequency of BNMN in the areas of eradication spraying but not in the area where lower rates were applied on sugar cane.

Further studies are needed to better characterize the potential genotoxic risk associated with the application of glyphosate for sugar cane maturation. The smaller number of subjects recruited in this study and small amount of information about the exposure precluded any conclusions. Many pesticides are used in conventional agriculture in Colombia and many pesticides are used in the production of coca (Solomon et al., 2007a, 2007b); however, there is not sufficient information to correlate the frequency of MN to the pesticide exposure.

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UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	**MONSANTO COMPANY'S NOTICE TO TAKE ORAL AND VIDEOTAPED DEPOSITION OF DR. CHRISTOPHER PORTIER**

To: All MDL plaintiffs, by and through, the Court's appointed co-lead counsel, Robin Greenwald of Weitz & Luxenberg, PC, Michael Miller of The Miller Firm, LLC, and Aimee Wagstaff of Andrus Wagstaff, PC

Please take notice that, pursuant to Rule 30 and Rule 45 of the Federal Rules of Civil Procedure, defendant Monsanto Company shall take the videotaped deposition upon oral examination of **Dr. Christopher Portier on September 5, 2017** before a person duly authorized to administer oaths. The deposition shall commence at **9:00 a.m. ET at Weitz & Luxenberg PC, 700 Broadway, New York, NY 10003**. The conduct of the deposition, including its continuation if necessary, shall be governed by Pretrial Order No. 7: Deposition Protocol (ECF No. 103) and Rule 30 of the Federal Rules of Civil Procedure. Dr. Portier shall produce any documents identified in Schedule A attached to his Document Subpoena, at least 10 days prior to the deposition.

DATED: August 16, 2017

Respectfully submitted,

/s/ Heather A. Pigman

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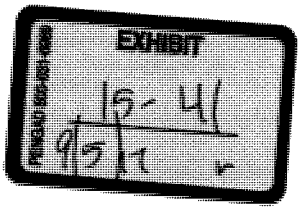


AO 88B (Rev. 02/14) Subpoena to Produce Documents, Information, or Objects or to Permit Inspection of Premises in a Civil Action

UNITED STATES DISTRICT COURT

for the

Northern District of California

IN RE: ROUNDUP PRODS. LIABILITY LITIG.
Plaintiff
v.
Defendant

Civil Action No. 16-md-2741-VC

SUBPOENA TO PRODUCE DOCUMENTS, INFORMATION, OR OBJECTS OR TO PERMIT INSPECTION OF PREMISES IN A CIVIL ACTION

To: Dr. Christopher Portier

(Name of person to whom this subpoena is directed)

☑ *Production:* **YOU ARE COMMANDED** to produce at the time, date, and place set forth below the following documents, electronically stored information, or objects, and to permit inspection, copying, testing, or sampling of the material: SEE ATTACHED SCHEDULE A

Place:	Date and Time:
Hollingsworth LLP, 1350 I St., NW Washington, D.C. 20005	08/26/2017 5:00 pm

☐ *Inspection of Premises:* **YOU ARE COMMANDED** to permit entry onto the designated premises, land, or other property possessed or controlled by you at the time, date, and location set forth below, so that the requesting party may inspect, measure, survey, photograph, test, or sample the property or any designated object or operation on it.

Place:	Date and Time:

The following provisions of Fed. R. Civ. P. 45 are attached – Rule 45(c), relating to the place of compliance; Rule 45(d), relating to your protection as a person subject to a subpoena; and Rule 45(e) and (g), relating to your duty to respond to this subpoena and the potential consequences of not doing so.

Date: 08/16/2017

CLERK OF COURT

OR

Signature of Clerk or Deputy Clerk

/s/ Heather Pigman
Attorney's signature

The name, address, e-mail address, and telephone number of the attorney representing *(name of party)* Monsanto, who issues or requests this subpoena, are:

Heather Pigman, 1350 I Street, NW Washington, D.C. 20005, hpigman@hollingsworthllp.com, 202-898-5800

Notice to the person who issues or requests this subpoena

If this subpoena commands the production of documents, electronically stored information, or tangible things or the inspection of premises before trial, a notice and a copy of the subpoena must be served on each party in this case before it is served on the person to whom it is directed. Fed. R. Civ. P. 45(a)(4).

Civil Action No. 16-md-2741-VC

PROOF OF SERVICE

(This section should not be filed with the court unless required by Fed. R. Civ. P. 45.)

I received this subpoena for *(name of individual and title, if any)* _____

on *(date)* _____ .

❒ I served the subpoena by delivering a copy to the named person as follows: _____

_____

_____ on *(date)* _____ ; or

❒ I returned the subpoena unexecuted because: _____

_____ .

Unless the subpoena was issued on behalf of the United States, or one of its officers or agents, I have also tendered to the witness the fees for one day's attendance, and the mileage allowed by law, in the amount of

$ _____ .

My fees are $ _____ for travel and $ _____ for services, for a total of $ 0.00 .

I declare under penalty of perjury that this information is true.

Date: _____

_____
Server's signature

_____
Printed name and title

_____
Server's address

Additional information regarding attempted service, etc.:

Federal Rule of Civil Procedure 45 (c), (d), (e), and (g) (Effective 12/1/13)

(c) Place of Compliance.

(1) ***For a Trial, Hearing, or Deposition.*** A subpoena may command a person to attend a trial, hearing, or deposition only as follows:

(A) within 100 miles of where the person resides, is employed, or regularly transacts business in person; or

(B) within the state where the person resides, is employed, or regularly transacts business in person, if the person

(i) is a party or a party's officer; or

(ii) is commanded to attend a trial and would not incur substantial expense.

(2) ***For Other Discovery.*** A subpoena may command:

(A) production of documents, electronically stored information, or tangible things at a place within 100 miles of where the person resides, is employed, or regularly transacts business in person; and

(B) inspection of premises at the premises to be inspected.

(d) Protecting a Person Subject to a Subpoena; Enforcement.

(1) ***Avoiding Undue Burden or Expense; Sanctions.*** A party or attorney responsible for issuing and serving a subpoena must take reasonable steps to avoid imposing undue burden or expense on a person subject to the subpoena. The court for the district where compliance is required must enforce this duty and impose an appropriate sanction—which may include lost earnings and reasonable attorney's fees—on a party or attorney who fails to comply.

(2) ***Command to Produce Materials or Permit Inspection.***

(A) *Appearance Not Required.* A person commanded to produce documents, electronically stored information, or tangible things, or to permit the inspection of premises, need not appear in person at the place of production or inspection unless also commanded to appear for a deposition, hearing, or trial.

(B) *Objections.* A person commanded to produce documents or tangible things or to permit inspection may serve on the party or attorney designated in the subpoena a written objection to inspecting, copying, testing, or sampling any or all of the materials or to inspecting the premises—or to producing electronically stored information in the form or forms requested. The objection must be served before the earlier of the time specified for compliance or 14 days after the subpoena is served. If an objection is made, the following rules apply:

(i) At any time, on notice to the commanded person, the serving party may move the court for the district where compliance is required for an order compelling production or inspection.

(ii) These acts may be required only as directed in the order, and the order must protect a person who is neither a party nor a party's officer from significant expense resulting from compliance.

(3) ***Quashing or Modifying a Subpoena.***

(A) *When Required.* On timely motion, the court for the district where compliance is required must quash or modify a subpoena that:

(i) fails to allow a reasonable time to comply;

(ii) requires a person to comply beyond the geographical limits specified in Rule 45(c);

(iii) requires disclosure of privileged or other protected matter, if no exception or waiver applies; or

(iv) subjects a person to undue burden.

(B) *When Permitted.* To protect a person subject to or affected by a subpoena, the court for the district where compliance is required may, on motion, quash or modify the subpoena if it requires:

(i) disclosing a trade secret or other confidential research, development, or commercial information; or

(ii) disclosing an unretained expert's opinion or information that does not describe specific occurrences in dispute and results from the expert's study that was not requested by a party.

(C) *Specifying Conditions as an Alternative.* In the circumstances described in Rule 45(d)(3)(B), the court may, instead of quashing or modifying a subpoena, order appearance or production under specified conditions if the serving party:

(i) shows a substantial need for the testimony or material that cannot be otherwise met without undue hardship; and

(ii) ensures that the subpoenaed person will be reasonably compensated.

(e) Duties in Responding to a Subpoena.

(1) ***Producing Documents or Electronically Stored Information.*** These procedures apply to producing documents or electronically stored information:

(A) *Documents.* A person responding to a subpoena to produce documents must produce them as they are kept in the ordinary course of business or must organize and label them to correspond to the categories in the demand.

(B) *Form for Producing Electronically Stored Information Not Specified.* If a subpoena does not specify a form for producing electronically stored information, the person responding must produce it in a form or forms in which it is ordinarily maintained or in a reasonably usable form or forms.

(C) *Electronically Stored Information Produced in Only One Form.* The person responding need not produce the same electronically stored information in more than one form.

(D) *Inaccessible Electronically Stored Information.* The person responding need not provide discovery of electronically stored information from sources that the person identifies as not reasonably accessible because of undue burden or cost. On motion to compel discovery or for a protective order, the person responding must show that the information is not reasonably accessible because of undue burden or cost. If that showing is made, the court may nonetheless order discovery from such sources if the requesting party shows good cause, considering the limitations of Rule 26(b)(2)(C). The court may specify conditions for the discovery.

(2) ***Claiming Privilege or Protection.***

(A) *Information Withheld.* A person withholding subpoenaed information under a claim that it is privileged or subject to protection as trial-preparation material must:

(i) expressly make the claim; and

(ii) describe the nature of the withheld documents, communications, or tangible things in a manner that, without revealing information itself privileged or protected, will enable the parties to assess the claim.

(B) *Information Produced.* If information produced in response to a subpoena is subject to a claim of privilege or of protection as trial-preparation material, the person making the claim may notify any party that received the information of the claim and the basis for it. After being notified, a party must promptly return, sequester, or destroy the specified information and any copies it has; must not use or disclose the information until the claim is resolved; must take reasonable steps to retrieve the information if the party disclosed it before being notified; and may promptly present the information under seal to the court for the district where compliance is required for a determination of the claim. The person who produced the information must preserve the information until the claim is resolved.

(g) Contempt.

The court for the district where compliance is required—and also, after a motion is transferred, the issuing court—may hold in contempt a person who, having been served, fails without adequate excuse to obey the subpoena or an order related to it.

For access to subpoena materials, see Fed. R. Civ. P. 45(a) Committee Note (2013).

SCHEDULE A

DEFINITIONS

1. The term "Communication," as used in these Requests, is intended to have the broadest possible meaning and shall include any contact or act by which information or knowledge is transmitted or conveyed between two or more persons and includes, without limitation: (1) written contact, including but not limited to letters, memoranda, PowerPoint presentations, email, text message, telegram, telex, internet-based meetings, or other written or electronic documents or files; (2) oral contact, whether by face-to-face meetings, internet-based meetings, video conferences, telephonic conversations, or otherwise; and (3) nonverbal acts intended to communicate or convey any meaning, understanding or other message.

2. "Concerns," "concerning," "relates," or "relating" shall mean and include contain or containing, constitute or constituting, describe or describing, discuss or discussing, refer or referring, state or stating, assess or assessing, and record or recording.

3. "Documents" shall be construed in the broadest sense and includes, but is not limited to, the original and any non-conforming copies of any and all written, printed, typed, graphic, photographic, visual or otherwise recorded matter of any kind or nature, and all microfilm, or electronic sound recording or transcripts thereof however produced or reproduced, including non-identical copies, whether different from the original by reason of any notation made on such copies or otherwise, writings, drawings, records and recordings of every kind and description, whether inscribed by hand or by mechanical, electronic, microfilm, photographic or other means, as well as audio or visual reproduction of all statements, conversations or events including, but not limited to, agreements, bids, bonds, bulletins, calendars and appointment books, checks, circulars, communications, contracts, correspondence, statements, telegrams, receipts, returns, summaries, data books, accounting records, including ledgers, vouchers and books of account, computer printouts, information storage, media diaries and diary entries, drawings and charts, including additions and revisions, estimates, evaluations, financial statements and records, instructions, inter- and intra-office communications, invoices, job site reports, investigative reports, audits, logs, memoranda of any type, minutes of all meetings, notes

of all types, orders, including change, proceed and purchase orders, questionnaires and surveys, photographs, price sheets, records, results of investigations, schedules including additions and revisions, statistical records, reports, analyses and studies of any kind, tape recordings, including any form of any recording of any telephone or other conversation, interview, conference, or meeting, and all contract and working papers as well as drawings, papers and files. A reference herein to any one or more of these types of documents shall be construed to include all other types of documents without limitations.

4. Words used in the singular shall, where the context permits, include the plural, and words used in the plural shall, where the context permits, include the singular.

5. "You" and "your" refers to the person served with and responding to these Requests.

6. "Roundup®/glyphosate litigation" refers to any lawsuit, litigation, or other matter, including, but is not limited to, the multidistrict litigation captioned, *In re Roundup Products Liability Litigation*, Case No. 3:16-md-02741-CV (N.D. Cal.), in which an individual has asserted or will assert, a claim against Monsanto Company ("Monsanto") asserting that the use of Monsanto's Roundup®-branded products has caused their non-Hodgkin's lymphoma ("NHL") or other cancers that have been or will be alleged.

REQUESTS FOR PRODUCTION

As stated in the foregoing Notice, you are required to produce the following documents:

1. All documents provided to you, or that you have, related to the Roundup®/glyphosate litigation that are not publicly or otherwise available.

2. All studies, literature, materials, research files, publications, treatises or any other documents that are not publicly or otherwise available that you have reviewed and upon which you rely and/or intend to rely upon as a basis for the opinions that you intend to offer in the Roundup®/glyphosate litigation or that were reviewed by you in working on, or rendering opinions in, the Roundup®/glyphosate litigation. This request includes all documents not cited in

your expert reports that contain data or other information considered by you in the course of formulating your opinions.

3. Your most recent curriculum vitae.

4. All billing records, invoices, or other documents reflecting time spent and/or fees charged by you (either directly or through your employer or other entity) in connection with the Roundup®/glyphosate litigation and/or consulting work regarding glyphosate, IARC, Roundup®, or Monsanto at C. Portier Consultations.

5. Any retainer letter, contract, agreement, or other document setting forth the retention of you to work in the Roundup®/glyphosate litigation.

6. A copy of all abstracts, articles, draft articles, books or book excerpts of which you are an author, co-author or editor which has as all or part of its subject matter NHL, glyphosate, and/ or Roundup®, that are not publicly or otherwise available.

7. A copy of all handouts, power points or other documents used by you at any lecture you have given on NHL, glyphosate, IARC, and/ or Roundup®, that are not publicly or otherwise available.

8. All documents and communications regarding glyphosate, NHL, Roundup®, or IARC sent to or received on or after January 1, 2013 from any current or former employee or current or former member of the International Agency for Research on Cancer (IARC) or IARC Working Group 112, Collegium Ramazzini or the Ramazzini Institute, December 2016 EPA Scientific Advisory Panel on glyphosate, media organizations such as U.S. Right to Know (USRTK) and Russia Today (RT), non-governmental organizations such as the Organic Consumers Association (OCA) or Natural Resources Defense Council (NRDC), regulatory bodies such as the California Office of Environmental Health Hazard Assessment (OEHHA), the United States Environmental Protection Agency (EPA) or the European Food Safety Authority (EFSA), governmental agencies such as the U.S. National Institute of Environmental Health Sciences (NIEHS) or the U.S. National Toxicology Program (NTP), or any other national or state regulatory body.

9. All documents, communications, or computer programs setting forth underlying mathematical formulations used to compute trend analyses and/or "P Hist" statistics discussed in animal toxicology section of original and revised report.

DATED: August 16, 2017

Respectfully submitted,

/s/ Heather A. Pigman

EXHIBIT 95 Part 5

W E I T Z
&
L U X E N B E R G
A PROFESSIONAL CORPORATION
• LAW OFFICES •
700 BROADWAY • NEW YORK, NY 10003
TEL. 212-558-5500 FAX 212-344-5461
WWW.WEITZLUX.COM

August 29, 2017

VIA EMAIL
John Kalas, Esq.
Hollingsworth, LLP
1350 I Street, N.W.
Washington, DC 20005

Re: *In Re: Roundup Products Liability Litigation*, MDL No. 2741,
Document Production for Dr. Portier

Dear Mr. Kalas:

As we discussed yesterday, and subject to Plaintiffs' objections served on August 23, 2017, attached are documents responsive to Schedule A attached to the Notice of Deposition for Dr. Christopher Portier.

Very truly yours,

Robin L. Greenwald

Encl.

Privileged and Confidential
Attorney Client Privilege
Attorney Work Product

In re Glyphosate/Roundup Litigation

March 29, 2015

Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

Expert Name
Christopher J. Portier, Ph.D.
Email [redacted]

Dear Dr. Portier:

This will confirm that Hunter W. Lundy, acting on behalf of the law firms of Lundy, Lundy, Soileau and South, LLP and Weitz & Luxenberg, PC ("Attorneys" or "Firms"), has retained you for the sole purpose of consulting with these Attorneys in connection with anticipated litigation involving claims arising from injury or damage caused, or potentially caused, by exposure to Roundup and/or other herbicides containing Glyphosate (the "Engagement"). The terms of the Engagement are as follows:

1. You are hereby engaged to provide expert consultation and analysis in connection with the cases to be filed (the "Roundup Cases"), relating to, without limitation, any area of expertise that you have or possess pertaining to the question of whether Roundup and/or Glyphosate-containing herbicides can cause adverse biological/physiological health effects in humans; relevant mechanisms of injury; any research or scientific studies that you have conducted or participated in conducting; and any other related issues.

Privileged and Confidential
Attorney Client Privilege
Attorney Work Product

2. All work conducted in connection with this Engagement as a consulting expert and/or a testifying expert witness pursuant to the direction, authority, and/or funding of the referenced Attorneys, including any reports, drafts, data, notes, work papers, correspondence, or other work documents you may generate or receive in connection with the Roundup Cases shall be considered and treated as confidential work product. All such documents and materials (and any information they contain that is not publicly available data or previously available to you) may be used only for purposes of this Engagement and may not be disclosed to anyone without our written consent in advance. This Engagement does not pertain to nor shall it affect your research and/or scientific studies, and it is expressly understood and acknowledged that we have not, nor will we fund, participate, sponsor or be involved in any of your past, present or future research or scientific studies.

3. In recognition of the confidential nature of this Engagement and subject to the terms of paragraph 2, you agree to not discuss or share any of this work, work product, analysis and/or opinions developed or prepared in connection with this Engagement with anyone else including, but not limited to, media organizations, trade journals, professional publications, members of the public, other purported experts, etc., and to notify us promptly if you receive:

   a. Any request to reveal information related to this Engagement or to examine, inspect or copy any documents you generate or receive; or

   b. Any actual or attempted service of a subpoena, summons or order purporting to require the disclosure of any such information or documents; and

   c. In consequence of such requests, subpoena(s), summons or order to require disclosure, the above-named law firm shall provide whatever legal services that are required to Christopher J. Portier without fee, any resultant out-of-pocket expenses, and payment of hourly rate.

Privileged and Confidential
Attorney Client Privilege
Attorney Work Product

4. You have assured us that you do not have any conflict of interest which might interfere with your performance of services contemplated by this Engagement, and you agree to avoid any such conflict during the term of this Engagement. More specifically, it is understood that until this matter is resolved (including any appeals), you will not accept any Roundup and/or Glyphosate-related engagement with any law firm that is a party to Roundup and/or Glyphosate-related litigation without our written consent in advance. However, if written consent is requested by Christopher J. Portier regarding another matter outside the specifics of this litigation, such consent shall not be unreasonably withheld. The request shall list the reasons why consent is requested. Should requested consent be withheld by Firms, they shall supply specific written reasons referencing the specific reasons listed in the written consent request. If Expert and Firms cannot agree, a single arbiter agreed upon by both parties shall decide.

5. Your fee for specific consultation, analysis and any requested report(s) shall be $450.00 (US Dollars) per hour in addition to reimbursement for any out-of-pocket expenses. You shall receive a retainer of $5,000.00 from which charges shall be drawn. You will send a monthly invoice as necessitated by the requested work which identifies the time spent and services rendered. Upon the depletion of the $5,000.00 retainer, payment will be made within 30 days from receipt of your invoice. Bills should be issued to the attention of Hunter W. Lundy at Lundy, Lundy, Soileau & South, LLP, 501 Broad Street, Lake Charles, LA 70601.

6. You will be working under the exclusive direction of Hunter W. Lundy, Matthew E. Lundy and Kristie M. Hightower with the law firm of Lundy, Lundy, Soileau & South, LLP, and Robin L. Greenwald with the law firm of Weitz and Luxenberg, PC.

7. Any and all work product created by you or on your behalf in whole or in part during the course of this Engagement, authorized by the Committee, shall be considered a work for hire and the property of the Firms.

8. You or we may terminate this agreement in writing at any time, in which event

you must stop work and bill only for the work performed up until receipt of the written termination. However, in the event of such termination, the restrictions described in paragraphs 2, 3 and 4 (related to work product generated) above will remain in effect absent a mutual agreement to the contrary. Such mutual agreement shall not be unreasonably withheld.

9. Any controversy, dispute or claim arising out of or relating to this Engagement or breach of this Agreement, shall be decided by a single arbitrator to be mutually selected in a privately administered arbitration to be held in _____, using the rules of the American Arbitration Association. The Firms and you expressly consent to personal jurisdiction in the courts of _____, and waive any objection thereto.

Please acknowledge that you accept these terms by signing the enclosed copy of this letter and returning it to us.

Sincerely,

LUNDY, LUNDY, SOILEAU & SOUTH, LLP

By:_____
Hunter W. Lundy

Agreed to by:

_____
Christopher J. Portier, Ph.D.

Dated: _____

INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

Invoice Date: 10/19/2015
Invoice #: 15002

Quantity	Date	Unit	Description	Rate	Amount Due
0.5	6/17/15	hr	Meet with H. Lundy at BIOEM meeting, general issues regarding Glyphosate	$450.00	$225.00
1	6/19/15	hr	Meet with H. Lundy and Robin Greenwald in Davis, CA, general issues regarding Glyphosate	$450.00	$450.00
2	7/9/15	hr	Background research on glyphosate and AML, cancers in the Ag. Health Study and onset time for NHL	$450.00	$900.00
3.5	10/19/15	hr	Reduce value of retainer (balance $5000.00) by cost this invoice (new balance $3425.00)	-$450.00	-$1575.00
				Total	$0.00

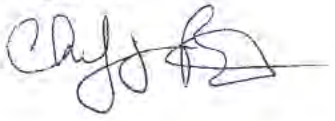
Reimbursement Information:

Name: Christopher Portier

[redacted]

[redacted]

Signature:



INVOICE

Christopher Portier

Regarding:

Bill to:
Glyphosate/Roundup Litigation
Attn: Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

Invoice Date: 3/29/2016
Invoice #: 15003

Quantity	Date	Unit	Description	Rate	Amount Due
2	12/4/15	hr	Phone call followed by research on glyphosate references	$450.00	$900.00
3	12/16/15	hr	Meet with Robin Greenwald and staff in NYC RE: Glyphosate	$450.00	$1350.00
3	3/11/16	hr	Meet with Hunter Lundy, Kristie Hightower and Rudie Soileau in Lake Charles	$450.00	$1350.00
3	3/11/16	hr	Travel to Lake Charles	$150.00	$450.00
3	3/11/16	hr	Travel from Lake Charles to New Orleans	$150.00	$450.00
			Credit from retainer	$3425.00	-$3425.00
				Total Invoice	$1085.00

Reimbursement Information:

Name: Christopher Portier
[redacted]

Signature:

INVOICE

Christopher Portier

Regarding:

Bill to:
Glyphosate/Roundup Litigation
Attn: Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

Invoice Date: 6/30/2016
Invoice #: 15004

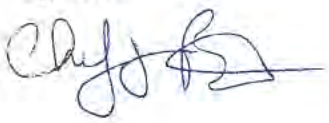
Quantity	Date	Unit	Description	Rate	Amount Due
8	5/12/16	hr	Read and evaluate EPA glyphosate document	$450.00	$3600.00
5	5/13/16	hr	Read and evaluate EPA glyphosate document	$450.00	$2250.00
4	5/14/16	hr	Read and evaluate EPA glyphosate document	$450.00	$1800.00
2	5/15/16	hr	Read and evaluate EPA glyphosate document	$450.00	$900.00
				Total Invoice	$8550.00

Reimbursement Information:

Name: Christopher Portier

[redacted]

Signature:



INVOICE

Christopher Portier

Regarding:

Bill to:
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 2/6/2017
Invoice #: 17001

Quantity	Date	Unit	Description	Rate	Amount Due
10	10/1/2016 to 12/31/2016	hr	Multiple phone meetings, reviews and background development	$450.00	$4,500.00
12	1/1/17 to 2/6/17	hr	Multiple phone meetings and slide preparation	$450.00	$5,400.00
1	1/31/17	tckt	Airline ticket for flight to and from San Francisco/NYC (see attached)	$7,777.71	$7,777.71
				Total Invoice	$17,677.71

Reimbursement Information:

Name: Christopher Portier

[redacted]

Signature:

INVOICE

Christopher Portier

Regarding:

Bill to:
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 3/7/2017
Invoice #: 17002

Quantity	Date	Unit	Description	Rate	Amount Due
17	2/8/17 to 2/26/17	hr	Slide preparation and discussion for "Science Day"	$450.00	$7,650.00
6	2/25/17	hr	Travel time to San Francisco	$100.00	$600.00
6.5	2/27/17	hr	"Science Day"	$450.00	$2,925.00
4	3/2/17	hr	Preparation of expert report	$450.00	$1,800.00
6	3/3/17	hr	Meet with legal team	$450.00	$2,700.00
5	3/5/17	hr	Travel time to home	$100.00	$500.00
1	2/25/17	cost	Taxi from airport to hotel in San Francisco	$50.00	$50.00
1	2/25/17	cost	Hotel in San Francisco	$560.50	$560.50
1	3/1/17	cost	Taxi to hotel in NYC	$62.84	$62.84
1	3/1/17	cost	Hotel in NYC	$601.40	$601.40
1	3/5/17	cost	Taxi to airport in NYC	$66.34	$66.34
				Total Invoice	$17,516.08

Reimbursement Information:

Name: Christopher Portier

[redacted]

Signature:

INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 4/4/2017
Invoice #: 17003

Quantity	Date	Unit	Description	Rate	Amount Due
163	Various dates	hr	Drafting of Expert Report (individual daily activities on Page 2)	$450.00	$73,350.00
			Total Invoice		$73,350.00

Reimbursement Information:

Name: Christopher Portier

[redacted]

Signature:

Quantity	Date	Units	Description	Rate	Charge
5.5	3/7/17	hr	Drafting of Expert Report	$450.00	$2,475.00
6.5	3/8/17	hr	Drafting of Expert Report	$450.00	$2,925.00
2	3/9/17	hr	Drafting of Expert Report	$450.00	$900.00
4	3/10/17	hr	Drafting of Expert Report	$450.00	$1,800.00
6	3/13/17	hr	Drafting of Expert Report	$450.00	$2,700.00
8	3/14/17	hr	Drafting of Expert Report	$450.00	$3,600.00
7	3/15/17	hr	Drafting of Expert Report	$450.00	$3,150.00
8	3/16/17	hr	Drafting of Expert Report	$450.00	$3,600.00
6	3/17/17	hr	Drafting of Expert Report	$450.00	$2,700.00
4	3/18/17	hr	Drafting of Expert Report	$450.00	$1,800.00
8	3/19/17	hr	Drafting of Expert Report	$450.00	$3,600.00
9	3/20/17	hr	Drafting of Expert Report	$450.00	$4,050.00
9	3/21/17	hr	Drafting of Expert Report	$450.00	$4,050.00
9	3/22/17	hr	Drafting of Expert Report	$450.00	$4,050.00
8	3/23/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/24/17	hr	Drafting of Expert Report	$450.00	$3,600.00
3	3/25/17	hr	Drafting of Expert Report	$450.00	$1,350.00
8	3/26/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/28/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/29/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/30/17	hr	Drafting of Expert Report	$450.00	$3,600.00
8	3/31/17	hr	Drafting of Expert Report	$450.00	$3,600.00
2	4/1/17	hr	Drafting of Expert Report	$450.00	$900.00
7	4/2/17	hr	Drafting of Expert Report	$450.00	$3,150.00
3	4/3/17	hr	Drafting of Expert Report	$450.00	$1,350.00
Totals					
163	25 days				$73,350.00

INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 6/18/2017
Invoice #: 17004

Quantity	Date	Unit	Description	Rate	Amount Due
72	Various dates	hr	Drafting of Expert Report (individual daily activities on Page 2)	$450.00	$32,400.00
			Total Invoice		$32,400.00

Reimbursement Information:

Name: Christopher Portier

[redacted]

Signature:

Quantity	Date	Units	Description	Rate	Charge
2	4/5/17	hr	Q&A	$450.00	$900.00
3	4/6/17	hr	Q&A, Work on expert report	$450.00	$1,350.00
4	4/7/16	hr	Read parts of various depositions	$450.00	$1,800.00
8	4/13/17	hr	Read FIFRA SAP Report, include in Expert Report	$450.00	$3,600.00
9	4/18/17	hr	Correct typos to Expert Report, explain certain parts, expand explanations of animal data	$450.00	$4,050.00
6	4/23/17	hr	Check all numbers and tables in expert report, clarify text	$450.00	$2,700.00
7	4/24/17	hr	Check all numbers and tables in expert report, clarify text	$450.00	$3,150.00
4	4/30/17	hr	Edit and refine Expert Report	$450.00	$1,800.00
9	5/1/17	hr	Edit and refine Expert Report	$450.00	$4,050.00
3	6/5/17	hr	Edit and refine Expert Report	$450.00	$1,350.00
4	6/6/17	hr	Edit and refine Expert Report	$450.00	$1,800.00
4	6/7/17	hr	Edit and refine Expert Report	$450.00	$1,800.00
5	6/8/17	hr	Edit and refine Expert Report	$450.00	$2,250.00
2	6/9/17	hr	Edit and refine Expert Report	$450.00	$900.00
2	6/13/17	hr	Edit and finalize final Expert Report	$450.00	$900.00
Totals					
72	15 days				$32,400.00

INVOICE

Christopher Portier

Regarding:

***Bill to*:**
Glyphosate/Roundup Litigation
Attn: Robin Greenwald, Esq.
Weitz & Luxenberg P.C.
700 Broadway, 5th Floor
New York, NY. 10003
Phone:212-558-5685
Fax: 212-344-5461
Email: RGreenwald@weitzlux.com

Invoice Date: 7/13/2017
Invoice #: 17005

Quantity	Date	Unit	Description	Rate	Amount Due
1	20-June to 19 July, 2017	ea	Airplane ticket for deposition in NYC in July, 2017 (cancelled)	$4,046.56	$4,046.56
			Total Invoice		$4,046.56

Reimbursement Information:

Name: Christopher Portier

[redacted]

Signature:

From: [redacted]
Subject: REPLY to Letter regarding EFSA Glyphosate Recommendations
Date: December 15, 2015 at 5:09:54 PM GMT+1
To: [redacted]
Cc: [redacted]

Dear Mr Portier,

Please find enclosed letter from Commissioner Andriukaitis.

Best regards,

Egidijus Dapkus
Assistant unknown.gif ¬ **European Commission** Cabinet of Commissioner Vytenis Andriukaitis Health & Food Safety BERL 08/359
+32 229 80729 [redacted]

From: Kurt Straif <[redacted]>
Subject: FW: IARC Monograph on Glyphosate
Date: November 11, 2015 at 11:04:48 PM GMT+1
To: "Chris Portier [redacted]" <[redacted]>

fyi

From: Kurt Straif **Sent:** 11 November 2015 23:04 **To:** [redacted] **Cc:** 'Landrigan, Philip' <[redacted]>
Subject: FW: IARC Monograph on Glyphosate

Dear Ellen,

I am a strong believer in open and transparent (and when needed provocative) discussion among reasonable people, and therefore I would like to respond to your email (appropriately forwarded by Phil, since I'm the first author of that letter and the Head of the IARC Monographs).

- Our response to the letter from our good friend Manolis was very nuanced, including the identification of scenarios where meta-analyses are not the magic cure for causal inference
- Cochrane reviews (even when focusing on RCTs) don't necessarily get it right (mammography screening being one such example)
- With our without meta-analyses, I would argue that the IARC Monographs are systematic reviews, and include a review of all published literature on cancer in humans and in animals pertinent to a given topic. Therefore, I don't understand why we are on weak grounds here.
- The Monograph on glyphosate included reviews of available meta-analyses (the most recent and comprehensive one reporting a statistically significant increased risk of NHL), but concluded that the qualitative review of the individual studies was more informative, and concluded that there is (only) "limited" evidence in humans.

Best,
Kurt

From: Landrigan, Philip [redacted] **Sent:** 11 November 2015 18:46 **To:** Kurt Straif [redacted] **Subject:** FW: IARC Monograph on Glyphosate

FYI

Philip J. Landrigan, MD, MSc, FAAP
Dean for Global Health
Arnhold Institute for Global Health
Professor of Preventive Medicine and Pediatrics
Icahn School of Medicine at Mount Sinai
12 16 Fifth Avenue, Room 556
New York, NY 10029

Tel: 212-824-7952

[redacted]

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WHO Collaborating Centre in Children's Environmental Health

From: Ellen Silbergeld [redacted] **Sent:** Wednesday, November 11, 2015 10:23 AM**To:** Landrigan, Philip**Cc:** [redacted] **Subject:** RE: IARC Monograph on Glyphosate

They are not the same. I think you and Kurt were co authors on a letter published in EHP in 2012 that recommended that IARC examine the use of meta-analyses and SR methods when possible and appropriate. **Use of Meta- analyses by IARC Working Groups**
http://dx.doi.org/10.1289/ehp.1205397

TO QUOTE YOUR LETTER: "With more epidemiological studies becoming

available for each agent, additional cancer sites being investigated, and relatively small effect esti-mates becoming center of the discussion, the need for meta-analyses is likely to increase."

I think this an example of how we are all on weak ground when each group does an assessment with a less than complete review of the literature

Ellen K Silbergeld, PhD
Professor, Environmental Health Sciences
Johns Hopkins Bloomberg School of Public Health
615 North Wolfe Street, Rm E6644
Baltimore MD 21205 USA
tel: 410 955 8678
fax: 443 287 6414

PLEASE NOTE: IF YOU DO NOT RECEIVE A PROMPT RESPONSE FROM ME TO AN EMAIL, PLEASE RESEND IT AS WE ARE HAVING ISSUES WITH OUR EMAIL SYSTEM. IF YOU STILL DO NOT RECEIVE A RESPONSE, YOU MAY HAVE TO CALL ME BY PHONE.

From: Landrigan, Philip [redacted] **Sent:** Wednesday, November 11, 2015 10:03 AM**To:** Ellen Silbergeld**Subject:** Re: IARC Monograph on Glyphosate

In my opinion an IARC review is Cochrane equivalent

Philip J. Landrigan, MD, MSc, FAAP
Dean for Global Health
Arnhold Institute for Global Health
Professor of Preventive Medicine & Pediatrics
Icahn School of Medicine at Mount Sinai
1216 Fifth Avenue, Room 556
New York, NY 10029

Tel: 1 212 824 7952

On Nov 11, 2015, at 9:50 AM, Ellen Silbergeld <[redacted]> wrote:

Phil: I have concerns that no one has done a systematic review on this topic...

Ellen K Silbergeld, PhD
Professor, Environmental Health Sciences
Johns Hopkins Bloomberg School of Public Health
615 North Wolfe Street, Rm E6644
Baltimore MD 21205 USA
tel: 410 955 8678
fax: 443 287 6414

PLEASE NOTE: IF YOU DO NOT RECEIVE A PROMPT RESPONSE FROM ME TO AN EMAIL, PLEASE RESEND IT AS WE ARE HAVING ISSUES WITH OUR EMAIL SYSTEM. IF YOU STILL DO NOT RECEIVE A RESPONSE, YOU MAY HAVE TO CALL ME BY PHONE.

From: Landrigan, Philip[redacted] **Sent:** Wednesday, November 11, 2015 9:26 AM**To:** Chris Portier**Cc:** Dariusz Leszczynski; ronald melnick;[redacted] pcl;[redacted] Bailer, A. John; Julia Gohlke; Dr. Fiorella Belboggi; Morando Morando Soffritti; Woodruff Tracey; Hillary Carpenter III; Harvey Checkoway; Jackson, Richard J.; Devra Davis;[redacted] Elena Craft; Dr Peter Di Marco PhD; Dr. Lutz Edler; Dr. Annette Kopp-Schneider; Silbergeld Ellen; Jon Freedman; Michael Gallo; Kenneth Portier; Ralph Portier; Steven hamburg; Joe Haseman; Tyrone Hayes; Irva Hertz-Picciotto; James Huff; [redacted] Tsuyoshi Nakamura; Ken Ramos; Michael Schwartz; Ray Tice; Sarah Vogel**Subject:** Re: IARC Monograph on Glyphosate

Chris

I stand with you on this. Please add my name

Phil Landrigan Philip J. Landrigan, MD, MSc, FAAP

Dean for Global Health
Arnhold Institute for Global Health
Professor of Preventive Medicine & Pediatrics
Icahn School of Medicine at Mount Sinai
1216 Fifth Avenue, Room 556
New York, NY 10029

Tel: 1 212 824 7952

On Nov 11, 2015, at 9:10 AM, Chris Portier <[redacted]> wrote:

Dear Colleagues,

For IARC Monograph 112, 17 scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The Working Group concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation of the IARC monograph results when they became available on July 29, 2015. During this period, the European Food Safety Agency (EFSA) was in the middle of a reassessment of the safety of glyphosate. The German Federal Institute for Risk Assessment (BfR) was the lead country agency in drafting the reassessment report. The draft, prior to the IARC Monograph, concluded there was no carcinogenic potential of glyphosate. In August of this year, following the release of the full Monograph on glyphosate, the BfR drafted an Addendum to their report that specifically addresses the Monograph review. This was presented to EFSA several weeks ago and leaked by the press.

This week, EFSA will release their reassessment of glyphosate. In this review, they will again conclude that glyphosate has no carcinogenic potential. This review is based on the BfR Addendum which has some severe scientific flaws. I am concerned that this evaluation, if it stands,

could weaken the effectiveness of the IARC Monograph Programme. I am also concerned that the serious flaws in the BfR Addendum, if not challenged, could continue to be used by regulatory agencies to dismiss critical science pertinent to a regulatory decision, including broad exclusion of literature data and epidemiological data.

The European Commission ENVI Committee will meet on December 1, 2015 to receive the reassessment report from EFSA. I have drafted a letter of concern that I wish to present to the ENVI Committee as they consider whether to accept or reject the EFSA evaluation. I would like to invite you to join with me in signing this open letter. I have obtained your names from many different lists, mostly from previous IARC monographs but also from other sources. It is possible I have included your name more than once on this list and I apologize for sending you multiple copies.

I am open to changes to improve the letter, but because of the short time-frame, I hope you can agree to sign on with only modest modifications (I am sending this to several hundred colleagues). I have included the letter but have not included the BfR Addendum or the Reassessment Report because of size. These are available at:

Addendum: http://www.mdr.de/fakt/fakt-glyphosat-bfr-bewertung100.html (NOTE: click on Herunterladen to download the report)
RAR: http://dar.efsa.europa.eu/dar-web/provision
The more important report is the Addendum.

If you agree to joining me in signing this letter, please respond by November 25 with the following that I can then add to my letter.

Title (Prof, Dr., …), Name
Position Title (e.g. Director, Named Chair, etc)
Affiliation
City, Country

I look forward to hearing from you.

Sincerely, Christopher Portier

<IARCWG112ResponseV3.docx>

From: FOUCART, Stéphane <[redacted]
Date: November 13, 2015 at 12:59:31 PM GMT+1
To: Chris Portier <[redacted]

Dear Chris Portier,

thank you so much for your time & help.
Please find attached the resulting article, due to be published this afternoon in the print edition (already on line).

again : thanks a lot for you explanations.
best
Stéphane

From: "Adriaanse, Paulien" <[redacted]
Subject: Your request for email address
Date: November 24, 2015 at 3:54:29 PM GMT+1
To: [redacted]

Dear Sir,

Please find below my email address for sending a copy of your letter to EFSA's PPR Panel.

Sincere regards,

Paulien Adriaanse

Paulien Adriaanse

Alterra
Team Environmental Risk Assessment
Senior scientific researcher LUMEN, room B.003 P.O. Box 47 6700 AA Wageningen tel. +31 317 481913
email: paulien.adriaanse@wur.nl
http://www.era.wur.nl

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From: Kathryn Guyton <[redacted]
Subject: FW: glyphosate in the press
Date: April 6, 2016 at 11:23:12 AM GMT+2
To: "Rusyn, Ivan" <[redacted], Chris Portier
[redacted]

Dear Chris, Dear Ivan,

The below may be of interest.

Chris, we gave your contact info to Kate K. of Reuters. I'll forward you the information we provided to her.

Best to you both from sunny Lyon,
Kate

From: Véronique Terrasse <[redacted]
Date: Wednesday 6 April 2016 at 11:09
To: Kurt Straif [redacted], Kate Guyton [redacted], Dana Loomis
[redacted]
Cc: Nicolas Gaudin <[redacted]
Subject: glyphosate in the press

Dear all,

Some lobbying activities on both sides..

Copa and Cogeca send letter to EU Commission & MEPs urging them to keep the herbicide active substance glyphosate on EU market, after EU Foo Safety Authority (EFSA) gave it green light (pdf)

Petition demands EPA revoke license for weed-killer ingredient

The Hill | 05/04/16 21:58

...Environmental Protection Agency (EPA) to revoke the license for ***glyphosate*** the active ingredient i Monsanto s herbicide Roundup. Recent tests.. .

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Véronique Terrasse
Press Officer, IARC Communications Group
Email: [redacted]
Web: www.iarc.fr
Tel: +33 4 72 73 83 66
Cell: +33 6 45 28 49 52

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From: Kathryn Guyton [redacted]
Subject: FYI
Date: April 6, 2016 at 11:26:45 AM GMT+2
To: Chris Portier <[redacted]

Hi Chris,
As mentioned.
Best,
Kate

From: Kathryn Guyton <[redacted]
Subject: Letter to Vol 112 Working Group
Date: April 7, 2016 at 8:55:57 PM GMT+2
To: Chris Portier <[redacted]

Dear Chris,
Please see the attached letter.
Best,
Kate

From: Kathryn Guyton <[redacted]
Subject: FW: Breaking news from EU Food Policy
Date: April 13, 2016 at 3:15:08 PM GMT+2
To: Ivan Rusyn [redacted] Chris Portier [redacted] Lauren Zeise <[redacted]

The latest on the EU vote on glyphosate today...
Best,
Kate

From: EU Food Policy [mailto:news@eufoodpolicy.com] **Sent:** 13 April 2016 14:18
Here's the latest breaking news from EU Food Policy:

MEPs call for 7-year limit on new glyphosate authorisation

MEPs have backed a resolution calling on the European Commission to renew the authorisation of the herbicide, glyphosate, for a maximum of seven years instead of the normal 15-year approval.
read more...
To access previous editions of EU Food Policy, use the Archive tab and select the edition required. When logging in, please remember to enter your email address in lower case, followed by your password. If you have any problems, don't hesitate to contact us.

Yours sincerely, *Patrick Bartlett Director EU Food Policy*
info@eufoodpolicy.com +44 208 567 4569

From: Kathryn Guyton [redacted]
Subject: FW: Reuters attacks IARC over glyphosate cancer link
Date: April 21, 2016 at 11:18:05 AM GMT+2
To: Chris Portier [redacted] Martyn Smith
[redacted]

Dear Chris, Dear Martyn,
Perhaps you did not realise it, but some of the sources in the Reuters article have a pro-industry history. ;-)
Happy reading,
Kate

Hope this is of some use to IARC; I understand they will respond to the recent attacks on them. Sources can be accessed in the online version here:
http://www.gmwatch.org/news/latest-news/16889

Claire Robinson
GMWatch

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From: "ED.Directorate" <[redacted]
Subject: RE: EFSA Glyphosate Recommendations
Date: February 9, 2016 at 3:24:39 PM GMT+1
To: IARC Director <[redacted]
Cc: ANDRIUKAITIS Vytenis <[redacted], HOGAN Phil <[redacted], PRATS MONNE Xavier <[redacted] MIKO Ladislav <[redacted] EFSA PESTICIDES PPR <[redacted] David Allen <[redacted], Kurt Straif <[redacted]

Dear Dr Wild,

In reply to your letter of 5 February 2016, please find attached Dr Url's response for your kind attention.

Yours sincerely,

Anna Azzali
Assistant to the Executive Director

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Via Carlo Magno 1A
43126 Parma (Italy)
Tel. +39 0521 036 201
Fax. +39 0521 036 0201
www.efsa.europa.eu
twitter.com/EFSA_EU **1__#$!@%!#__unknown.jpg ¬**
youtube.com/EFSAchannel **2__#$!@%!#__unknown.jpg ¬**

From: Margot Geesink [redacted] **On Behalf Of** IARC Director
Sent: 05 February 2016 16:11 **To:** URL Bernhard; ED.Directorate **Cc:** ANDRIUKAITIS Vytenis; CAB ANDRIUKAITIS WEBPAGE; HOGAN Phil; PRATS MONNE Xavier; MIKO Ladislav; [redacted] EFSA PESTICIDES PPR; David Allen; Kurt Straif; IARC Director **Subject:** FW: EFSA Glyphosate Recommendations

Dear Dr Url,

Please find attached a letter from Dr Christopher Wild.

Yours sincerely,

Margot Geesink
Personal Assistant to Dr Christopher P. Wild, Director,
International Agency for Research on Cancer (IARC)
150 cours Albert-Thomas
69008 Lyon, France
Tel. +33-4-72738577; Fax +33-4-72738564
E-mail: [redacted] www.iarc.fr

From: AZZALI Anna [redacted] **On Behalf Of** ED.Directorate **Sent:** 13 January 2016 10:57 **To:** Chris Portier [redacted] **Cc:** ANDRIUKAITIS Vytenis [redacted] HOGAN Phil [redacted] PRATS MONNE Xavier [redacted] IARC Director [redacted] MIKO Ladislav [redacted] **Subject:** RE: EFSA Glyphosate Recommendations

Dear Professor Portier,

In reply to your letter dated 27 November 2015, please find attached Dr. Url's response for your kind attention.

Yours sincerely,

Anna Azzali
Assistant to the Executive Director

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Via Carlo Magno 1A
43126 Parma (Italy)
Tel. +39 0521 036 201
Fax. +39 0521 036 0201
www.efsa.europa.eu
twitter.com/EFSA_EU **1__#$!@%!#__unknown.jpg ¬**
youtube.com/EFSAchannel **2__#$!@%!#__unknown.jpg ¬**

From: Chris Portier [redacted] **Sent:** 27 November 2015 09:57
To: CAB ANDRIUKAITIS WEBPAGE; ANDRIUKAITIS Vytenis **Cc:** URL Bernhard; [redacted] EFSA PESTICIDES PPR; HOGAN Phil; MIKO Ladislav; [redacted] **Subject:** EFSA Glyphosate Recommendations

Dear Commissioner Andriukaitis,

Attached to this email is a letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety Agency (EFSA) decision that the widely used herbicide, glyphosate "is

unlikely to pose a carcinogenic hazard to humans." We ask that you read our letter and share it with those who will be advising you on accepting or rejecting EFSA's decision. We would greatly appreciate your sharing this with the members of the Standing Committee on Plants, Animals, Food and Feed before their next meeting on December 10, 2015. I will be in Brussels from November 30 to December 2. If you believe it would be helpful for me to discuss these concerns with you or your staff in person, please send email to this address or call +41 79 605 79 58.

Thank you for your attention to this important issue.

Sincerely,

Prof. Christopher J. Portier

cc: Mr. Phil Hogan, European Commissioner for Agriculture and Human Development
Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety
Dr. Bernhard Url, Executive Director, EFSA
Dr. Giovanni La Via, Chair, ENVI Committee
EFSA Panel on Plant Protection Products and their Residues
Mr. Christian Schmidt, Minister of Food and Agriculture
Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)
Professor Dr. Dr. Andreas Hensel, President, BFR
Dr. Christopher Wild, Director, IARC
Mr. Jim Jones, Assistant Administrator, USEPA

From: "ED.Directorate" [redacted]
Subject: RE: EFSA Glyphosate Recommendations
Date: January 13, 2016 at 10:57:15 AM GMT+1
To: [redacted]
Cc: ANDRIUKAITIS Vytenis <[redacted],
HOGAN Phil [redacted]
[redacted] PRATS MONNE Xavier
[redacted]
[redacted] MIKO Ladislav
[redacted]

Dear Professor Portier,

In reply to your letter dated 27 November 2015, please find attached Dr. Url's response for your kind attention.

Yours sincerely,

Anna Azzali
Assistant to the Executive Director

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Via Carlo Magno 1A
43126 Parma (Italy)
Tel. +39 0521 036 201
Fax. +39 0521 036 0201
www.efsa.europa.eu
twitter.com/EFSA_EU **1__#$!@%!#__unknown.jpg ¬**
youtube.com/EFSAchannel **2__#$!@%!#__unknown.jpg ¬**

From: Chris Portier [redacted] **Sent:** 27 November 2015 09:57
To: CAB ANDRIUKAITIS WEBPAGE; ANDRIUKAITIS Vytenis **Cc:** URL Bernhard; [redacted] EFSA PESTICIDES PPR; HOGAN Phil; MIKO Ladislav; [redacted] **Subject:** EFSA Glyphosate Recommendations

Dear Commissioner Andriukaitis,

Attached to this email is a letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety Agency (EFSA) decision that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you read our letter and share it with those who will be advising you on accepting or rejecting EFSA's decision. We would greatly appreciate your sharing this with the members of the Standing Committee on Plants, Animals, Food and Feed before their next meeting on December 10, 2015. I will be in Brussels from November 30 to December 2. If you believe it would be helpful for me to discuss these concerns with you or your staff in person, please send email to this address or call [redacted]

Thank you for your attention to this important issue.

Sincerely,

Prof. Christopher J. Portier

cc: Mr. Phil Hogan, European Commissioner for Agriculture and Human Development
Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety
Dr. Bernhard Url, Executive Director, EFSA
Dr. Giovanni La Via, Chair, ENVI Committee
EFSA Panel on Plant Protection Products and their Residues
Mr. Christian Schmidt, Minister of Food and Agriculture
Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)
Professor Dr. Dr. Andreas Hensel, President, BFR
Dr. Christopher Wild, Director, IARC
Mr. Jim Jones, Assistant Administrator, USEPA

From: Kathy Burns [redacted]
Subject: RE: REPLY to Letter regarding EFSA Glyphosate Recommendations
Date: January 18, 2016 at 5:04:29 PM GMT+1
To: 'Chris Portier' [redacted]

This is fantastic. Your efforts on this have made all the difference in moving towards transparency and hopefully a more legitimate EFSA (if that can even be hoped for).

From: Chris Portier [redacted] **Sent:** Monday, January 18, 2016 10:55 AM **To:** Dr. Christopher Portier [redacted] **Subject:** Fwd: REPLY to Letter regarding EFSA Glyphosate Recommendations

FYI. I guess we had some impact.

C.

Begin forwarded message:

From: Kate Trollope <[redacted]
Subject: RE: REPLY to Letter regarding EFSA Glyphosate Recommendations
Date: January 18, 2016 at 4:39:43 PM GMT+1
To: 'Chris Portier' <[redacted]

As discussed, please find article below on EU experts' involvement in the EFSA assessment. Prior to this article, we found that one expert was someone EFSA had already launched a "breach of trust" against a few years ago when he was on their pesticides panel but failed to say that he worked for a consultancy, Melete, which worked for chemical firms. However, this person, Prof Galli was due to attend the teleconference on glyphosate but did not actually tune in so he was invited to participate but did not in the end!

We have also run an article about the fact that the wife of the EFSA head of the pesticides unit ran a chemical consultancy until a few weeks ago.

And we have found that many of the declarations of interest that EFSA publishes for its pesticide experts are blank because the experts refuse to fill them in and EFSA has no power to make them do so!

Best regards, Kate

Secrecy deepens over EU experts involved in glyphosate verdict

The secrecy over the identity of the EU member state experts involved in deciding that glyphosate is safe has deepened after the vast majority refused to allow their name to be made public.

In an effort to be more transparent about the procedure used in the EU for evaluation of pesticides, the European Food Safety Authority (EFSA) asked the 75 experts, who work for member states, if it could publish a list of their names. But only 14 people agreed to be identified, including two who were invited in their personal capacity.

These were Marianne Balmer of the Swiss research institute, Agroscope, and Veronique Poulsen, of the French food safety agency, ANSES.

Following the contrasting verdicts over glyphosate from EFSA and the International Agency for Research on Cancer, a number of organisations applied through the access-to-documents legislation for a list of the 75 experts involved at EFSA.

But none of the five individuals who work at the Federal Institute for Risk Assessment, BfR, which was the rapporteur on glyphosate, would be identified. And most experts working in other member states took a similar stance.

Dirk Detken, head of legal at EFSA, said the Authority was "committed to high standards of transparency and engagement in the risk assessment process, aiming at generating trust and credibility".

But he said this was subject to rules regarding personal data protection and "the

commitment ensured by the subsidiarity principle underpinning the peer review process involving member states".
Therefore, EFSA had asked the experts involved if the fact that they represented their administration at the expert meetings could be made public.
Most said no but EFSA has provided the names of the institutions involved, which brings clarity, as well as the names of people who were prepared to be identified.
Those who refused to be identified work at the following organisations:

- the Austrian food safety agency, AGES, (4)
- the Greek Benaki institute (4)
- the Dutch board for the authorisation of plant protection products and biocides (5)
- the Bulgarian food safety agency (4)
- the Hungarian Central Agricultural Office (1)
- the Central Institute in the Czech Republic (2)
- the Chemicals Regulation Directorate in the UK (5)
- the Danish Environmental Protection Agency (3)
- the Directorate of Food and Veterinary Affairs in Portugal (1)
- the Finnish Safety and Chemicals Agency (2)
- the French food safety agency, ANSES, (5)
- the Italian Centre for Pesticides (5)
- the Norwegian Food Safety Authority (2)
- National Food Chain Safety Office (1)
- the National Institute of Public Health (1)
- the National Reference Laboratory in Slovakia (1)
- the Scientific Institute of Health in Belgium (1)
- the State Plant Service in Lithuania (1)
- the Germany Environment Agency (4)
- the Slovakian Water Research Institute (1)
- Croatia (1)

Those prepared to be identified included Sten Flodstrom, of the Swedish Chemicals Agency, which argued in a minority Opinion that glyphosate could be carcinogenic.
Others identified include Audra Paltanaviciene, State Plant Service, Ministry of Agriculture, Lithuania; Liga Brence, of the State Plant Protection Service in Latvia; Lucija Perharic, of the National Institute of Public Health in Slovenia; Ana Fandino Carro, of the National Institute for Agricultural and Food Research Technology in Spain; Christian Schlitt and Luca Tosti, of the Italian Centre for Pesticides; Laura Maccalman, of the UK Institute of Occupational Medicine; Wim Hooghe, of the Belgian Federal Public Service Health; Thomasina Barron, of the Department of Agriculture in Ireland; Susy Brescia, of the UK Chemicals

Regulation Directorate; and Eugenia Chaideftou, of the Benaki Institute in Greece.
NGOs have requested the documents and, no doubt, in the coming weeks will be looking into any declarations of interest made.
Corporate Europe Observatory last month launched a €5,000 fundraising campaign to raise funds for an investigation.
EFSA has already published on its website a list of all its member state experts involved in pesticide work. But this does not tell you which particular substances they have been involved in.
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The pesticides risk assessment is done differently to the panel system used for other regulated products such as food additives or GMOs and relies on experts sent by member states, not experts appointed to a panel by the management board.

EFSA pesticides supremo declares wife's chemical interests

The European Food Safety Authority's head of pesticides has revealed that until a few weeks ago his wife ran a private consulting company working for the chemical industry.
Jose Tarazona, head of the EFSA pesticides unit, makes the disclosure in a declaration of interest (DoI) form, which was signed on 2 December.
Dr Tarazona, who presided over EFSA's high profile work on glyphosate, says his wife, Maria Jose Ramos Peralonso, is an expert on hazard and risk communication of chemicals and had her own consulting company, Green Planet Environmental Consulting.
He says she gave advice to public and private bodies on the implementation of REACH, CLP and the communication of hazards and risks.
"She covered industrial and consumer (but not food or feed) products, thus no direct involvement in matters related to EFSA activities. No contracts with private companies since I am EFSA staff," he adds.
A number of organisations requested a copy of Dr Tarazona's declaration of

interest following EFSA's verdict that glyphosate was unlikely to cause cancer, in contrast to the opposite verdict of the International Agency for Cancer Research's.
He was the key staff member at EFSA involved in the assessment and represented EFSA at its press conference and in the European Parliament debate.
The requests for the DoI were made in November and early December and suddenly a new DoI was signed on 2 December. This stated that Dr Tarazona's wife had ended her consultancy in November.
This has created the perception that the consulting firm shut only as people asked more questions about Dr Tarazona's interests.
However, a spokesman for EFSA said that the closure of the consulting firm was a purely personal decision and was taken some time ago.
There was no link between NGOs asking for the DoI and the company closing, he said.
And Dr Tarazona had always declared his wife's interest on his DoI and needed to update his DoI because of the firm's closure.
The EFSA spokesman also stressed that the consulting firm had never been involved in work related to pesticides, or, in particular, to glyphosate.
Dr Tarazona became head of EFSA's pesticides unit in October 2013 after working for the European Chemicals Agency for four years.
Under EFSA independence rules, senior staff have to submit a DoI which includes any interests of "close family members".

EFSA under pressure to publish names of glyphosate experts

The European Food Safety Authority is under pressure to publish the names of exactly who actively contributed to its assessment of glyphosate and their declarations of interest.
This follows the disclosure that some member state experts involved on EFSA's pesticide working groups have refused to provide a declaration of interest.
One of them was the subject of a breach of trust procedure at EFSA in 2011 because he failed to declare interests with chemical firms.
This week, the head of legal affairs at EFSA, Dirk Detken, said that although this scientist, Corrado Galli, was appointed by Italy for the purpose of the assessment, in fact he had failed to attend the discussion.
Following the revelations about Prof Galli, *EU Food Policy* submitted an access-to-documents request to Mr Detken, asking for copies of all the comments made by Prof Grilli, including those made at the teleconference.
Mr Detken replied: "Although Corrado Galli was put forward by Italy as one of its

experts to participate in the teleconference (teleconference 117), together with member state scientists during the peer review, Dr Galli did not attend, meaning that the documents you seek with your request do not exist."
EU Food Policy asked EFSA several times two weeks ago why Prof Galli was allowed to participate and this is the first time that EFSA has said that he did not. Before, we were told that it was up to member states to put forward their experts and that EFSA itself had no control over them, and no power to force them to make a declaration of interest.
EFSA has published the names of all its experts in several working groups on pesticides and the unscreened DoIs of those experts willing to submit one. But so far, it has not issued a list of which experts made written comments and which attended the teleconference.

Back

From: Kate Trollope <[redacted]
Subject: RE: REPLY to Letter regarding EFSA Glyphosate Recommendations
Date: January 18, 2016 at 4:39:43 PM GMT+1
To: 'Chris Portier' <[redacted]

As discussed, please find article below on EU experts' involvement in the EFSA assessment. Prior to this article, we found that one expert was someone EFSA had already launched a "breach of trust" against a few years ago when he was on their pesticides panel but failed to say that he worked for a consultancy, Melete, which worked for chemical firms. However, this person, Prof Galli was due to attend the teleconference on glyphosate but did not actually tune in so he was invited to participate but did not in the end!

We have also run an article about the fact that the wife of the EFSA head of the pesticides unit ran a chemical consultancy until a few weeks ago.

And we have found that many of the declarations of interest that EFSA publishes for its pesticide experts are blank because the experts refuse to fill them in and EFSA has no power to make them do so!

Best regards, Kate

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Secrecy deepens over EU experts involved in glyphosate verdict

The secrecy over the identity of the EU member state experts involved in deciding that glyphosate is safe has deepened after the vast majority refused to allow their name to be made public.
In an effort to be more transparent about the procedure used in the EU for evaluation of pesticides, the European Food Safety Authority (EFSA) asked the

75 experts, who work for member states, if it could publish a list of their names.
But only 14 people agreed to be identified, including two who were invited in their personal capacity.
These were Marianne Balmer of the Swiss research institute, Agroscope, and Veronique Poulsen, of the French food safety agency, ANSES.
Following the contrasting verdicts over glyphosate from EFSA and the International Agency for Research on Cancer, a number of organisations applied through the access-to-documents legislation for a list of the 75 experts involved at EFSA.
But none of the five individuals who work at the Federal Institute for Risk Assessment, BfR, which was the rapporteur on glyphosate, would be identified.
And most experts working in other member states took a similar stance.
Dirk Detken, head of legal at EFSA, said the Authority was "committed to high standards of transparency and engagement in the risk assessment process, aiming at generating trust and credibility".
But he said this was subject to rules regarding personal data protection and "the commitment ensured by the subsidiarity principle underpinning the peer review process involving member states".
Therefore, EFSA had asked the experts involved if the fact that they represented their administration at the expert meetings could be made public.
Most said no but EFSA has provided the names of the institutions involved, which brings clarity, as well as the names of people who were prepared to be identified.
Those who refused to be identified work at the following organisations:

- the Austrian food safety agency, AGES, (4)
- the Greek Benaki institute (4)
- the Dutch board for the authorisation of plant protection products and biocides (5)
- the Bulgarian food safety agency (4)
- the Hungarian Central Agricultural Office (1)
- the Central Institute in the Czech Republic (2)
- the Chemicals Regulation Directorate in the UK (5)
- the Danish Environmental Protection Agency (3)
- the Directorate of Food and Veterinary Affairs in Portugal (1)
- the Finnish Safety and Chemicals Agency (2)
- the French food safety agency, ANSES, (5)
- the Italian Centre for Pesticides (5)
- the Norwegian Food Safety Authority (2)
- National Food Chain Safety Office (1)
- the National Institute of Public Health (1)
- the National Reference Laboratory in Slovakia (1)
- the Scientific Institute of Health in Belgium (1)

- the State Plant Service in Lithuania (1)
- the Germany Environment Agency (4)
- the Slovakian Water Research Institute (1)
- Croatia (1)

Those prepared to be identified included Sten Flodstrom, of the Swedish Chemicals Agency, which argued in a minority Opinion that glyphosate could be carcinogenic.

Others identified include Audra Paltanaviciene, State Plant Service, Ministry of Agriculture, Lithuania; Liga Brence, of the State Plant Protection Service in Latvia; Lucija Perharic, of the National Institute of Public Health in Slovenia; Ana Fandino Carro, of the National Institute for Agricultural and Food Research Technology in Spain; Christian Schlitt and Luca Tosti, of the Italian Centre for Pesticides; Laura Maccalman, of the UK Institute of Occupational Medicine; Wim Hooghe, of the Belgian Federal Public Service Health; Thomasina Barron, of the Department of Agriculture in Ireland; Susy Brescia, of the UK Chemicals Regulation Directorate; and Eugenia Chaideftou, of the Benaki Institute in Greece.

NGOs have requested the documents and, no doubt, in the coming weeks will be looking into any declarations of interest made.

Corporate Europe Observatory last month launched a €5,000 fundraising campaign to raise funds for an investigation.

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From: Chris Portier [redacted] **Sent:** 18 January 2016 13:58

To: kate trollope <[redacted] **Subject:** Re: REPLY to Letter regarding EFSA Glyphosate Recommendations

+41 79 605 7958

On Jan 18, 2016, at 2:48 PM, kate trollope [redacted] wrote:

Yes I would. What number can I reach you on this afternoon. Kate

From: Chris Portier [redacted] **Sent:** 18 January 2016 13:18
To: kate trollope**Subject:** Re: REPLY to Letter regarding EFSA Glyphosate Recommendations**Importance:** High

Kate,

If you wish to chat about the response, I would be happy to talk with you.

C.

On Jan 14, 2016, at 9:56 AM, kate trollope [redacted] wrote:

Dear Prof Portier

I was wondering if you had any response to the letter you received yesterday from EFSA?

I look forward to hearing from you.

Kind regards, Kate
Kate Trollope
Editor
EU Food Policy

www.eufoodpolicy.com

00 44 208 579 0192

From: Chris Portier [redacted] **Sent:** 21 December 2015 14:10
To: kate trollope **Subject:** Re: REPLY to Letter regarding EFSA Glyphosate Recommendations

That was my read on the letter as well. Except the part about ECHA… not sure what happens if they decide to classify as carcinogenic.

On Dec 21, 2015, at 3:07 PM, kate trollope [redacted] wrote:

Thanks very much. I received this from the European Commission last week when they put it on Twitter. I would be grateful if you could let me know when you get the letter from EFSA, addressing the scientific points.

I would also like to know if you have any reaction to the letter from Mr Andriukaitis? He seemed to be saying that the Commission is legally bound to do what EFSA says.

Thanks, Kate

From: Chris Portier [redacted] **Sent:** 21 December 2015 13:59
To: kate trollope **Subject:** Fwd: REPLY to Letter regarding EFSA Glyphosate Recommendations

FYI

Begin forwarded message:

From: [redacted]
Subject: REPLY to Letter regarding EFSA Glyphosate Recommendations
Date: December 15, 2015 at 5:09:54 PM GMT+1
To: [redacted]
Cc: [redacted]

Dear Mr Portier,

Please find enclosed letter from Commissioner Andriukaitis.

Best regards,

Egidijus Dapkus
Assistant

From: "Lowit, Anna" <[redacted]
Subject: FW: Sorry
Date: June 24, 2016 at 8:18:40 PM GMT+2
To: [redacted]

Hi Chris

Jim Jones forwarded me some files from you. thanks for sending them. I have a quick Q for you.

in this PPT file, what is the citation(s) for the metaanalysis of the animal tumor data?

Thanks
Anna

Sent from my Windows Phone

From: Jones, Jim
Sent: 6/24/2016 7:43 AM
To: Housenger, Jack; Lowit, Anna
Subject: FW: Sorry

As per my conversation with Jack. Jim

-----Original Message-----
From: Chris Portier[redacted]
Sent: Thursday, June 23, 2016 2:17 PM
To: Jones, Jim <[redacted]
Subject: Sorry

Jim,

I had an error in one Table that I had to correct. New version attached.

C,

From: "Lowit, Anna" <[redacted]
Subject: RE: Sorry
Date: June 24, 2016 at 9:11:58 PM GMT+2
To: Chris Portier <[redacted]

Ditto on the terse emails, it's too easy on the phone to be quick and even rude! I do it too.

Thanks for the quick response.

Would you mind sharing the code? I'm interested in the analysis, it's a different approach to the data compared to all the others "floating around".

Sent from my Windows Phone

From: Chris Portier
Sent: 6/24/2016 2:22 PM
To: Lowit, Anna
Subject: Re: Sorry

Anna,

Oh, and I wanted to say Hi Anna. Sometimes my emails are a bit short.

If you need any background from me, I'll be happy to help you out. I am also in DC if you want to meet and discuss this.

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On Jun 24, 2016, at 2:18 PM, Lowit, Anna <[redacted] wrote:
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C,

<FiguresandTablesEPA.pptx>

From: "Lowit, Anna" <[redacted]
Subject: RE: Sorry
Date: June 27, 2016 at 2:17:34 AM GMT+2
To: Chris Portier [redacted]

Thanks!

Sent from my Windows Phone

From: Chris Portier
Sent: 6/26/2016 6:42 PM
To: Lowit, Anna
Subject: Re: Sorry

Anna,

Per your request. I believe these are all of the files you will need. Let me know if these do not work for you. I had some minor errors in the tables again because I was not taking direction into account for the trend test (up or down). That is now fixed.

C.

From: "Lowit, Anna" <[redacted]
Subject: RE: Sorry
Date: June 24, 2016 at 9:23:09 PM GMT+2
To: Chris Portier [redacted]

That would be great ☺

Sent from my Windows Phone

From: Chris Portier
Sent: 6/24/2016 3:14 PM
To: Lowit, Anna
Subject: Re: Sorry

No problem. Shall I clean it up a bit first. I can get it to you by monday.

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C,

<FiguresandTablesEPA.pptx>

From: Tom Bender [redacted]
Subject: GYPHOSATE ARTICLE
Date: March 14, 2016 at 9:42:21 PM GMT+1
To: [redacted]

Thank you and your colleagues for your recent article in inadequacy of evaluation of toxicity and danger of herbicides. I don't know if you have seen the attached recent articles, but to me, they offer an even deeper perspective. Evaluating the toxicity of a herbicide based on just its "active" ingredient is profoundly deceptive. Many of the "inert" ingredients are also toxic, and their combinations even MORE toxic. The first study shows that 8 out of 9 Roundup products tested were UP TO 1000 TIMES AS TOXIC as the rating for glyphosate. And it is important to acknowledge that all these studies are based on very short test exposures. Long and/or repeated exposures are, of course, even more toxic.

The second article is based on Freedom Of Information documents EPA was forced to provide, which show that Monsanto knew back in the early '80s the toxicity of glyphosate, and that they AND EPA worked together to bury and hide that information.

There also is important recent information on the LARGER effects of VERY LOW exposure levels of herbicides damaging DNA and with effects continuing to future generations.

It would be wonderful for some of this information to be examined/incuded in a study so we get beyond this "possible" toxicity.

Thanks,
Tom

Tom Bender
Sustainable Architecture and Economics
38755 Reed Rd.
Nehalem OR 97131

503-368-6294
[redacted]
www.tombender.org

From: Kathryn Guyton <[redacted]
Subject: Le Monde
Date: March 16, 2016 at 5:50:24 PM GMT+1
To: [redacted]

Hi Chris,
Can we find a few minutes to chat w Stephane F? Perhaps early afternoon today or tomorrow morning? Let me know when works,
Kate

Envoyé de mon iPhone

From: Kathryn Guyton [redacted]
Subject: FW: Don't renew its authorisation, urge MEPs - Glyphosate
Date: March 23, 2016 at 10:43:07 AM GMT+1
To: "Rusyn, Ivan" [redacted] Chris Portier
[redacted]

From: Véronique Terrasse [redacted]
Date: Wednesday 23 March 2016 at 05:19
To: Kurt Straif [redacted], Dana Loomis [redacted], Kate Guyton [redacted]
Cc: IARC Director [redacted], Nicolas Gaudin [redacted]
Subject: Don't renew its authorisation, urge MEPs - Glyphosate

Dear all,

Below is Bloomberg's coverage following the MEPs' call to stop the relicensing of Glyphosate:

"The non-binding resolution calls on the EU executive to table a new draft. MEPs want the European Commission and the European Food Safety Authority to "immediately disclose all the scientific evidence that has been a basis for the positive classification of glyphosate and the proposed re-authorisation, given the overriding public interest in disclosure".

Next steps

The motion for a resolution, co-signed by Katerina Konecn (GUE/NGL, CZ), Bas Eickhout (Greens/EFA, NL) Piernicola Pedicini (EFDD, IT), on behalf of their respective political groups, and MEPs Mark

Demesmaeker (ECR, BE), Sirpa Pietikainen (EPP, FI) and Frederique Ries (ALDE, BE), will be ***put to a vote at the 11-14 April plenary session in Strasbourg****.*

National experts sitting in the Standing Committee on Plants, Animals, Food and Feed (Phytopharmaceuticals Section) **will vote to adopt or reject the Commission proposal by qualified majority in May. If there is no such majority, it will be up to the European Commission to decide.**

http://www.bloomberg.com/research/markets/news/article.asp?docKey=600-201603221059M2 EUPR 766c0000051ccac3 3600-1

Press release from the European Parliament

http://www.europarl.europa.eu/portal/en

Véronique

unknown.png ¬

Véronique Terrasse
Press Officer, IARC Communications Group
Email: [redacted]
Web: www.iarc.fr
Tel: +33 4 72 73 83 66
Cell: [redacted]

unknown.png ¬

From: Kathryn Guyton [redacted]
Subject: FW: Glyphosate: article, NRDC blog
Date: March 29, 2017 at 4:22:20 PM GMT+2
To: Christopher Portier [redacted]

As discussed in http://time.com/4711846/roundup-weed-killer-cancer/, please see attached article.
See also https://www.nrdc.org/experts/jennifer-sass/split-within-epa-glyphosate-carcinogenicity.

From: Kathryn Guyton <[redacted]
Subject: Fwd: Sutherland Investigative Report "Is Glyphosate Legal" and the US NIH RoC
Date: March 17, 2016 at 4:03:08 PM GMT+1
To [redacted]

Envoyé de mon iPhone

Begin forwarded message:

From: Véronique Terrasse [redacted]
Date: 17 March 2016 at 08:34:20 GMT-5
To: Kurt Straif <[redacted], Kathryn Guyton <[redacted]
Dana Loomis <[redacted]
Cc: Nicolas Gaudin <[redacted]
Subject: FW: Sutherland Investigative Report "Is Glyphosate Legal" and the US NIH RoC

Quite impressive overview from a regular citizen..

Véronique Terrasse
Press Officer, IARC Communications Group
Email: [redacted]
Web: www.iarc.fr
Tel: +33 4 72 73 83 66
Cell: [redacted]

From: IARC Communications **Sent:** 17 March 2016 14:02**To:** Véronique Terrasse**Cc:** Nicolas Gaudin**Subject:** FW: Sutherland Investigative Report "Is Glyphosate Legal" and the US NIH RoC

FYI

Bernadette

From: Donald Sutherland [redacted] **Sent:** jeudi 17 mars 2016 12:33**To:** IARC Communications**Subject:** Sutherland Investigative Report "Is Glyphosate Legal" and the US NIH RoC

Good Morning Christopher Wild,
I am a USDA certified organic vegetable farmer in Hopkinton, MA USA and a freelance writer.
I wanted to alert you and the IARC my nomination of glyphosate and its products to the US NIH Report on Carcinogens have been accepted.
Also, I have writen a report "Is Glyphosate Legal" for you and the IARC review.
Please contact me if you have any questions.

Best Wishes,
Donald Sutherland
Hopkinton, MA USA
Long Life Farm
Http://www.longlifefarm.com
Member of the Northeast Organic Farmers Association (NOFA)
Member of the Society of Environmental Journalists (SEJ) Is Glyphosate Legal?
By Donald Sutherland

It is spring time and millions of pounds of the world's most common herbicide are being applied to the agricultural land in the United States.
http://npic.orst.edu/factsheets/archive/glyphotech.html
http://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2012&map=GLYPHOSATE&hilo=L

This year the United States Department of Environmental Protection (EPA), who license and regulate glyphosate and its 750 products, must decide if the herbicide is safe for prenatal, infant, child, and adult

consumption in food crops and products- and the agency is stalling.

The EPA's sister European Food Safety Authority (EFSA) is also stalling its' reauthorization of glyphosate under a peer review re-evaluation of EU's list of approved active substances.
http://www.efsa.europa.eu/

Currently, France, Italy, Sweden, and the Netherland's are opposed to the relicensing of glyphosate, and Germany is abstaining.
http://www.theguardian.com/environment/2016/mar/08/eu-vote-on-controversial-weedkiller-licence-postponed-glyphosate

In the United States the EPA is under a federal mandate requiring the agency to re-evaluate all pesticides on a 15-year cycle.
http://www.epa.gov/pesticide-reevaluation
http://www.epa.gov/ingredients-used-pesticide-products/glyphosate

The federal regulatory agencies (EPA, USDA, FDA) who establish food safety regulations claim the world's most commonly used herbicide is as safe as table salt if used under directions.

So, why doesn't the EPA reregister the license for glyphosate use in agriculture?

In 2015 the World Health Organization's International Agency for Research on Cancer (IARC) assessed glyphosate and its products as a probable human carcinogenic health risk, and this year the California state government intends to list the herbicide as a carcinogen.

The California Office of Environmental Health Assessment (OEHHA) intends to list glyphosate as a carcinogen under the mandates of state law Proposition 65 (The Safe Drinking Water and Toxic Enforcement Act of 1986).
http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/090415LCset27.html

"The law requires that certain substances identified by the International Agency for Research on Cancer (IARC) be listed as known to cause cancer under Proposition 65. Labor Code section 6382(b)(1) refers to substances identified as human or animal carcinogens by IARC."
http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/090415LCset27.html

So far, the EPA hasn't agreed with the California OEHHA and World Health Organization's IARC assessment of glyphosate and its products as a human carcinogenic health risk.
http://monographs.iarc.fr/ENG/Monographs/vol112/mono112-09.pdf#page89
https://www.iarc.fr/en/media-centre/iarcnews/pdf/MonographVolume112.pdf
http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/090415LCset27.html

Clinical, peer reviewed studies by science, industry, and government bodies show glyphosate kills plants and bacteria by interfering with an enzyme producing aromatic amino acids which are essential for life in plants, bacteria and humans.
http://www.epa.gov/sites/production/files/2015-06/documents/glyphosate-417300_2015-06-29_txr0057175.pdf
http://www.monsanto.com/glyphosate/pages/how-does-glyphosate-work.aspx
https://en.m.wikipedia.org/wiki/Glyphosate

The EPA and glyphosate manufacturers admit consumers absorb glyphosate in minute amounts from food and drinking water, but assure us decades of clinical studies show it only harms plant life and passes harmlessly through the body in urination.

"All labeled uses of glyphosate are safe for human health and supported

by one of the most extensive worldwide human health databases ever compiled on an agricultural product," states Dr. Philip Miller, Vice President Global Regulatory Affairs, Monsanto.
http://news.monsanto.com/news/monsanto-disagrees-iarc-classification-glyphosate

Not so, says an international contingent of scientists.

These scientists, using peer reviewed clinical data, defend the IARC assessment glyphosate poses a human health risk.
http://www.zeit.de/wissen/umwelt/2015-11/glyphosat-offener-brief.pdf
https://www.researchgate.net/publication/283490944_Glyphosate_pathways_to_modern_diseases_IV_cancer_and_related_pathologies
http://www.mdpi.com/1099-4300/15/4/1416
http://www.nejm.org/doi/full/10.1056/NEJMp1505660?rss=searchAndBrowse
http://www.enveurope.com/content/26/1/14

They argue the US EPA and EFSA have cited biased industry sponsored clinical data to make their case glyphosate is safe, and didn't consider the low dose effects in prenatal, infants, and children.
http://www.efsa.europa.eu/en/efsajournal/pub/4302

"The science consisted solely of toxicologic studies commissioned by the herbicide manufacturers in the 1980s and 1990s and never published, not an uncommon practice in U.S. pesticide regulation," says Philip J. Landrigan, M.D., and Charles Benbrook, Ph.D. in their New England Journal of Medicine report GMOs, Herbicides, and Public Health.
http://www.nejm.org/doi/full/10.1056/NEJMp1505660?rss=mostEmailed

"These studies predated current knowledge of low-dose, endocrine-mediated, and epigenetic effects and were not designed to detect them. The risk assessment gave little consideration to potential

health effects in infants and children, thus contravening federal pesticide law," Landrigan and Benbrook say.
http://www.nejm.org/doi/full/10.1056/NEJMp1505660?rss=searchAndBrowse

The exponential increase in the agricultural use of glyphosate over the past two decades and its' correlation with human health issues involving neurological, intestinal, and cancer disorders, is hotly contested by both sides of the glyphosate safety debate.

"I personally believe that glyphosate is the main reason why we have an epidemic in autism. I think it's also responsible for the rise in Non-Hodgkin's lymphoma, pancreatic cancer, thyroid cancer, inflammatory bowel disease, ADHD, COPD, alzheimer's, diabetes, obesity, and probably several other chronic conditions that we face today," says
Stephanie Seneff, a senior research scientist at the Massachusetts Institute of Technology (MIT).
https://www.researchgate.net/publication/283490944_Glyphosate_pathways_to_modern_diseases_IV_cancer_and_related_pathologies
http://www.mdpi.com/1099-4300/15/4/1416

I don't agree with the WHO's designation as "probably carcinogenic," she says. "I think it is definitely carcinogenic."

The stakes are huge in this political scientific schism.

The future of the global proprietary owned agro-industry glyphosate ready genetically modified organism (GMO) crops lies in the resolution of the split between the World Health Organization's IARC and the US EPA & EFSA.

Food manufacturers using GMO crops also have a huge stake at risk if glyphosate is banned or restricted.

Over 90% of US corn, soy, and sugar beet crops are grown with glyphosate, and these GMO crops and their products constitute over 80% of processed food products. Glyphosate is also used in wheat production.
http://www.ers.usda.gov/media/1282246/err162.pdf
http://www.ers.usda.gov/media/1424185/eib124.pdf

Kellogg's, a Fortune 500 food manufacturer, acknowledges grains purchased on the open market contain agricultural herbicide residues including glyphosate and are consumed by customers in their processed products.
http://www.gmofreeusa.org/food-testing/kelloggs/kelloggs-froot-loops/

"Nearly all crops in the US are treated with herbicides and pesticides, and may leave behind very low residue levels on some foods," says a customer service Kellogg Company spokesman.

"In the US, the acceptable level of pesticide and herbicide use in crops is set by the Environmental Protection Agency (EPA) based on, a standard of reasonable certainty that the use would cause no harm to human health or the environment," says the company spokesman.

US federal agencies in charge of protecting the public's health with a "standard of reasonable certainty", EPA, USDA, and FDA, state they have never tested glyphosate residue in federal aggregate food crop tests (outside of a USDA Soy 2011 test), because manufacturer and EPA cited laboratory tests claim there is no human health risk. They also insist glyphosate herbicides are safe if used under direction.
http://www.epa.gov/pesticides/health/
http://www.epa.gov/pesticides
http://www.monsanto.com/glyphosate/pages/default.aspx
http://www.monsanto.com/iarc-roundup/pages/default.aspx

These same federal agencies also authorized the safety of "Roundup ready" transgenic genetically modified organisms (GMOs) crops as

"substantially equivalent to nature", and give GMO glyphosate ready crops a pass from federal food testing requirements.
http://www.fda.gov/food/guidanceregulation/guidancedocumentsregulatoryinformation/labelingnutrition/ucm059098.htm
http://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/introduction-biotechnology-regulation-pesticides#overview

It's a complicated byzantine federal process proving glyphosate isn't a health risk to humans.

But, when it is unraveled a secret is found - the licensing of glyphosate and its products is in violation of the federal laws governing pesticides.

Under the Federal Food Drug and Cosmetic Act (FFDCA) and the Food Quality Protection Act (FQPA) aggregate testing of food crops and products is mandated for all pesticide residue tolerances to account for the accumulated exposures of the herbicide's chemical residue in commonly consumed food.
http://www.epa.gov/laws-regulations/summary-food-quality-protection-act
http://www.epa.gov/laws-regulations/summary-federal-food-drug-and-cosmetic-act

US federal agencies (EPA, USDA, FDA) claim there is no government aggregate food testing of glyphosate residues, so the EPA uses "available information".
http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0132-0009

The EPA also admits to waiving the FQPA Safety Factor additional tenfold risk margin of safety for pesticide maximum residue levels (MRLs) protecting the safety of the most vulnerable population group - prenatal, infants, and children.
http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0

132-0009
http://www.epa.gov/sites/production/files/2015-07/documents/determ.pdf
http://www.epa.gov/laws-regulations/summary-federal-food-drug-and-cosmetic-act
http://www2.epa.gov/pesticide-tolerances/about-pesticide-tolerances
http://www.ecfr.gov/cgi-bin/text-idx?SID=14480e45fa5ca0522865d765eec6bb72&mc=true&node=se40.24.180_1364&rgn=div8

Clinical laboratory glyphosate health risk testing data cited by the EPA Hazard Identification Assessment Review Committee (HIARC) is used in the federal agency's Office of Pesticide Programs (OPP) and Health Effects Division (HED) ruling the safety of infants and children is adequately protected if the FQPA Safety Factor were reduced to 1X instead of 10X.
http://www.monsanto.com/glyphosate/pages/default.aspx
http://www.monsanto.com/iarc-roundup/pages/default.aspx
http://www.epa.gov/pesticide-contacts/contacts-office-pesticide-programs-health-effects-division#teb
http://www.epa.gov/pesticides

For now, the EPA insists glyphosate and its MRLs, established before the herbicide was declared a probable carcinogenic health risk by the World Health Organization, is safe for humans.
http://www.epa.gov/oppsrrd1/reregistration/REDs/factsheets/0178fact.pdf
http://www.ecfr.gov/cgi-bin/text-idx?SID=14480e45fa5ca0522865d765eec6bb72&mc=true&node=se40.24.180_1364&rgn=div8

"If you are asking if glyphosate is safe, then yes, we have said that that glyphosate does not cause unreasonable adverse effects to human health and the environment so long as it is used according to the pesticide labels," says Khue Nguyen, ChemicalReview Manager, Risk Management and Implementation Branch 1
PesticideRe-evaluation Division, Office of Pesticide Programs, EPA

"EPA regulates pesticides, which means we deal primarily with pesticide policy and we determine what appears on the pesticide labels. We do not do food safety inspections or testing on food/feed commodities. To be clear, we set tolerances for all pesticides that are used on food/feed commodities. A pesticide having a tolerance or multiple tolerances does not mean that it is unsafe," says Nguyen.

Section408(b)(2)(A)(i) of the Federal Food Drug and Cosmetics Act states that EPA can establish a tolerance for a pesticide chemical residue in or on food only if EPA determines that the tolerance is safe. "Safe" is then defined as a "reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures.
http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/FDCActChapterIVFood/
http://www.epa.gov/laws-regulations/summary-federal-food-drug-and-cosmetic-act

Consumer advocates claim without the government providing a transparent aggregate testing of glyphosate chemical residue in food there is no total accounting for the public's cumulative exposure to the herbicide in a daily diet, and no safety MRL can be established.

"The legal process for tolerance setting must be based on human health effects from dietary exposures. However, without data on actual residues on these crops, this cannot be verified. We have challenged EPA's tolerance setting before and will continue to do so," says Nichelle Harriott, Science and Regulatory Director, Beyond Pesticides.
http://www.beyondpesticides.org

In a little publicized federal government sponsored program called the IR-4 Project the USDA, EPA, and glyphosate manufacturers do test glyphosate tolerance residue on crops, but without transparency to the public.

The United States Department of Agriculture funded IR-4 Project partnering with the EPA, state government agencies, glyphosate manufacturers, and universities have been testing glyphosate residues in food crops and feed to facilitate the herbicide's use in agriculture.
http://ir4.rutgers.edu

IR-4 sounds like a federal secret, but when it petitioned the Environmental Protection Agency(EPA) in the federal register to increase food crop MRL residue tolerance levels of the world's most popular herbicide it gave away its cover.
http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0132-0009

The IR-4 petition went unnoticed in the shadow of Monsanto's (an IR-4 member) EPA petition, and was approved by the EPA (also an IR-4 member).
http://www.regulations.gov/#%21docketDetail;D=EPA-HQ-OPP-2012-0132
https://www.gpo.gov/fdsys/pkg/FR-2013-05-01/pdf/2013-10316.pdf
http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0132-0009

Headquartered in Princeton, N.J., the IR-4 operates as a "unique" partnership between the USDA, EPA, the National Institute of Food and Agriculture (NIFA), the Agricultural Research Service (ARS), the State Agricultural Experiment Stations (SAES), agrochemical industry, universities, commodity groups, and growers.
http://nifa.usda.gov/topics
http://ir4.rutgers.edu/directory.cfm?nd=nd&letter=B

Monsanto, Syngenta, DuPont, Dow, Bayer, and BASF are listed in the IR-4 directory.
http://ir4.rutgers.edu/directory.cfm?nd=nd&letter=B

With a staff of over 125 full time members the mission statement for the IR-4 Project is to "facilitate registration of sustainable pest management technology for specialty crops and minor uses."

Specialty crops tested by IR-4 include commonly consumed food crops (ie. fruits, vegetables, nuts, herbs, spices,) and non-food plants and flowers used in landscape.

"As some background, for more than 50 years, the USDA funded IR-4 Project is the only resource for facilitating registrations of conventional chemical pesticides, biopesticides, and organic products for growers of specialty crops and other minor uses (specialty uses) in the United States. These are uses not supported by registrants. IR-4 is a partnership with government, industry and growers," says Jerry J. Baron, Ph.D, Executive Director, IR-4 Project.

"We typically develop residue exposure data to assist EPA with their risk assessment. Basically we apply the test product the way the farmer would potentially use the pesticide or biopesticide. When the crop is mature, we harvest the raw agriculture commodity and analyze for the presences of the chemical, biochemical and/or metabolites, " says Baron.

What was the IR-4's urgent need to exponentially increase the herbicide residue levels on such foods as carrots, sweet potatoes, fruits, grains, and berries?

"The IR-4 Project received multiple request for assistance to facilitate modifications to the registration of glyphosate from public sector scientists with USDA and the State Agricultural Experiment Stations. These requests were reviewed during IR-4 Project Food Use Workshops and classified as high priority," says Baron.

The IR-4 insists there is no conflict of interest with government regulatory bodies and glyphosate industry manufacturers collectively

using their testing data to petition the EPA in the federal register to increase glyphosate MRL levels for crops.
http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2012-0132-0009

"Though IR-4's data development is independent of the companies, IR-4 submissions are coordinated with the companies. Due to provisions of the Pesticide Registration Improvement Act, IR-4 submissions are often classified as part of a company submission," says the IR-4 Executive Director.

The IR-4 also insists their hidden glyphosate residue data developed under USDA and EPA testing standards is "different" from the USDA MRL monitoring data used in national USDA food survey's to protect the health of the public.

"The data IR-4 develops is much different than glyphosate monitoring data by EPA and USDA ; we are fully removed from that activity. USDA just released a report within the last couple of weeks from their Pesticide Data Program out of the Agriculture Marketing Service. You may find some glyphosate monitoring data in that sample set," says Baron.

The USDA Pesticide Data Program (PDP)Annual Summary report is conducted by the USDA Agricultural Marketing Service (AMS) to collect data on pesticide/herbicide residues in over 10,000 samples of fruit, vegetables, fresh and processed products, and infant formulas throughout the US using the MRL tolerances set by the EPA. This PDP data is presented to the public to assure consumers the food they feed their families is safe.
https://www.ams.usda.gov/sites/default/files/media/2014%20PDP%20Annual%20Summary.pdf

"Ultimately, if the EPA determines a pesticide is not safe for our families it is removed from the market," states the USDA in their 2014

PDP report.
http://www.ams.usda.gov/sites/default/files/media/PDP%20factsheet.pdf

The USDA admit they don't test in the PDP for the mostly commonly used herbicide in the US (glyphosate) in food crops and food products - except for a USDA soy test in 2011.
https://www.ams.usda.gov/sites/default/files/media/2014%20PDP%20Annual%20Summary.pdf

"The PDP tests a wide variety of domestic and imported foods using a sound statistical program and the most current laboratory methods. Glyphosate is not detectable using the multi-residue methods (MRM) the PDP testing laboratories use and would require a specialized method. Glyphosate requires the single analyte method to test for residues," says Peter Wood, spokesman for the Public Affairs Office of the USDA AMS.

When asked why didn't the USDA PDP use USDA funded IR-4 glyphosate residue MRL data for those foods listed in the annual survey the USDA spokesman said, "the report does not include data from other sources."

Why then doesn't the USDA use the single analyte method used in the 2011, PDP testing of 300 soybean samples for glyphosate and its metabolite AMPA (aminomethylphosphonic acid)?
http://www.ams.usda.gov/sites/default/files/media/2011%20PDP%20Annual%20Summary.pdf

"USDA and EPA specialists discuss the selection of commodities and pesticides for testing. With USDA's scientific input and EPA's data needs, EPA makes the determination which commodities and pesticides are tested," says Wood.

"Currently, the U.S. Food and Drug Administration (FDA) is testing corn and soybean grains for glyphosate residues. EPA is waiting on the

results from FDA testing before making the determination if additional data is needed for its ongoing evaluation of glyphosate tolerances to ensure that the levels set by EPA meet the safety standards prescribed by the law," he says.
http://www.fda.gov/Food/FoodScienceResearch/TotalDietStudy/ucm184293.htm

The FDA is responsible for enforcing EPA pesticide tolerances, but admits it is the first time they have ever tested for glyphosate MRLs in any food commodity.

"FDA has not routinely looked for glyphosate in its pesticide monitoring regulatory program for several reasons, including that available methods for detecting glyphosate were selective residue methods that would have been very expensive and labor intensive to implement in FDA field labs," says Charlotte Lian, Ph.D., Plant Products Branch, Division of Plant Products and Beverages, Office of Food Safety Center for Food Safety and Applied Nutrition, Food and DrugAdministration
http://www.fda.gov/downloads/Food/ComplianceEnforcement/ucm073186.pdf

"FDA is aware of the 2015 IARC World Health Organization's assessment of glyphosate. In the U.S., risk assessments of pesticides are conducted by EPA," says Lian.

How was glyphosate and 750 products licensed without abiding by the aggregate tolerance residue testing data mandates for risk assessments under the Food Quality Protection Act?

The EPA dodges the question.

Anne Overstreet, Chief Communication Services Branch, Field and External Affairs Division Office of Pesticide Programs, Environmental

Protection Agency says, "the Federal Food, Drug, and Cosmetic Act states: To make the safety finding, EPA *considers*, among other things: the toxicity of the pesticide and its break-down products, aggregate exposure to the pesticide in foods and from other sources of exposure, and any special risks posed to infants and children."

"While testing for aggregate exposure is nearly impossible – people eat different foods, combinations of foods, and amounts of foods – EPA uses *models* to assess likely aggregate exposure and adds an additional safety factor to further protect consumers, especially children, as required by the Food Quality Protection Act," she continues. http://www.epa.gov/laws-regulations/summary-food-quality-protection-act

"In setting tolerances, EPA must make a finding that the tolerance is "safe," with safe being defined as meaning that there is a "reasonable certainty that no harm will result from aggregate exposure to the pesticide residue," she says.

Anne Overstreet then refers to the USDA PDP aggregate exposure testing as proof consumers shouldn't worry about pesticides residues on their food - even though the 2014 PDP didn't test for glyphosate.

"The PDP data demonstrate that overall pesticide residues found on foods tested are at levels below the tolerances established by EPA and pose no safety concern. Based on the PDP data, consumers can feel confident about eating a diet that is rich in fresh fruits and vegetables," says Overstreet.

"Glyphosate residue data are not part of 2014 PDP sampled pesticides. To find out whether FDA has plans to test for glyphosate residues, please contact FDA directly," she says.

This type of circular non-answer on glyphosate's safety is how the EPA has been stalling their decision to reregister the herbicide and its products - while permitting its' continued use.

And after exposing a generation to glyphosate, the EPA also refuses to answer if the herbicide's current MRL tolerance residue levels are in violation of the FQPA Safety Factor protecting prenatal, infants, and children.

"The real question is whether the EPA was in violation of the law when glyphosate was approved then and now," says Jonathan Evans, Environmental Health Legal Director and Senior Attorney for the Center for Biological Diversity.

Donald Sutherland is a freelance writer, USDA certified organic vegetable farmer, member of the Northeast Organic Farmers Association (NOFA), and the Society of Environmental Journalists (SEJ).
https://www.linkedin.com/in/donaldsutherland
He farms with his wife Laura, and their two daughters Mei and Li, in Hopkinton, Ma
Long Life Farm
http://www.longlifefarm.com
His last story on food was published in Food Safety News.
http://www.foodsafetynews.com/author/dsutherland/#.Vq-RRvA8KrU

Begin forwarded message:

From: "Lunn, Ruth (NIH/NIEHS) [E]" [redacted] **Date:** January 14, 2016 at 4:23:33 PM EST **To:** Donald Sutherland

[redacted] **Subject: FW: [NTP Web] Received nomination to the National Toxicology Program**

Dear Mr. Sutherland, This email acknowledges your nomination of glyphosate and its products for review for possible listing in the Report on Carcinogens and the list of websites/documents supporting your nomination. The process for preparing the Report of Carcinogen is available at http://ntp.niehs.nih.gov/go/rocprocess; please see Part 1 of the process for steps regarding nominations and selection of candidate substances. We appreciate your interest in the Report on Carcinogens and National Toxicology Program and your previous correspondence regarding this topic. Sincerely, Ruth M. Lunn, DrPH Director, Office of the Report on Carcinogens Division of the National Toxicology Program, NIEHS Phone: 919-316-4637 Mailing address PO Box 12233, MD K2-14 Research Triangle Park, NC 27709 Courier 530 Davis Dr., Room 2138 Morrisville, NC 27560 On 1/7/16, 10:05 AM, "NTP Website" <ntpweb-noreply@ntp.niehs.nih.gov> wrote:

The following has been submitted as a nomination.

Name: Donald Sutherland
Telephone: 508-497-3676
Email: [redacted]
Affiliation Type: Individual
Additional Contact Information: The best way to contact me is by email: [redacted]

From: Kathryn Guyton [redacted]
Subject: Fwd: Correction in NR article
Date: May 5, 2016 at 11:47:08 AM GMT+2
To: [redacted]

Et voila. Thanks to Ivan for alerting me to this article!

Envoyé de mon iPhone

Begin forwarded message:

From: Kathryn Guyton [redacted]
Date: 5 May 2016 at 11:40:34 GMT+2
To: [redacted]
Cc: [redacted] Kurt Straif [redacted] Nicolas Gaudin [redacted], Véronique Terrasse [redacted]
Subject: Correction in NR article

Dear Sir, Dear Madam,

I hereby request correction of false and defamatory statements in the recent NR article below.

The presentation in question noted that many studies had examined a link to breast cancer with some pesticides (not herbicides in particular), a factual statement. Further, a publication that I coauthored in The Lancet Oncology reached the opposite conclusion from "clear indications of a link to breast cancer" that you attribute to me in your article. Contrary to your assertion of a "total lack of objectivity", our publications states specifically: "Although more than 40 studies conducted since 1993 were reviewed, no clear association was found between breast cancer and DDT or DDE"

http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00081-9/fulltext

I will look forward to your reply.

Sincerely yours,

Kate Z. Guyton PhD DABT
Monographs Section
International Agency for Research on Cancer
150, cours Albert Thomas
69372 Lyon Cedex 08
France
Tel: [+33] (0)4 72 73 86 54
[redacted]

The lead author of the glyphosate report, Kathryn Guyton, gave a speech in 2014 to an NGO group — before the review process had begun — in which she stated that the herbicide studies planned for 2015 had shown clear indications of a link to breast cancer, demonstrating her total lack of objectivity.

Read more at:
http://www.nationalreview.com/article/434845/WHO-cancer-agency-bad-science-labels-glyphosate-probably-carcinogenic

From: Kathryn Guyton <[redacted]
Subject: Fwd: Clarification- NR article
Date: May 5, 2016 at 12:19:15 AM GMT+2
To: "[redacted]

Envoyé de mon iPhone

Begin forwarded message:

From: Kathryn Guyton <[redacted]
Date: 4 May 2016 at 22:59:11 GMT+2
To: Kurt Straif <[redacted] Dana Loomis <[redacted]
"Nicolas Gaudin" <[redacted]
Subject: Clarification- NR article

Dear Kurt, Dear Dana,

I have spoken to Chris Portier, and EDF is taking steps to correct false statements about him/EDF in the NR article. I have taken the step of contacting NR by phone and noting that false and potentially defamatory statements about me have appeared in their article, and asking what steps had been taken to verify any of the facts presented. I was told to contact the below NR folks in writing, and have drafted this email for your review and further comment.

Bonne soiree,
Kate

Dear Sir, Dear Madam,

I was wondering what steps could be taken to correct the record concerning false and potentially defamatory statements in this article: http://www.nationalreview.com/article/434845/WHO-cancer-a

gency-bad-science-labels-glyphosate-probably-carcinogenic, particularly:

The lead author of the glyphosate report, Kathryn Guyton, gave a speech in 2014 to an NGO group — before the review process had begun — in which she stated that the herbicide studies planned for 2015 had shown clear indications of a link to breast cancer, demonstrating her total lack of objectivity.

The presentation in question noted that many studies had examined a link to breast cancer with some pesticides (not herbicides in particular), a factual statement. Further, a publication that I coauthored in The Lancet Oncology reached the opposite conclusion from "clear indications of a link to breast cancer", specifically: "Although more than 40 studies conducted since 1993 were reviewed, no clear association was found between breast cancer and DDT or DDE measured in samples of blood or adipose taken in adulthood" http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(15)00081-9/fulltext

I will look forward to your reply.

With kind regards,

nbrown@nationalreview.com
kconnell@nationalreview.com

From: Kurt Straif [redacted]
Subject: FW: Conflict of Interest Concerns Cloud Meeting as International Experts Review Herbicide Risks | U.S. Right to Know
Date: May 12, 2016 at 10:26:48 PM GMT+2
To: "Christopher Portier [redacted]
"Emmerig Hedwig (Ref. Biotechnologie und Bioethik)"
[redacted]

FYI, Boobis is Chair of the current JMPR meeting and Moretto vice-Chair.
http://usrtk.org/pesticides/conflict-of-interest-concerns-cloud-meeting-as-international-experts-review-herbicide-risks/

From: Kathryn Guyton [redacted]
Subject: Fwd: Breaking news from EU Food Policy
Date: May 17, 2016 at 4:26:08 PM GMT+2
To: [redacted]

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1_#$!@%!#_unknown.png ¬

From: Kathryn Guyton <[redacted]
Subject: FW: Latest issue from EU Food Policy
Date: May 20, 2016 at 3:11:40 PM GMT+2
To: Ivan Rusyn [redacted] Christopher Portier
[redacted]

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5_#$!@%!#_unknown.png ¬

From: Kurt Straif <[redacted]
Date: Friday 20 May 2016 11:30
To: Nicolas Gaudin <[redacted]
Subject: FW: Latest issue from EU Food Policy

As usual,
Merci, Kurt

From: EU Food Policy [mailto:news@eufoodpolicy.com] **Sent:** 20 May 2016 11:00 **To** [redacted] **Subject:** Latest issue from EU Food Policy

unknown.jpg ¬
Hi Mr Straif,

The latest edition is ready for you to view at www.eufoodpolicy.com. You can download this week's full newsletter or read all the top stories and analysis online. If you have any problems please email info@eufoodpolicy.com. These are some of this week's headlines:

EU will act over EFSA palm oil Opinion - Commission Read more... **Swedish agency launches probe into glycidyl levels in food**Read more... **Glyphosate - member states fail to support nine year renewal**Read more... **Ombudsman to probe "EU pilot" system for infringement cases**Read more... **EFSA pesticide expert advises CEFIC chemical lobby**Read more... **Choices label is not "licence" to eat more, finds study**Read more... **Action Plan on mutual recognition changes published**Read more... **Glyphosate unlikely to cause cancer, says WHO/FAO panel**Read more... **WHO/FAO conclusions on glyphosate irrelevant to renewal, say critics**Read more... **WHO defends glyphosate experts**Read more...

Also in the latest issue

US tells Commission to act over French BPA ban Commission rules out EU ecolabel for fish Launch of new standard for measuring food waste Andriukaitis promises raft of food waste measures Eating bigger breakfast doesn't dramatically cut lunch calories A colour on a food packet is worth a thousand words Coke under attack over marketing pledges BfR endocrine consensus breaks as participants give different message Dutch raids over country of origin fraud FSA board supports major changes to delivery of scientific advice Commission censure motion collapses Commission takes case-by-case view of East-West food quality divide FSA to look after mandatory CCTV in slaughter houses EU could ban DNP supplements TTIP - more conspiracy theories than Middle Ages, says Andriukaitis

Swedish government looks at new plan on reformulation Health NGOs say advertising reforms don't go far enough EFSA seeks experts to serve for just one year MEPs hold another non-binding vote on GMOs Hogan calls for more substantial proposals from US in TTIP EFSA gives green light to liquid absorber EFSA issues positive verdict on GM food contact ingredient Dieticians call on Parliament to act on obesity EFSA issues verdict on material to extend shelf life of wine Italy notifies changes in national olive oil labelling law In brief

To access previous editions of EU Food Policy, use the Archive tab and select the edition required. When logging in, please remember to enter your email address in lower case, followed by your password. If you have any problems, don't hesitate to contact us.

Yours sincerely, *Patrick Bartlett Director EU Food Policy*
info@eufoodpolicy.com +44 208 567 4569

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From: Kathryn Guyton [redacted]
Subject: Fwd: Emailing: EUFoodPolicy_ECHA.pdf, EUFoodPolicy_MEPs-vote.pdf, EUFoodPolicy_mediation.pdf
Date: March 22, 2016 at 1:06:47 PM GMT+1
To: [redacted]

Envoyé de mon iPhone

Begin forwarded message:

From: Kurt Straif [redacted]
Date: 22 March 2016 at 08:04:06 GMT-4
To: Dana Loomis <[redacted] Kathryn Guyton [redacted]
Nicolas Gaudin <[redacted] Véronique Terrasse
[redacted]
Subject: Emailing: EUFoodPolicy_ECHA.pdf, EUFoodPolicy_MEPs-vote.pdf, EUFoodPolicy_mediation.pdf

Dear all,

I have managed to get trial access to EUFoodPolicy and have now downloaded and attached fyi the recent 3 possibly important, short articles.

Kurt

Your message is ready to be sent with the following file or link attachments:

EUFoodPolicy_ECHA.pdf
EUFoodPolicy_MEPs-vote.pdf
EUFoodPolicy_mediation.pdf

From: Kathryn Guyton [redacted]
Subject: FW: RAC-40_Invitation to IARC_glyphosate
Date: February 7, 2017 at 10:12:52 AM GMT+1
To: Christopher Portier [redacted]

Hi Chris,
Did you also receive this invitation? I'll be in the US 4-17 March, and know you will also be at SOT (as will Jose T). I can check if someone else can attend from IARC.
Kate

From: ECHA Committee Risk Assessment <rac@echa.europa.eu>
Date: Tuesday, 7 February 2017 at 09:00
To: Kate Guyton [redacted]
Cc: BOWMER Tim [redacted] VAN HAELST Anniek [redacted], Kurt Straif [redacted], ECHA Committee Risk Assessment [redacted]
Subject: RAC-40_Invitation to IARC_glyphosate

RE: 40th meeting of the Committee for Risk Assessment (6-10 March and 14-15 March 2017)

For the attention of IARC - glyphosate

Dear Dr Kate Z. Guyton,

Please find attached your invitation to the 40th Meeting of the Committee for Risk Assessment (RAC-40). Glyphosate is scheduled to be discussed on Wednesday 8 March at 11.30 – 18.30 and on Wednesday 15 March at 09.15-11.15 Helsinki time. The working language of the meeting will be English.

Preparation for the meeting
The provisional Draft Agenda and the provisional timelines are attached to this invitation.

Practicalities
You are kindly asked to make your own travel and any hotel

arrangements. A list of local hotels is available on request.

Please confirm your attendance, and for any further information or assistance you may need, please contact RAC Secretariat (rac@echa.europa.eu).

Data protection notice
This meeting will be video recorded for minute taking purposes. The recordings will only be accessible to the Secretariat and will be permanently deleted once no longer needed. Please note that the minutes, which are published on the ECHA website, include a list of participants. The European Chemicals Agency will ensure on its part that your personal data is processed as required by Regulation (EC) No 45/2001 on the protection of individuals with regard to the processing of personal data by the Community institutions and bodies and on the free movement of such data. You have the right to access and rectify that data. To exercise these rights, please contact the data controller at rac@echa.europa.eu
For any further information or assistance you may need, please contact the RAC Secretariat (rac@echa.europa.eu).

Best regards,

Leila Kokkola Committee for Risk Assessment (RAC) Unit B.1 - Committees Secretariat European Chemicals Agency Annankatu 18, P.O. Box 400, FI-00121 Helsinki, Finland Tel. +358 9 6861 8288
[redacted]
http://echa.europa.eu/
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From: "Peltonen Kimmo (Tukes)" <[redacted]
Subject: glycophosphate
Date: March 6, 2017 at 5:08:52 PM GMT+1
To: Tuomisto Jouko <[redacted], "Chris Portier
[redacted] "Putkonen Tiina (Tukes)"
[redacted]

Dear Jouko, Chris and Tiina,

I have contacted EFSA and ECHA and the message is clear. They will not participate any meeting or share any data dealing with glycophosphate before ECHA's opinion is adopted and released. When that will happen – your guess is as good as mine.

I talked today with Jose Tarazona from EFSA and he made a proposal to have a meeting which has a more general topic focusing methodological differences between WHO/EU in chemical risk assessment. Furthermore he suggested that one should have 5 different pesticides and some industrial chemicals as examples.

Please, let me know your thoughts about the more general workshop, which could preferentially be a joint one with all parties.

Sorry to disappoint you, but I don't see any point of trying to arrange a meeting on this subject anymore.

All the best,

Kimmo

Kimmo Peltonen Pääjohtaja | Director General

Turvallisuus- ja kemikaalivirasto (Tukes) | Finnish Safety and Chemicals Agency
PL 66 (Opastinsilta 12 B), 00521 Helsinki, FINLAND
Puh. 040 5002 614 | Tel. +358 40 5002 614
[redacted]

Tukes: Suojan tuoja – turvallisen toiminnan edistäjä ja mahdollistaja.

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¬5__#$!@%!#__unknown.jpg ¬

From: [redacted]
Subject: Automatic reply: EFSA Glyphosate Recommendations
Date: November 27, 2015 at 9:57:24 AM GMT+1
To: [redacted]

We acknowledge receipt of your email. If your message concerns a request for a meeting or a petition please see the information below.

Important notice on Transparency: Meetings with organisations or self-employed individuals

I would like to draw your attention to the Commission's new policy on transparency which entered into force on 1 December 2014. More details can be found here.

Before we can proceed with your request for a meeting, could you please confirm whether you, or your organisation, are registered in the Transparency Register and provide your Register ID number? If you are not registered, you are kindly invited to register on this website. The meeting can only take place once we have received the confirmation of your registration.

Please be aware that the European Commission is committed to enhanced transparency. Therefore, Commissioners and their Cabinets only meet organisations or self-employed individuals that are registered in the EU's Transparency Register.

Petitions

Replies to petitions are published on the Transparency Portal of the European Commission.

From: Sönke Guttenberg - Harald Ebner MdB [redacted]
Subject: AW: EFSA Glyphosate Recommendations
Date: November 27, 2015 at 9:58:57 AM GMT+1
To: Chris Portier [redacted]

Thank you! Then I will start sending now.

Von: Chris Portier [redacted] **Gesendet:** Freitag, 27. November 2015 09:58 **An:** Sönke Guttenberg - Harald Ebner MdB **Betreff:** Fwd: EFSA Glyphosate Recommendations

It has been sent.

Begin forwarded message:

From: Chris Portier [redacted]
Date: November 27, 2015 at 9:56:57 AM GMT+1
To: [redacted]
Cc: [redacted]

Subject: EFSA Glyphosate Recommendations

Dear Commissioner Andriukaitis,

Attached to this email is a letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and write to you at this time to

express our deep concern over the recent European Food Safety Agency (EFSA) decision that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you read our letter and share it with those who will be advising you on accepting or rejecting EFSA's decision. We would greatly appreciate your sharing this with the members of the Standing Committee on Plants, Animals, Food and Feed before their next meeting on December 10, 2015. I will be in Brussels from November 30 to December 2. If you believe it would be helpful for me to discuss these concerns with you or your staff in person, please send email to this address or call +41 79 605 79 58.

Thank you for your attention to this important issue.

Sincerely,

Prof. Christopher J. Portier

cc: Mr. Phil Hogan, European Commissioner for Agriculture and Human Development
Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety
Dr. Bernhard Url, Executive Director, EFSA
Dr. Giovanni La Via, Chair, ENVI Committee
EFSA Panel on Plant Protection Products and their Residues
Mr. Christian Schmidt, Minister of Food and Agriculture
Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)
Professor Dr. Dr. Andreas Hensel, President, BFR
Dr. Christopher Wild, Director, IARC
Mr. Jim Jones, Assistant Administrator, USEPA

From: FOUCART, Stéphane <[redacted]
Subject: bombshell
Date: March 16, 2017 at 10:07:17 PM GMT+1
To: Chris Portier <[redacted] Chris Portier <[redacted]

Hi Chris

you NEED to check out this file (New documents unsealed). It is so huge I am not sure I properly understand : did Monsanto itself had serious evidence that glyphosate is a potential clastogenic compound, back in 1999 ??? look at exhibit 5 !! I would very much appreciate your interpretation of the content of the file (released the very day ECHA said glyphosate is not a CMR !!)

best regards
Stef

--
Stéphane Foucart
Le Monde
service Planète/Science - *Environment/Science desk*
80 boulevard Auguste Blanqui
75 707 Paris cedex 13
tel. +33 1 57 28 27 02
[redacted]

From: Volker Barth <[redacted]
Subject: engl version - documentary on risk assessment / glyphosate
Date: January 17, 2016 at 11:45:53 AM GMT+1
To: Chris Portier <[redacted]

Dear Chris

EFSA spread the news about your letter, and meeting with the Commission coming up.

Nice to see your irritation is still unsatisfied about EFSA and BfR at present. My guess is that they were bought by the bio-organic farm industry, as it is a clear case, the more openly their work is flawed, the more customers will switch of to the organic food counter. But that is just a guess.

Just in case, the engl version has just been translated, is officially not yet published, but is already asked for by various European Broadcasters, and can be used for review and internal communication.

https://vimeo.com/141141148
PW agriculture

what I sometimes wonder, if the procedures of EFSA and the EC Commission
are in perfect harmony - what they seem to be

or if the commission is totally uninterested or simply unaware that e.g. the BfR risk asssessment was entirely prewritten/preformulated by the industry Glyphosate Task Force GTF, and not by BfR.
(As declared in plain sight on the original BfR report on page one, which is referred in the movie at TC 31:18)

(interestingly the job was granted by GTF to the same intertek team, which later re-evaluated the IARC work - with central author Williams GM)

Well, if you find time on such a beautiful day to watch the movie - now it is in English, and please let me know if you detect any wrong interpretation of your words or science immediately

over here the snow seems to stay, means likely we can xcountry ski to Gruene Woche the upcoming week

hope all is well on your side

with greetings

Volker

--
soweit, mit herzlichen Grüssen

Ihr

Volker Barth

Anthro Media

Documentary and iTV Production
Nature, Science, and Living History

Nansenstr. 19
D- 12047 Berlin

tel :: +49 (0) 30 62 7278 62
fax :: +49 (0) 30 62 7278 32
[redacted]

LONGER ARE
PASSIVELY DATA MINED, BUT ACTIVELY MONITORED

From: FOUCART, Stéphane <[redacted]
Subject: EPA ORD OPP glyphosate
Date: March 14, 2017 at 11:32:24 AM GMT+1
To: Chris Portier <[redacted] Chris Portier [redacted]

FYI

http://www.lemonde.fr/planete/article/2017/03/14/glyphosate-discorde-a-l-agence-de-protection-de-l-environnement-americaine_5094158_3244.html

best
Stef

--
Stéphane Foucart
Le Monde
service Planète/Science - *Environment/Science desk*
80 boulevard Auguste Blanqui
75 707 Paris cedex 13
tel. +33 1 57 28 27 02
[redacted]

From: FOUCART, Stéphane [redacted]
Subject: glyphosate letter
Date: December 7, 2015 at 2:22:16 PM GMT+1
To: Chris Portier [redacted]

Dear Chris Portier,

I hope this message finds you well. I mentioned the letter to european authorities on glyphosate at the last paragraph of my weekly column (here http://abonnes.lemonde.fr/idees/article/2015/12/07/petits-arrangements-avec-la-verite_4826110_3232.html for subscribers, and in the print edition, PDF attached).

Please do not hesitate to send updates if necessary (these last days, the timing was bad in France, virtually all environmental journalists are working on the COP21).

best regards,
Stéphane

From: FOUCART, Stéphane <[redacted]
Subject: Fwd: Gly
Date: March 8, 2016 at 5:04:26 PM GMT+1
To: Chris Portier <[redacted]

FYI

From: Christopher Watts <[redacted]
Subject: Fwd: Ramazzini Institute
Date: September 7, 2016 at 1:30:31 PM GMT+2
To: [redacted]

Christopher,

I am following up on our recent introduction to try to schedule a short call to hear your insights into the Ramazzini Institute.

I'm conducting some background research to try to better understand the aims and the activities of the Institute.

It's not for any specific article or publication, at this stage, so our conversation will be off the record, for background only.

Would you like to suggest a time that is convenient for you?

Thank you very much for letting me know.

Kind regards,

Christopher.

---------- Forwarded message ----------
From: **Devra Davis** [redacted]
Date: 10 August 2016 at 17:26
Subject: Re: Ramazzini Institute
To: Christopher Watts <[redacted]
Cc: Chris Portier <[redacted]

yes....also recommend Christopher Portier, copied here

Devra Davis, PhD MPH
Fellow American College of Epidemiology

Visiting Prof. Hebrew Univ. Hadassah Medical Center & Ondokuz Mayis Univ. Medical School
Associate Editor, Frontiers in Radiation and Health
President Environmental Health Trust
P.O. Box 58
Teton Village, WY 83025

Web: EHTRUST.ORG
Please Sign up for the EHT Newsletter
Follow me on Twitter @DevraLeeDavis
www.facebook.com/devra.davis
www.facebook.com/EHTrust

See our new music video: "A Little Chat"
http://ehtrust.org/music-video-on-cell-phone-safety/

Disconnect:the truth about cell phone radiation
http://amzn.to/1OGZJwT

The Secret History of the War on Cancer
http://amzn.to/1FIMzfJ

On Wed, Aug 10, 2016 at 12:43 AM, Christopher Watts [redacted] wrote:

Dear Dr Davis,

I am conducting some background research on the Ramazzini Institute to try to get greater insight into its goals and its activities.

Would you be available for a short off-the-record briefing by phone in the coming 1-2 weeks to share your insights and experiences of the institute, please?

Alternatively, are you able to recommend me any names of other well-placed individuals who are familiar with the institute?

I would be grateful for any support you are able to offer. Thank you very much for letting me know.

Yours sincerely, Christopher Watts.

--
Christopher Watts
Contributing Editor
The Economist Group
[redacted]

--
Christopher Watts
Contributing Editor
The Economist Group
[redacted]

From: Kathryn Guyton <[redacted]>
Subject: Glyphosate-Information requests
Date: April 1, 2016 at 3:25:41 PM GMT+2
To: [redacted] "Blair, Aaron (NIH/NCI) [V]" <[redacted]> Bill Jameson <[redacted]> "Kromhout, J. (Hans)" <[redacted]> frank lecurieux <[redacted]> Teresa Rodriguez <[redacted]> Consolato Sergi <[redacted]> Chris Portier <[redacted]>
Cc: Kurt Straif <[redacted]> Dana Loomis <[redacted]>

Dear Vol 112 Working Group members,

Although you are not employed by a US state or federal institution, you may find of interest that two state universities in the US have received information requests, issued under US state open records laws, concerning the IARC evaluation of glyphosate. IARC is not in a position to offer legal advice concerning such information requests. However, it is the position of IARC that Working Group members prepare all materials on behalf of IARC, and not as part of their official employment duties; and that IARC is the sole owner of all such materials. IARC does not encourage participants to retain working drafts of documents after the related Monograph has been published.

Don't hesitate to inform us if you have similarly received such information requests, or if we can facilitate or help with any responses.

With kind regards,
Kate

Kate Z. Guyton PhD DABT
Responsible Officer, Volume 112

Monographs Section
International Agency for Research on Cancer 150, cours Albert Thomas
69372 Lyon Cedex 08
France Tel: [+33] (0)4 72 73 86 54
[redacted]

From: Carey Gillam <careygillamnewsnow@gmail.com>
Subject: Here is the article
Date: September 29, 2016 at 5:55:39 PM GMT+2
To: Christopher Portier <[redacted]

http://www.huffingtonpost.com/carey-gillam/upcoming-epa-meetings-on_b_12245584.html

--

Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@gmail.com
www.careygillam.com
https://twitter.com/careygillam

From: Geets Siobhan [redacted]
Subject: AW: press inquiry glyphosate
Date: December 1, 2015 at 11:17:22 AM GMT+1
To: Chris Portier <[redacted]

Great, when can I call in the afternoon? I think it is a six hour time difference?

Mit freundlichen Grüßen Mag. Siobhan Geets Redaktion
unknown.gif ¬ **Wiener Zeitung GmbH** Media Quarter Marx 3.3 (
Anfahrtsplan) 1030 Wien I Maria-Jacobi-Gasse 1 T: +43 1 206 99-315
[redacted] I http://www.wienerzeitung.at

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Von: Chris Portier [redacted] **Gesendet:** Montag, 30. November 2015 18:40 **An:** Geets Siobhan **Betreff:** Re: press inquiry glyphosate

I am available tomorrow afternoon or now.

==========

Text entered on a small quadrilateral of aluminosilicate glass using thick fingers with a confused spelling checker running on a processor more powerful than the combined computing power of the planet when I started college and sent over digitally-controlled electromagnetic fields that are probably scrambling my brain. Mistakes are inevitable.

On Nov 30, 2015, at 18:06, Geets Siobhan [redacted] wrote:

Dear Prof. Portier,

I am writing to you on behalf of the Austrian daily newspaper „Wiener

Zeitung", we would like to print an interview with you on the dangers of glyphosate.
Are you available on phone or Skype in the next days?
I hope we'll be able to talk about this very important subject soon!

Sincerely,
best wishes from Vienna,

Siobhán Geets

Mag. Siobhan Geets Redaktion <image001.gif> **Wiener Zeitung GmbH** Media Quarter Marx 3.3 (Anfahrtsplan)
1030 Wien | Maria-Jacobi-Gasse 1 T: +43 1 206 99-315
[redacted] | http://www.wienerzeitung.at

<image002.gif>

From: Carey Gillam <careygillamnewsnow@yahoo.com>
Subject: Re: can you review this please??
Date: September 27, 2016 at 9:03:17 PM GMT+2
To: Chris Portier [redacted]
Reply-To: Carey Gillam <careygillamnewsnow@yahoo.com>

Thank you for the quick reply. I have another question for you, if and when you have time to address it. I'm interested in the EPA scientist listing as sitting on the IARC working group... A Matthew T. Martin. He appears to have no involvement with the EPA's own cancer assessments of glyphosate. Did he agree wholeheartedly with the rest of the working group, as far as you recall? Do you know much about his position? He seems fairly young. He is listed as a research Biologist at the EPA's National Center for Computational Toxicology in North Carolina. I wonder if he was in that role last year when he was on the IARC working group, or if he has been since reassigned. Do you know anything about him??

Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@yahoo.com
carey@usrtk.org
https://twitter.com/careygillam
http://www.careygillam.com/

From: Chris Portier <[redacted]
To: Carey Gillam <careygillamnewsnow@yahoo.com>
Sent: Tuesday, September 27, 2016 1:52 PM
Subject: Re: can you review this please??

I have no concerns with your quotes. A very balanced article I think.

On Sep 27, 2016, at 8:17 PM, Carey Gillam <careygillamnewsnow@yahoo.com> wrote:

I have an article I plan to publish perhaps tomorrow. Can you please look over these few paragraph excerpts and tell me if you see anything inaccurate??

The company clearly does not welcome the public scrutiny the meetings bring, but it should be satisfied that the EPA has no intention of contradicting Monsanto's claims of glyphosate's safety. After all, earlier this month the EPA publicized a 227-page "evaluation" of glyphosate's cancer-causing potential that ended with a "proposed" conclusion that glyphosate was "'not likely to be carcinogenic to human' at doses relevant to human health risk assessment."

To its credit, the EPA did issue several caveats in that report, acknowledging that numerous research studies do link glyphosate to cancer, but offering various explanations as to why the agency doesn't believe those study results are significant. The agency also added a host of qualifiers, including stating that the data it was relying on was largely limited and outdated. And the EPA specifically noted that "with the increased use of glyphosate following the introduction of glyphosate-tolerant crops in 1996, there is a need for more recent studies…" The EPA also offered a specific caveat with respect to research tying glyphosate to non-Hodgkin lymphoma (NHL), saying: "There are conflicting views on how to interpret the overall results for NHL. Some believe that the data are indicative of a potential association between glyphosate exposure and risk of NHL."

The EPA's appearance of aligning with Monsanto over independent international scientists with decades of specific

experience in cancer research, angers many in the scientific community who say the EPA is straying from established scientific principles and ignoring key evidence so it can keep the corporate interests who profit from glyphosate herbicides happy

"This chemical is a probable human carcinogen by any reasonable definition. It is nonsense to say otherwise," said Christopher Portier, former director of the National Center for Environmental Health and Agency for Toxic Substances and Disease Registry at the U.S. Centers for Disease Control and Prevention (CDC). Prior to that role, Portier spent 32 years with the National Institute of Environmental Health Sciences (NIEHS), where he served as the NIEHS associate director, director of the Environmental Toxicology Program, and associate director of the National Toxicology Program. In retirement, Portier, who was an "invited specialist" to the IARC review on glyphosate, has done some part-time work for the Environmental Defense Fund.

Portier and more than 90 other international scientists have issued a detailed report laying out the specific research that ties glyphosate to cancer both in animal studies and in human observations. The scientists said the only way for the EPA or other regulatory bodies to discount the evidence is to bend well-established rules for scientific evaluations. They say available human evidence shows an association between glyphosate and a blood cancer called non-Hodgkin lymphoma; while significant carcinogenic effects are seen in laboratory animals for rare kidney and other types of tumors. There is also "strong evidence of genotoxicity and oxidative stress," including findings of DNA damage in the peripheral blood of people exposed to glyphosate, the scientists said.
"The most appropriate and scientifically based evaluation of the cancers reported in humans and laboratory animals as well as supportive mechanistic data is that glyphosate is a probable human carcinogen*,"* the report states. *"On the basis of this*

conclusion and in the absence of evidence to the contrary, it is reasonable to conclude that glyphosate formulations should also be considered likely human carcinogens."

"The EPA is in a bad spot with this. The pushback really has come out of the industry based on things that are not scientifically sound," said Maarten Bosland, one of the authors of the report on glyphosate research. Bosland is director of the Center for Global Health Outreach Department of Pathology at the University of Chicago /Illinois and holds a Ph.D. in experimental pathology. "The amount of money that is involved in this compound is gigantic. It's a worldwide conglomerate of financial interests that are affected by this."

It seems more than coincidental that the EPA's rationale for dismissing scientific studies that IARC said showed cancer links closely dovetails with the findings of a 16-member Monsanto-funded panel. That group of 16 scientists, all but four of whom had previously worked either as employees or consultants for Monsanto, issued a report in 2015 that supported Monsanto's contention that there is no real evidence that glyphosate can cause cancer. Leading the work was Gary M. Williams, director of environmental pathology and toxicology at New York Medical College, who has a long history of publishing positive findings about glyphosate while working as a consultant for Monsanto. Williams was an author of one of Monsanto's most-touted studies, a 2000 research report that concluded glyphosate is not only not a carcinogen, but "is considered to be practically nontoxic."

Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@yahoo.com
carey@usrtk.org
https://twitter.com/careygillam
http://www.careygillam.com/

From: Carey Gillam <careygillamnewsnow@gmail.com>
Subject: Re: CD-1 mouse study
Date: June 7, 2017 at 6:11:14 PM GMT+2
To: Chris Portier <[redacted]

One quick quote perhaps? I'm writing about Monsanto's manipulation of the kidney study results, or their efforts to convince regulators of their industry-friendly "interpretation." I see dog studies, rats, mice, rabbits, etc..that show tumors, reduced pregnancy rates, other negative impacts, and yet the data all eventually are discounted by regulators as not statistically significant. Can you offer a reader-friendly quote addressing this?
Carey

On Mon, Jun 5, 2017 at 9:32 PM, Chris Portier [redacted] wrote:
The kidney tumors in the 1983 study are definitely important. When the two 24 month mouse studies are combined, the kidney tumors are statistically significant. Individually, when historical controls are used against the rates seen in the 1983 study, the finiding is highly statistically significant. The argument used by the regulatory agencies that these tumors fall within the range of historical controls is an incorrect statistical comparison and a mor rigorous approach needs to be used - this leads to significance as noted by IARC. In general, all four mouse studies in CD-1 mice showed some positive trend in kidney tumors that, when combined, is highly significant. The same is true for hemangiosarcomas in male mice and malignant lymphoma in male mice in the 18-month studies. They are all important.

C.

On Jun 6, 2017, at 4:37 AM, Carey Gillam <careygillamnewsnow@gmail.com> wrote:

Hello again - I'm writing up a piece about the twisted path of the 1983 CD-1 mouse study that has appeared fairly pivotal when it comes to glyphosate carcinogenicity classifications. You know the saga of the non-existent tumor in the control group that then appeared after Monsanto enlisted an outside pathologist to review tissue slides.
I'm wondering how you view this study and how much weight it carries, or

does not carry, in your evaluations of the research surrounding glyphosate and cancer.
You are aware, I believe, that the plaintiffs' attorneys in the Roundup cancer litigation in San Francisco received court approval to review the tissue slides. I'd be most interested in your view on that study. This is the one prepared by BioDynamics for Monsanto's submission to EPA.

--
Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@gmail.com
www.careygillam.com
https://twitter.com/careygillam

--
Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@gmail.com
www.careygillam.com
https://twitter.com/careygillam

From: Kathryn Guyton <[redacted]
Subject: Re: EFSA "criteria"
Date: November 17, 2015 at 5:12:54 PM GMT+1
To: Chris Portier
Cc: "Rusyn, Ivan"[redacted]

Apologies, they are both wrong- should be:
·Carcinoma [P=0.037]
Adenoma or carcinoma (combined)[P=0.034]

From: Chris Portier <[redacted]
Date: Tuesday 17 November 2015 at 17:09
To: Kate Guyton <[redacted]
Subject: Re: EFSA "criteria"

One of these p-values is wrong.

On Nov 17, 2015, at 4:30 PM, Kathryn Guyton <[redacted] wrote:
Dear Chris, Dear Ivan,

We have noted that EFSA has invoked a number of "additional criteria" in a weight of evidence approach in concluding "no evidence of carcinogenicity" of glyphosate in experimental animals.

I append for your review and comment a preliminary review of the criteria referenced by EFSA (see below), identifying relevant IARC and OECD guidance, and (consistent with the IARC systematic review approach) indicating the applicability of each to the two studies that provided "sufficient evidence" of carcinogenicity in the Monograph.

Many thanks,
Best from Lyon,
Kate

http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/4302.pdf

No evidence of carcinogenicity was confirmed by the large majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pair-wise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/MTD, lack of pre- neoplastic lesions and/or being within historical control range. The statistical significance found in trend analysis (but not in pair-wise comparison) per se was balanced against the former considerations.
<Additional criteria- EFSA.docx>

From: Kathryn Guyton [redacted]
Subject: Re: EFSA Glyphosate Recommendations
Date: November 27, 2015 at 10:59:16 AM GMT+1
To: Chris Portier [redacted]

AWESOME! FYI, it will be me and Chris Wild at the ENVI meeting.
Kate

From: Chris Portier [redacted]
Date: Friday 27 November 2015 at 10:26
To: Kate Guyton [redacted] Kurt Straif [redacted]
Subject: Fwd: EFSA Glyphosate Recommendations

Embargoed until monday.

Begin forwarded message:
From: Chris Portier [redacted]
Date: November 27, 2015 at 9:56:57 AM GMT+1
[redacted]
Subject: EFSA Glyphosate Recommendations

Dear Commissioner Andriukaitis,

Attached to this email is a letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety

Agency (EFSA) decision that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you read our letter and share it with those who will be advising you on accepting or rejecting EFSA's decision. We would greatly appreciate your sharing this with the members of the Standing Committee on Plants, Animals, Food and Feed before their next meeting on December 10, 2015. I will be in Brussels from November 30 to December 2. If you believe it would be helpful for me to discuss these concerns with you or your staff in person, please send email to this address or call [redacted]

Thank you for your attention to this important issue.

Sincerely,

Prof. Christopher J. Portier

cc: Mr. Phil Hogan, European Commissioner for Agriculture and Human Development

Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety

Dr. Bernhard Url, Executive Director, EFSA

Dr. Giovanni La Via, Chair, ENVI Committee

EFSA Panel on Plant Protection Products and their Residues

Mr. Christian Schmidt, Minister of Food and Agriculture

Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection

and Food Safety (BVL)

Professor Dr. Dr. Andreas Hensel, President, BFR

Dr. Christopher Wild, Director, IARC

Mr. Jim Jones, Assistant Administrator, USEPA

From: [redacted]
Subject: RE: EFSA Glyphosate Recommendations
Date: December 4, 2015 at 4:49:01 PM GMT+1
To: [redacted]
Cc: [redacted]

Dear Mr Portier,

Thank you for your prompt reply. Unfortunately, the Commissioner will not be in Brussels after 17 December so in this case, we would like to instead offer a meeting on 8 January at 13:00-14:00, would this be suitable?

Best regards,

Tuuli Kytölä

From: Chris Portier [redacted] **Sent:** Friday, December 04, 2015 3:54 PM**To:** KYTOLA Tuuli (CAB-ANDRIUKAITIS)**Cc:** CHAZE Nathalie (CAB-ANDRIUKAITIS); DAPKUS Egidijus (CAB-ANDRIUKAITIS); LIUTVINSKAITE Dovile (CAB-ANDRIUKAITIS)**Subject:** Re: EFSA Glyphosate Recommendations

Dear Tuuli Kytölä,

I am honored that the Commissioner would take the time out of his busy schedule to meet with me. The issue of glyphosate carcinogenicity is one that is important to everyone in Europe on both economic and safety levels and it is important that we all have a clear understanding of what the data are implying. Regretfully, I will be flying to the United States on December 11 and will be unavailable at that time. I will return from the United States on December 17 but have a commitment on December 18. I am free the following week if that could be arranged.

Sincerely,

Prof. Christopher Portier

On Dec 4, 2015, at 1:04 PM, [redacted] wrote:

Dear Mr Portier,

On behalf of Commissioner Vytenis Andriukaitis, I would like to thank you for your e-mail of 27 November 2015, sharing concerns about the EFSA Glyphosate Recommendations.

The Commissioner would be available for a meeting with you on 11 December at 13:30-14:30, would this be suitable for you?

Yours sincerely,

Tuuli Kytölä Assistant <image001.gif> **European Commission**
Cabinet of Commissioner Vytenis Andriukaitis Health and Food Safety
BERL 08/376 +32 229 58938 [redacted]

From: Chris Portier [redacted] **Sent:** Friday, November 27, 2015 9:57 AM**To:** CAB ANDRIUKAITIS WEBPAGE; ANDRIUKAITIS Vytenis (CAB-ANDRIUKAITIS)**Cc:** URL Bernhard (EFSA); LA VIA Giovanni (EP); [redacted] HOGAN Phil (CAB-HOGAN); MIKO Ladislav (SANTE); [redacted] **Subject:** EFSA Glyphosate Recommendations

Dear Commissioner Andriukaitis,

Attached to this email is a letter from 96 prominent epidemiologists, toxicologists, statisticians and molecular biologists from 25 countries. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety

Agency (EFSA) decision that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you read our letter and share it with those who will be advising you on accepting or rejecting EFSA's decision. We would greatly appreciate your sharing this with the members of the Standing Committee on Plants, Animals, Food and Feed before their next meeting on December 10, 2015. I will be in Brussels from November 30 to December 2. If you believe it would be helpful for me to discuss these concerns with you or your staff in person, please send email to this address or call [redacted]

Thank you for your attention to this important issue.

Sincerely,

Prof. Christopher J. Portier

cc: Mr. Phil Hogan, European Commissioner for Agriculture and Human Development

Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety

Dr. Bernhard Url, Executive Director, EFSA

Dr. Giovanni La Via, Chair, ENVI Committee

EFSA Panel on Plant Protection Products and their Residues

Mr. Christian Schmidt, Minister of Food and Agriculture

Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection

and Food Safety (BVL)

Professor Dr. Dr. Andreas Hensel, President, BFR

Dr. Christopher Wild, Director, IARC

Mr. Jim Jones, Assistant Administrator, USEPA

<EFSA-Glyphosate-Letter.pdf>

From: Carey Gillam <careygillamnewsnow@gmail.com>
Subject: Re: FYI - maybe we can talk again
Date: October 25, 2016 at 11:44:43 PM GMT+2
To: Chris Portier <[redacted]

There is also this out today. They are really turning up the heat now on EPA, moving from attacking IARC credibility to threatening careers of EPA officials, including pointing fingers at Jim Jones, the top pesticide program guy at EPA. The fact that they are so focused on obtaining emails from anyone EXCEPT Monsanto Co, (which we know there are Monsanto emails to and from EPA on this topic) shows how the wind is blowing. I think they are pushing so hard to get EPA to officially and finally repudiate the cancer connection both to hopefully influence EU decision and to use as lever to try to halt or limit the MDL. Anyway, this is latest from DC:
https://science.house.gov/sites/republicans.science.house.gov/files/documents/10.25.16%20SST%20Letter%20to%20Administrator%20McCarthy%20re%20Glyphosate.pdf

On Tue, Oct 25, 2016 at 1:55 PM, Chris Portier [redacted] wrote:

NIH needs public examination after giving millions to rogue UN agency

By: Bruce Chassy
Published: October 24, 2016
Source: The Hill
http://thehill.com/blogs/pundits-blog/healthcare/302484-nih-needs-public-examination-after-giving-millions-to-rouge-un

The National Institutes of Health (NIH) is being **called** on the carpet to explain why it gave tens of millions of dollars to the International Agency for Research on Cancer (IARC), a United Nations agency that has been accused of "**quackery**" and "**cherry picking**" its facts.

The NIH agreed to appear before Rep. **Jason Chaffetz**'s House Oversight Committee — but only on the condition that the hearing is closed-press and off-limits to the public. We don't even know the exact date the hearing will be held.

Meanwhile, the NIH is **stonewalling** FOIA requests for its emails with IARC staff, claiming — absurdly — that U.S. freedom of information laws somehow don't apply to U.S. government employees communicating with the IARC.

Why all the secrecy? The growing scandal over the IARC's finding that the widely used herbicide glyphosate is "probably carcinogenic" to humans has nothing do with national security, terrorism or classified information.

Congress simply wants the NIH to explain its support and staff involvement with an agency that has been widely criticized for its shoddy science and plagued by questions of bias. Science claims upon which public health policies are set demand transparency, expert review and demonstrated replicability.

Because of the IARC's flawed assessment and its unprecedented political lobbying, glyphosate's re-approval is now threatened in Europe, and the U.S. Environmental Protection Agency has delayed what should have been an easy re-approval. Losing glyphosate would be a **massive blow** to American farmers, consumers and the agricultural economy.

If we want the American people to continue to trust the integrity of our regulatory system, the NIH needs to answer the questions raised by the IARC's actions.

In March of this year, David Zaruk **published a series** detailing the conflicts of interest of the IARC's "independent expert," Chris Portier.

An ex-staffer at the NIH's sub-agency, the National Institute for Environmental Health Sciences (NIEHS), Portier drove the current IARC monograph process, determining which chemicals would be reviewed and influencing who would be selected to participate on the review panels — all the while taking a pay check

from the anti-pesticide Environmental Defense Fund.

Despite the IARC's purported strict conflict of interest rules, which it routinely uses to exclude scientists with any connection to industry, the agency covered up Portier's activist connections for years, identifying him only as "retired" from the NIEHS.

Portier isn't the only one in the IARC's revolving door of activist groups and those who profit by disparaging chemicals. Other monograph panelists with undisclosed conflicts include:

- Martyn Smith, reported to be a founding incorporator of the Council for Education and Research on Toxics (CERT) — an activist litigator group that sues companies over cancer claims **linked** to California Prop 65 issues — and an expert **witness** in lawsuits against chemical and pharmaceutical companies;

- Mary Wolff, an advisory board member of the anti-pesticide NGOs **Breast Cancer Action** and the **Silent Spring Institute**; and

- R. Thomas Zoeller, advisory board member of the anti-pesticide **Organic Center**.

Others, like **Aaron Blair**, **Isabelle Baldi**, **Matthew Ross** and **Ivan Rusyn**, frequently collaborate in activist conferences, co-publish papers with activists, or publicly lobby to ban pesticides. Many also serve as expert witnesses for lawsuits claiming chemicals cause cancer and are positioned to directly profit from the IARC's skewed and misleading hazard-based cancer rankings.

Congress needs to know what role the NIEHS has played in all of this, to wit:

- What role did the NIEHS and other U.S. government employees have in the IARC monograph process?

- Was the NIEHS aware of Chris Portier's and others' conflicts of interest when it provided millions in taxpayer funds to the IARC?

- Will the NIH comply with U.S. law and release their FOIA communications with the IARC to the public?

•

Finally, serious concerns have been raised about NIH and EPA procedures involving Chris Portier's brother, Kenneth Portier. The two sat on multiple **NIEHS** and **EPA** panels and other meetings without disclosing their relationship — even when Ken sat in review of Chris's work.

Despite declaring his belief that glyphosate should be taken off the market and the fact that his brother's reputation as an expert claiming glyphosate causes cancer is directly tied to the review findings, Kenneth Portier has been named to sit on EPA's glyphosate review panel.

Given this troubling conflict of interest, will the NIH and EPA disclose who recommended Kenneth Portier to this panel, release any official correspondence with Kenneth Portier and his brother Chris, and ask Kenneth Portier to make public any correspondence he has had with Chris regarding glyphosate?

The NIH needs to divulge what it knew and when it knew it. It must comply with U.S. transparency laws and rectify any internal conflicts that led to U.S. taxpayer dollars funding a rogue U.N. agency.

That's how things are supposed to be done in the United States. Not in secret, behind closed doors.

Chassy served as a researcher at the NIH for 21 years before moving to the University of Illinois at Urbana-Champaign as a department head and assistant dean, and is now professor emeritus of Food Science and Human Nutrition.

--

Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@gmail.com
www.careygillam.com

https://twitter.com/careygillam

From: Carey Gillam <careygillamnewsnow@gmail.com>
Subject: Re: Glyphosate Letter
Date: May 30, 2017 at 10:34:43 PM GMT+2
To: Chris Portier [redacted]

Thank you! Hey, I shared this on social media outlets but would like to write more if possible. It seems it has gotten quite a bit of attention in European press. Have you gotten much interest from U.S. journalists?
And can you illuminate for me the key distinctions or additions in this letter from the excellent piece you and the other scientists put out last year that made similar points: in essence, European regulators are ignoring and/or missing increases in tumor responses.
What are the newest, salient points, if you can direct me?
And have you heard anything back from Juncker's office, EFSA or EChA?
Best regards,
Carey

On Sat, May 27, 2017 at 7:55 AM Chris Portier <[redacted] wrote:
Carey,

FYI. Please treat this as embargoed until Monday, May 29 at 1:00 pm CET.

C.

From: Carey Gillam <careygillamnewsnow@gmail.com>
Subject: Re: glyphosate questions from a reporter
Date: September 21, 2016 at 1:45:36 PM GMT+2
To: Chris Portier <[redacted]

Thank you - I have to get my little chickens (children) off to school and then will be free by 9 a.m central/10 ET. I'd be grateful if you would call. My cell is[redacted]
Best regards,
Carey

On Wed, Sep 21, 2016 at 6:17 AM, Chris Portier <[redacted] wrote:
I am able to speak today before noon Eastern Standard time. Phone is [redacted] If you prefer, I can call you since I have unlimited international calling.

C.

On Sep 20, 2016, at 6:57 PM, Carey Gillam <careygillamnewsnow@gmail.com> wrote:

Greetings Dr. Portier- Prof. Bosland was kind enough to share your email address and your phone number. I'm hoping to arrange a time to talk to you via phone, or perhaps to ask you a few questions via email, if you prefer. I'm a reporter/researcher looking into a range of concerns surrounding glyphosate for a book I'm writing on the topic. I'm using expert voices like yours to help guide readers through this complicated, but important, issue. So with all that in mind, I'm asking if you might have time to speak on the phone Wednesday, or if you might entertain some questions via email?
If you need to know more about me, you can look at my work here http://www.huffingtonpost.com/author/careygillamnewsnow-194 and here http://www.reuters.com/journalists/carey-gillam/
My latest story from last week http://www.huffingtonpost.com/carey-gillam/fda-finds-monsantos-weed_b_12008680.html got 133,000 Facebook 'likes' on the HuffPo website, so people are reading about glyphosate!
Please let me know if we can speak.

--
Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@gmail.com
www.careygillam.com
https://twitter.com/careygillam

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Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@gmail.com
www.careygillam.com
https://twitter.com/careygillam

From: "Sass, Jennifer" <[redacted]
Subject: RE: Glyphosate SAP Hearing
Date: December 12, 2016 at 6:13:06 PM GMT+1
To: Chris Portier <[redacted]

Great - thanks!

-----Original Message-----
From: Chris Portier [redacted]
Sent: Monday, December 12, 2016 12:10 PM
To: Sass, Jennifer
Subject: Re: Glyphosate SAP Hearing

I I'll send you a revised version in word. Thanks for sharing this.

Sent from my iPad

On Dec 12, 2016, at 17:51, Sass, Jennifer [redacted] wrote:

Thanks for pulling this together Chris - you are truly a superhero.

My problem is that I won't be able to attend the SAP either, since it is now overlapping with the NIEHS BSC, and I have to be at NIEHS for that. I'll be able to webinar into the SAP on Friday, but will have to miss Tue-Thurs. Aargh.

Kristi Pullen is unable to attend the SAP for me, since she got pulled into another all-day meeting. I'm going to have to get an intern or someone without technical ability to attend and just give a word of introduction and then circulate my comments. I can also include yours at that time. Getting them circulated in writing is probably best anyway, so the panelists can refer to them at the appropriate times.

My scheduled comment time is Thurs AM. Let me know if you'd like me to include your comments. I can put them together as a one-page from you, and have them circulated on Thurs AM along with mine.

-----Original Message-----
From: Chris Portier [redacted]
Sent: Monday, December 12, 2016 7:23 AM
To: Sass, Jennifer
Subject: Glyphosate SAP Hearing

Jenn,

Dr. Joe Haseman has submitted comments to the SAP that are critical of my analysis. I only noticed these yesterday so I will not have an opportunity to respond in writing to the SAP. I was wondering if you could find someone who is speaking who could present my comments to the committee. I have drafted below something simple and easily read. I don't know the rules, but if they could hand over additional written comments, this would be helpful. But if they could just make a few observations in their prepared talk, this would help as well. I am concerned that Dr. Haseman's comments will carry great weight, especially if he is present. Here are the points I would make:

Major Points:

1. Dr. Haseman's analysis of p-values across the fifteen studies is flawed because (1) some of these studies are not valid tests of the compound as noted by the EFSA, EPA and others; (2) The approach is inappropriate for rare tumors and (3) the approach does not address the issue of the same tumor site appearing in multiple studies in the male mouse (he groups his analysis with rats and mice to say the three findings occur by chance in the male mice).

2. Dr. Haseman's dismissal of the tumor findings in mice fails to clarify the picture. For tumors with low historical control rates, the exact test has very limited power and it is where historical controls should be used to characterize the response (e.g. the p-value of 0.062 calculated by Dr. Haseman and estimated by me for the 2 tumors in the high dose of the 1997 study is the smallest p-value possible under the exact test as this is the most extreme case for a marginal of two tumors). The historical control data set I used was that cited by EPA. The IARC used a different study but for simplicity in my presentation, I used the study cited by EPA. For this rare tumor, the p-value calculated by the historical controls is very

significant in 3 studies. This is even more obvious for hemangiosarcomas where the historical control base cited by the EPA shows no tumors in 26 control groups for 18 months; the 1997 study saw 2 tumors in the high dose group. If nothing else, the SAP should request that EPA use a formal test of significance of historical controls in these evaluations.

3. EPA, in their document, compares the results from the 18 month mouse studies with those of the 24 month studies and concludes they are inconsistent. The analysis presented with the poly-3 adjusted pooled data is an attempt to address this question rigorouusly; if the studies were indeed inconsistent, then any trend in the data should be removed by the pooled analysis. Dr. Haseman's comments fail to address this part of the arguments by the EPA.

Minor Points:

1. The Poly-3 adjustments are used appropriately. EPA based their analysis on tumor counts and did not provide the actual survival for the animals. The analysis was simply an attempt to make the 18-month studies match the 24-month studies. There was no attempt to hide the fact that the 24-month study denominators would not change. I could only use the data available to me.

2. The randomization test (20,00 random samples) I used to estimate the exact p-value for the trend test is sufficient to give reasonable p-values. While it is simple to calculate p-values for responses at the extreme, this is much more difficult for the pooled data and I did not have access to a program to calculate truly exact p-values. The one randomization test was applied to all of my exact analyses.

3. Dr. Haseman is not actually reviewing the EPA evaluation but pretty much only my comments to the analyses. Both he and Dr. Tarone correctly point out the flaws in using the approximate trend test p-value. What he fails to see is the limitations of any of these tests for rare tumors which are the last 2 columns in my response to Dr. Tarone.

4. I did not play a significant role in the IARC review; I was an invited specialist. In that capacity I did not write any of the report or participate in the discussion to finally list glyphosate as a "Probable Human Carcinogen".

The positive findings for renal tubule adenomas (0/49, 0/49, 1/50, 3/50) in the 1983 study by the IARC Working Group was based upon both p-value and historical control data but is also significant under the exact test. The finding of a significant effect on hemangiosarcomas in the 1993 study is significant by the exact test and the test against historical controls. The IARC could only evaluate 2 of the mouse studies.

C.

From: Carey Gillam <careygillamnewsnow@gmail.com>
Subject: Re: Industry complaint about Infante here if you are interested
Date: October 19, 2016 at 10:22:07 PM GMT+2
To: Chris Portier [redacted]

http://www.huffingtonpost.com/carey-gillam/epa-bows-to-chemical-indu_b_12563438.html

On Tue, Oct 18, 2016 at 2:15 PM, Carey Gillam <careygillamnewsnow@gmail.com> wrote:
http://191hmt1pr08amfq62276etw2.wpengine.netdna-cdn.com/wp-content/uploads/2016/01/CLA-Comments-on-SAP-Disqualification-10-12-16.pdf

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Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@gmail.com
www.careygillam.com
https://twitter.com/careygillam

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Best regards,
Carey Gillam
913-526-6190
careygillamNewsNow@gmail.com
www.careygillam.com
https://twitter.com/careygillam

From: Erika Sanders <[redacted]
Subject: RE: Invitation to speak on CHE call on glyphosate, Thur April 28
Date: April 8, 2016 at 5:57:49 PM GMT+2
To: 'Chris Portier' [redacted]
Cc: 'Lorelei CHE Walker' <[redacted]

Wonderful, Dr. Portier. We're so pleased.

Yes, the "technology" for these calls is really simple. You simply need to dial in to a phone number I'll send you (with an access code).

The only other thing you would need is access to your computer or other device to view your own slides, if you choose to use them. We post them as PDFs on the call's webpage on our website and participants download them to their own devices and follow along on their own. Everyone advances their own slides. So, as you move through your presentation you simply need to say "next slide" or let the audience know what number slide you're on. This isn't a webinar, so no connecting via computer or need for other equipment of any kind.

I will be posting the call announcement on our webpage today. **If you had a moment to send me a brief bio to use and a preferred photo** (I can also look online), then I'll get you added as a speaker. Once that webpage is up, I'll send additional logistical details to the whole group next week.

You would have about 12 minutes or so for your presentation. We do leave time for some Q&A following all the presentations with participants. The call will last a total of 1 hour.

We very much appreciate your willingness to participate. It feels important to have IARC's evaluation of glyphosate represented.

If you have any further questions at this time, please be in touch. Otherwise, you'll be hearing more from us next week.

Best,

Erika

Erika Sanders
CHE Programs Administrative Coordinator
[redacted]
360-331-7904
www.HealthandEnvironment.org

From: Chris Portier [redacted] **Sent:** Friday, April 8, 2016 6:45 AM **To:** Erika Sanders [redacted] **Cc:** Kate Guyton [redacted] Lorelei CHE Walker [redacted] **Subject:** Re: Invitation to speak on CHE call on glyphosate, Thur April 28

Erika,

I assume I would do this from my office via electronic means. If that is true, I am happy to help you out.

C.

On Apr 7, 2016, at 6:30 PM, Erika Sanders [redacted] wrote:

Thank you, Dr. Guyton, for you quick response.

Dr. Portier, we would of course be delighted if you would consider joining the call on April 28th as a speaker to discuss IARC's evaluation of glyphosate. The details are below, but if I can answer any questions, please don't hesitate to be in touch.

Best,
Erika

Erika Sanders
CHE Programs Administrative Coordinator
[redacted]
360-331-7904
www.HealthandEnvironment.org

From: Kathryn Guyton [redacted] **Sent:** Thursday, April 7, 2016 7:37 AM **To:** Erika Sanders <[redacted] **Cc:** 'Lorelei CHE Walker' <[redacted]>; Chris Portier [redacted] **Subject:** Re: Invitation to speak on CHE call on glyphosate, Thur April 28

Dear Erika,

Thank you for your email, and for the kind invitation. Unfortunately, I wouldn't be able to provide the presentation you request. May I kindly suggest you contact Professor Chris Portier, cc'd here, as he may be willing to help.

With best regards,
Kate

Kate Z. Guyton PhD DABT
Monographs Section
International Agency for Research on Cancer 150, cours Albert Thomas
69372 Lyon Cedex 08
France Tel: [+33] (0)4 72 73 86 54
[redacted]

From: Erika Sanders <[redacted] **Date:** Wednesday 6 April 2016 at 19:17 **To:** [redacted] Kate Guyton [redacted] **Cc:** 'Lorelei CHE Walker' <[redacted] **Subject:** Invitation to speak on CHE call on glyphosate, Thur April 28

Dear Dr. Guyton,

I am the Programs Administrative Coordinator with the Collaborative on the Health and the Environment (CHE, see: http://www.healthandenvironment.org). Lisette van Vliet, director of the Health and Environment Alliance (HEAL) in Brussels recommended I reach out to you with an invitation to speak on an upcoming teleconference CHE is hosting on glyphosate and health on **Thursday April 28, 2016 at noon US Eastern**.

Dr. Belpoggi of the Ramazzini Institute in Italy, an author of the recently released consensus statement Concerns over us of glyphosate-based herbicides associated with exposures: a consensus statement(February 17, 2016, Environmental Health),has agreed to speak both to the consensus statement's recommendations as well as to her own research on glyphosate and health. Lisette will speak as well to the policy considerations of glyphosate research and recent policy movement in the EU.

We would like to invite you to speak to IARC's evaluation of glyphosate.

Our overall aim for this call is to give participants an understanding of the latest science on glyphosate, where leading institutions such as IARC stand on its potential human health impacts and what policy recommendations are being made, particularly in the EU.

The teleconference would last one hour. If you agree to speak that will give us 3 speakers, so you would each have approximately 12 minutes or so to present. You're welcome to use slides to accompany your remarks.

Our teleconferences are attended by environmental health researchers, medical professionals, government representatives (EPA, NIEHS, etc.), NGO representatives and some members of the general public. We typically have 75-100 participants. They last for one hour, and include a brief Q&A period following the speaker presentations.

Again, the call is scheduled for Thursday April 28th. If you can join us, you'd only need to send me a brief bio and a photo you'd like me to use for our

advertising. I will then send you additional logistical information for the call.

Thank you for your consideration.

Best,

Erika

Erika Sanders
CHE Programs Administrative Coordinator
[redacted]
360-331-7904
www.HealthandEnvironment.org

From: Kathryn Guyton <[redacted]
Subject: Re: Joint FAO/WHO Meeting on Pesticide Residues - JMPR summary report
Date: May 16, 2016 at 3:51:52 PM GMT+2
To: Chris Portier <[redacted]

Yes. I'm still in Geneva, through tomorrow…

From: Chris Portier <[redacted]
Date: Monday 16 May 2016 at 15:15
To: Kate Guyton <[redacted]
Subject: Re: Joint FAO/WHO Meeting on Pesticide Residues - JMPR summary report

And, do we need to chat?

On May 16, 2016, at 1:14 PM, Kathryn Guyton <[redacted] wrote:

Envoyé de mon iPhone

Begin forwarded message:

A Joint Meeting of the Food and Agriculture Organization of the United Nations (FAO) Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization (WHO) Core Assessment Group on Pesticide Residues (JMPR) was held at WHO Headquarters, Geneva (Switzerland), from 9 to 13 May 2016. **Diazinon**, **glyphosate** and **malathion** were placed on the agenda by the JMPR Secretariat, based on the recommendation of the last session of JMPR to re-evaluate these compounds given the number of new studies that had become available since their last full assessments. The

extracts of the results of the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) have now been published under the following link: http://www.who.int/foodsafety/jmprsummary2016.pdf?ua=1 You will also find a set of Q&As following this link: http://www.who.int/foodsafety/faq/en/ **For media queries, please contact** Paul Garwood Telephone: +41 22 791 1578 Mobile: [redacted] Email: [redacted] Christian Lindmeier Telephone: +41 22 791 1948 Mobile: [redacted] E-mail: [redacted]

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From: ECHA Committee Risk Assessment <rac@echa.europa.eu>
Subject: RE: Portier slides for ECHA Committee Risk Assessment
Date: November 21, 2016 at 4:21:40 PM GMT+1
To: Chris Portier [redacted]
Cc: Lisette van Vliet [redacted], Dolores Romano [redacted] Tatiana Santos [redacted], pcl [redacted] DVORAKOVA Dana [redacted] ECHA Committee Risk Assessment [redacted]

Dear Chris,
Thank you for your quick response and for the slides!
Best regards,
Dana

-----Original Message-----
From: Chris Portier [redacted]
Sent: 21 November 2016 17:18
To: ECHA Committee Risk Assessment <rac@echa.europa.eu>
Cc: Lisette van Vliet [redacted] Dolores Romano [redacted] Tatiana Santos [redacted] pcl [redacted]
Subject: Portier slides for ECHA Committee Risk Assessment

Dear Dana,

Per your request through Tatiana Santos and Peter Clausing, I have attached my slides.

C. Portier

From: Chris Portier <[redacted]
Subject: Re: query to you.
Date: August 4, 2017 at 3:33:52 PM GMT+2
To: Carey Gillam <carey@careygillam.com>

The European Parliament is not like the US House or Senate. They take these discussions seriously and ask reasonable questions (in my experience). There will be some members who clearly are on one side of the issue or the other, but many fall in between. You can certainly expect to be attacked by Monsanto and I expect to be attacked by both BfR and EFSA. But that is the nature of the beast.

C.

On Aug 4, 2017, at 1:44 PM, Carey Gillam <carey@careygillam.com> wrote:
I see you are slated to speak to Euro Parl hearing Oct. 11 as am I.
I hope you are planning to attend.
I also see BfR and EFSA and Monsanto on agenda.
Is there any reason I should be skeptical about participation?
And thank you for your reply. I know you are quite busy.
Bests,
Carey

On Fri, Aug 4, 2017 at 4:20 AM, Chris Portier <[redacted]> wrote:
On point 1, I agree that this appears to be a deceit by the Agency asking about formulations only after the fact,

On point 2, by statute, EPA is required to base their decision on the active ingredient (glyphosate) and not the formulated product. So, in doing there evaluations, they tend to ignore studies regarding the formulated product and they don't necessarily feel they even need to know about the adjuvants.

Sorry I took so long to reply, I have been busy. I found more positive tumors in the publicly available glyphosate data and I am trying to decide what is worth doing at this point to expose how poorly these data have been evaluated.

C.

On Aug 2, 2017, at 9:56 PM, Carey Gillam <carey@careygillam.com> wrote:

I have some EPA emails and notes that show the agency trying in April 2016 to get information from Monsanto about formulated Roundup products

An EPA scientist wrote this: "EPA was interested in any data or information Monsanto may have on how the formulations may differ from data on the active ingredient and surfactants independently of one another." The notes go on to ask for information about changes in Monsanto's Roundup formulation "over the years." "Monsanto indicated that up until 2000, nearly all glyphosate products on the market were its Roundup formulation which used some form of tallow amine as a surfactant. Afterwards, the properties of surfactants used and the ratio of surfactant to active ingredient were changed in most formulations… EPA suggested that Monsanto provide in writing any information that documents the changes of glyphosate formulations over time and across the globe."

This comes three months after the same EPA official Khue Nguyen reassured a concerned member of the public who had been asking questions. Nguyen told that man this: "Often, glyphosate products contain water, dyes, and/or surfactants that help facilitate movement of glyphosate into the plant…" . "While manufacturers of pesticide products do not always disclose all "other ingredients" on their labels…. they are required to disclose those ingredients to EPA. Inert ingredients in a product such as Roundup are not of concern for the consumer when pesticide products are used according to the label."

To me this is troubling because
1. it appears that the EPA is acting as though it has all the information it needs on formulated Roundup products to assure they are safe while at the same time asking Monsanto to provide it with information on what its using and in what ratio in these formulated Roundup products.
2. Why is EPA asking Monsanto for information on formulations in 2016, after

some 40 years of this stuff being on the market? Shouldn't EPA already know in detail what is out there and have the database to show its safe if its telling consumers its safe?

Obviously, I'm aware of Monsanto's own internal discussions of formulations v. glyphosate-only research and I'm aware of the studies that have shown formulations to be more toxic.
I'm simply asking you if the language I've shared above, which is pulled verbatim from these EPA records, indicates to you a hypocrisy or perhaps even a deceit by the agency. Or just a lack of knowledge? I may be reading it all wrong or not considering factors I'm not aware of and thought you had the experience and background to address this.
I'd welcome your comments.
Bests,
Carey

Friday, August 18, 2017 at 12:57:17 PM Central European Summer Time

Subject: RE: Public Hearing on "The Monsanto papers and glyphosate" in the European Parliament on 11 October 2017 - invitation
Date: Friday, August 18, 2017 at 12:20:14 PM Central European Summer Time
From: NEUMANN Nina
To: [redacted]
CC: Portier Chris (TGX), MITTERMAYER Felix
Attachments: image001.png

Dear Prof Dr Portier,

Thank you for your email.

We are delighted that you will participate in the public hearing in the European Parliament, and we will send you further information in early September.

Best wishes

Nina Neumann

From: Portier Chris (TGX) [redacted]
Sent: 18 August 2017 10:57
To: NEUMANN Nina
Subject: Re: Public Hearing on "The Monsanto papers and glyphosate" in the European Parliament on 11 October 2017 - invitation

Dear Ms. Neumann,

Did I answer this email? It went to my Maastricht account that I seldom check. I would be happy to participate. Please address any further emails to [redacted]

C.

From: NEUMANN Nina [redacted]
Date: Friday, August 4, 2017 at 10:57 AM
To: "Portier Chris (TGX)" [redacted]
Cc: MITTERMAYER Felix [redacted]
Subject: RE: Public Hearing on "The Monsanto papers and glyphosate" in the European Parliament on 11 October 2017 - invitation

Dear Prof. Dr. Portier,

Considering the importance that many of our Members attach to your presence at the public hearing in the European Parliament on the Monsanto papers and glyphosate, I allow myself to re-send our invitation (just in case my previous email got lost).

Thank you very much in advance.

Best wishes,

Nina Neumann

From: NEUMANN Nina
Sent: 28 July 2017 16:57
To: [redacted]
Cc: MITTERMAYER Felix [redacted]
Subject: Public Hearing on "The Monsanto papers and glyphosate" in the European Parliament on 11 October 2017 - invitation

Dear Prof. Dr. Portier,

The Committee on the Environment, Public Health and Food Safety (ENVI) and the Committee on Agriculture and Rural Development (AGRI) of the European Parliament will hold a joint Public Hearing entitled "The Monsanto papers and glyphosate" on Wednesday, 11 October, from 9h00 to 12h30, in the premises of the European Parliament in Brussels.

The aim is to discuss the credibility of scientific studies behind both the decision of US regulatory agencies to authorise the plant protection product Roundup™, as well as the conclusions of the EU risk assessment agencies ECHA and EFSA regarding its active substance glyphosate, with a specific focus on the questions raised by the so-called Monsanto papers. The hearing is expected to give a good insight into the matters at stake and to provide Parliament with the necessary information to decide on possible follow-up action.

Given your profile as one of the leading scientists familiar with the risk assessment of glyphosate, the Members of both committees would highly appreciate it if you could speak at this event and present your views.

Considering the fact that the hearing is already in a few weeks' time, we would be grateful if you could let us know as soon as possible whether you will be able to speak at this public hearing.

Many thanks in advance!

Best wishes,

Nina Neumann

Nina NEUMANN
Administrator for a parliamentary body

European Parliament
IPOL
Directorate for Economic and Scientific Policies
Secretariat of the Committee on the Environment, Public Health and Food Safety
BRU - SQM 10Y020 - Tel. +32 228 46022
[redacted]
www.europarl.europa.eu

Friday, August 18, 2017 at 12:57:17 PM Central European Summer Time

Subject: Automatic reply: Public Hearing on "The Monsanto papers and glyphosate" in the European Parliament on 11 October 2017 - invitation
Date: Friday, August 18, 2017 at 10:57:03 AM Central European Summer Time
From: NEUMANN Nina
To: Portier Chris (TGX)

Thank you for your email. Please note that I am on leave until 30 August. I will be back in the office on 31 August.

Friday, August 18, 2017 at 12:57:17 PM Central European Summer Time

Subject: RE: Public Hearing on "The Monsanto papers and glyphosate" in the European Parliament on 11 October 2017 - invitation
Date: Friday, August 4, 2017 at 10:52:02 AM Central European Summer Time
From: NEUMANN Nina
To: Portier Chris (TGX)
CC: MITTERMAYER Felix
Attachments: image001.png

Dear Prof. Dr. Portier,

Considering the importance that many of our Members attach to your presence at the public hearing in the European Parliament on the Monsanto papers and glyphosate, I allow myself to re-send our invitation (just in case my previous email got lost).

Thank you very much in advance.

Best wishes,

Nina Neumann

> **From:** NEUMANN Nina
> **Sent:** 28 July 2017 16:57
> **To:** [redacted]
> **Cc:** MITTERMAYER Felix [redacted]
> **Subject:** Public Hearing on "The Monsanto papers and glyphosate" in the European Parliament on 11 October 2017 - invitation
>
> Dear Prof. Dr. Portier,
>
> The Committee on the Environment, Public Health and Food Safety (ENVI) and the Committee on Agriculture and Rural Development (AGRI) of the European Parliament will hold a joint Public Hearing entitled "The Monsanto papers and glyphosate" on Wednesday, 11 October, from 9h00 to 12h30, in the premises of the European Parliament in Brussels.
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>
> Many thanks in advance!

Best wishes,

Nina Neumann

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[redacted]
www.europarl.europa.eu

Friday, August 18, 2017 at 12:57:17 PM Central European Summer Time

Subject: Public Hearing on "The Monsanto papers and glyphosate" in the European Parliament on 11 October 2017 - invitation
Date: Friday, July 28, 2017 at 4:57:10 PM Central European Summer Time
From: NEUMANN Nina
To: Portier Chris (TGX)
CC: MITTERMAYER Felix
Attachments: image001.png

Dear Prof. Dr. Portier,

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BRU - SQM 10Y020 - Tel. +32 228 46022
[redacted]
www.europarl.europa.eu

From: no-reply@echa.europa.eu
Subject: Your ECHA submission data: glyphosate (ISO); N-(phosphonomethyl)glycine, 1071-83-6, 213-997-4
Date: July 8, 2016 at 9:21:09 PM GMT+2
To: [redacted]

Your submission is successfully received. Your reference number is 702fd2a8-3afd-41ea-ac94-fc89eb76cbd5. This message has been generated automatically by comments.echa.europa.eu
Substance Name: glyphosate (ISO); N-(phosphonomethyl)glycine
CAS Number: 1071-83-6
EC Number213-997-4

IARC Monograph Review Process and Glyphosate

Christopher J. Portier, Ph.D.

Cancer by Glyphosate – how dangerous is the herbicide?

Deutscher Bundestag, Berlin

June 6, 2015

The IARC Monographs Program

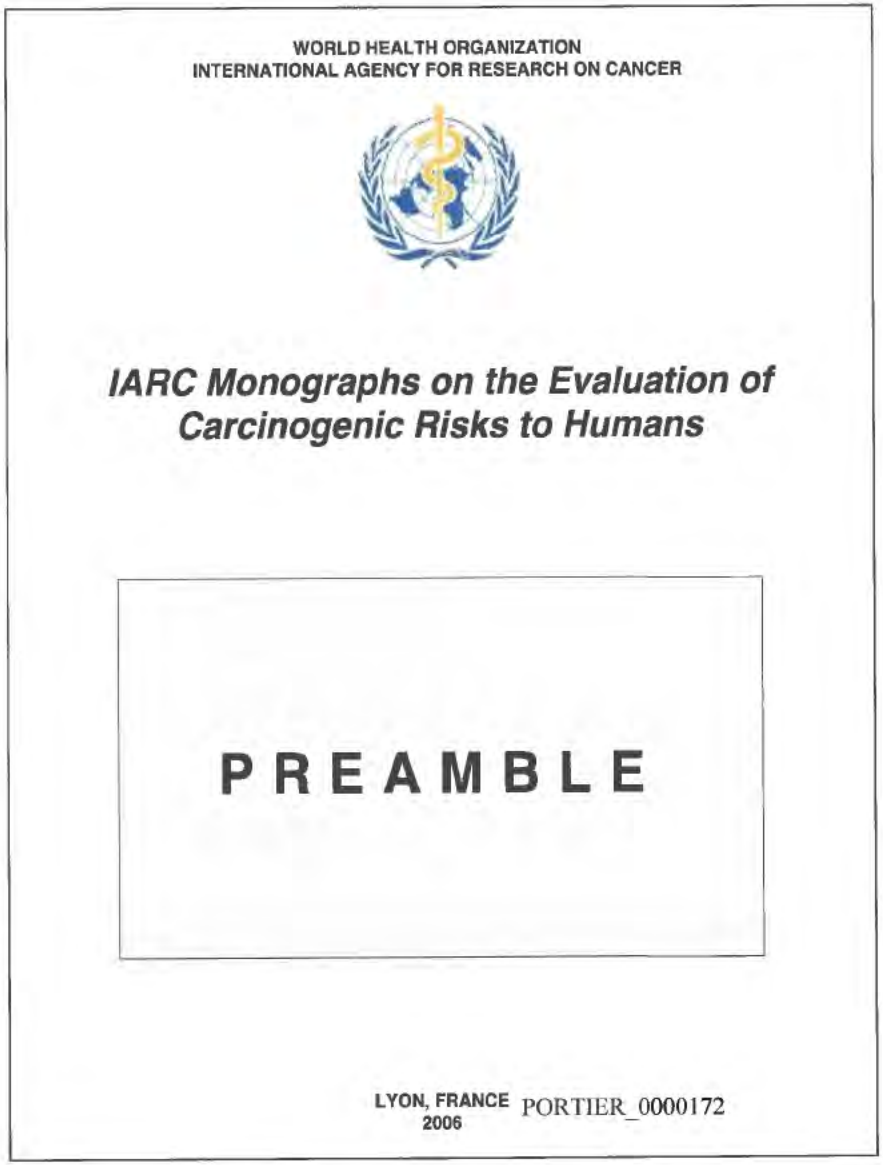
- IARC Monographs Evaluate
  - Chemicals
  - Complex substances and mixtures
  - Occupational exposures
  - Physical and biological agents
  - Personal habits

The IARC Monographs Program

- 980 Agents have been reviewed
  - 116 **known** human carcinogens
    - Group 1
  - 73 **probable** human carcinogens
    - Group 2A
  - 287 **possible** human carcinogens
    - Group 2B
  - 503 **not classifiable**
    - Group 3
  - 1 **probably not** carcinogenic

IARC Monographs Process

- Written Guidelines
  - Public Document
  - Who? What? How?
  - Roles
  - Responsibilities
  - Instructions
    - Review
    - Summary of Evidence



IARC Monograph 112 Process

- Working Group Members
  - No real or apparent conflicts of interest
    - Formal process, written declarations of interest
  - Membership
    - Working Group members – review, evaluate
    - Invited Specialist – review only
    - Representatives – government, observe only
    - Observers – interested party, observe only
    - Secretariat – support the Working Group

IARC Monograph Timeline

- 1 year before Monograph Meeting
  - Meeting announced
  - Call for experts
  - Call for data
- 8 months before Monograph Meeting
  - Working Group membership selected
  - Request for observer status opened
  - Draft sections of Monograph developed by Working Group Members

IARC Monograph Timeline

- 1 month before Monograph Meeting
  - Call for data closed
  - Draft sections distributed to Working Group members for review and comment
- At Monograph Meeting
  - Finalize review of all literature
  - Evaluate the evidence in each category
  - Complete the overall evaluation

IARC Monograph Timeline

- 1-2 weeks after Monograph Meeting
  - Publish summary in Lancet Oncology
- 4-12 months after Monograph Meeting
  - Finalize Monograph and publish

The IARC Monograph

Preamble

General Remarks

Several *Monographs* in one volume:

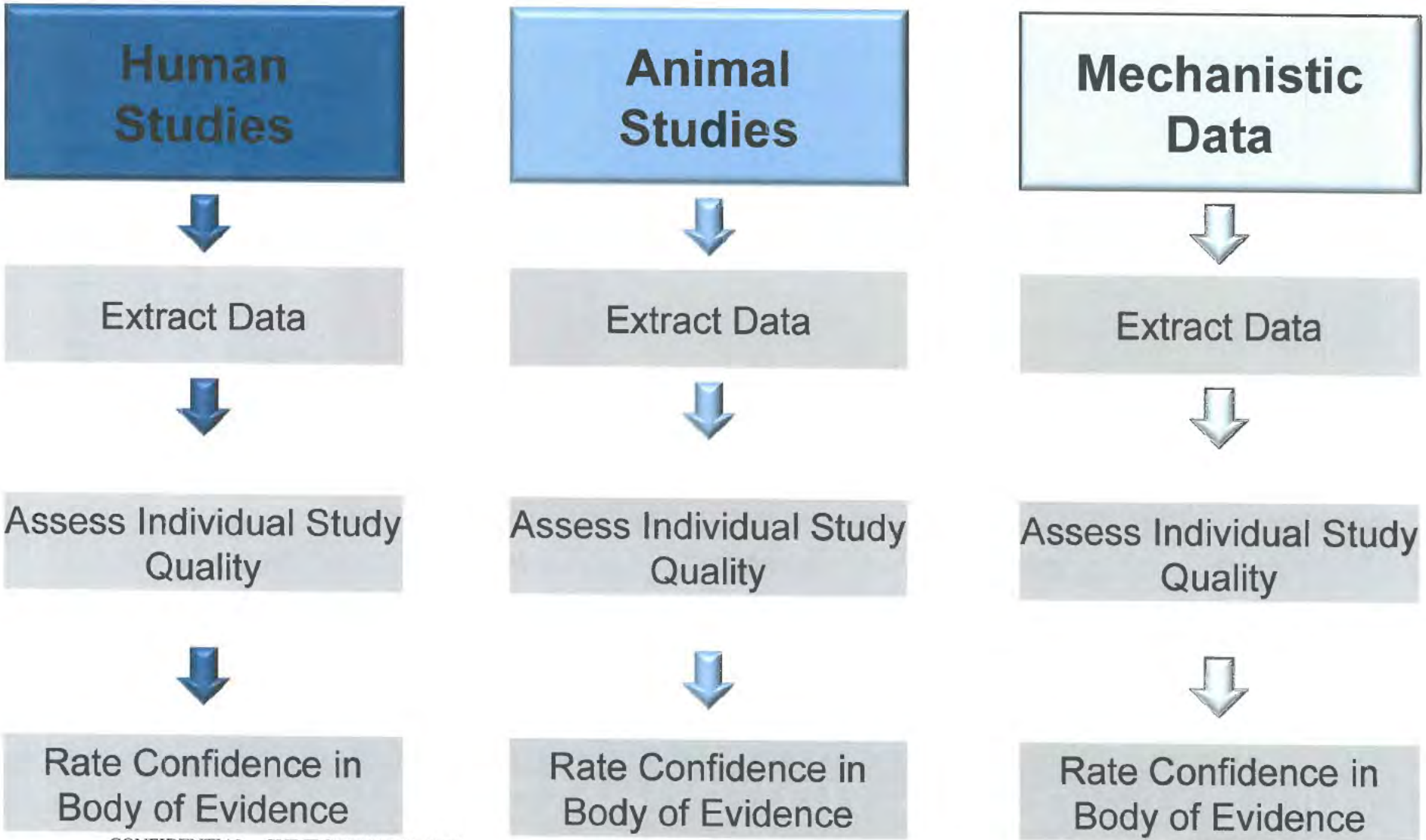
1. Exposure data
2. Cancer in humans
3. Cancer in animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

References

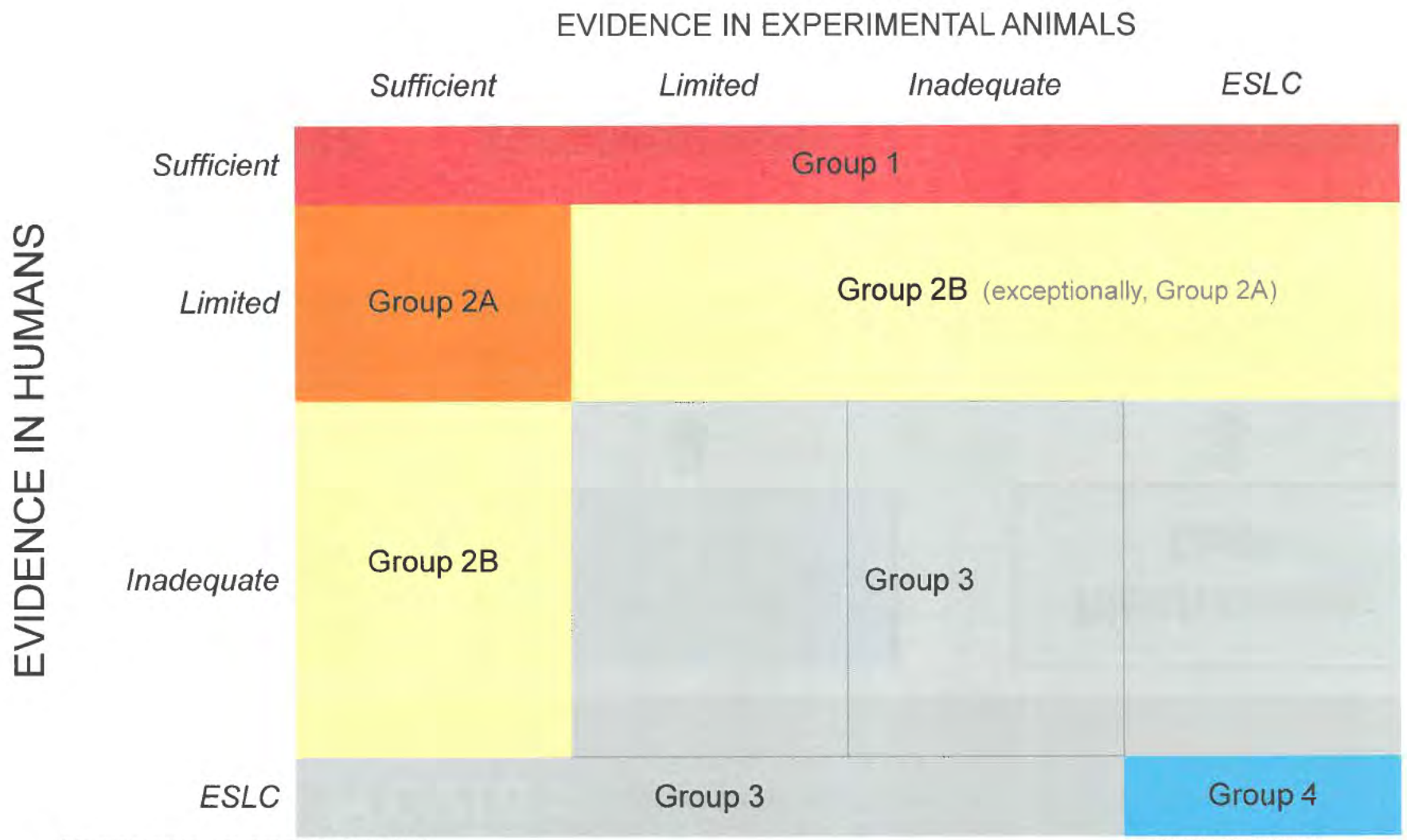
What is reviewed?

- Systematic review of human, experimental and mechanistic data
- All pertinent epidemiological studies and cancer bioassays
- Representative mechanistic data
- Studies must be publicly available
  - Sufficient detail to review
  - Reviewers cannot have been associated with the study

Evidence Review



IARC Overall Evaluation – Prof. Rusyn



Modified from Vincent Cogliano, IARC

Evaluating Human Evidence
Preamble Part B, Section 6(a)

- Sufficient Evidence
  - Causal relationship is **established**
  - Chance, bias and confounding ruled out with reasonable confidence
- Limited Evidence
  - Causal interpretation is **credible**
  - Chance, bias and confounding could not be ruled out with reasonable confidence

Evaluating Human Evidence
Preamble Part B, Section 6(a)

- Inadequate Evidence
  - Studies permit no conclusion regarding causality
- Evidence suggesting lack of carcinogenicity
  - Several strong studies showing consistent lack of positive association
  - Conclusion limited to cancer sites and conditions studied

Glyphosate - Background

- Broad-spectrum, non-selective herbicide
- First synthesized by Cilag (1950) as a possible drug
- Re-synthesized by Monsanto (1970)
- Patent expired [1991, 2000 (US)]
- Hundreds of trade names
- Approximately 91 producers in 20 countries

Glyphosate - Background

- Believed to be the most heavily used herbicide in the world
  - 2012 production volume > 700 million kg
- Production has increased sharply in recent years
  - Genetically modified glyphosate-resistant crop varieties
- Exposure pathways
  - Air (during spraying)
  - Water
  - Food

Glyphosate – Human Evidence

- Literature
  - US Agricultural Health Study (AHS)
  - Multiple independent case-control studies

Glyphosate – Human Evidence

- Epidemiological studies of cancer in humans
  - More than 2 studies
    - Non-Hodgkin Lymphoma (NHL)
    - Multiple Myeloma (MM)
  - Two studies
    - Leukemia, breast cancer, prostate cancer
  - One Study
    - Adult brain, oesophageal, stomach, prostate, soft-tissue sarcoma, lung, oral cavity, colorectal, pancreas, kidney, bladder, melanoma

Glyphosate – Key Epidemiology Studies for Non-Hodgkin Leukemia

Study	Type	Size
Agricultural Health Study *(Alavanja et al., 2003)*	Cohort – pesticide applicators and spouses	52 395 (+32 347 spouses)
US Midwest *(De Roos et al., 2003)*	Pooled analysis of 3 case-control studies	NHL: 650 cases, 1933 controls
Cross-Canada *(McDuffie et al., 2001)*	Population-based case-control	517 cases, 1506 controls
Swedish Case-Control Study *(Eriksson et al., 2008)*	Population-based case-control study	910 cases, 1016 control
Swedish Case-Control Study *(Hardell et al., 1999)*	Population-based case-control study	404 cases, 741 control (limited power)

Glyphosate Evaluation – Human Evidence

- Limited Evidence for NHL
  - Causal interpretation is **credible**
  - Chance, bias and confounding could not be ruled out with reasonable confidence
- Basis
  - De Roos et al., 2003 (US), McDuffie et al., 2001 (Canada), Eriksson et al., 2008 (Sweden)
    - Positive association
    - Adjustment for other pesticides
  - Agricultural Health Study
    - No additional support for association, does not contradict

Monograph should be available in July!

Questions?

Carcinogenicity of Glyphosate
A Systematic Review of the Available Evidence

Christopher J. Portier, Ph.D.

Swiss Society of Toxicology

18 November, 2016, Basel

Glyphosate - Background

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- Exposure pathways
  - Air (during spraying)
  - Water
  - Food

Recent Cancer Assessments of Glyphosate

- IARC – March, 2015
  - Probable human carcinogen
- EFSA – November, 2015
  - Unlikely to pose a carcinogenic hazard to humans
- Portier et al. – January, 2016
  - Probable human carcinogen
- WHO/JMPR – March, 2016
  - Unlikely to pose a carcinogenic risk to humans from exposure through the diet
- ECHA – May, 2016 (draft)
  - no hazard classification for carcinogenicity is warranted
- USEPA – September, 2016 (draft)
  - Not likely to be carcinogenic to humans at doses relevant to human health risk assessment

Comparison Across Evaluations

Study	Authors Known	COI Made Public	Proprietary Studies	Open Literature	Guidelines	Evaluated Dose-Response
IARC	Yes	Yes	No	Yes	Yes	No
EFSA	No	No	Yes	Yes	Yes	No
Portier	Yes	Yes	Yes	Yes	Yes	No
JMPR	Yes	?	Yes	Yes	Yes	Yes
ECHA	No	No	Yes	Yes	Yes	No
EPA	?	Some	Yes	Yes	Yes	No

Why are they different?

- Human Data
  - Limited evidence versus Insufficient Evidence
- Animal Cancer Studies
  - Sufficient Evidence versus Insufficient Evidence
- Mechanisms
  - Genotoxic or not genotoxic
  - Induces oxidative stress is or is not important

IARC: Evaluating Human Evidence
Preamble Part B, Section 6(a)

- Sufficient Evidence
  - Causal relationship is **established**
  - Chance, bias and confounding ruled out with reasonable confidence
- Limited Evidence
  - Causal interpretation is **credible**
  - Chance, bias and confounding could not be ruled out with reasonable confidence

IARC: Evaluating Human Evidence
Preamble Part B, Section 6(a)

- Inadequate Evidence
  - Studies permit no conclusion regarding causality
- Evidence suggesting lack of carcinogenicity
  - Several strong studies showing consistent lack of positive association
  - Conclusion limited to cancer sites and conditions studied

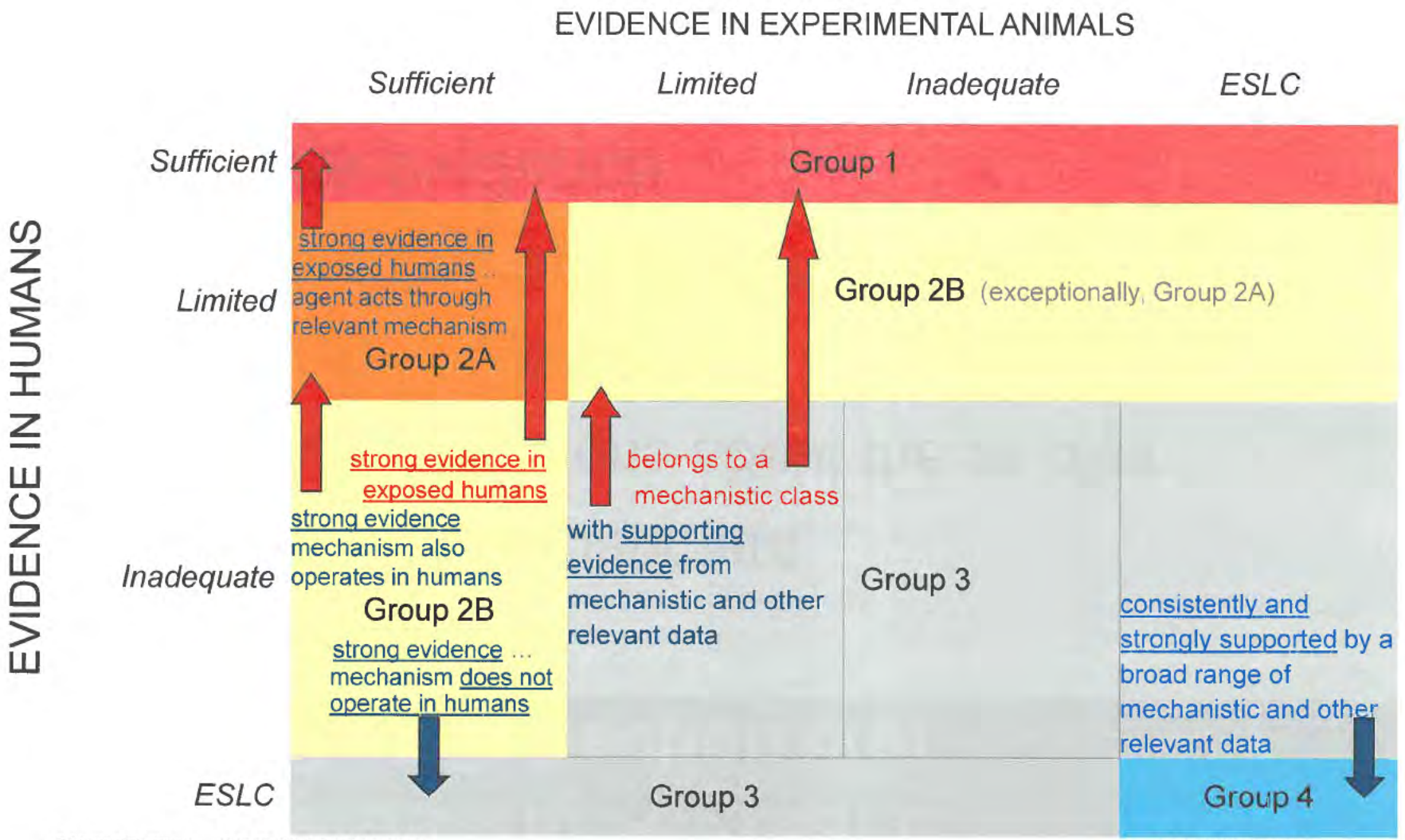
IARC: Evaluating Animal Evidence
Preamble Part B, Section 6(a)

- Sufficient Evidence
  - Causal relationship established
  - Two or more species of animals or two or more studies
  - One study where malignant neoplasms occur to an unusual degree
    - Incidence (rare tumors)
    - Site (unusual tumors)
    - Age at onset
    - Strong findings at multiple sites

IARC: Evaluating Animal Evidence
Preamble Part B, Section 6(a)

- Limited Evidence
  - Single positive experiment
  - Unresolved questions about the studies
  - Only benign neoplasms
  - Only promoting activity demonstrated
- Inadequate evidence
- Evidence suggesting lack of carcinogenicity
  - All studies negative or inadequate
  - At least two well-conducted negative studies

IARC Overall Evaluation



Modified from Vincent Cogliano, IARC

CLP Guidance on Carcinogenicity
(continued)

- The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:
  - human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
  - animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).
- In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing **limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals**

Guidance on the Application of the CLP Criteria, ECHA (2015)

Table 1: Human Epidemiology Studies

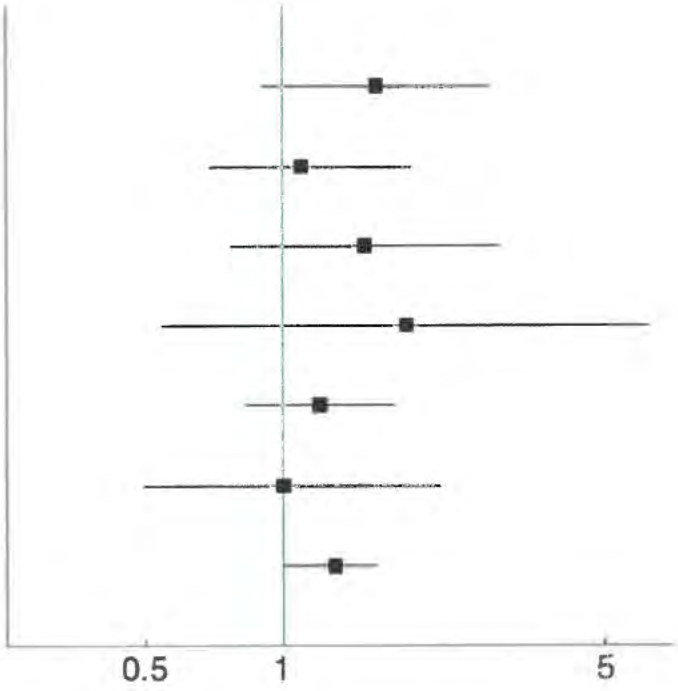
Study	Type	Size	Findings	Exposed Cases
Agricultural Health Study *(De Rooset al., 2005)*	Cohort – licensed pesticide applicators	52 395 (+32 347 spouses), 92 cases, 4-8 years follow-up	1.1 (0.7-1.9) C 0.7 (0.4-1.4) 21-56% tertile compared to <20% tertile 0.9 (0.5-1.6) 21-56% tertile compared to >57% tertile (31 cases no quantification of exposure)	73
US Midwest *(De Roos et al., 2003)*	Pooled analysis 3 case-control studies	NHL: 650 cases, 1933 controls	2.1 (1.1-4) U 1.6 (0.9-2.8) C	36 36
Cross-Canada *(McDuffie et al., 2001)*	Population-based case-control study	517 cases, 1506 controls	1.2 (0.83-1.74) U 1.0 (0.63-1.57) ≤2 d/Y 2.12 (1.2-3.73) >2 d/Y	51 28 23
Swedish Case-Control Study *(Eriksson et al., 2008)*	Population-based case-control study	910 cases, 1016 control	2.02 (1.1-3.71) U 1.51 (0.77-2.94) C 1.69 (0.7-4.07) ≤10 d/Y 2.36 (1.04-5.37) >10 d/Y 1.11 (0.24-5.08) ≤10 Y 2.26 (1.16-4.4) >10 Y	29 29 12 17 NR NR
Swedish Case-Control Study *(Hardell et al., 1999)*	Population-based case-control study	404 cases, 741 control (limited power)	2.3 (0.4-1.3) U 5.8 (0.6-5.4) C (not specified)	4 NR
France Case-Control *(Orsi et al, 2009)*	Hospital-based case-control study	244 cases, 456 controls	1.0 (0.5-2.2) U	12
Swedish Case-Control Study *(Hardell et al., 2002)*	Population-based case-control study	515 cases, 1141 controls	3.04 (1.08-8.5) U 1.85 (0.55-6.2) C (not specified)	8 8
US Case-Control Study *(Lee et al., 2004)*	Population-based case-control study	872 cases, 2381controls	1.4 (0.98-2.1) U – no asthma 1.2 (0.4-3.3) U - asthma	53 6

Meta Analyses

Study	Included Studies	Findings
Schinasi and Leon, 2014	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.5 (1.1-2.0)
IARC Monograph Working Group	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.3 (1.103-1.65) – used adjusted risk estimates from Hardell et al., 2003 and Eriksson et al., 2008
Chang and Delzell, 2016	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.3 (1.0-1.6)

Tree Plot of Epidemiology Studies
(using analyses corrected for potential confounders)

Study	RR	Lower	Upper	Weight
De Roos et al. (2003)	1.600	0.900	2.800	16.2
De Roos et al. (2005)	1.100	0.700	1.900	21.0
Eriksson et al., (2008)	1.510	0.770	2.940	11.6
Hardell et al. (2002)	1.850	0.550	6.200	3.6
McDuffie et al. (2001)	1.200	0.830	1.740	38.1
Oris et al. (2009)	1.000	0.500	2.200	9.5
Meta-Analysis	1.300	1.000	1.600	100.0



Chang and Delzell (2016)

Summary of Human Evidence

- Limited Evidence in Humans
  - IARC, Portier et al.
- Insufficient evidence in humans
  - EFSA, ECHA, EPA
- Did not evaluate
  - WHO/JMPR

Carcinogenicity Studies in Male Mice

Year	Strain	Length[1]	Top Dose[2]	Renal Tumors	Hemangio-sarcomas	Malignant Lymphoma
1983[5]	Crl:CD-1	24	4,841	+[3]		
1993[5]	?:CD-1	24	1,000		+	+/-[4]
1997	CrJ:CD-1	18	4,843	+	+	+
2001	SW	18	1,460	+		+/-[6]
2009	Crl:CD-1	18	810			+

1 – months; 2 – mg/kg bw/day; 3 - + indicates a p-value of <0.05 as calculated by BfR using the Armitage linear trend test in proportions; 4 – p=0.08; 5 – studies evaluated in IARC review; 6 – p=0.053

+ indicates studies evaluated by IARC

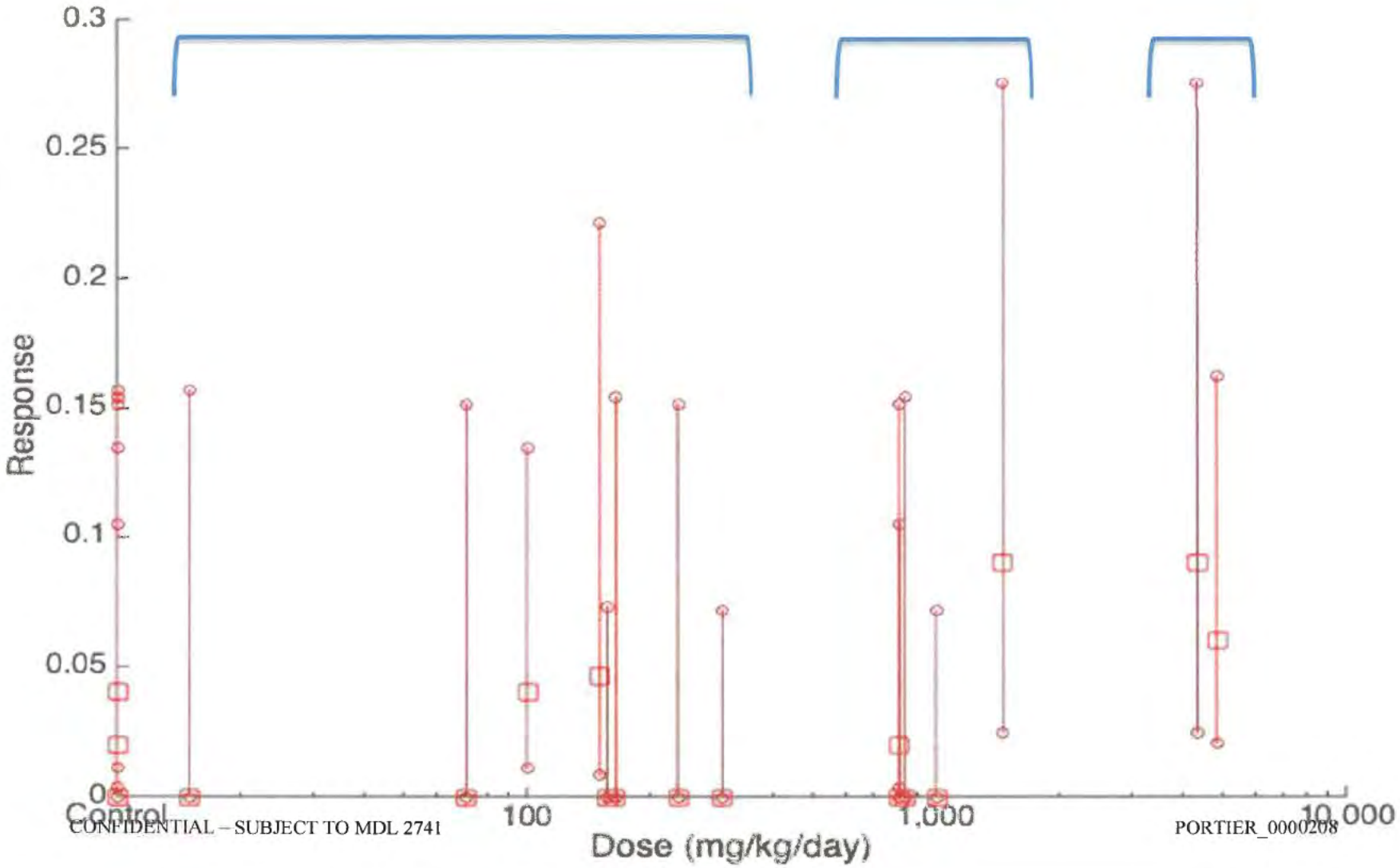
Tale based on Table 5.3-1 in the EFSA Renewal Assessment Report, Addendum I (8/31/2015)

Analysis of Male Mouse Renal Tumors From the Individual Studies

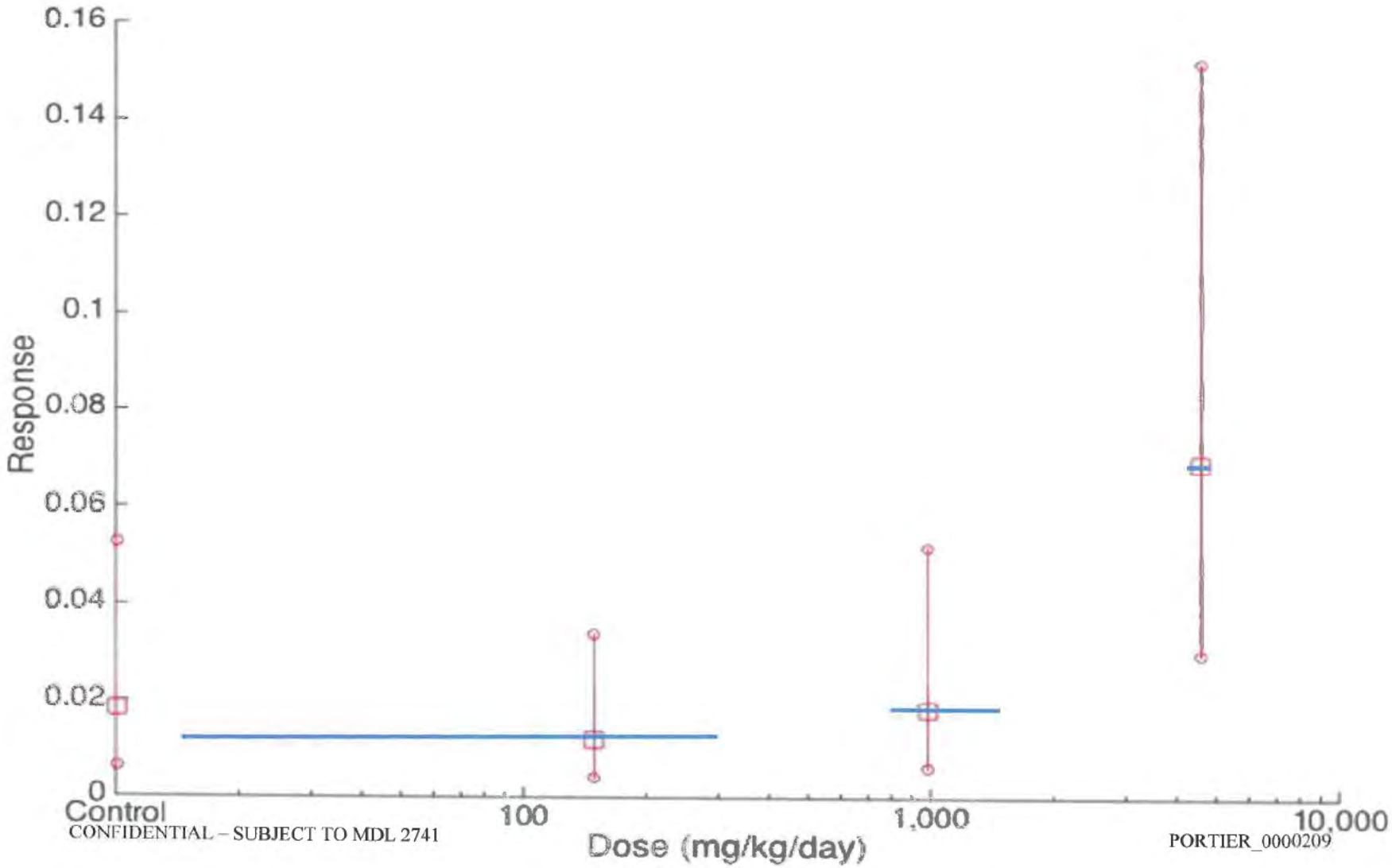
Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)[1]
1983	Crl:CD-1	24	157, 814, 4841	1/50, 0/49, 1/50, 3/50	**0.03 (0.03)**
1993	?:CD-1	24	100, 300, 1000	2/50, 2/50, 0/50, 0/50	0.94 (0.94)
1997	CrJ:CD-1	18	165, 838, 4348	0/50, 0/50, 0/50, 2/50	**0.008 (0.009)**
2001	SW	18	15, 151, 1460	0/49, 0/49, 1/50, 2/50	**0.04 (0.04)**
2009	Crl:CD-1	18	71, 234, 810	0/51, 0/51, 0/51, 0/51	-

1 – Poly-3 adjustment used to predict response at 24 months from response at 18 months; see Bailer and Portier (1988)

Renal tumors in male mice poly-3 adjusted showing individual dose groups



Renal tumors in male mice poly-3 adjusted and clustered by similar doses



Renal Tumors in Male Mice

Study	Approx. Trend	Exact Trend	Historical Trend
Knezevich and Hogan, 1983	0.033	0.063	0.009
Atkinson, 1993b	0.94	0.982	1
Sugimoto, 1997	0.008	0.061	0.009
Kumar, 2001	0.04	0.059	0.011
Wood et al., 2009b	0.5	1	0.629
All experiments combined	<0.001	0.003	0.004
All CD-1 Studies Combined	<0.001	0.005	0.008
All experiments combined, doses<1500	0.212	0.209	0.206
All CD-1 experiments combined, doses<1000	0.851	0.856	0.867

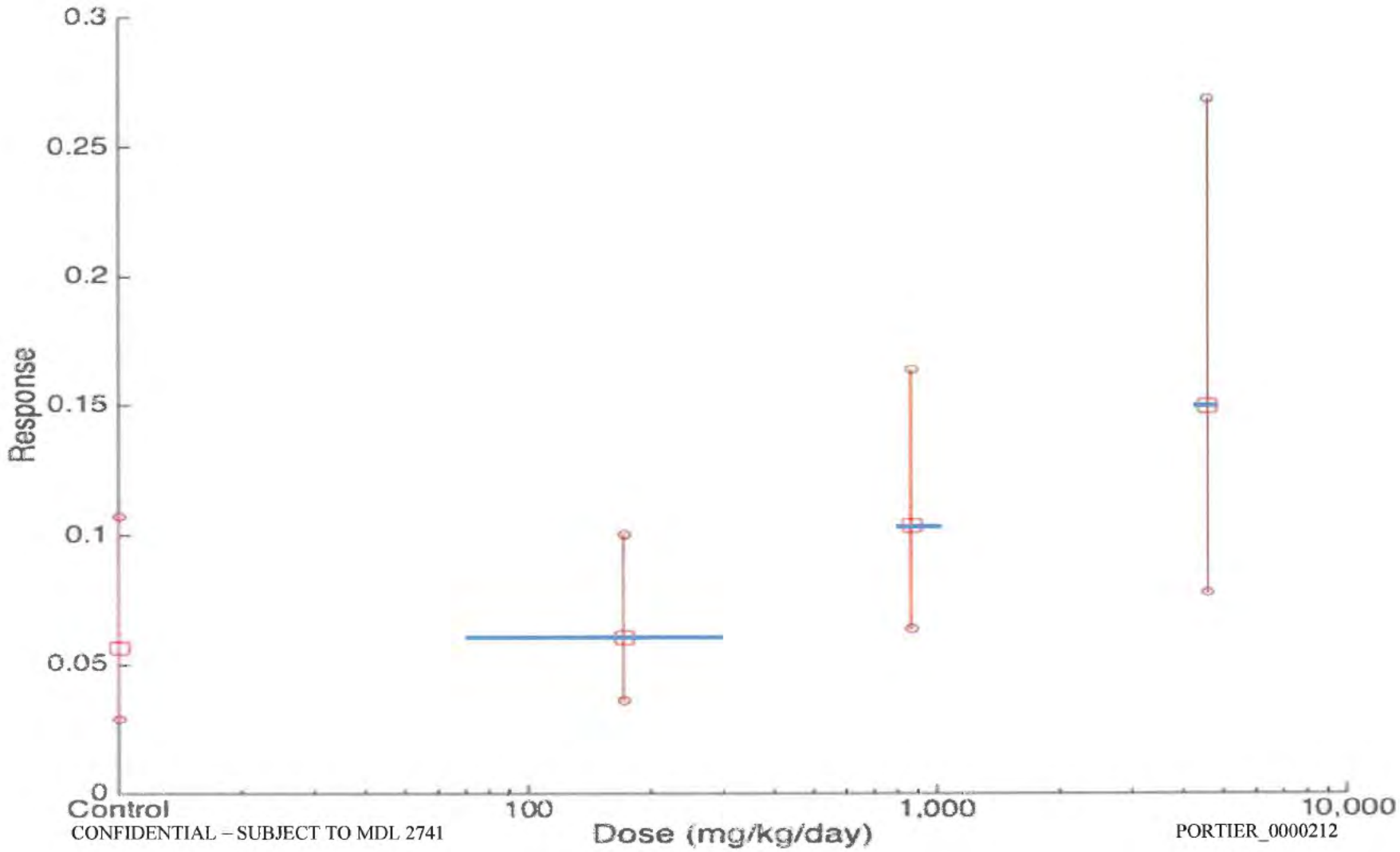
Historical trend test is based upon historical control data from Giknis and Clifford (2005)

Analysis of Male Mouse Malignant Lymphoma From the Individual Studies

Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)[1]
1983	Crl:CD-1	24	157, 814, 4841	2/50, 5/49, 4/50, 2/50	0.51 (0.51)
1993	?:CD-1	24	100, 300, 1000	4/50, 2/50, 1/50, 6/50	0.08 (0.08)
1997	CrJ:CD-1	18	165, 838, 4348	2/50, 2/50, 0/50, 6/50	**0.008 (0.012)**
2001	SW	18	15, 151, 1460	10/49, 15/49, 16/49, 19/49	**0.05 (0.09)**
2009	Crl:CD-1	18	71, 234, 810	0/51, 1/51, 2/51, 5/51	**0.004 (0.005)**

1 – Poly-3 adjustment used to predict response at 24 months from response at 18 months; see Bailer and Portier (1988)

Malignant lymphomas in male CD-1mice poly-3 adjusted and clustered by similar doses



Malignant Lymphomas in Male Mice

Study	Approx. Trend	Exact Trend	Historical Trend
Knezevich and Hogan, 1983	0.515	0.736	0.484
Atkinson, 1993b	0.076	0.095	0.087
Sugimoto, 1997	0.008	0.02	0.013
Kumar, 2001	0.053	0.105	0.072
Wood et al., 2009b	0.004	0.008	0.007
All experiments combined	0.173	0.426	0.172
All CD-1 Studies Combined	0.015	0.084	0.021
All experiments combined, doses<1500	<0.001	0.002	0.001
All CD-1 experiments combined, doses<1000	0.031	0.036	0.039

Historical trend test is based upon historical control data from Giknis and Clifford (2005)

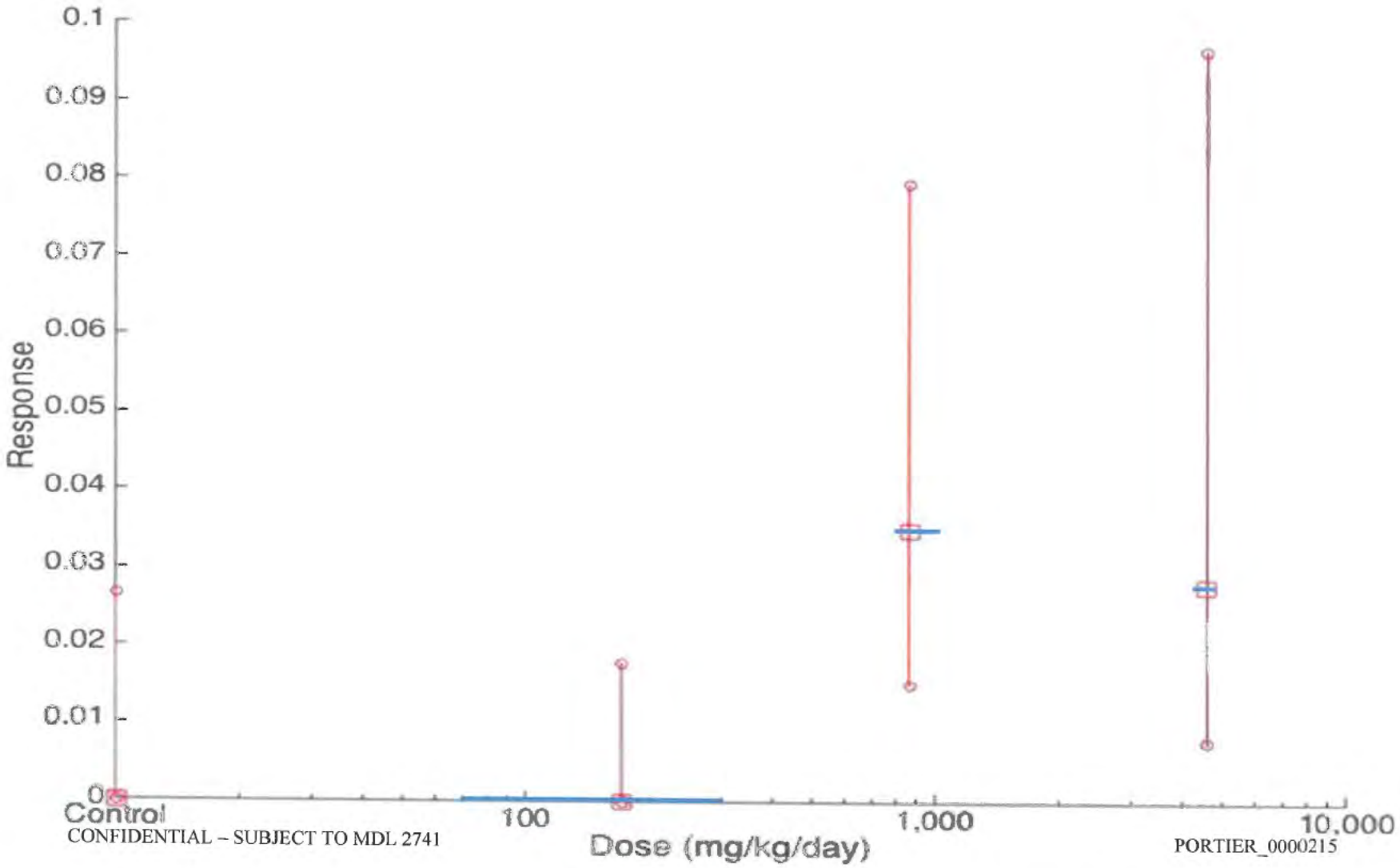
Analysis of Male Mouse Hemangiosarcomas From the Individual Studies

Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)[1]
1983	Crl:CD-1	24	157, 814, 4841	0/50, 0/49, 1/50, 0/50	0.63 (0.63)
1993	?:CD-1	24	100, 300, 1000	0/50, 0/50, 0/50, 4/50	**0.0004 (0.0004)**
1997	CrJ:CD-1	18	165, 838, 4348	0/50, 0/50, 0/50, 2/50	**0.008 (0.009)**
2001	SW	18	15, 151, 1460	0/50, 0/50, 2/50, 0/50	0.724 (0.724)
2009	Crl:CD-1	18	71, 234, 810	0/51, 0/51, 0/51, 0/51[2]	0.5 (0.50

1 – Poly-3 adjustment used to predict response at 24 months from response At 18 months; see Bailer and Portier (1988)

2 – EChA Table 42 lists tumor counts for this study of 2/51, 1/51, 2/51 and 1/51. However, these rates include hemangiomas from liver and kidney, making them different from the other studies and not applicable for the comparisons that follow

Hemangiosarcomas in male CD-1 mice poly-3 adjusted and clustered by similar



Hemangiosarcomas in Male Mice

Study	Approx. Trend	Exact Trend	Historical Trend
Knezevich and Hogan, 1983	0.628	0.5	0.592
Atkinson, 1993b	<0.001	0.004	<0.001
Sugimoto, 1997	0.008	0.061	0.021
Kumar, 2001	0.5	0.494	0.621
Wood et al., 2009b	0.5	1	0.49
All experiments combined	0.041	0.056	0.060
All CD-1 Studies Combined	0.024	0.044	0.041
All experiments combined, doses<1500	0.007	0.016	0.014
All CD-1 experiments combined, doses<1000	<0.001	<0.001	<0.001

Historical trend test is based upon historical control data from Giknis and Clifford (2005)

Carcinogenicity Studies in Rats

Year	Strain	Length[1]	Top Dose[2]	Finding
+Atkinson et al., 1993	SD	24	1000	none
+Lankas, 1981	SD	26	~32	inadequate dose, testicular tumors (M), pancreas islet cell aden. (M, weak)
+Stout & Ruecker, 1990	SD	24	1183	liver aden. (M), pancreas islet cell aden. (M), thyroid aden. (F)
Enemoto, 1997	SD	24	1127	none
Pavkov & Wyand, 1987	SD	24	41.8	inadequate dose and purity

1 – months; 2 – mg/kg bw/day;
+ indicates studies evaluated by IARC

Carcinogenicity Studies in Rats

Year	Strain	Length[1]	Top Dose[2]	Finding
+Seralini et al., 1993	SD	24	2250 mg/L in water	inadequate, mammary tumors
+Suresh, 1996	Wistar	24	886	none
Wood et al., 2004	Wistar	24	1229.7	mammary gland tumors (F)
Brammer, 2001	Wistar	24	1,498	Liver aden. (M)
+Chru-scielska et al., 2000	Wistar	24	2250 mg/L in water	inadequate documentation
+Syngenta , 1996	Wistar	12	1409	Inadequate length of study

1 – months; 2 – mg/kg bw/day;

+ indicates studies evaluated by IARC

Summary of Animal Cancer Data

- Sufficient Evidence
  - IARC, Portier et al.
- Insufficient Evidence
  - EFSA, ECHA, USEPA, WHO/JMPR
    - Excluded high dose effects
    - Used historical controls inappropriately
    - Generally excluded trend tests
    - Down-played or ignored consistency across mouse studies

Glyphosate Monograph – Mechanistic and Other Considerations:

Key Characteristic of Carcinogens #2 (Genotoxic)

Agent	Strength of the evidence	Evidence base includes	Endpoints considered in the evaluation
Glyphosate	Strong	1. ***Largely positive*** studies: • in human cells *in vitro*, • in mammalian model systems *in vivo* and *in vitro*, • studies in other non-mammalian organisms 2. ***Generally positive*** studies in liver *in vivo* in mammals 3. ***Mixed*** results for kidney and bone marrow *in vivo* in mammals 4. ***Consistently negative*** results from tests in bacterial assays	• Biomarkers of DNA adducts • Biomarkers of various types of chromosomal damage
Glyphosate formulations	Strong	1. ***Evidence in exposed humans***: • three studies of genotoxicicity endpoints in community residents exposed to glyphosate formulations, two of which reported positive associations • one of these studies examined subjects before and after aerial spraying and found a significant increase in micronuclei after exposure in 3 of 4 different geographical areas 2. ***Largely positive*** studies: • in human cells *in vitro*, • in mammalian model systems *in vivo* and *in vitro*, • studies in other non-mammalian organisms 3. ***Generally negative*** results from tests in bacterial assays 4. The ***pattern*** of tissue specificity of genotoxicity endpoints observed with glyphosate formulations is similar to that observed with glyphosate alone	• Chromosomal damage (micronuclei) in circulating blood cells from humans • Biomarkers of DNA adducts • Biomarkers of various types of chromosomal damage
AMPA	Moderate	1. Two human *in vitro* studies 2. One mammalian *in vivo* study 3. One mammalian *in vitro* study 4. One study in eel	While the number of studies is not large, all of the studies were ***positive***

Glyphosate Monograph – Mechanistic and Other Considerations:

Key Characteristic of Carcinogens #5 (Oxidative Stressor)

Agent	Strength of the evidence	Evidence base includes	Endpoints considered in the evaluation
Glyphosate	Strong	1. Rodent studies *in vivo* (including similar effects observed in many tissues) 2. Rodent cells *in vitro* 3. Human cells *in vitro*	• Lipid peroxidation markers • Oxidative DNA adducts • Dysregulation of antioxidant enzymes • Some studies challenged this mechanism experimentally (*e.g.*, by co-administering antioxidants)
Glyphosate formulations	Strong		
AMPA	Strong		

What have I learned from disagreements with EPA, EFSA and EChA?

- Almost impossible to reproduce a regulatory decision
  - Lack of access to data
  - Subjective decisions made with unclear justification
    - Weight-of-evidence
  - Lack of strict adherence to guidelines
- Independent evaluations (like that done by IARC) are critical in order to keep all of the groups involved in regulatory decisions honest
- EC needs an outside set of experts, with no conflicts of interest, to review these types of risk assessments in an open forum

What needs to be done?

- Transparency of regulatory decisions needs to be re-evaluated
  - Authors and any conflicts need to be made public
  - Reviewers and any conflicts need to be made public
  - Literature used to make these decisions need to be made public
- Relationship between industry and regulatory communities needs to be carefully reviewed and guidelines put into place
- Scientific review and oversight of regulatory decisions needs to be done in an open and transparent fashion

Glyphosate Cancer Classification

Christopher J. Portier, Ph.D.

17 May, 2017

EAPCCT Meeting

Basel, Switzerland

IARC Working Group Classifies Glyphosate as "Probably Carcinogenic to Humans"

NATURE | NEWS: EXPLAINER

Widely used herbicide linked to cancer

As the World Health Organization's research arm declares glyphosate a probable carcinogen, *Nature* looks at the evidence.

Roundup weedkiller 'probably' causes cancer, says WHO study

The Monsanto product – the world's most widely used herbicide – contains glyphosate, which may also be carcinogenic for non-Hodgkin's lymphoma

A Top Weedkiller Could Cause Cancer. Should We Be Scared?

ROUNDUP AND RISK ASSESSMENT

By Michael Specter April 10, 2015

A farmer sprays glyphosate across his cornfield.

Participants

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Representatives

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[3] Christopher J. Portier receives a part-time salary from the Environmental Defense Fund, a United States–based non-profit environmental advocacy group.
[4] Amira Ben Amara attended as a representative of the National Agency of Sanitary and Environmental Control of Products, Tunisia.
[5] Catherine Eiden attended as a representative of the United States Environmental Protection Agency.
[6] Marie-Estelle Gouze attended as a representative of ANSES, France.
[7] Jesudoss Rowland attended as a representative of the United States Environmental Protection Agency.

IARC Working Group Findings

- Consistent positive association for NHL but bias and confounding possible
- Renal tumors (1 study) and hemangiosarcomas (1 study) in mice (2 studies evaluated)
- Pancreas islet-cell tumors (2 studies), liver adenomas (1 study), Thyroid C-cell adenomas (1 study) in rats (5 studies evaluated)
- Genotoxicity and oxidative stress

Regulatory Authorities

- EFSA – November, 2015
  - Unlikely to pose a carcinogenic hazard to humans
- WHO/JMPR – March, 2016
  - Unlikely to pose a carcinogenic risk to humans from exposure through the diet
- ECHA – March, 2017
  - no hazard classification for carcinogenicity is warranted
- USEPA – September, 2016 (draft)
  - Not likely to be carcinogenic to humans at doses relevant to human health risk assessment
- Australia Pesticides and Veterinary Medicines Authority – 2015
  - the use of glyphosate in Australia does not pose a cancer risk to humans

CLP Guidance on Carcinogenicity

- Category 1: Known or presumed human carcinogens
  - Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence
  - Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence

Guidance on the Application of the CLP Criteria, ECHA (2015)

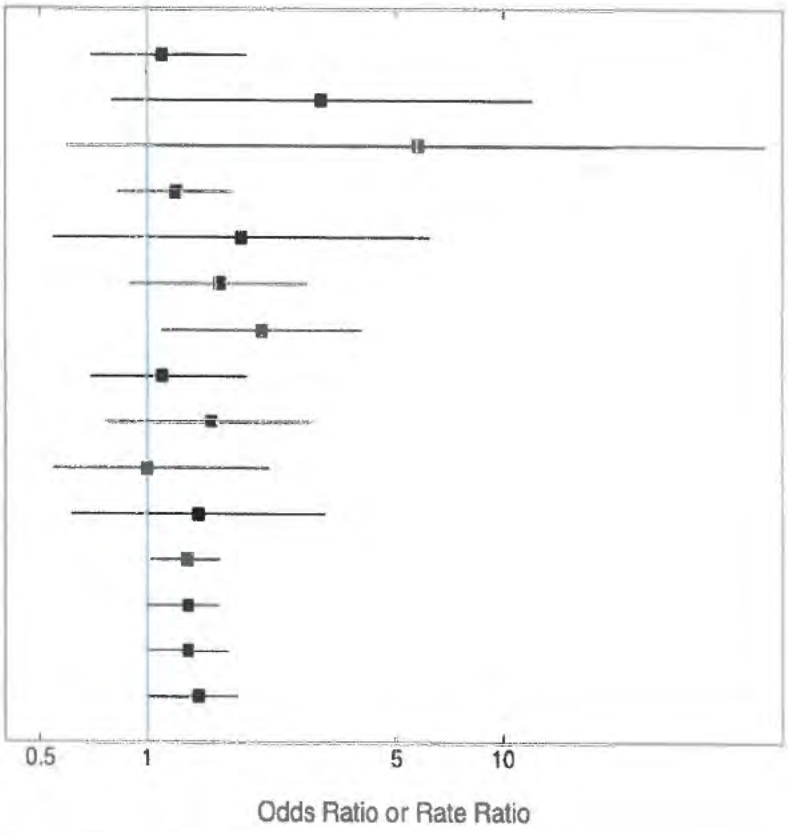
CLP Guidance on Carcinogenicity
(continued)

- The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:
  - human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
  - animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).
- In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing **limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals**

Guidance on the Application of the CLP Criteria, ECHA (2015)

Epidemiology Data – Non-Hodgkin Lymphoma

Study	RR	Lower	Upper	Weight (Model 1)
Cantor et al. (1992)	1.10	0.70	1.90	0.0
Nordstrom et al. (1998)	3.10	0.80	12.00	0.0
Hardell and Eriksson (1999)	5.80	0.60	54.00	0.0
McDuffie et al. (2001)	1.20	0.83	1.74	38.1
Hardell et al. (2002)	1.85	0.55	6.20	3.6
De Roos et al. (2003)	1.60	0.90	2.80	16.2
logistic regression	2.10	1.10	4.00	0.0
De Roos et al. (2005)	1.10	0.70	1.90	21.0
Eriksson et al., (2008)	1.51	0.77	2.94	11.6
Orsi et al. (2009)	1.00	0.55	2.20	3.6
Hohenadel et al. (2011)	1.40	0.62	3.15	0.0
Meta-Analysis: Model 1	1.30	1.03	1.60	
Meta-Analysis: Model 2	1.30	1.00	1.60	
Meta-Analysis: Model 3	1.30	1.00	1.70	
Meta-Analysis: Model 4	1.40	1.00	1.80	



Limited Evidence of Carcinogenicity

- EChA: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
- IARC: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Human Data Conclusions

EFSA – very limited?

From the wealth of epidemiological studies, the majority of experts concluded that there is very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma, overall inconclusive for a causal or clear associative relationship between glyphosate and cancer in human studies. Minority views nevertheless were expressed that there was either inadequate or limited evidence of an association. [redacted]

IARC Working Group – limited evidence

There is *limited evidence* in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma.

Reasons used by EFSA to dismiss positive findings in an animal study?

- The trend test was significant but the pair-wise tests were not and/or
- Studies were not consistent and/or
- No positive results at doses below 1000 mg/kg/day and/or
- No dose-response for pre-malignant lesions and/or
- The response was within the historical control range.

Are these reasonable?

Probability of a False Positive Error[1] When Excluding Positive Trend Tests with Responses Inside the Historical Control Range

# Historical Controls Groups	Expected Control Response		
	0.05	0.10	0.20
None	0.056	0.052	0.055
5	0.046	0.046	0.051
10	0.032	0.036	0.036
20	0.020	0.024	0.028
50	0.007	0.013	0.013

1 – doses used are 0, 1, 2, and 4 with 50 animals per group and with the expected response in all dose groups equal to the expected control response, 10,000 simulations

Probability of Detecting a True Positive [1] When Excluding Positive Trend Tests with Responses Inside the Historical Control Range

# Historical Controls Groups	Expected Control Response		
	0.05	0.10	0.20
None	0.404	0.613	0.900
5	0.365	0.591	0.896
10	0.307	0.551	0.886
20	0.252	0.496	0.861
50	0.165	0.398	0.798

1 – doses used are 0, 1, 2, and 4 with 50 animals per group and with the expected response in the high dose group equal to twice (2x) the expected control response and other doses with proportionate response, 10,000 simulations

Use of Historical Controls

- IARC Recommendations
  - Use a formal statistical method
  - *"Generally not appropriate to discount a tumor response that is statistically significantly increased in comparison to concurrent controls by arguing it falls within the range of concurrent controls"*
  - Can be used for rare tumors

Major Tumors in CD-1 Mice

Summary of significance tests for 5 tumors from 4 studies in CD-1 Mice

Study	Months on Study	Neoplasm				
		Hemangio-sarcoma (male)	Hemangi-sarcoma (female)	Malignant Lymphoma (male)	Kidney Tumor (male)	Lung Adeno-carcinoma (male)
Sugimoto 1997	18	+/+++[1]	+++/+++	++/++	+/+++	-/-
Wood 2009	18	-/-	-/-	+++/+++	-/-	++/++
Sugimoto & Wood Pooled		++/+++	+++/+++	+++/+++	++/+++	-/-
Atkinson 1993	24	+++/+++	-/-	+/+	-/-	-/-
Knezevich 1983	24	-/-	NA	-/-	+/++	-/-
Atkinson & Knezevich Pooled		-/-	NA	-/-	++/+	-/-
All CD-1 Studies Pooled		++/++	+++/+++	+/+	+++/+++	-/-

[1]entries are p_{Trend}/p_{Hist} with values: – p>0.1, + 0.1≥p>0.05, ++ 0.05≥p>0.01, +++ p≤0.01

Major Tumors in Rats

Table 8: Summary of significance tests for 5 tumors from 7 studies in Rats

Study	Strain	Neoplasm						
		Liver Adenomas (males)	Mammary Gland Tumors (females)	Thyroid C-Cell Tumors (females)	Thyroid C-Cell Tumors (males)	Thyroid Follicular Cell Tumors (males)	Testis Interstitial Cell Tumors (male)	Kidney Adenomas (males)
Brammer (2001)	Wistar	+++[1]	-					
Wood (2009)		-	+++					
Suresh (1996)		-	-					
Pooled Wistar Rats		++	++					
Lankas (1981)	Sprague Dawley	-		+	-	-	++	-
Enemoto (1997)		-		-	-	-	-	+++
Atkinson et al. (1993)		-		+	-	++	-	-
Stout and Ruecker (1990)		++		-	+	-	-	-
Pooled Sprague-Dawley Rats		++		-	++	-	-	++

[1]entries are p_{Trend}/p_{Hist} with values: – p>0.1, + 0.1≥p>0.05, ++ 0.05≥p>0.01, +++ p≤0.01

Observed versus expected tumor sites with significant trends

Species	Strain	Sex	Total Sites[1]	Exp. <0.05	Obs. <0.05	Tumors[2] p<0.05	Exp. <0.01	Obs. <0.01	Tumors p<0.01
Rat (7 studies)	Sprague-Dawley (4 studies)	M	86	4.3	4	TICT, TFAC, KA, HA	0.9	2	TICT, KA
		F	102	5.1	1	TCCC	1.0	1	TCCC
	Wistar (3 studies)	M	64.5	3.2	2	HA, SK	0.6	1	HA
		F	76.5	3.8	2	MC, MAC	0.8	1	MAC
Mouse (5 studies)	CD-1 (4 studies)	M	42	2.1	8	KA, KC, KAC, H(2)[3], ML(2), LAC	0.4	5	KA,KC, H(2), ML
		F	60	3	1	H	0.6	1	H
	Albino (1 study)	M	10.5	0.5	0		0.1	0	
		F	15	0.8	0		0.2	0	
Rats (7 studies)	All (7 studies)	M	150.5	7.5	6	TICT, KA, HA(2), TFAC, SK	1.5	3	TICT, KA, HA
		F	178.5	8.9	3	TCCC, MC, MAC	1.8	2	TCCC, MAC
		Both	329	16.5	9	TICT, KA, HA(2), TFAC, SK, TCCC, MC, MAC	3.3	5	TICT, KA, HA, TCCC, MAC
Mice (5 studies)	All (5 studies)	M	52.5	2.6	8	KA, KC, KAC, H(2), ML(2), LAC	0.5	5	KA,KC, H(2), ML
		F	75	3.8	1	H	0.7	1	H
		Both	127.5	6.4	9	KA, KC, KAC, H(3)[3], ML(2), LAC	1.3	6	KA,KC, H(3), ML
All (12 studies)	All (12 studies)	M	203	10.1	14	TICT, KA(2), HA(2), TFAC, SK, KC, KAC, H(2), ML(2), LAC	2.0	8	TICT, HA, KA(2),KC, H(2), ML
		F	253.5	12.7	4	TCCC, MC, MAC, H	2.5	3	TCCC, MAC, H
		Both	456.5	22.8	18	TICT, KA(2), HA(2), TFAC, SK, KC, KAC, H(3), ML(2), LAC, TCCC, MC, MAC	4.6	11	TICT, HA, KA(2), KC, H(3), ML, TCCC, MAC

[1]Number of sites examined is based upon suggestions by Dr. J. Haseman in his written testimony to the EPA; male mice – 10.5 sites; female mice – 15 sites; male rats – 21.5 sites; female rats – 25.5 sites

[2]Tumor abbreviations are: KA – kidney adenoma; KC – kidney carcinoma; KAC – kidney adenoma or carcinoma; H – hemangiosarcoma; HA – hepatocellular adenoma; LAC – lung adenoma or adenocarcinoma; ML – malignant lymphoma; MC – mammary gland carcinoma; MAC

Sufficient Evidence in Animals

- ECHA
  - a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites
- IARC – exactly the same

Limited Evidence in Animals

- ECHA
  - the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.
- IARC – exactly the same

Conclusions

EFSA

[redacted] No evidence of carcinogenicity was confirmed by the large majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pair-wise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/MTD, lack of pre-neoplastic lesions and/or being within historical control range. The statistical significance found in trend analysis (but not in pair-wise comparison) *per se* was balanced against the former considerations. [redacted]

IARC Working Group

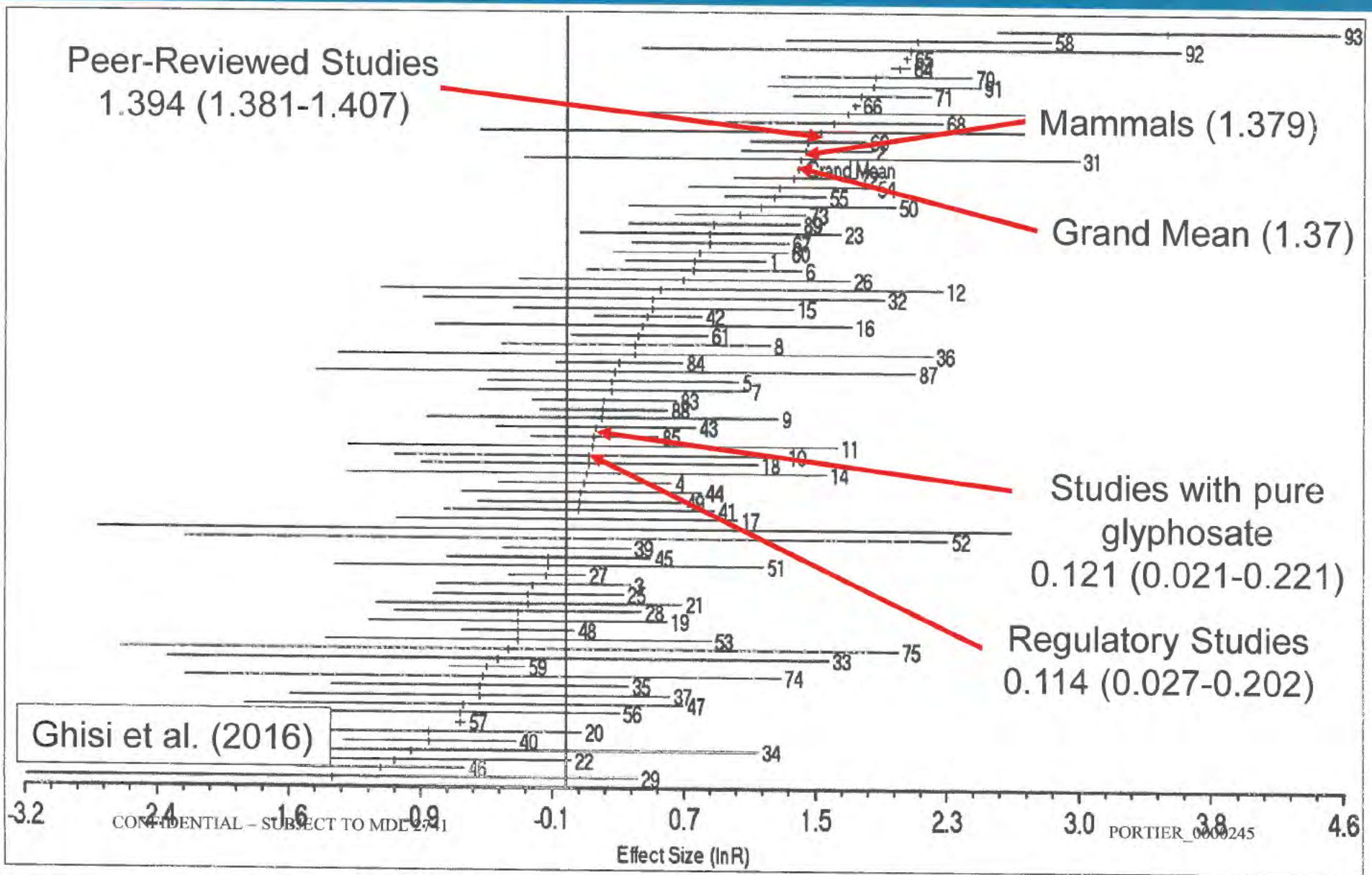
There is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate.

Summary of in vivo and in vitro genetox studies of glyphosate and glyphosate formulations in mammals[1]

In vivo or in vitro	Species	Cell type or tissue	Glyphosate[2]		Glyphosate Formulations	
			Number Positive	Number Negative	Number Positive	Number Negative
In vivo	Humans	Peripheral blood			2	1
in vitro	Humans	lymphocytes	5	2(1)	2	
		Hep 2	1			
		GM 38 HT1080	1			
		GM 5757	1			
		TR146	1		1	
In vivo	Swiss CD-1 Mouse	Liver/Kidney	1	1	2	
In vivo (micro-nucleus assay)	NMRI mouse	Erythrocytes		4(3)		2(1)
	Swiss CD-1 mouse		1		2	
	Balb C mouse		1			
	$B6C3F_1$ mouse			1		
	Swiss mouse		1(1)			3(2)
	CD-1 mouse		2(2)	1(1)	2 (2)	6 (6)
	Swiss albino mouse		1(1)	3(3)	1	
	C57BL mouse					1
	Mouse (not specified)				1	
	Rats (all)			2(1)		1(1)
In vitro	Mouse	L5178 lymphoma		2(2)		
	Chinese hamster	Lung		3(3)		
	Chinese hamster	ovary	1	1		
	Fischer rat	liver		1		
	Rat	Lymphocytes		1(1)		
	Bovine	Lymphocytes	1		2	

[1]each entry in the table corresponds to a single study where a study is positive if at least one valid positive finding emerged from the study p<0.05; entries in the table are only for studies where data was available to review including data from EFSA[88] and Kier and

Forest Plot of Micronucleus Frequency



Conclusions

EFSA

[redacted]During the teleconference 117, the experts also agreed to the conclusion of the RMS, that for the active substance glyphosate no classification for mutagenicity is warranted. However, there were two minority views, that a Comet assay should be requested for confirmation.

IARC Working Group

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.

Is seeing the studies important?

Tumors with significant ($p<0.05$) trends in the carcinogenicity studies not cited in the EFSA and EChA Risk Assessments

Study (Species)	Tumor type Sex; Incidences	p-value (one-sided)
Sugimoto, 1997 (Mouse)	Total number of animals with malignant neoplasms Males; 5/50, 5/50, 11/50, 16/50	0.004
Wood et al., 2009 (Mouse)	Lung adenocarcinomas Males; 5/51, 5/51, 7/51, 11/51	0.038
Atkinson et al., 1993 (Rat)	Thyroid follicular cell adenomas and carcinomas Males; 0/50, 0/21, 0/17, 2/21, 2/49	0.036
Suresh, 1996 (Rat)	Thyroid c-cell Carcinomas Females; 1/47, 0/49, 2/50, 6/47	0.003
Enomoto, 1997 (Rat)	Kidney adenoma Males; 0/50, 0/50, 0/50, 4/50	0.004
Brammer, 2001 (Rat)	Hepatocellular Adenoma Males; 0/52, 2/52, 0/52, 5/52	0.009
Wood et al., 2009 (Rat)	Skin Keratocanthoma Males; 2/51, 3/51, 0/51, 6/51	0.034
Wood et al., 2009 (Rat	Mammary gland adenocarcinomas Males; 2/51, 3/51, 1/51, 6/51	0.046

Take Home Messages

- Transparency is necessary
- Guidelines should be peer-reviewed and applied uniformly
- Proper statistical methods need to be applied and understood

Glyphosate Carcinogenicity

Christopher J. Portier, Ph.D.

Fachanlass: Pesticid-Zukunft Schweiz

28 September, 2016, Bern

Recent Cancer Assessments of Glyphosate

- IARC – March, 2015
  - Probable human carcinogen
- EFSA – November, 2015
  - Unlikely to pose a carcinogenic hazard to humans
- Portier et al. – January, 2016
  - Probable human carcinogen
- WHO/JMPR – March, 2016
  - Unlikely to pose a carcinogenic risk to humans from exposure through the diet
- ECHA – May, 2016 (draft)
  - no hazard classification for carcinogenicity is warranted
- USEPA – September, 2016 (draft)
  - Not likely to be carcinogenic to humans at doses relevant to human health risk assessment

Comparison Across Evaluations

Study	Authors Known	COI Made Public	Proprietary Studies	Open Literature	Guidelines	Followed Guidelines	Evaluated Dose-Response
IARC	Yes	Yes	No	Yes	Yes	Yes	No
EFSA	No	No	Yes	Yes	Yes	No	No
Portier	Yes	Yes	Yes	Yes	Yes	Yes	No
JMPR	Yes	?	Yes	Yes	Yes	Yes	Yes
ECHA	No	No	Yes	Yes	Yes	No	No
EPA	?	Some	Yes	Yes	Yes	No	No

Why are they different?

- Human Data
  - Limited evidence versus Insufficient Evidence
- Animal Cancer Studies
  - Sufficient Evidence versus Insufficient Evidence
- Mechanisms
  - Genotoxic or not genotoxic
  - Induces oxidative stress is or is not important

Table 1: Human Epidemiology Studies

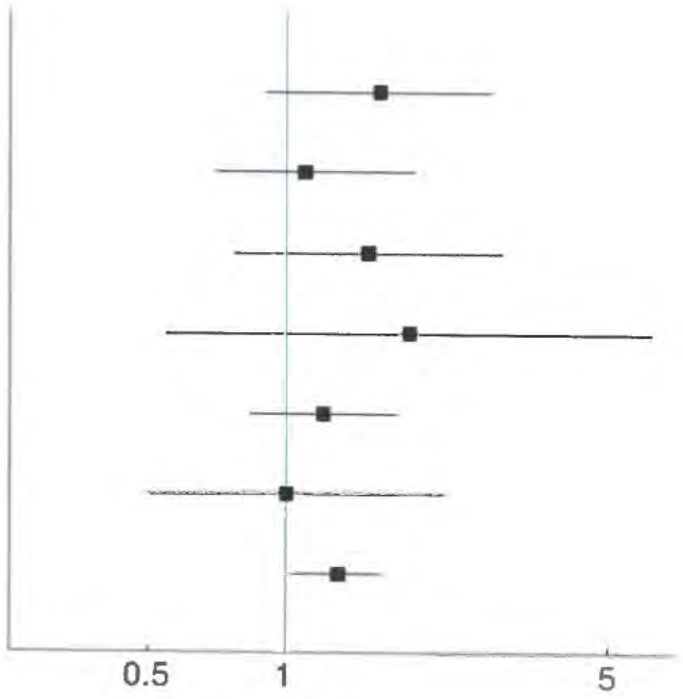
Study	Type	Size	Findings	Exposed Cases
Agricultural Health Study *(De Rooset al., 2005)*	Cohort -- licensed pesticide applicators	52 395 (+32 347 spouses), 92 cases, 4-8 years follow-up	1.1 (0.7-1.9) C 0.7 (0.4-1.4) 21-56% tertile compared to <20% tertile 0.9 (0.5-1.6) 21-56% tertile compared to >57% tertile (31 cases no quantification of exposure)	73
US Midwest *(De Roos et al., 2003)*	Pooled analysis 3 case-control studies	NHL: 650 cases, 1933 controls	2.1 (1.1-4) U 1.6 (0.9-2.8) C	36 36
Cross-Canada *(McDuffie et al., 2001)*	Population-based case-control study	517 cases, 1506 controls	1.2 (0.83-1.74) U 1.0 (0.63-1.57) ≤2 d/Y 2.12 (1.2-3.73) >2 d/Y	51 28 23
Swedish Case-Control Study *(Eriksson et al., 2008)*	Population-based case-control study	910 cases, 1016 control	2.02 (1.1-3.71) U 1.51 (0.77-2.94) C 1.69 (0.7-4.07) ≤10 d/Y 2.36 (1.04-5.37) >10 d/Y 1.11 (0.24-5.08) ≤10 Y 2.26 (1.16-4.4) >10 Y	29 29 12 17 NR NR
Swedish Case-Control Study *(Hardell et al., 1999)*	Population-based case-control study	404 cases, 741 control (limited power)	2.3 (0.4-1.3) U 5.8 (0.6-5.4) C (not specified)	4 NR
France Case-Control *(Orsi et al, 2009)*	Hospital-based case-control study	244 cases, 456 controls	1.0 (0.5-2.2) U	12
Swedish Case-Control Study *(Hardell et al., 2002)*	Population-based case-control study	515 cases, 1141 controls	3.04 (1.08-8.5) U 1.85 (0.55-6.2) C (notspecified)	8 8
US Case-Control Study *(Lee et al., 2004)*	Population-based case-control study	872 cases, 2381controls	1.4 (0.98-2.1) U – no asthma 1.2 (0.4-3.3) U - asthma	53 6

Table 2: Meta Analyses

Study	Included Studies	Findings
Schinasi and Leon, 2014	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.5 (1.1-2.0)
IARC Monograph Working Group	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.3 (1.103-1.65) – used adjusted risk estimates from Hardell et al., 2003 and Eriksson et al., 2008
Chang and Delzell, 2016	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.3 (1.0-1.6)

Figure 1: Tree Plot of Epidemiology Studies
(using analyses corrected for potential confounders)

Study	RR	Lower	Upper	Weight
De Roos et al. (2003)	1.600	0.900	2.800	16.2
De Roos et al. (2003)	1.100	0.700	1.900	21.0
Eriksson et al., (2008)	1.510	0.770	2.940	11.6
Hardell et al. (2002)	1.850	0.550	6.200	3.6
McDuffie et al. (2001)	1.200	0.830	1.740	38.1
Oris et al. (2009)	1.000	0.500	2.200	9.5
Meta-Analysis	1.300	1.000	1.600	100.0



Chang and Delzell (2016)

Summary of Human Evidence

- Limited Evidence in Humans
  - IARC, Portier et al.
- Insufficient evidence in humans
  - EFSA, ECHA, EPA
- Did not evaluate
  - WHO/JMPR

Table 3: Carcinogenicity Studies in Male Mice

Year	Strain	Length[1]	Top Dose[2]	Renal Tumors	Hemangio-sarcomas	Malignant Lymphoma
1983[5]	Crl:CD-1	24	4,841	+[3]		
1993[5]	?:CD-1	24	1,000		+	+/-[4]
1997	CrJ:CD-1	18	4,843	+	+	+
2001	SW	18	1,460	+	**Data Not Available**	+/-[6]
2009	Crl:CD-1	18	810			+

1 – months; 2 – mg/kg bw/day; 3 - + indicates a p-value of <0.05 as calculated by BfR using the Armitage linear trend test in proportions; 4 – p=0.08; 5 – studies evaluated in IARC review; 6 – p=0.054

Table 4: Analysis of Male Mouse Renal Tumors From the Individual Studies

Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)
1983	Crl:CD-1	24	157, 814, 4841	1/50, 0/49, 1/50, 3/50	**0.03 (0.03)**
1993	?:CD-1	24	100, 300, 1000	2/50, 2/50, 0/50, 0/50	0.94 (0.94)
1997	CrJ:CD-1	18	165, 838, 4348	0/50, 0/50, 0/50, 2/50	**0.008 (0.009)**
2001	SW	18	15, 151, 1460	0/49, 0/49, 1/50, 2/50	**0.04 (0.04)**
2009	Crl:CD-1	18	71, 234, 810	0/51, 0/51, 0/51, 0/51	-

Table 5: Pooled Analysis of Male CD-1 Mouse Renal Tumors

Year	Strain	p-Trend (p-poly3)
CD-1 Combined	CD-1	**0.001 (0.001)**
CD-1 Combined and Doses Pooled[1]	CD-1	**0.001(0.001)**
CD-1 Combined, doses>1000 dropped	CD-1	0.85 (0.86)
CD-1 Combined, doses>1000 dropped and Doses Pooled[2]	CD-1	0.80 (0.80)

[1] – Doses were combined as follows: all controls, doses between 0 and 310 mg/kg/day, doses between 310 and 1500 mg/kg/day, and doses greater than 1500 mg/kg/day. Average doses in each pooled group were used in the analysis. [2]- Doses were combined as follows: all controls, doses between 0 and 310 mg/kg/day, and doses between 310 and 1500 mg/kg/day. Average doses in each pooled group were used in the analysis.

Figure 2: Renal tumors in male mice poly-3 adjusted showing individual dose groups

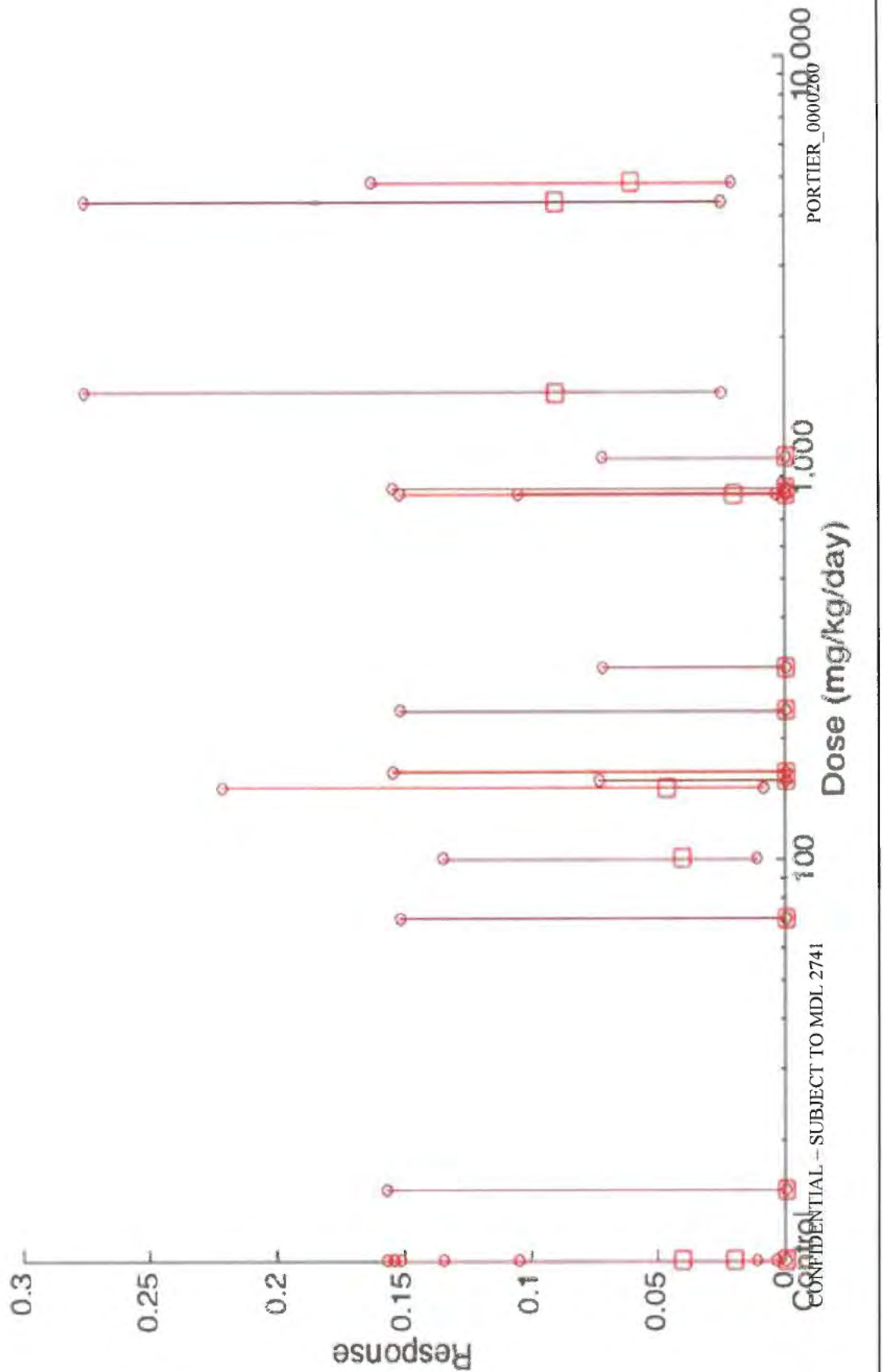


Figure 3: Renal tumors in male mice poly-3 adjusted and clustered by similar doses

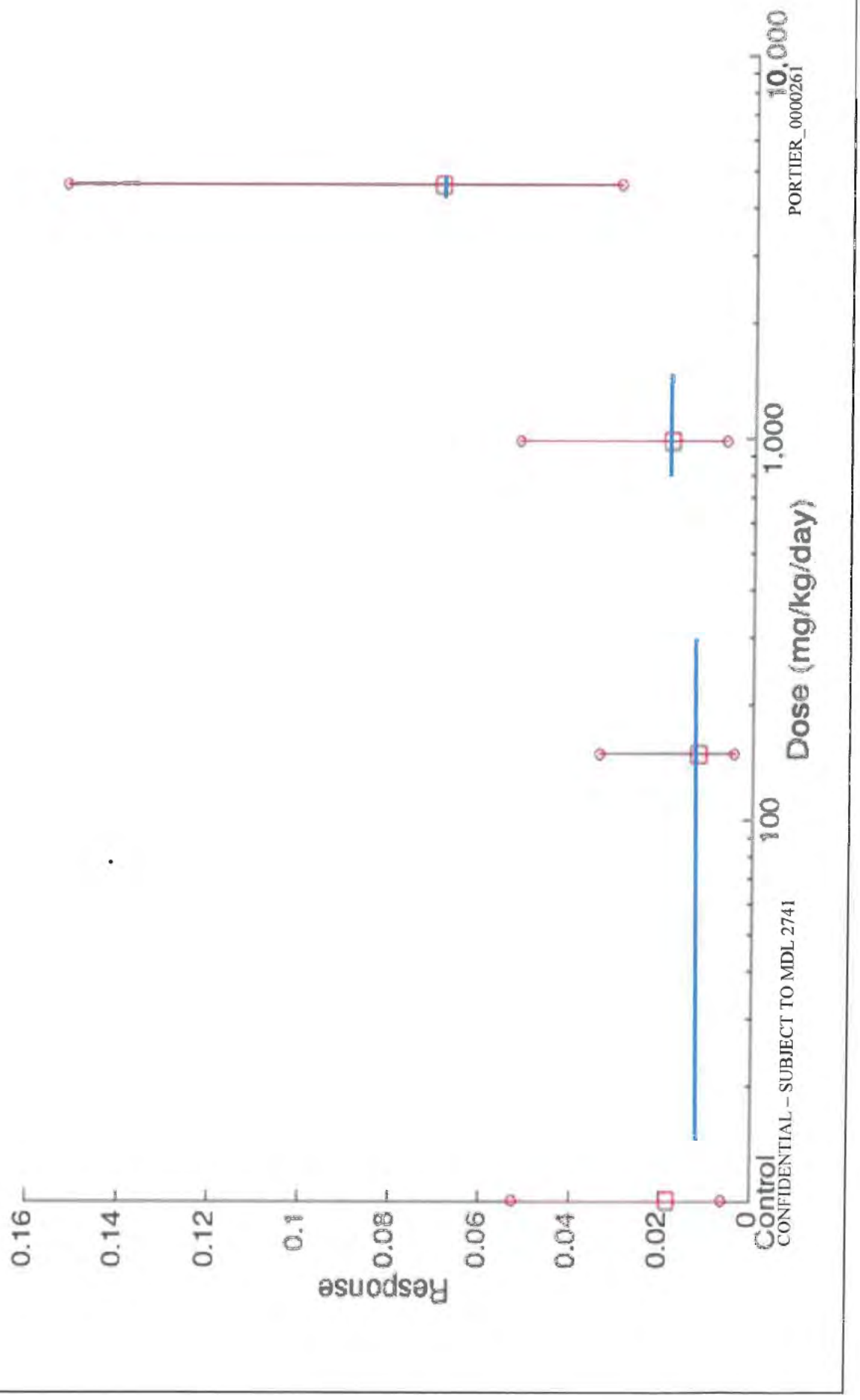


Table 6: Analysis of Male Mouse Malignant Lymphoma From the Individual

Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)
1983	Crl:CD-1	24	157, 814, 4841	2/50, 5/49, 4/50, 2/50	0.51 (0.51)
1993	?:CD-1	24	100, 300, 1000	4/50, 2/50, 1/50, 6/50	0.08 (0.08)
1997	CrJ:CD-1	18	165, 838, 4348	2/50, 2/50, 0/50, 6/50	**0.008 (0.012)**
2001	SW	18	15, 151, 1460	10/49, 15/49, 16/49, 19/49	**0.05 (0.09)**
2009	Crl:CD-1	18	71, 234, 810	0/51, 1/51, 2/51, 5/51	**0.004 (0.005)**

Table 7: Pooled Analysis of Male Mouse Malignant Lymphoma

Year	Strain	p-Trend (p-poly3)
CD-1 Combined	CD-1	0.02 (0.01)
CD-1 Combined and Doses Pooled[1]	CD-1	0.01(0.009)
CD-1 Combined, doses>1000 dropped	CD-1	0.03 (0.05)
CD-1 Combined, doses>1000 dropped and Doses Pooled[2]	CD-1	0.04 (0.04)

[1] – Doses were combined as follows: all controls, doses between 0 and 310 mg/kg/day, doses between 310 and 1500 mg/kg/day, and doses greater than 1500 mg/kg/day. Average doses in each pooled group were used in the analysis. [2]- Doses were combined as follows: all controls, doses between 0 and 310 mg/kg/day, and doses between 310 and 1500 mg/kg/day. Average doses in each pooled group were used in the analysis.

Figure 5: Malignant lymphomas in male CD-1 mice poly-3 adjusted showing individual dose

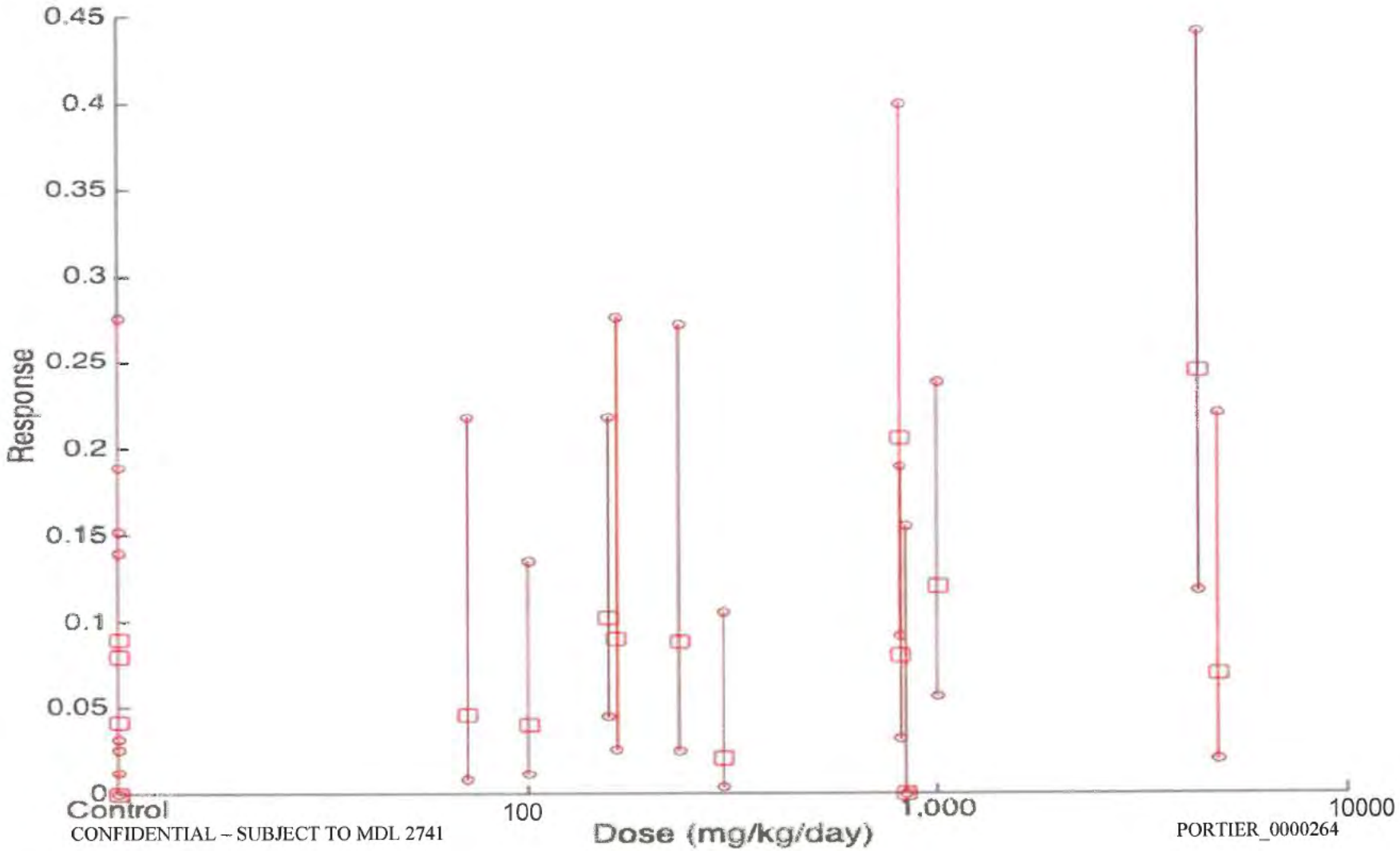


Figure 6: Malignant lymphomas in male CD-1mice poly-3 adjusted and clustered by similar doses

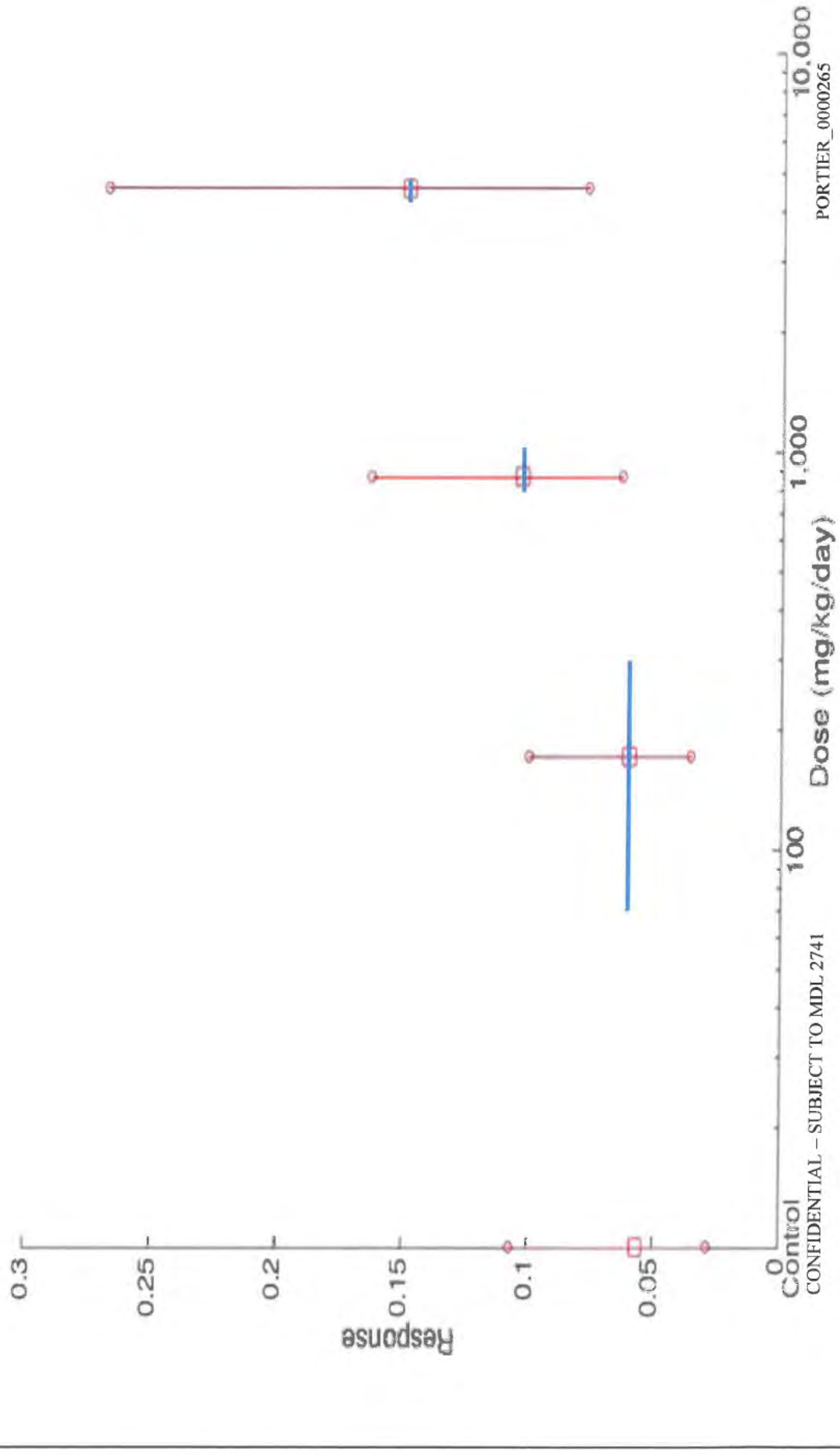


Table 8: Analysis of Male Mouse Hemangiosarcomas From the Individual

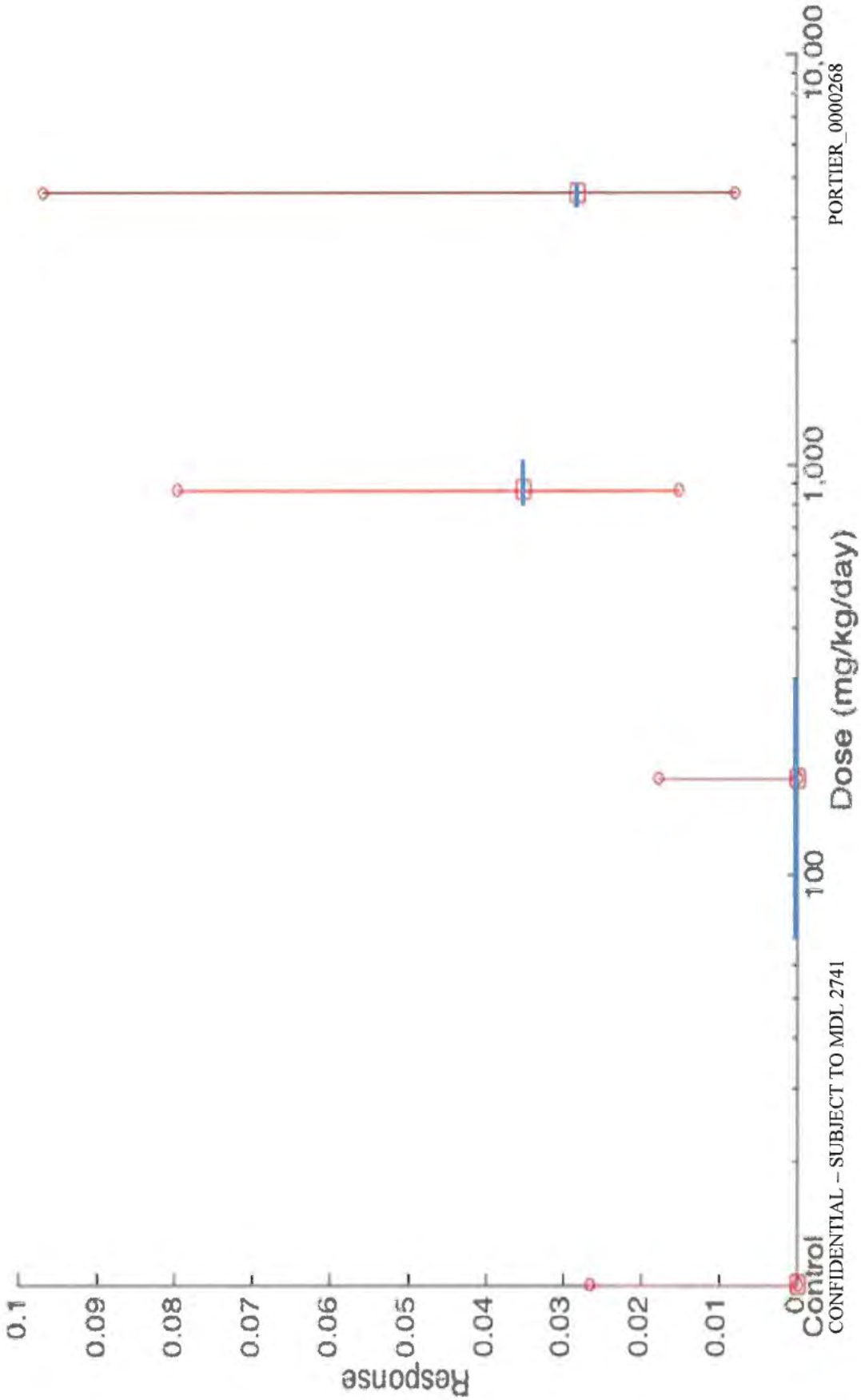
Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)
1983	Crl:CD-1	24	157, 814, 4841	0/50, 0/49, 1/50, 0/50	0.63 (0.63)
1993	?:CD-1	24	100, 300, 1000	0/50, 0/50, 0/50, 4/50	**0.0004 (0.0004)**
1997	CrJ:CD-1	18	165, 838, 4348	0/50, 0/50, 0/50, 2/50	**0.008 (0.009)**
2001	SW	18	15, 151, 1460	No Data	-
2009	Crl:CD-1	18	71, 234, 810	0/51, 0/51, 0/51, 0/51	-

Table 9: Pooled Analysis of Male Mouse Hemangiosarcomas

Year	Strain	p-Trend (p-poly3)
CD-1 Combined	CD-1	0.02 (0.03)
CD-1 Combined and Doses Pooled[1]	CD-1	0.02 (0.02)
CD-1 Combined, doses>1000 dropped	CD-1	<0.0001 (<0.0001)
CD-1 Combined, doses>1000 dropped and Doses Pooled[2]	CD-1	0.0003 (0.0003)

[1] – Doses were combined as follows: all controls, doses between 0 and 310 mg/kg/day, doses between 310 and 1500 mg/kg/day, and doses greater than 1500 mg/kg/day. Average doses in each pooled group were used in the analysis. [2] – Doses were combined as follows: all controls, doses between 0 and 310 mg/kg/day, and doses between 310 and 1500 mg/kg/day. Average doses in each pooled group were used in the analysis.

Figure 8: Hemangiosarcomas in male CD-1 mice poly-3 adjusted and clustered by



Summary of Animal Cancer Data

- Sufficient Evidence
  - IARC, Portier et al.
- Insufficient Evidence
  - EFSA, ECHA, USEPA, WHO/JMPR
    - Dismissed high dose effects
    - Used historical controls inappropriately
    - Dismissed trend tests
    - Down-played or ignored consistency across mouse studies

EFSA/ECHA (draft) compared to IARC

- Agreed with the IARC on *limited evidence* in humans
  - dismissed the association as "insufficiently consistent" with no justification.
- Dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies
  - Inappropriate historical control dataset used in an incorrect manner and ignoring established guidelines cited in their report
  - Trend test not convincing, Doses too high
- Down-weighted laboratory and human evidence of genotoxicity.
- Confirmed glyphosate induces oxidative stress
  - Not relevant for cancer because no other indications

EPA (draft) compared to IARC

- Disagreed with the IARC on *limited evidence* in humans
  - dismissed the association
- Dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies
  - Inappropriate historical control dataset used in an incorrect manner and ignoring established guidelines cited in their report
  - Trend test not convincing, Doses too high
- Down-weighted laboratory and human evidence of DNA damage as a marker of genotoxicity
- Confirmed glyphosate induces oxidative stress
  - Not relevant for cancer because no other indications

What have we learned from these disagreements?

- Almost impossible to reproduce a regulatory decision
  - Lack of access to data
  - Subjective decisions made with little justification
  - Lack of strict adherence to guidelines
- Independent evaluations (like that done by IARC) are critical in order to keep all of the groups involved in regulatory decisions honest
- EC needs an outside set of experts, with no conflicts of interest, to review these types of risk assessments in an open forum

What needs to be done?

- Transparency of regulatory decisions needs to be re-evaluated
  - Authors and any conflicts need to be made public
  - Reviewers and any conflicts need to be made public
  - Literature used to make these decisions need to be made public
- Relationship between industry and regulatory communities needs to be carefully reviewed and guidelines put into place
- Scientific review and oversight of regulatory decisions needs to be done in an open and transparent fashion

Glyphosate Carcinogenicity

Christopher J. Portier, Ph.D.

Fachanlass: Pesticid-Zukunft Schweiz

28 September, 2016, Bern

Recent Cancer Assessments of Glyphosate

- IARC – March, 2015
  - Probable human carcinogen
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  - unlikely to pose a carcinogenic risk to humans from exposure through the diet
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  - no hazard classification for carcinogenicity is warranted
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  - Not likely to be carcinogenic to humans at doses relevant to human health risk assessment

Comparison Across Evaluations

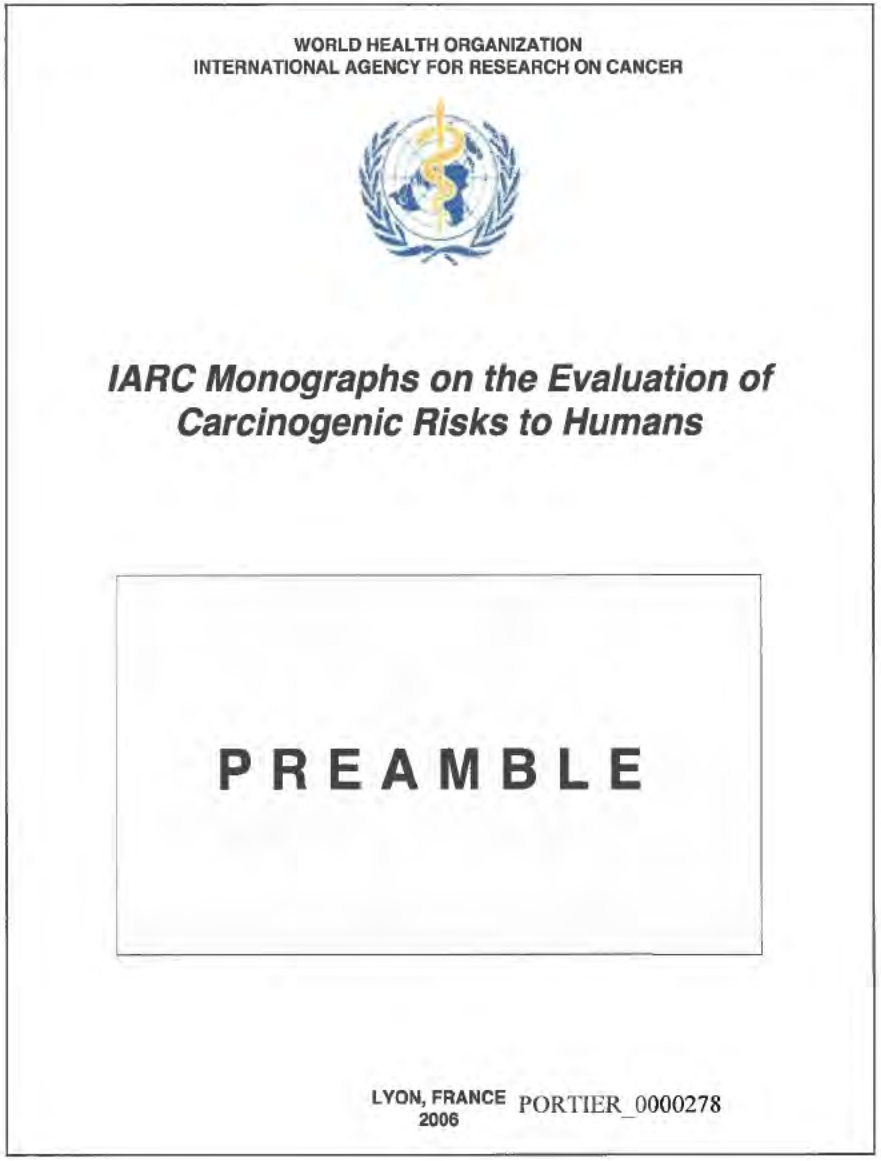
Study	Authors Known	COI Made Public	Proprietary Studies	Open Literature	Guidelines	Followed Guidelines	Evaluated Dose-Response
IARC	Yes	Yes	No	Yes	Yes	Yes	No
EFSA	No	No	Yes	Yes	Yes	No	No
Portier	Yes	Yes	Yes	Yes	Yes	Yes	No
JMPR	Yes	?	Yes	Yes	Yes	Yes	Yes
ECHA	No	No	Yes	Yes	Yes	No	No
EPA	?	Some	Yes	Yes	Yes	No	No

The IARC Monographs Program

- IARC Monographs Evaluate
  - Chemicals
  - Complex substances and mixtures
  - Occupational exposures
  - Physical and biological agents
  - Personal habits

IARC Monographs Process

- Written Guidelines
  - Public Document
  - Who? What? How?
  - Roles
  - Responsibilities
  - Instructions
    - Review
    - Summary of Evidence



IARC Monograph 112 Process

- Working Group Members
  - No real or apparent conflicts of interest
    - Formal process, written declarations of interest
  - Membership
    - Working Group members – review, evaluate
    - Invited Specialist – review only
    - Representatives – government, observe only
    - Observers – interested party, observe only
    - Secretariat – support the Working Group

IARC Monograph Timeline

- 1 year before Monograph Meeting
  - Meeting announced
  - Call for experts
  - Call for data
- 8 months before Monograph Meeting
  - Working Group membership selected
  - Request for observer status opened
  - Draft sections of Monograph developed by Working Group Members

IARC Monograph Timeline

- 1 month before Monograph Meeting
  - Call for data closed
  - Draft sections distributed to Working Group members for review and comment
- At Monograph Meeting
  - Finalize review of all literature
  - Evaluate the evidence in each category
  - Complete the overall evaluation

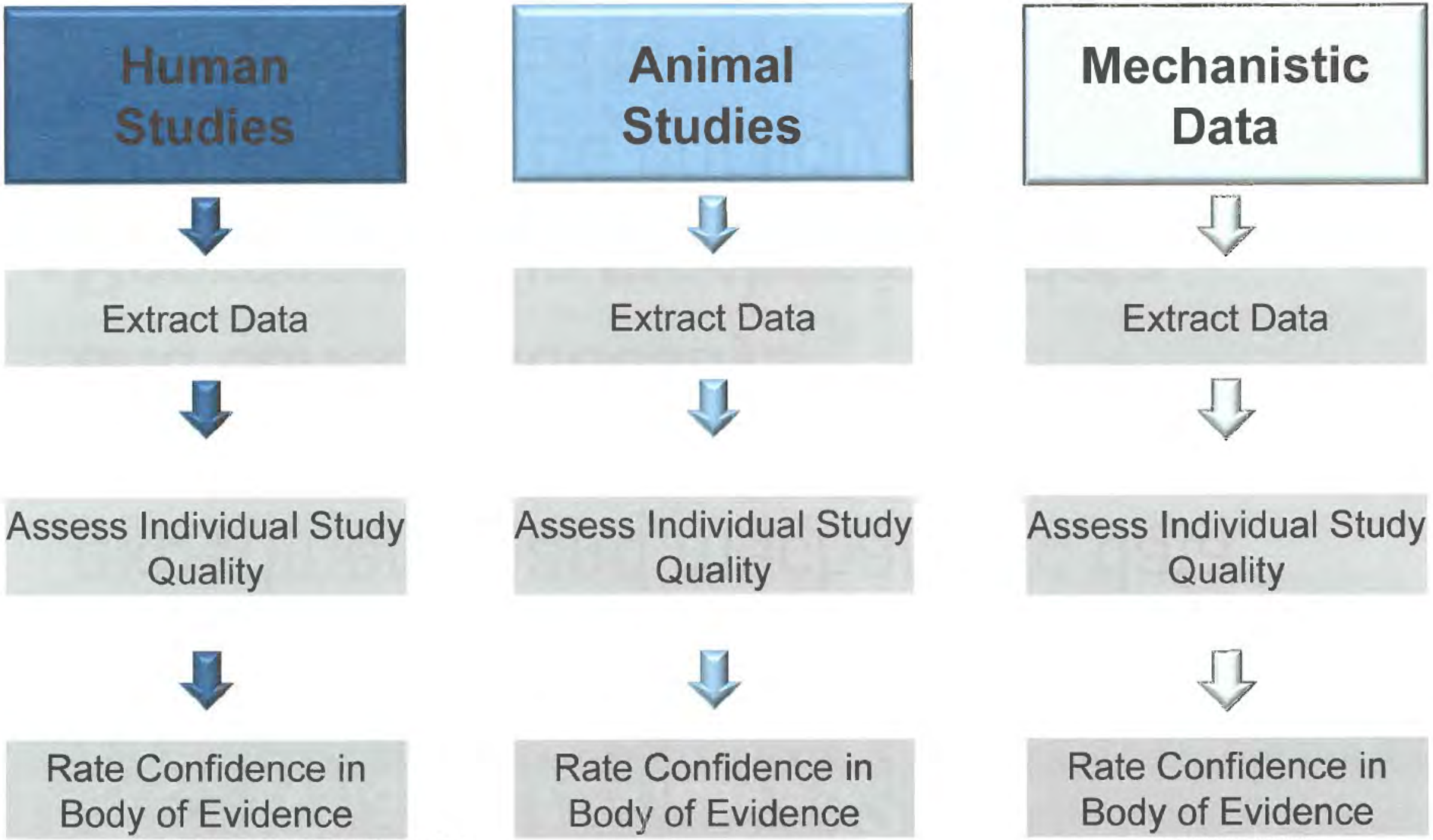
IARC Monograph Timeline

- 1-2 weeks after Monograph Meeting
  - Publish summary in Lancet Oncology
- 4-12 months after Monograph Meeting
  - Finalize Monograph and publish

IARC: What is reviewed?

- Systematic review of human, experimental and mechanistic data
- All pertinent epidemiological studies and cancer bioassays
- Representative mechanistic data
- Studies must be publicly available
  - Sufficient detail to review
  - Reviewers cannot have been associated with the study

IARC: Evidence Review



IARC: Evaluating Human Evidence
Preamble Part B, Section 6(a)

- Sufficient Evidence
  - Causal relationship is **established**
  - Chance, bias and confounding ruled out with reasonable confidence
- Limited Evidence
  - Causal interpretation is **credible**
  - Chance, bias and confounding could not be ruled out with reasonable confidence

IARC: Evaluating Human Evidence
Preamble Part B, Section 6(a)

- Inadequate Evidence
  - Studies permit no conclusion regarding causality
- Evidence suggesting lack of carcinogenicity
  - Several strong studies showing consistent lack of positive association
  - Conclusion limited to cancer sites and conditions studied

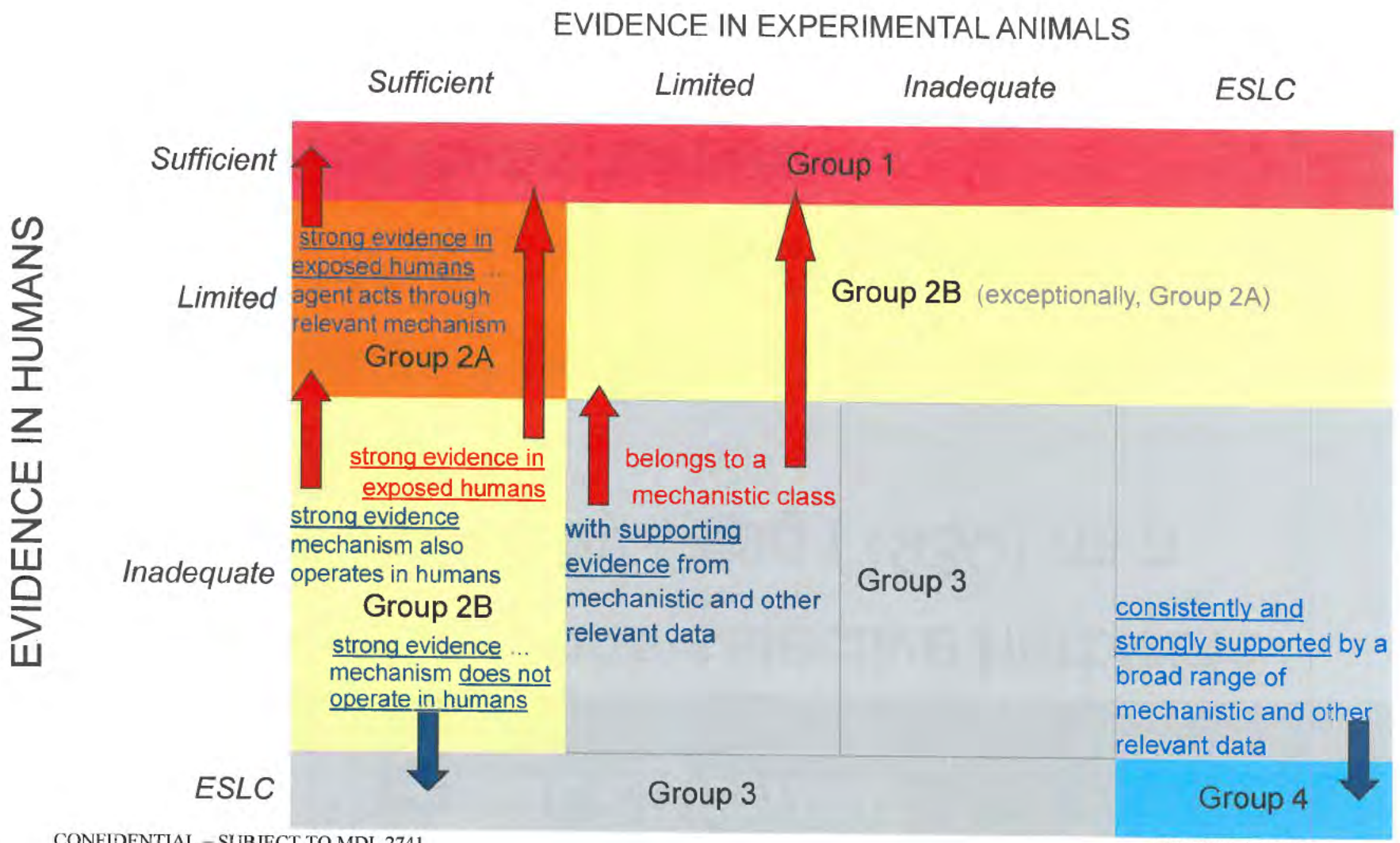
IARC: Evaluating Animal Evidence
Preamble Part B, Section 6(a)

- Sufficient Evidence
  - Causal relationship established
  - Two or more species of animals or two or more studies
  - One study where malignant neoplasms occur to an unusual degree
    - Incidence (rare tumors)
    - Site (unusual tumors)
    - Age at onset
    - Strong findings at multiple sites

IARC: Evaluating Animal Evidence
Preamble Part B, Section 6(a)

- Limited Evidence
  - Single positive experiment
  - Unresolved questions about the studies
  - Only benign neoplasms
  - Only promoting activity demonstrated
- Inadequate evidence
- Evidence suggesting lack of carcinogenicity
  - All studies negative or inadequate
  - At least two well-conducted negative studies

IARC Overall Evaluation



Modified from Vincent Cogliano, IARC

Glyphosate - Background

- Broad-spectrum, non-selective herbicide
- First synthesized by Cilag (1950) as a possible drug
- Re-synthesized by Monsanto (1970)
- Patent expired [1991, 2000 (US)]
- Hundreds of trade names
- Approximately 91 producers in 20 countries

Glyphosate - Background

- Believed to be the most heavily used herbicide in the world
  - 2012 production volume > 700 million kg
- Production has increased sharply in recent years
  - Genetically modified glyphosate-resistant crop varieties
- Exposure pathways
  - Air (during spraying)
  - Water
  - Food

Glyphosate – Human Evidence

- Literature
  - US Agricultural Health Study (AHS)
  - Multiple independent case-control studies

Glyphosate – Human Evidence

- Epidemiological studies of cancer in humans
  - More than 2 studies
    - Non-Hodgkin Lymphoma (NHL)
    - Multiple Myeloma (MM)
  - Two studies
    - Leukemia, breast cancer, prostate cancer
  - One Study
    - Adult brain, oesophageal, stomach, prostate, soft-tissue sarcoma, lung, oral cavity, colorectal, pancreas, kidney, bladder, melanoma

Glyphosate – Key Epidemiology Studies for Non-Hodgkin Leukemia

Study	Type	Size
Agricultural Health Study *(Alavanja et al., 2003)*	Cohort – pesticide applicators and spouses	52 395 (+32 347 spouses), 92 cases, 4-8 years follow-up
US Midwest *(De Roos et al., 2003)*	Pooled analysis of 3 case-control studies	NHL: 650 cases, 1933 controls
Cross-Canada *(McDuffie et al., 2001)*	Population-based case-control	517 cases, 1506 controls
Swedish Case-Control Study *(Eriksson et al., 2008)*	Population-based case-control study	910 cases, 1016 control
Swedish Case-Control Study *(Hardell et al., 1999)*	Population-based case-control study	404 cases, 741 control (limited power)

IARC Glyphosate Evaluation
Human Evidence

- **Limited Evidence** for NHL
  - Causal interpretation is **credible**
  - Chance, bias and confounding could not be ruled out with reasonable confidence
- Basis
  - De Roos et al., 2003 (US), McDuffie et al., 2001 (Canada), Eriksson et al., 2008 (Sweden)
    - Positive association
    - Adjustment for other pesticides
  - Agricultural Health Study
    - No additional support for association, does not contradict
  - Positive meta-analysis

IARC Evidence in Experimental Animals

- 1 mouse feeding (glyphosate) study showed significant trend in the incidence of ***renal tubule adenoma or carcinoma*** (combined) in male mice; renal tubule carcinoma is a rare tumor
- 1 mouse feeding (glyphosate) study showed significant trend in the incidence of ***haemangiosarcoma*** in male mice
- 2 rat feeding (glyphosate) studies showed significant increase in the incidence of *pancreatic islet cell adenoma* (a benign tumor) in male rats
- 1 mouse study (GLY formulation) showed positive effect on *skin cancer* in an initiation-promotion study
- Several other oral feeding (glyphosate) and drinking water (glyphosate and glyphosate formulation) studies in rats showed no significant effects

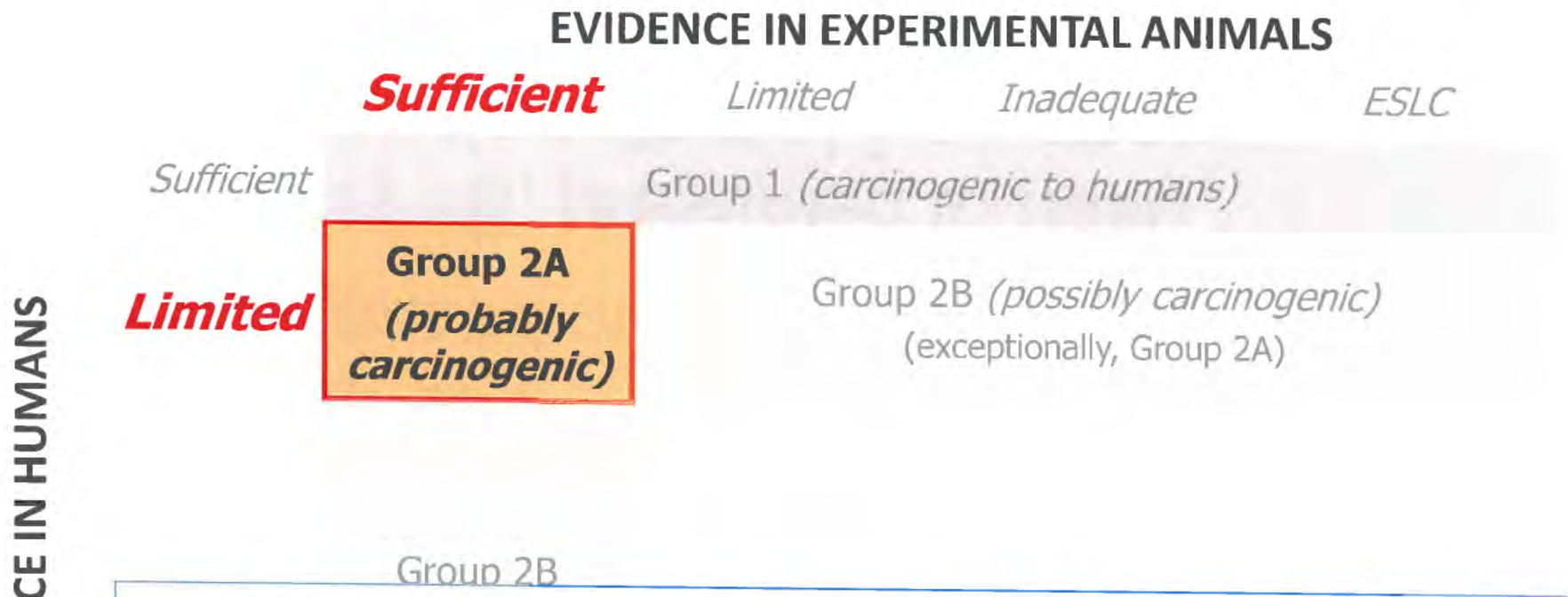
IARC Glyphosate Evaluation
Human Evidence

- **Sufficient Evidence** in experimental animals
  - More than two independent studies showing a significant, biologically relevant cancer finding

IARC Mechanistic Evidence

Key characteristic	Strength of Evidence
1. Electrophilic or ability to undergo metabolic activation	Glyphosate is ***not*** electrophilic
2. Genotoxic	Strong (G, GF)
3. Alters DNA repair or causes genomic instability	No data
4. Epigenetic Alterations	No data
5. Oxidative Stressor	Strong (G, GF and AMPA)
6. Induces chronic inflammation	No data
7. Immunosuppressant	Weak
8. Modulates receptor-mediated effects	Weak
9. Immortalization	No data
10. Alters cell proliferation, cell death, or nutrient supply	Weak

IARC Glyphosate Monograph
Overall Evidence



"*for […] glyphosate, the* ***mechanistic evidence provided independent support of the 2A classification*** *based on evidence of carcinogenicity in humans and experimental animals*"

(The Lancet Oncology; March 20, 2015)

CLP Guidance on Carcinogenicity

- Category 1: Known or presumed human carcinogens
  - Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence
  - Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence

Guidance on the Application of the CLP Criteria, ECHA (2015)

CLP Guidance on Carcinogenicity
(continued)

- The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:
  - human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
  - animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).
- In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing **limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals**

Guidance on the Application of the CLP Criteria, ECHA (2015)

EFSA – What is reviewed for reassessment?

- All new data since the last review
- All endpoints
  - Including non-cancer endpoints
- Assessment is based upon
  - Reassessment document provided by industry
    - BfR and EFSA comment on document
    - Analysis of study results based upon submitted documents
  - All pertinent epidemiological studies and cancer bioassays
  - Representative mechanistic data
  - Studies may not be publicly available
  - Reviewers submit Declaration of Interests
    - Some of these are blank?

EFSA Glyphosate Review
Animal Carcinogenicity

Year	Strain	Length[1]	Top Dose[2]	Renal Tumors	Hemangio-sarcomas	Malignant Lymphoma
1983[5]	Crl:CD-1	24	4,841	+[3]		
1993[5]	?:CD-1	24	1,000		+	
1997	CrJ:CD-1	18	4,843	+	+	+
2001	SW	24	1,460	+		+/-[4]
2009	Crl:CD-1	18	810			+

1 – months; 2 – mg/kg bw/day; 3 - + indicates a p-value of <0.05 as calculated by BfR using the Armitage linear trend test in proportions; 4 – p=0.066; 5 – studies evaluated in IARC review

Historical Control Data used: collected 1987-96, 51 control groups from Crl:CD-1 mice from7 different research laboratories using mice from 3 different Charles River Laboratories production sites with sacrifice at ages 18-24 months

Renal Adenoma: 41 studies no tumors, 3 studies 1 tumor, 2 studies 2 tumors
Renal Carcinoma: 42 studies no tumors, 4 studies 1 tumor

EFSA compared to IARC

- Agreed with the IARC on *limited evidence* in humans
  - dismissed the association as "insufficiently consistent" with no justification.
- Dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies
  - Inappropriate historical control dataset used in an incorrect manner and ignoring established guidelines cited in their report
  - Trend test not convincing, Doses too high
- Down-weighted laboratory and human evidence of genotoxicity.
- Confirmed glyphosate induces oxidative stress
  - Not relevant for cancer because no other indications

Carcinogenicity of Glyphosate
A Systematic Review of the Available Evidence

Christopher J. Portier, Ph.D.

21 November, 2016,

Recent Cancer Assessments of Glyphosate

- IARC – March, 2015
  - Probable human carcinogen
- EFSA – November, 2015
  - Unlikely to pose a carcinogenic hazard to humans
- Portier et al. – January, 2016
  - Probable human carcinogen
- FAO/WHO Joint Meeting on Pesticides Residue (JMPR) – March, 2016
  - Unlikely to pose a carcinogenic risk to humans from exposure through the diet
- CLP Proposal (Germany, BAuA, Federal Institute for Occupational Safety and Health) – May, 2016 (draft)
  - no hazard classification for carcinogenicity is warranted
- USEPA – September, 2016 (draft)
  - Not likely to be carcinogenic to humans at doses relevant to human health risk assessment

Table 1: Human Epidemiology Studies

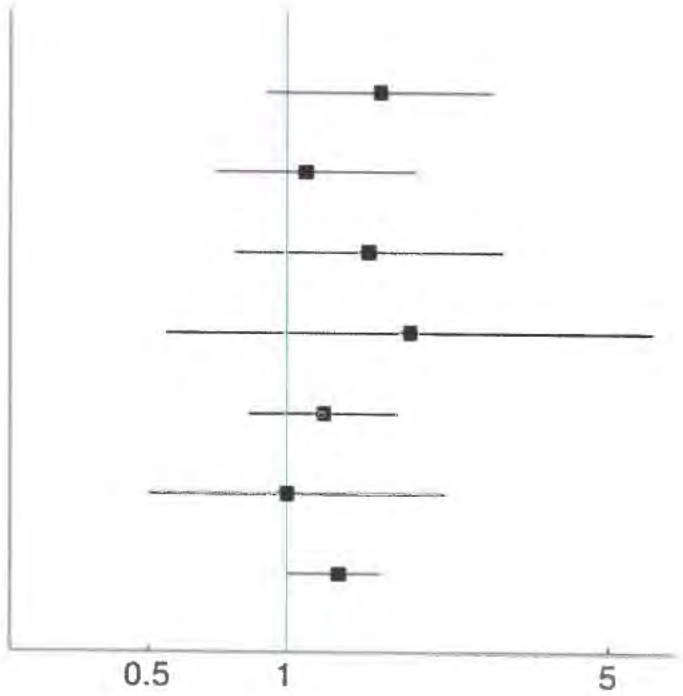
Study	Type	Size	Findings	Exposed Cases
Agricultural Health Study *(De Rooset al., 2005)*	Cohort – licensed pesticide applicators	52 395 (+32 347 spouses), 92 cases, 4-8 years follow-up	1.1 (0.7-1.9) C 0.7 (0.4-1.4) 21-56% tertile compared to <20% tertile 0.9 (0.5-1.6) 21-56% tertile compared to >57% tertile (31 cases no quantification of exposure)	73
US Midwest *(De Roos et al., 2003)*	Pooled analysis 3 case-control studies	NHL: 650 cases, 1933 controls	2.1 (1.1-4) U 1.6 (0.9-2.8) C	36 36
Cross-Canada *(McDuffie et al., 2001)*	Population-based case-control study	517 cases, 1506 controls	1.2 (0.83-1.74) U 1.0 (0.63-1.57) ≤2 d/Y 2.12 (1.2-3.73) >2 d/Y	51 28 23
Swedish Case-Control Study *(Eriksson et al., 2008)*	Population-based case-control study	910 cases, 1016 control	2.02 (1.1-3.71) U 1.51 (0.77-2.94) C 1.69 (0.7-4.07) ≤10 d/Y 2.36 (1.04-5.37) >10 d/Y 1.11 (0.24-5.08) ≤10 Y 2.26 (1.16-4.4) >10 Y	29 29 12 17 NR NR
Swedish Case-Control Study *(Hardell et al., 1999)*	Population-based case-control study	404 cases, 741 control (limited power)	2.3 (0.4-13) U 5.8 (0.6-5.4) C (not specified)	4 NR
France Case-Control *(Orsi et al, 2009)*	Hospital-based case-control study	244 cases, 456 controls	1.0 (0.5-2.2) U	12
Swedish Case-Control Study *(Hardell et al., 2002)*	Population-based case-control study	515 cases, 1141 controls	3.04 (1.08-8.5) U 1.85 (0.55-6.2) C (not specified)	8 8
US Case-Control Study *(Lee et al., 2004)*	Population-based case-control study	872 cases, 2381controls	1.4 (0.98-2.1) U – no asthma 1.2 (0.4-3.3) U - asthma	53 6

Meta Analyses

Study	Included Studies	Findings
Schinasi and Leon, 2014	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.5 (1.1-2.0)
IARC Monograph Working Group	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.3 (1.103-1.65) – used adjusted risk estimates from Hardell et al., 2003 and Eriksson et al., 2008
Chang and Delzell, 2016	McDuffie et al., 2001; Hardell et al., 2002; De Roos et al., 2003 and 2005; Eriksson et al., 2008; Orsi et al., 2009)	1.3 (1.0-1.6)

Tree Plot of Epidemiology Studies
(using analyses corrected for potential confounders)

Study	RR	Lower	Upper	Weight
De Roos et al. (2003)	1.600	0.900	2.800	16.2
De Roos et al. (2005)	1.100	0.700	1.900	21.0
Eriksson et al., (2008)	1.510	0.770	2.940	11.6
Hardell et al. (2002)	1.850	0.550	6.200	3.6
McDuffie et al. (2001)	1.200	0.830	1.740	38.1
Oris et al. (2009)	1.000	0.500	2.200	9.5
Meta-Analysis	1.300	1.000	1.600	100.0



Chang and Delzell (2016)

Summary of Human Evidence

- Limited Evidence in Humans
  - IARC, Portier et al.
- Insufficient evidence in humans
  - EFSA, CLP Proposal, EPA (draft)
- Definition of Limited Evidence (CLP Guidance, 2015; IARC 2006)
  - limited evidence of carcinogenicity: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence. (3.6.2.2.3.a)

Carcinogenicity Studies in Male Mice

Year	Strain	Length[1]	Top Dose[2]	Renal Tumors	Hemangio-sarcomas	Malignant Lymphoma
1983[5]	Crl:CD-1	24	4,841	+[3]		
1993[5]	?:CD-1	24	1,000		+	+/-[4]
1997	CrJ:CD-1	18	4,843	+	+	+
2001	SW	18	1,460	+		+/-[6]
2009	Crl:CD-1	18	810			+

1 – months; 2 – mg/kg bw/day; 3 - + indicates a p-value of <0.05 as calculated by BfR using the Armitage linear trend test in proportions; 4 – p=0.08; 5 – studies evaluated in IARC review; 6 – p=0.053

+ indicates studies evaluated by IARC

Table based on Table 5.3-1 in the EFSA Renewal Assessment Report, Addendum I (8/31/2015)

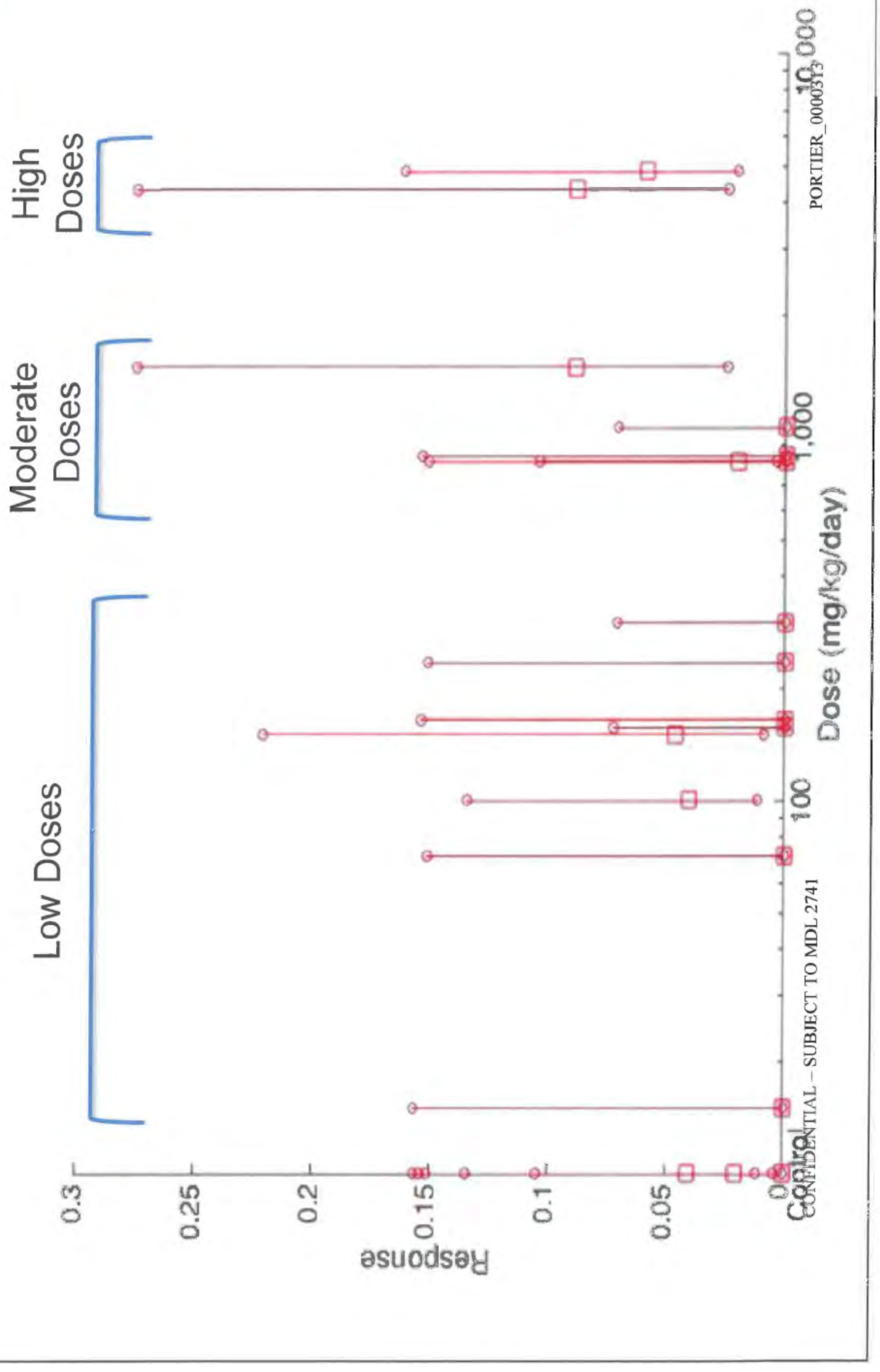
Analysis of Male Mouse Renal Tumors[1] From the Individual Studies

Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)[2]
1983	Crl:CD-1	24	157, 814, 4841	1/50, 0/49, 1/50, 3/50	**0.03 (0.03)**
1993	?:CD-1	24	100, 300, 1000	2/50, 2/50, 0/50, 0/50	0.94 (0.94)
1997	CrJ:CD-1	18	165, 838, 4348	0/50, 0/50, 0/50, 2/50	**0.008 (0.009)**
2001	SW	18	15, 151, 1460	0/49, 0/49, 1/50, 2/50	**0.04 (0.04)**
2009	Crl:CD-1	18	71, 234, 810	0/51, 0/51, 0/51, 0/51	-

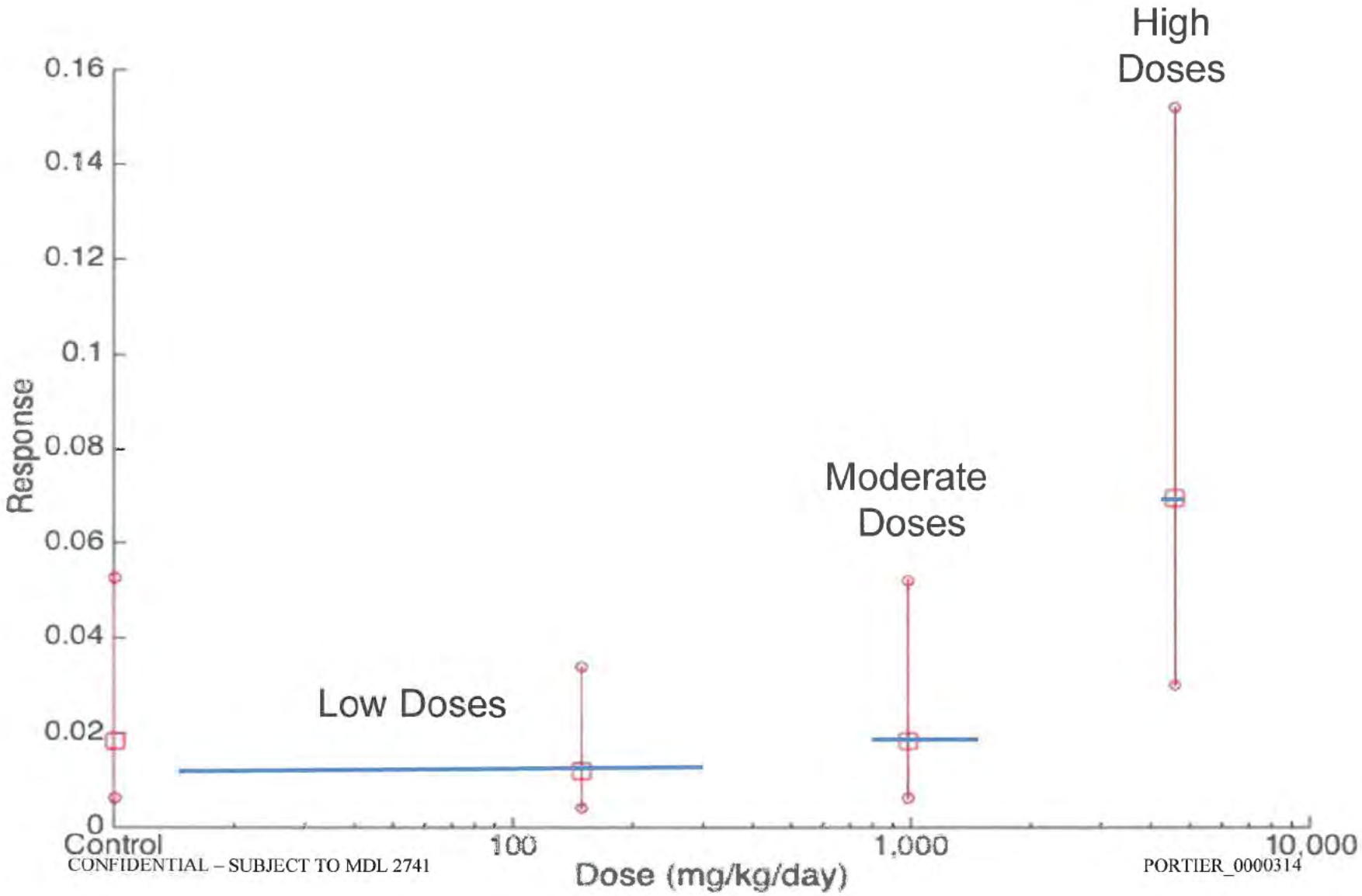
1 – Giknis and Clifford, 2005 historical control rate=0.0038, 43 of 52 studies had no tumors, 7 had 1 tumor and 2 had 2 tumors

2 – Poly-3 adjustment used to predict response at 24 months from response at 18 months; see Bailer and Portier (1988)

Renal tumors in male mice poly-3 adjusted showing individual dose groups



Renal tumors in male mice poly-3 adjusted and clustered by similar doses



Renal Tumors in Male Mice

Study	Approx. Trend	Exact Trend[1]	Historical Trend[2]
Knezevich and Hogan, 1983	0.033	0.063	0.009
Atkinson, 1993b	0.94	0.982	1
Sugimoto, 1997	0.008	0.061	0.009
Kumar, 2001	0.04	0.059	0.011
Wood et al., 2009b	0.5	1	0.629
All experiments combined	<0.001	0.003	0.004
All CD-1 Studies Combined	<0.001	0.005	0.008
All experiments combined, doses<1500	0.212	0.209	0.206
All CD-1 experiments combined, doses<1000	0.851	0.856	0.867

1 – Exact test is based upon a permutation test with fixed marginals.

2 - Historical trend test is based upon historical control data from Giknis and Clifford (2005)

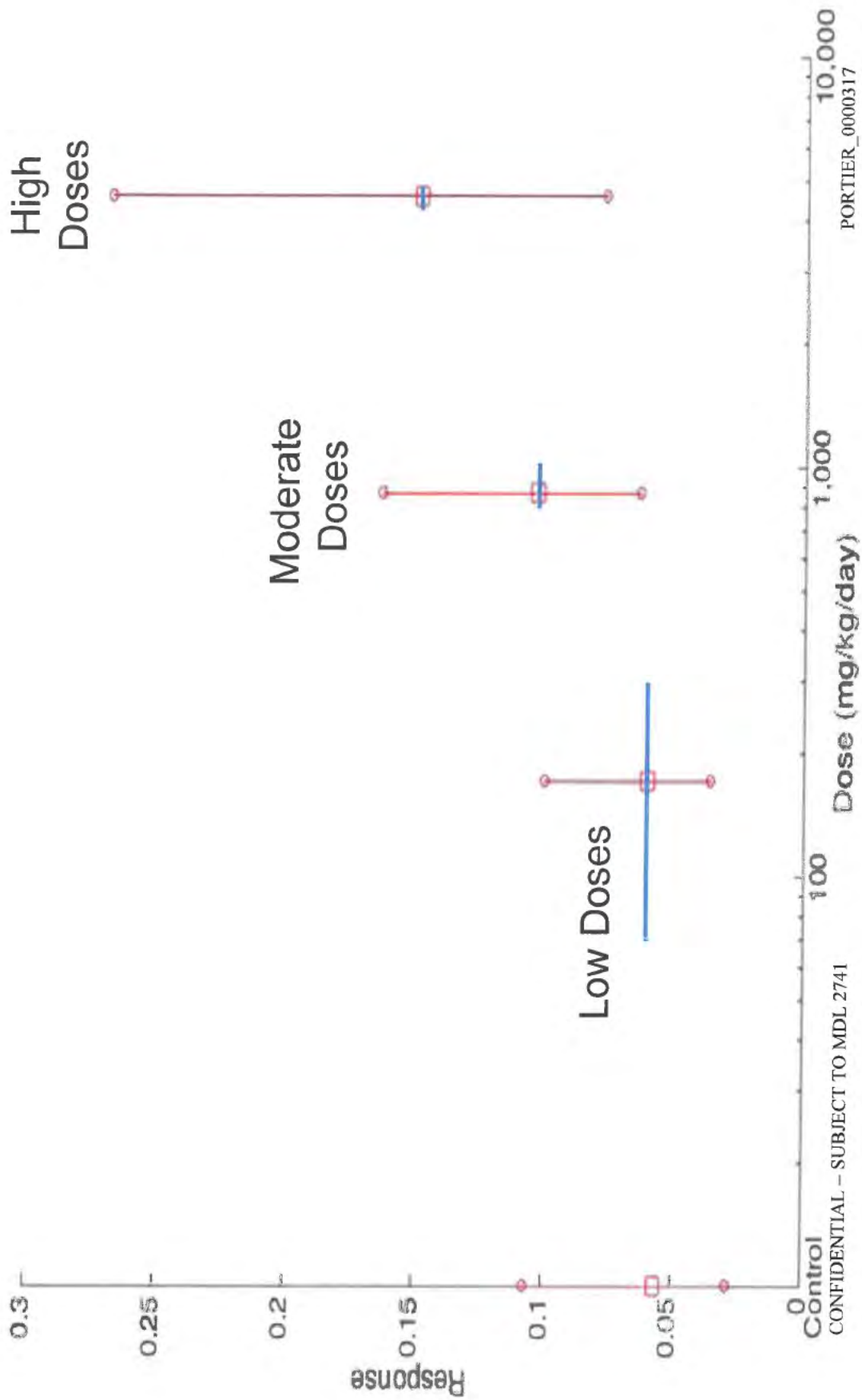
Analysis of Male Mouse Malignant Lymphoma From the Individual Studies

Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)[2]
1983	Crl:CD-1	24	157, 814, 4841	2/50, 5/49, 4/50, 2/50	0.51 (0.51)
1993	?:CD-1	24	100, 300, 1000	4/50, 2/50, 1/50, 6/50	0.08 (0.08)
1997	CrJ:CD-1	18	165, 838, 4348	2/50, 2/50, 0/50, 6/50	**0.008 (0.012)**
2001	SW	18	15, 151, 1460	10/49, 15/49, 16/49, 19/49	**0.05 (0.09)**
2009	Crl:CD-1	18	71, 234, 810	0/51, 1/51, 2/51, 5/51	**0.004 (0.005)**

1 – Giknis and Clifford, 2005 historical control rate=0.045 (0.027 in 18 month and 0.06 in 24 month), 8 of 26 18-month studies had no tumors, 3 of 26 24-month studies had no tumors

2 – Poly-3 adjustment used to predict response at 24 months from response at 18 months, see Bailer and Portier (1988)

Malignant lymphomas in male CD-1mice poly-3 adjusted and clustered by similar doses



Malignant Lymphomas in Male Mice

Study	Approx. Trend	Exact Trend[1]	Historical Trend[2]
Knezevich and Hogan, 1983	0.515	0.736	0.484
Atkinson, 1993b	0.076	0.095	0.087
Sugimoto, 1997	0.008	0.02	0.013
Kumar, 2001	0.053	0.105	0.072
Wood et al., 2009b	0.004	0.008	0.007
All experiments combined	0.173	0.426	0.172
All CD-1 Studies Combined	0.015	0.084	0.021
All experiments combined, doses<1500	<0.001	0.002	0.001
All CD-1 experiments combined, doses<1000	0.031	0.036	0.039

1 – Exact test is based upon a permutation test with fixed marginals.
2 - Historical trend test is based upon historical control data from Giknis and Clifford (2005)

Analysis of Male Mouse Hemangiosarcomas[1] From the Individual Studies

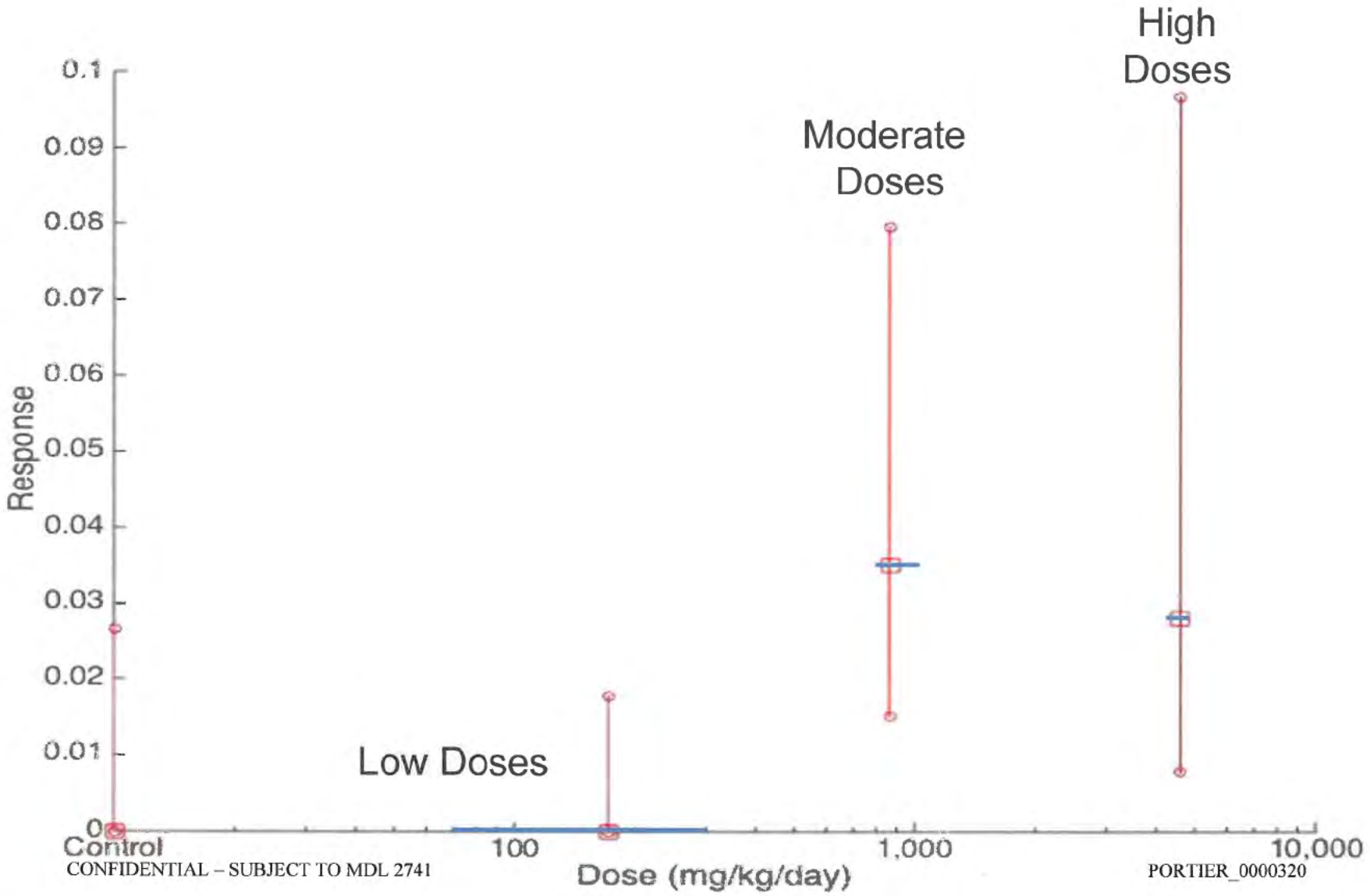
Year	Strain	Length	Doses (mg/kg/d)	Response	p-Trend (p-poly3)[2]
1983	Crl:CD-1	24	157, 814, 4841	0/50, 0/49, 1/50, 0/50	0.63 (0.63)
1993	?:CD-1	24	100, 300, 1000	0/50, 0/50, 0/50, 4/50	**0.0004 (0.0004)**
1997	CrJ:CD-1	18	165, 838, 4348	0/50, 0/50, 0/50, 2/50	**0.008 (0.009)**
2001	SW	18	15, 151, 1460	0/50, 0/50, 2/50, 0/50	0.724 (0.724)
2009	Crl:CD-1	18	71, 234, 810	0/51, 0/51, 0/51, 0/51[3]	0.5 (0.50

1 – Giknis and Clifford, 2005 historical control rate=0.01 (0 in 18 month and 0.018 in 24 month), all of 26 18-month studies had no tumors, 18 of 26 24-month studies had no tumors

2 – Poly-3 adjustment used to predict response at 24 months from response at 18 months; see Bailer and Portier (1988)

3 – CLP Proposal Table 42 lists tumor counts for this study of 2/51, 1/51, 2/51 and 1/51. However, these rates include hemangiomas from liver and kidney, making them different from the other studies and not applicable for the comparisons that follow

Hemangiosarcomas in male CD-1 mice poly-3 adjusted and clustered by similar



Hemangiosarcomas in Male Mice

Study	Approx. Trend	Exact Trend[1]	Historical Trend[2]
Knezevich and Hogan, 1983	0.628	0.5	0.592
Atkinson, 1993b	<0.001	0.004	<0.001
Sugimoto, 1997	0.008	0.061	0.021
Kumar, 2001	0.5	0.494	0.621
Wood et al., 2009b	0.5	1	0.49
All experiments combined	0.041	0.056	0.060
All CD-1 Studies Combined	0.024	0.044	0.041
All experiments combined, doses<1500	0.007	0.016	0.014
All CD-1 experiments combined, doses<1000	<0.001	<0.001	<0.001

1 – Exact test is based upon a permutation test with fixed marginals.
2 - Historical trend test is based upon historical control data from Giknis and Clifford (2005)

Carcinogenicity Studies in Rats

Year	Strain	Length[1]	Top Dose[2]	Finding
+Atkinson et al., 1993	SD	24	1000	none
+Lankas, 1981	SD	26	~32	inadequate dose, testicular tumors (M), pancreas islet cell aden. (M, weak)
+Stout & Ruecker, 1990	SD	24	1183	liver aden. (M), pancreas islet cell aden. (M), thyroid aden. (F)
Enemoto, 1997	SD	24	1127	none
Pavkov & Wyand, 1987	SD	24	41.8	inadequate dose and purity

1 – months; 2 – mg/kg bw/day;
+ indicates studies evaluated by IARC

Carcinogenicity Studies in Rats

Year	Strain	Length[1]	Top Dose[2]	Finding
+Seralini et al., 1993	SD	24	2250 mg/L in water	inadequate, mammary tumors
+Suresh, 1996	Wistar	24	886	none
Wood et al., 2004	Wistar	24	1229.7	mammary gland tumors (F)
Brammer, 2001	Wistar	24	1,498	Liver aden. (M)
+Chru-scielska et al., 2000	Wistar	24	2250 mg/L in water	inadequate documentation
+Syngenta , 1996	Wistar	12	1409	Inadequate length of study

1 – months; 2 – mg/kg bw/day;
+ indicates studies evaluated by IARC

Summary of Animal Cancer Data

- Sufficient Evidence
  - IARC, Portier et al.
- Insufficient Evidence
  - EFSA, CLP Proposal, USEPA, WHO/JMPR
- Definition of Sufficient Evidence (CLP Guidance, 2015; IARC, 2006)
  - sufficient evidence of carcinogenicity: a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.
  - A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites

Glyphosate Monograph – Mechanistic and Other Considerations:

Key Characteristic of Carcinogens #2 (Genotoxic)

Agent	Strength of the evidence	Evidence base includes	Endpoints considered in the evaluation
Glyphosate	Strong	1. ***Largely positive*** studies: • in human cells *in vitro*, • in mammalian model systems *in vivo* and *in vitro*, • studies in other non-mammalian organisms 2. ***Generally positive*** studies in liver *in vivo* in mammals 3. ***Mixed*** results for kidney and bone marrow *in vivo* in mammals 4. ***Consistently negative*** results from tests in bacterial assays	• Biomarkers of DNA adducts • Biomarkers of various types of chromosomal damage
Glyphosate formulations	Strong	1. ***Evidence in exposed humans***: • three studies of genotoxicicity endpoints in community residents exposed to glyphosate formulations, two of which reported positive associations • one of these studies examined subjects before and after aerial spraying and found a significant increase in micronuclei after exposure in 3 of 4 different geographical areas 2. ***Largely positive*** studies: • in human cells *in vitro*, • in mammalian model systems *in vivo* and *in vitro*, • studies in other non-mammalian organisms 3. ***Generally negative*** results from tests in bacterial assays 4. The ***pattern*** of tissue specificity of genotoxicity endpoints observed with glyphosate formulations is similar to that observed with glyphosate alone	• Chromosomal damage (micronuclei) in circulating blood cells from humans • Biomarkers of DNA adducts • Biomarkers of various types of chromosomal damage
AMPA	Moderate	1. Two human *in vitro* studies 2. One mammalian *in vivo* study 3. One mammalian *in vitro* study 4. One study in eel	While the number of studies is not large, all of the studies were ***positive***

Glyphosate Monograph – Mechanistic and Other Considerations:

Key Characteristic of Carcinogens #5 (Oxidative Stressor)

Agent	Strength of the evidence	Evidence base includes	Endpoints considered in the evaluation
Glyphosate	Strong	1. Rodent studies *in vivo* (including similar effects observed in many tissues) 2. Rodent cells *in vitro* 3. Human cells *in vitro*	• Lipid peroxidation markers • Oxidative DNA adducts • Dysregulation of antioxidant enzymes • Some studies challenged this mechanism experimentally (*e.g.*, by co-administering antioxidants)
Glyphosate formulations	Strong		
AMPA	Strong		

Conclusions

- Glyphosate should be listed as a Category 1B Carcinogen
  - animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen)[1]
  - In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals[1]
  - In this case limited evidence in humans and sufficient in animals

1. Guidance on the Application of the CLP Criteria, Table 3.6.1 (2015)

IARC Monograph Review Process and Glyphosate

Christopher J. Portier, Ph.D.

December, 2015

The IARC Monographs Program

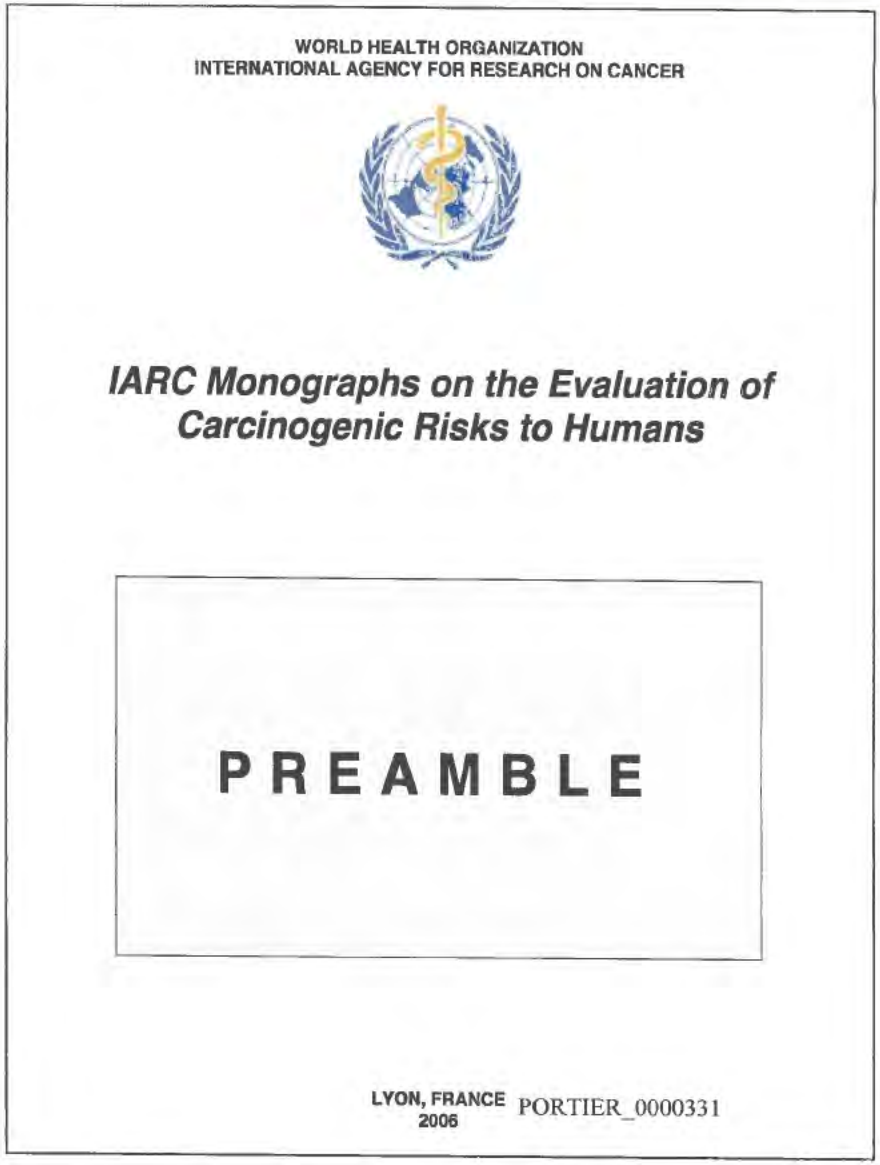
- IARC Monographs Evaluate
  - Chemicals
  - Complex substances and mixtures
  - Occupational exposures
  - Physical and biological agents
  - Personal habits

The IARC Monographs Program

- 980 Agents have been reviewed
  - 116 **known** human carcinogens
    - Group 1
  - 73 **probable** human carcinogens
    - Group 2A
  - 287 **possible** human carcinogens
    - Group 2B
  - 503 **not classifiable**
    - Group 3
  - 1 **probably not** carcinogenic

IARC Monographs Process

- Written Guidelines
  - Public Document
  - Who? What? How?
  - Roles
  - Responsibilities
  - Instructions
    - Review
    - Summary of Evidence



IARC Monograph 112 Process

- Working Group Members
  - No real or apparent conflicts of interest
    - Formal process, written declarations of interest
  - Membership
    - Working Group members – review, evaluate
    - Invited Specialist – review only
    - Representatives – government, observe only
    - Observers – interested party, observe only
    - Secretariat – support the Working Group

IARC Monograph Timeline

- 1 year before Monograph Meeting
  - Meeting announced
  - Call for experts
  - Call for data
- 8 months before Monograph Meeting
  - Working Group membership selected
  - Request for observer status opened
  - Draft sections of Monograph developed by Working Group Members

IARC Monograph Timeline

- 1 month before Monograph Meeting
  - Call for data closed
  - Draft sections distributed to Working Group members for review and comment
- At Monograph Meeting
  - Finalize review of all literature
  - Evaluate the evidence in each category
  - Complete the overall evaluation

IARC Monograph Timeline

- 1-2 weeks after Monograph Meeting
  - Publish summary in Lancet Oncology
- 4-12 months after Monograph Meeting
  - Finalize Monograph and publish

The IARC Monograph

Preamble

General Remarks

Several *Monographs* in one volume:

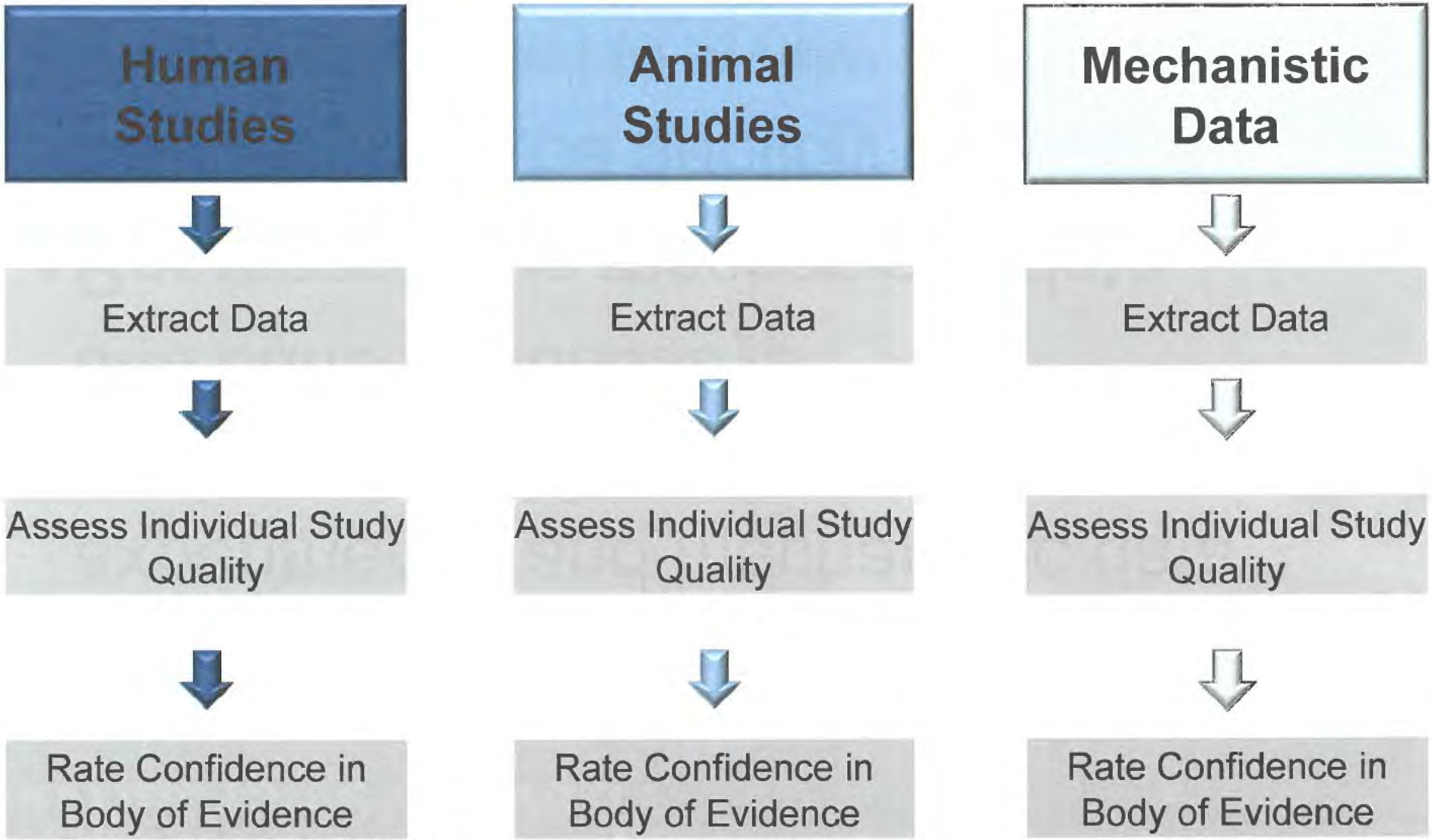
1. Exposure data
2. Cancer in humans
3. Cancer in animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

References

What is reviewed?

- Systematic review of human, experimental and mechanistic data
- All pertinent epidemiological studies and cancer bioassays
- Representative mechanistic data
- Studies must be publicly available
  - Sufficient detail to review
  - Reviewers cannot have been associated with the study

Evidence Review



Glyphosate - Background

- Broad-spectrum, non-selective herbicide
- First synthesized by Cilag (1950) as a possible drug
- Re-synthesized by Monsanto (1970)
- Patent expired [1991, 2000 (US)]
- Hundreds of trade names
- Approximately 91 producers in 20 countries

Glyphosate - Background

- Believed to be the most heavily used herbicide in the world
  - 2012 production volume > 700 million kg
- Production has increased sharply in recent years
  - Genetically modified glyphosate-resistant crop varieties
- Exposure pathways
  - Air (during spraying)
  - Water
  - Food

Glyphosate – Human Evidence

- Literature
  - US Agricultural Health Study (AHS)
  - Multiple independent case-control studies

Glyphosate – Human Evidence

- Epidemiological studies of cancer in humans
  - More than 2 studies
    - Non-Hodgkin Lymphoma (NHL)
    - Multiple Myeloma (MM)
  - Two studies
    - Leukemia, breast cancer, prostate cancer
  - One Study
    - Adult brain, oesophageal, stomach, prostate, soft-tissue sarcoma, lung, oral cavity, colorectal, pancreas, kidney, bladder, melanoma

Glyphosate – Key Epidemiology Studies for Non-Hodgkin Leukemia

Study	Type	Size
Agricultural Health Study *(Alavanja et al., 2003)*	Cohort – pesticide applicators and spouses	52 395 (+32 347 spouses), 92 cases, 4-8 years follow-up
US Midwest *(De Roos et al., 2003)*	Pooled analysis of 3 case-control studies	NHL: 650 cases, 1933 controls
Cross-Canada *(McDuffie et al., 2001)*	Population-based case-control	517 cases, 1506 controls
Swedish Case-Control Study *(Eriksson et al., 2008)*	Population-based case-control study	910 cases, 1016 control
Swedish Case-Control Study *(Hardell et al., 1999)*	Population-based case-control study	404 cases, 741 control (limited power)

Evaluating Human Evidence
Preamble Part B, Section 6(a)

- Sufficient Evidence
  - Causal relationship is **established**
  - Chance, bias and confounding ruled out with reasonable confidence
- Limited Evidence
  - Causal interpretation is **credible**
  - Chance, bias and confounding could not be ruled out with reasonable confidence

Evaluating Human Evidence
Preamble Part B, Section 6(a)

- Inadequate Evidence
  - Studies permit no conclusion regarding causality
- Evidence suggesting lack of carcinogenicity
  - Several strong studies showing consistent lack of positive association
  - Conclusion limited to cancer sites and conditions studied

Glyphosate Evaluation – Human Evidence

- **Limited Evidence** for NHL
  - Causal interpretation is **credible**
  - Chance, bias and confounding could not be ruled out with reasonable confidence
- Basis
  - De Roos et al., 2003 (US), McDuffie et al., 2001 (Canada), Eriksson et al., 2008 (Sweden)
    - Positive association
    - Adjustment for other pesticides
  - Agricultural Health Study
    - No additional support for association, does not contradict

Evidence in Experimental Animals

- 1 mouse feeding (glyphosate) study showed significant trend in the incidence of ***renal tubule adenoma or carcinoma*** (combined) in male mice; renal tubule carcinoma is a rare tumor
- 1 mouse feeding (glyphosate) study showed significant trend in the incidence of ***haemangiosarcoma*** in male mice
- 2 rat feeding (glyphosate) studies showed significant increase in the incidence of *pancreatic islet cell adenoma* (a benign tumor) in male rats
- 1 mouse study (GLY formulation) showed positive effect on *skin cancer* in an initiation-promotion study
- Several other oral feeding (glyphosate) and drinking water (glyphosate and glyphosate formulation) studies in rats showed no significant effects

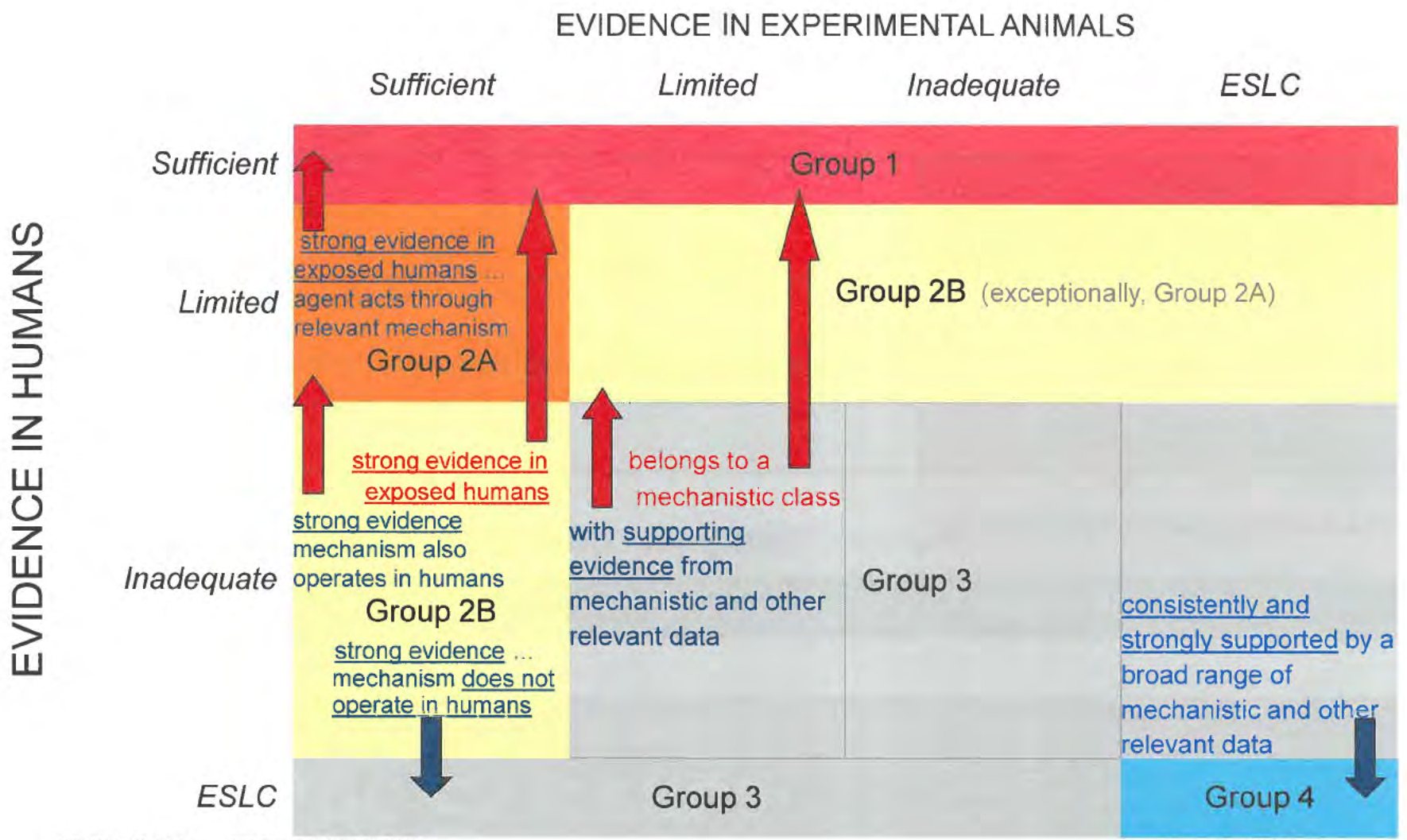
Glyphosate Evaluation – Human Evidence

- **Sufficient Evidence** in experimental animals
  - More than two independent studies showing a significant, biologically relevant cancer finding

Mechanistic Evidence

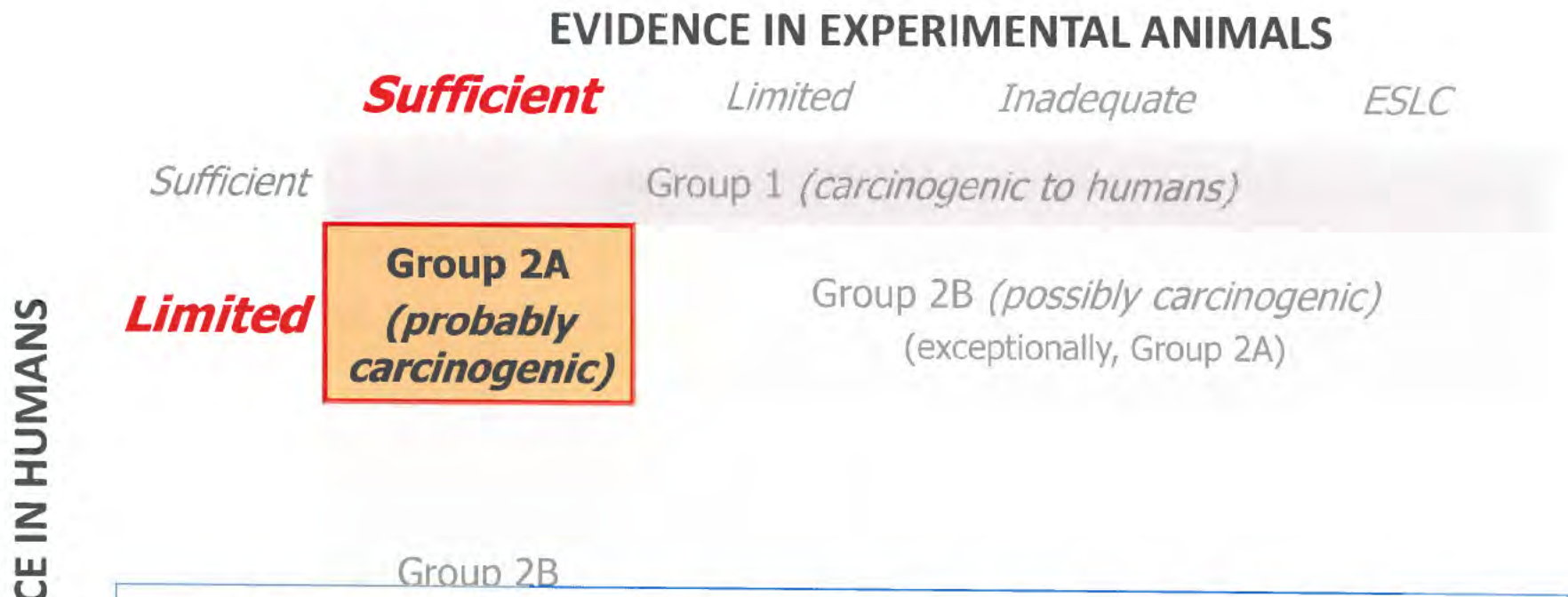
Key characteristic	Strength of Evidence
1. Electrophilic or ability to undergo metabolic activation	Glyphosate is ***not*** electrophilic
2. Genotoxic	Strong (G, GF)
3. Alters DNA repair or causes genomic instability	No data
4. Epigenetic Alterations	No data
5. Oxidative Stressor	Strong (G, GF and AMPA)
6. Induces chronic inflammation	No data
7. Immunosuppressant	Weak
8. Modulates receptor-mediated effects	Weak
9. Immortalization	No data
10. Alters cell proliferation, cell death, or nutrient supply	Weak

IARC Overall Evaluation



Modified from Vincent Cogliano, IARC

Glyphosate Monograph – Overall Evidence



"*for […] glyphosate, the* ***mechanistic evidence provided independent support of the 2A classification*** *based on evidence of carcinogenicity in humans and experimental animals*"

(The Lancet Oncology; March 20, 2015)

EFSA Glyphosate Review
Animal Carcinogenicity

Year	Strain	Length[1]	Top Dose[2]	Renal Tumors	Hemangio-sarcomas	Malignant Lymphoma
1983[5]	Crl:CD-1	24	4,841	+[3]		
1993[5]	?:CD-1	24	1,000		+	
1997	CrJ:CD-1	18	4,843	+	+	+
2001	SW	24	1,460	+		+/-[4]
2009	Crl:CD-1	18	810			+

1 – months; 2 – mg/kg bw/day; 3 - + indicates a p-value of <0.05 as calculated by BfR using the Armitage linear trend test in proportions; 4 – p=0.066; 5 – studies evaluated in IARC review

Historical Control Data used: collected 1987-96, 51 control groups from Crl:CD-1 mice from7 different research laboratories using mice from 3 different Charles River Laboratories production sites with sacrifice at ages 18-24 months

Renal Adenoma: 41 studies no tumors, 3 studies 1 tumor, 2 studies 2 tumors
Renal Carcinoma: 42 studies no tumors, 4 studies 1 tumor

EFSA compared to IARC

- Agreed with the IARC on *limited evidence* in humans
  - dismissed the association as "insufficiently consistent" with no justification.
- Dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies
  - Inappropriate historical control dataset used in an incorrect manner and ignoring established guidelines cited in their report
  - Trend test not convincing, Doses too high
- Down-weighted laboratory and human evidence of genotoxicity.
- Confirmed glyphosate induces oxidative stress
  - Not relevant for cancer because no other indications

CLP Guidance on Carcinogenicity

- Category 1: Known or presumed human carcinogens
  - Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence
  - Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence

Guidance on the Application of the CLP Criteria, ECHA (2015)

CLP Guidance on Carcinogenicity
(continued)

- The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:
  - human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
  - animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).
- In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing **limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals**

Guidance on the Application of the CLP Criteria, ECHA (2015)

Hide and Seek

Glyphosate Cancer Risks and the European Pesticide Regulatory Process

Christopher J. Portier, Ph.D.

11 May, 2017

Maastricht University

IARC Working Group Classifies Glyphosate as "Probably Carcinogenic to Humans"

NATURE | NEWS: EXPLAINER

Widely used herbicide linked to cancer

As the World Health Organization's research arm declares glyphosate a probable carcinogen, *Nature* looks at the evidence.

Roundup weedkiller 'probably' causes cancer, says WHO study

The Monsanto product – the world's most widely used herbicide – contains glyphosate, which may also be carcinogenic for non-Hodgkin's lymphoma

A Top Weedkiller Could Cause Cancer. Should We Be Scared?

ROUNDUP AND RISK ASSESSMENT

By Michael Specter April 10, 2015

A farmer sprays glyphosate across his cornfield.

Participants

Consolato Maria Sergi

Department of Laboratory Medicine and Pathology
University of Alberta
Edmonton, Alberta
Canada

Andrea 't Mannetje

Centre for Public Health Research
Massey University, Wellington Campus
Wellington
New Zealand

Lauren Zeise

Reproductive and Cancer Hazard Assessment
California Environmental Protection Agency
Oakland, CA
USA

Invited Specialist

Christopher J. Portier [retired] [3]

National Center for Environmental Health and Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention
Atlanta, GA
USA

Representatives

Amira Ben Amara [unable to attend] [4]

Agence Nationale de Contrôle Sanitaire et Environnementale des Produits (ANCSEP)
Montplaisir, Tunis
Tunisia

Catherine Eiden [unable to attend] [5]

Office of Pesticide Programs
United States Environmental Protection Agency
Washington, DC
USA

Marie-Estelle Gouze [6]

French Agency for Food, Environment and Occupational Health Safety (ANSES)
Maisons-Alfort
France

Jesudoss Rowland [7]

Office of Pesticide Programs
United States Environmental Protection Agency
Washington, DC
USA

[3] Christopher J. Portier receives a part-time salary from the Environmental Defense Fund, a United States–based non-profit environmental advocacy group.
[4] Amira Ben Amara attended as a representative of the National Agency of Sanitary and Environmental Control of Products, Tunisia.
[5] Catherine Eiden attended as a representative of the United States Environmental Protection Agency.
[6] Marie-Estelle Gouze attended as a representative of ANSES, France.
[7] Jesudoss Rowland attended as a representative of the United States Environmental Protection Agency.

Glyphosate - Background

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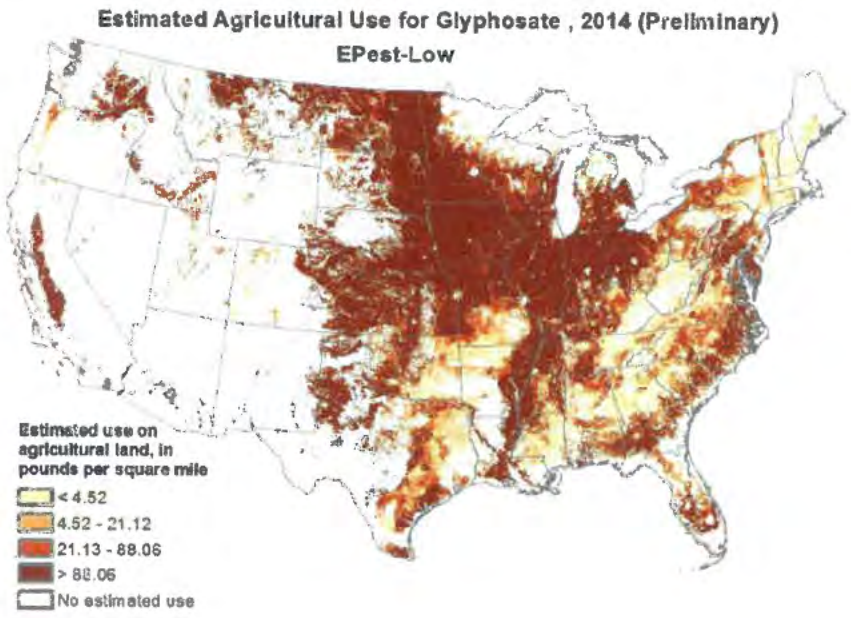
- Hundreds of trade names
- Approximately 91 producers in 20 countries

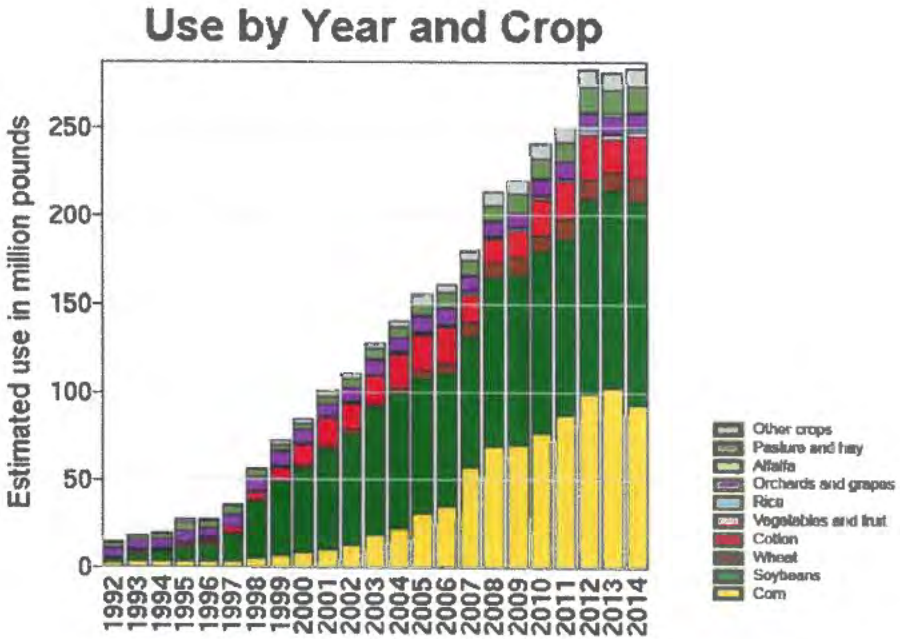
Glyphosate - Background

- Believed to be the most heavily used herbicide in the world
  - 2012 production volume > 700 million kg (approximately 3 times the adult human biomass population of The Netherlands[1])
- Production has increased sharply in recent years
  - Genetically modified glyphosate-resistant crop varieties
- Exposure pathways
  - Air (during spraying)
  - Water
  - Food

[1] "*The weight of nations: an estimation of adult human biomass*", Walpole et al., 2012, BMC Public Health, 12:439

US use of Glyphosate





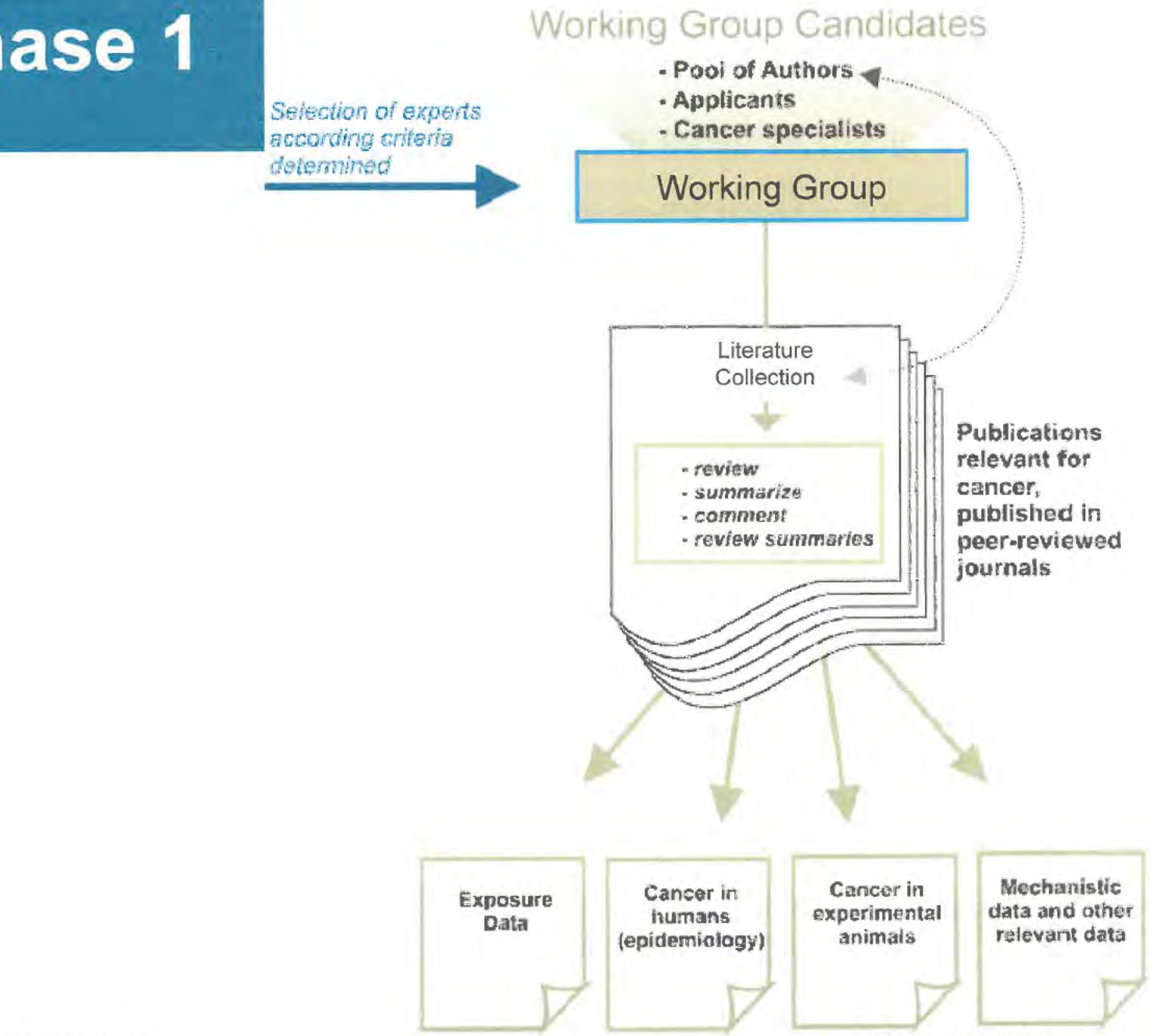
IARC Working Group Findings

- Consistent positive association for NHL but bias and confounding possible
- Renal tumors (1 study) and hemangiosarcomas (1 study) in mice (2 studies evaluated)
- Pancreas islet-cell tumors (2 studies), liver adenomas (1 study), Thyroid C-cell adenomas (1 study) in rats (5 studies evaluated)
- Genotoxicity and oxidative stress

Regulatory Authorities

- EFSA – November, 2015
  - Unlikely to pose a carcinogenic hazard to humans
- WHO/JMPR – March, 2016
  - Unlikely to pose a carcinogenic risk to humans from exposure through the diet
- ECHA – March, 2017
  - no hazard classification for carcinogenicity is warranted
- USEPA – September, 2016 (draft)
  - Not likely to be carcinogenic to humans at doses relevant to human health risk assessment
- Australia Pesticides and Veterinary Medicines Authority – 2015
  - the use of glyphosate in Australia does not pose a cancer risk to humans

IARC Phase 1

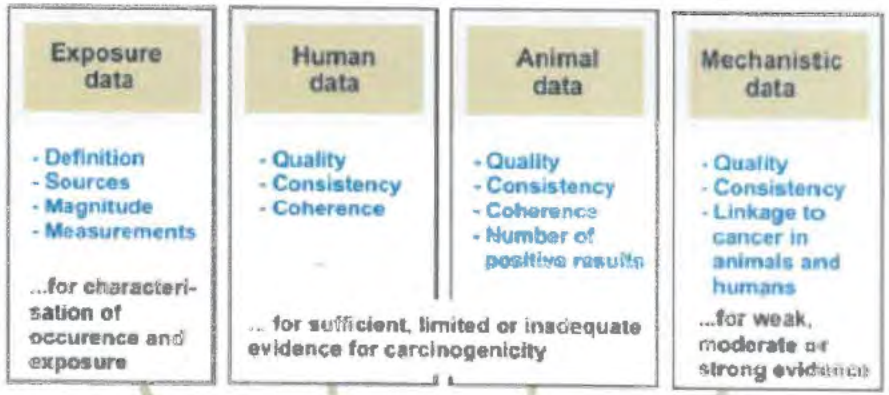


IARC Phase 2

Guidance on evaluating carcinogenicity

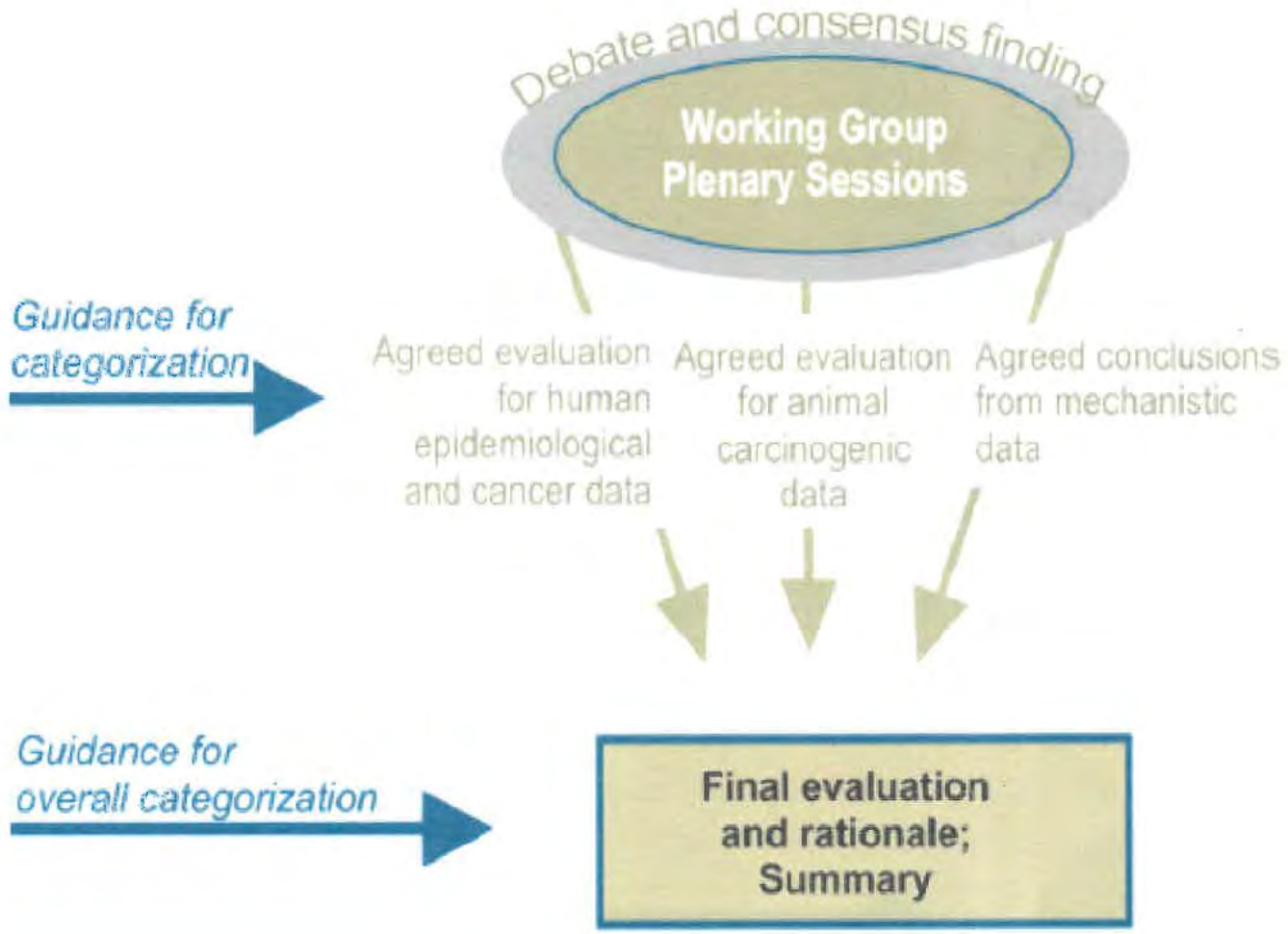
Work in Subgroups evaluating:

Evaluation Criteria



Wording and suggested evaluation | Wording and suggested evalutation | Wording and suggested mechanisms

IARC Final Phase



IS GLYPHOSATE PROBABLY CARCINOGENIC? PROBABLY NOT!

September 8, 2015 by James Gurney · in Blog Post, GMOs

THE LEAGUE OF NERDS

IARC S Ruling On Glyphosate Ignores The Science

The Risk-Monger

Monsanto Disagrees with IARC Classification for Glyphosate

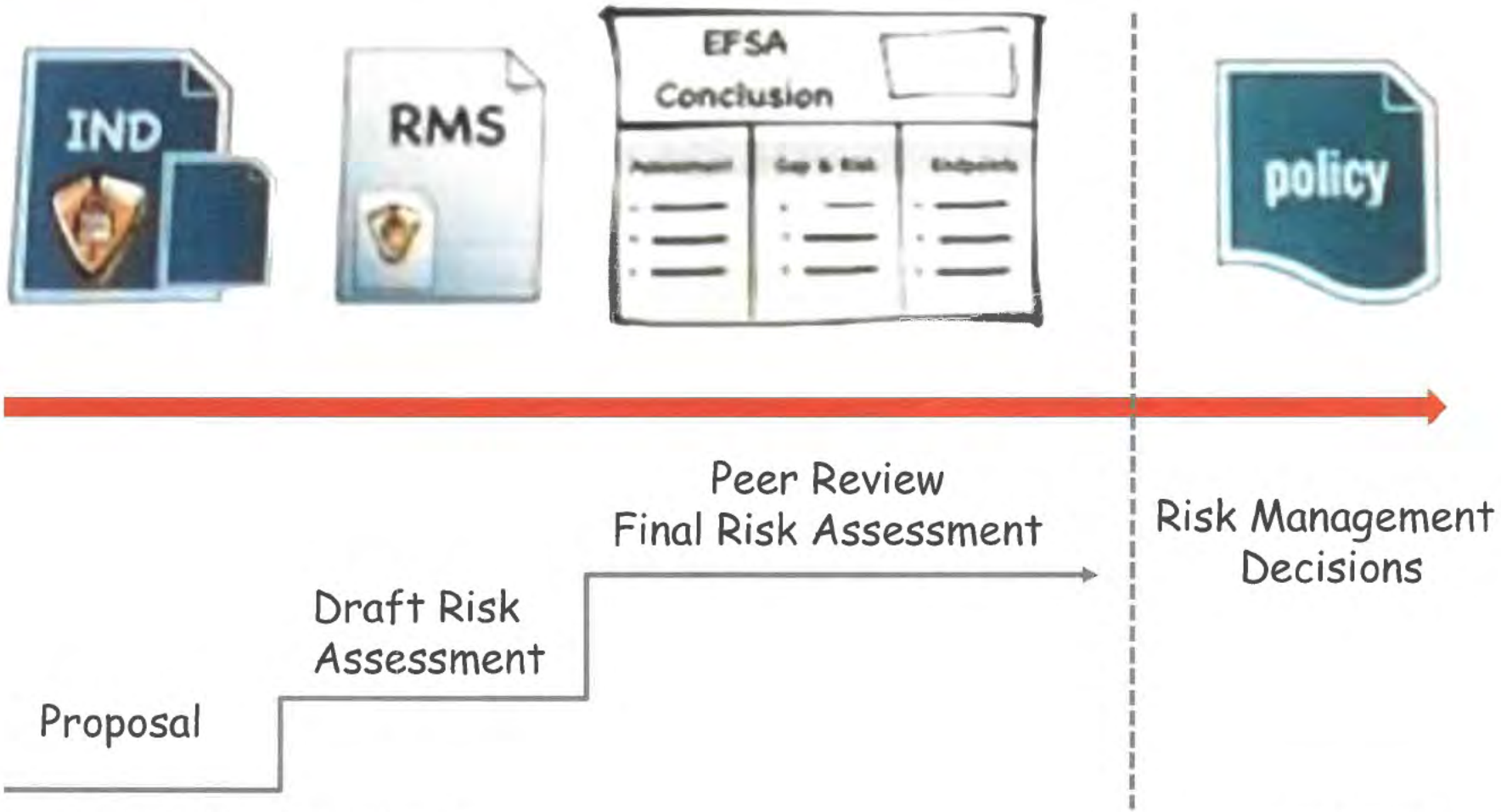
WHAT THE IARC 2A RATING FOR GLYPHOSATE REALLY MEANS

Reuters attacks IARC over glyphosate cancer link

Claire Robinson reports on a hit piece titled "Who says bacon is bad?", which quotes industry-linked sources to smear the cancer agency that judged glyphosate a probable carcinogen

PORTIER_0000367

Pesticide Peer Review in the EU



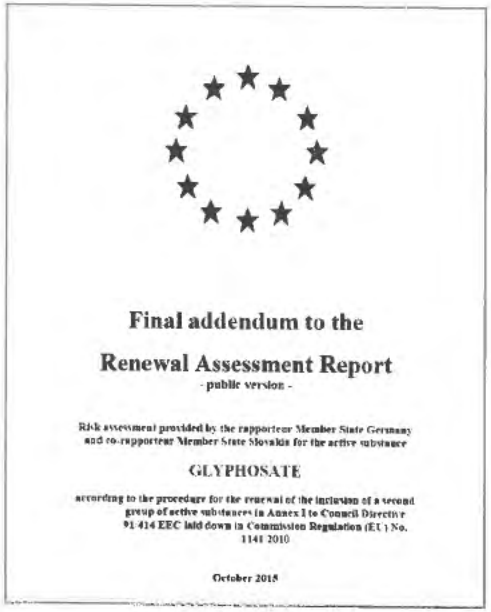
Modified from slide by J. Tarazona

Documents from EFSA Peer Review

Scientific Peer-Reviewed Literature

Industry Proprietary Research Reports

RMS → Comments → EFSA



Final addendum to the

Renewal Assessment Report

- public version -

Risk assessment provided by the rapporteur Member State Germany and co-rapporteur Member State Slovakia for the active substance

GLYPHOSATE

according to the procedure for the renewal of the inclusion of a second group of active substances in Annex I to Council Directive 91-414 EEC laid down in Commission Regulation (EU) No. 1141 2010

October 2015

European Food Safety Authority

efsa

European Food Safety Authority

Peer Review Report on Glyphosate

- Comments on the assessment report and addendum 1
- Reporting tables and commenting table on addendum 1
- Pesticides peer review meeting reports
- Evaluation tables
- Comments on the additional information assessment
- Comments on the draft EFSA conclusion and updated EFSA conclusion

efsa

CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate

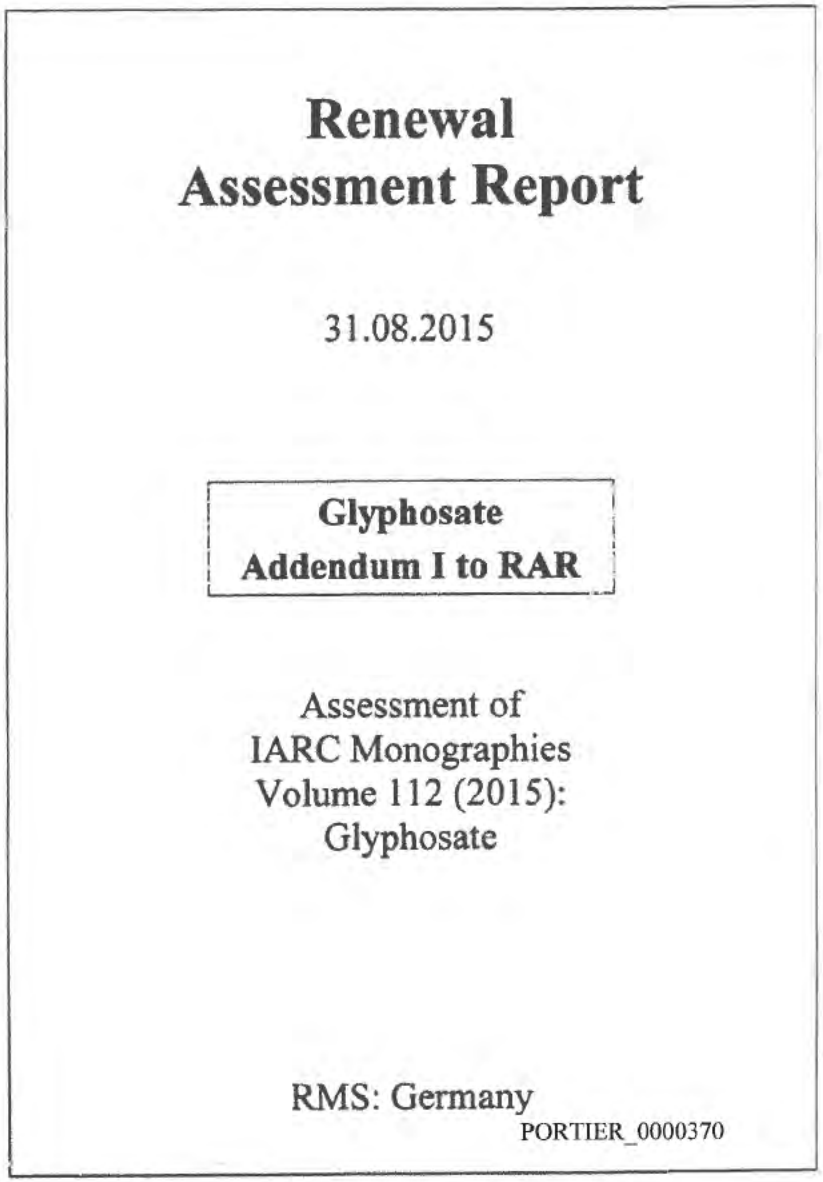
European Food Safety Authority (EFSA)

ABSTRACT

Modified from slide by J. Tarazona

Bundesinstitut für Risikobewertung (BfR)

- Responsible Member State (RMS)
- No consistent positive association in human data
- No indication of cancer risk in 7 rat and 5 mouse studies
- No mechanistic data to support finding
- IARC looked at fewer studies than BfR



Renewal Assessment Report

31.08.2015

Glyphosate
Addendum I to RAR

Assessment of
IARC Monographies
Volume 112 (2015):
Glyphosate

RMS: Germany

PORTIER_0000370

Scientific Response (96 Scientists)

- BfR agreed on limited evidence in humans
  - dismissed the association as insufficiently consistent with no justification.
- BfR dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcomas in 2 mouse studies and malignant lymphomas in 2 mouse studies
  - inappropriate historical control dataset used in an incorrect manner and ignoring the OECD guidelines
  - BfR incorrectly discarded all of the glyphosate-induced carcinogenic findings in animals as chance occurrences.
- BfR ignored important laboratory and human evidence of genotoxicity
- BfR confirmed that glyphosate induces oxidative stress
  - dismissed this finding for lack of any other finding to support cancer causation because they had dismissed all of the other evidence


Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA)

PORTIER_0000371

Response

EU scientists in row over safety of Glyphosate weedkiller

Dispute over possible carcinogenic effects of the widely used w
ahead of an EU decision on its continued use

SPECIAL REPORTS | Mon Apr 18, 2016 | 4:42pm EDT

Is your weed killer carcinogenic?

EFSA accuses world-class cancer experts of engaging in 'Facebook science'

Blogpost by **franziska achterberg** - December 8, 2015 at 14:06

Scientists take sides: Who's right about glyphosate?

The head of the EU's food safety body rips critics for 'Facebook science'

Posted Apr. 18th, 2016 *by* Kate Kelland

Questions you might ask

- Who wrote the original draft report?
  - European Glyphosate Task Force
    - a consortium of companies joining resources and efforts in order to renew the European glyphosate registration with a joint submission
    - ADAMA Agan Ltd., Agria S.A., Agro Trade GmbH, Albaugh UK Limited, Arysta Lifesciences SAS, Barclay Chemicals (Manufacturing) Ltd., Brokden SL, BROS Spółka z ograniczoną odpowiedzialnością spółka komandytowa, Cheminova A/S, Coromandel International Ltd, EXCEL CROP CARE(Europe) NV, Helm AG, Industrias Afrasa S.A., **Monsanto Europe S.A./N.V.,** Nufarm GmbH & Co KG, Rotam Agrochemical Europe Limited, Sapec Agro S.A., Sinon Corporation, Société Financière de Pontarlier, Syngenta Limited, United Phosphorus Ltd, Wynca UK Limited

Table B.2.9-6: Proposed risk mitigation measures for the achievement of an acceptable risk for non-target plants in off-field areas

~~Intended uses~~	~~Application rate (g a.s./ha)~~	~~Buffer strip (m) without drift reduction~~	~~Buffer strip (m) with x % drift reduction~~
~~Orchard crops, vine including citrus & tree nuts*~~	~~1 x 2880~~	~~10 m~~	~~1m 90%~~
	~~1 x 2160~~	~~10 m~~	~~1m 90%~~
	~~3 x 1440~~	~~10 m~~	~~1m 90%~~
~~All crops (all seeded and transplanted crops)~~	~~2 × 2160~~	~~trigger not reached~~	~~5m 75%~~
	~~2 × 1440~~	~~trigger not reached~~	~~5m 75%~~
	~~1 × 1440~~	~~10m~~	~~1m 90%~~
	~~1 × 1080~~	~~10m~~	~~1m 90%~~
~~Cereals, Oilseeds (pre-harvest) **~~	~~1 x 2160~~	~~trigger not reached~~	~~5m 90%~~
	~~1 × 1440~~	~~trigger not reached~~	~~5m 75%~~
	~~1 × 1080~~	~~trigger not reached~~	~~5m 75%~~
	~~1x 720 g~~	~~10 m~~	~~1m 90%~~
Intended uses	**Application rate (g a.s./ha)**	**Buffer strip (m) without drift reduction**	**Buffer strip (m) with x % drift reduction**
Orchard crops, vine including citrus & tree nuts*	1 x 2880	10 m	1 m-90%
	1 x 2160	10 m	1 m-90%
	3 x 1440	10 m	1 m-90%
All crops (all seeded and transplanted crops)	2 × 2160	trigger not reached	5m-75%
	2 × 1440	trigger not reached	5m-75%
	1 × 1440	10m	1 m-90%
	1 × 1080	10m	1 m-90%
Cereals, Oilseeds (pre-harvest) **	1 x 2160	trigger not reached	5m-75%
	1 × 1440	10m	1 m-90%
	1 × 1080	10m	1 m-90%
	1x 720 g	5m	1 m-75%

Sample comments in document

Conclusion by the Notifiers

Based on the study results the NOAEL in rats after chronic exposure to glyphosate acid for 24 month is 6000 ppm (corresponding to 361 mg/kg bw/day in males and 437 mg/kg bw/day in females). It is concluded that glyphosate technical is not carcinogenic in rats.

RMS comment:

The study is considered acceptable. We agree with the description of the study and its findings and support the conclusions including the NOAEL. It was surprising that the salivary gland findings reported by Milburn (1996, TOX2000-1998) were not confirmed although the study was run in the same laboratory employing rats of the same strain. No further remarks.

1st study: [redacted] 1981

Reference: IIA 5.5.2 05
Report: [redacted] (1981)
A Lifetime Feeding Study
of Glyphosate (ROUNDUP Technical) in Rats
[redacted]
Data owner: Monsanto
Study Project No.: 77-2062
Date: 1981-09-18
not published. TOX2000-595
Guidelines: Not stated: In general accordance with OECD 453 (1981)
Deviations: None
GLP: no
Acceptability: *See RMS comment*

Dates of experimental work: In-life: 1978-07-12 to 1980-09-04

Materials and methods

Test material:
Identification: Glyphosate acid (Round-up technical material)
Description: Fine White powder
Lot Batch #: XHJ-64
Purity: 98.7 % w/w
Stability of test compound: At least 45 days when stored at -20 °C.
Vehicle and/or positive control: Diet

Species: Rat
Strain: Sprague-Dawley CD
Source: [redacted]
Age: 28 days (on delivery). 41 days at initiation of delivery
Sex: Males and females
Weight at dosing: Males: 155.0 – 156.6 g (mean values); females: 136.0 – 138.4 g (mean values)
Acclimation period: 12 days.
Diet Food: Standard laboratory diet (Purina Lab Chow) *ad libitum*. Freshly prepared weekly
Water: Mains automated water system (Elizabethtown Water Company). *ad libitum*
Housing: Individually in elevated stainless steel cages.
Environmental conditions: Temperature: Monitored but values are not stated
Humidity: not stated
Air changes: not stated
12 hours light/dark cycle

In life dates: 12-07-1978 to 04-09-1980

Epidemiology Studies in RAR

2.2 Case–control studies on non-Hodgkin lymphoma, multiple myeloma, and leukaemia

16 studies have been reported in section 2.2 of the IARC monograph and are summarized including comments of the RMS in Table 2.2-1.

Two of these 16 studies did not mention glyphosate ([redacted] 2001, ASB2015-8037 and [redacted] 1990, ASB2013-11501).

Five studies reported no increased risk of non-Hodgkin lymphoma and/or leukaemia or multiple myeloma. ([redacted] 1990, TOX2003-999; [redacted] 1992, ASB2015-7885; [redacted] 2012, ASB2012-11865; [redacted] 2004a, ASB2015-8238, and [redacted] 2009, ASB2012-11985).

Some of the reported studies had according to the IARC assessment in agreement with the RMS assessment a limited or even very limited power to assess effects of glyphosate. In three studies only 4 exposed cases have been compared with 2, 3 or 5 control subjects ([redacted] 2013, ASB2014-7523; [redacted] 1999, ASB2012-11838; and [redacted] 1998, TOX1999-687).

Further studies reported different, contradictory results. Depending from the used method of statistical analysis the risk was increased in some cases or not increased in other cases.

The relevant studies on non-Hodgkin lymphoma have been selected by [redacted] (2014, ASB2014-4819) to perform a meta-analysis. For the analysis of an association between glyphosate and non-Hodgkin lymphoma the following studies have been used: [redacted] 2003, ASB2012-11606; [redacted] 2005a, ASB2012-11605; [redacted] 2008, ASB2012-11614; [redacted] 2002, ASB2012-11839; [redacted] 2001, ASB2011-364, and [redacted] 2009, ASB2012-11985.

Furthermore, for the analysis of an association between glyphosate and B cell lymphoma 2 studies have been used: [redacted] 2008, ASB2012-11614 and [redacted] 2013, ASB2014-7523.

2 of the 6 studies used for the analysis of non-Hodgkin lymphoma reported no increased risk of non-Hodgkin lymphoma ([redacted] 2005a, ASB2012-11605 and [redacted] 2009, ASB2012-11985).

3 of the above cited 7 studies were considered by IARC to have limited or even very limited power ([redacted] 2002, ASB2012-11839 and [redacted] 2013, ASB2014-7523) or a low participation rate ([redacted] 2001, ASB2011-364).

Finally, IARC referred in a publication in Lancet ([redacted] 2015, ASB2015-7076) to 3 studies ([redacted] 2003, ASB2012-11606; [redacted] 2001, ASB2011-364, and [redacted] 2008, ASB2012-11614) in context with the conclusion that there was limited evidence in humans for carcinogenicity of glyphosate. These 3 studies are discussed by RMS in Table 2.2-2.

Questions you might ask
(continued)

- Who reviewed the report at BfR?
  - Unknown
- Who reviewed the study for EFSA?
  - Partially known
  - COI unavailable on most reviewers

Glyphosate Back in the News – Regulation, Revolving Doors, Pesticides & Politics

Posted on 19 March, 2017 by Oliver Moore in Main stories // 1 Comment

By Oliver Moore

The chair of the ECHA committee, Tim Bowmer, worked for two consultancies in the chemical sector for 20 years, including as business development manager and senior account manager. His contract with the organisations ended the day before he started his employment as chair of ECHA's Risk Assessment Committee.

US Congressman Calls for DOJ Investigation into EPA-Monsanto Glyphosate Collusion

Posted on Mar 17 2017 - 3:20pm *by* Sustainable Pulse

« PREVIOUS | NEXT »

Categorized as
Breaking News
News
Sustainable

U.S. Congressman Ted Lieu issued a strongly worded statement this week regarding reports that unsealed court documents raise new
Monsanto weed killer Roundup and its chief ingred

UN/WHO panel in conflict of interest row over glyphosate cancer risk

Chairman of UN's joint meeting on pesticide residues co-runs scientific institute which received donation from Monsanto, which uses glyphosate

EPA Official Accused of Helping Monsanto 'Kill' Cancer Study

Joel Rosenblatt, Lydia Mulvany & Peter Waldman

March 14, 2017, 7:18 PM GMT+1 *Updated on* March 15, 2017, 1:44 AM GMT+1

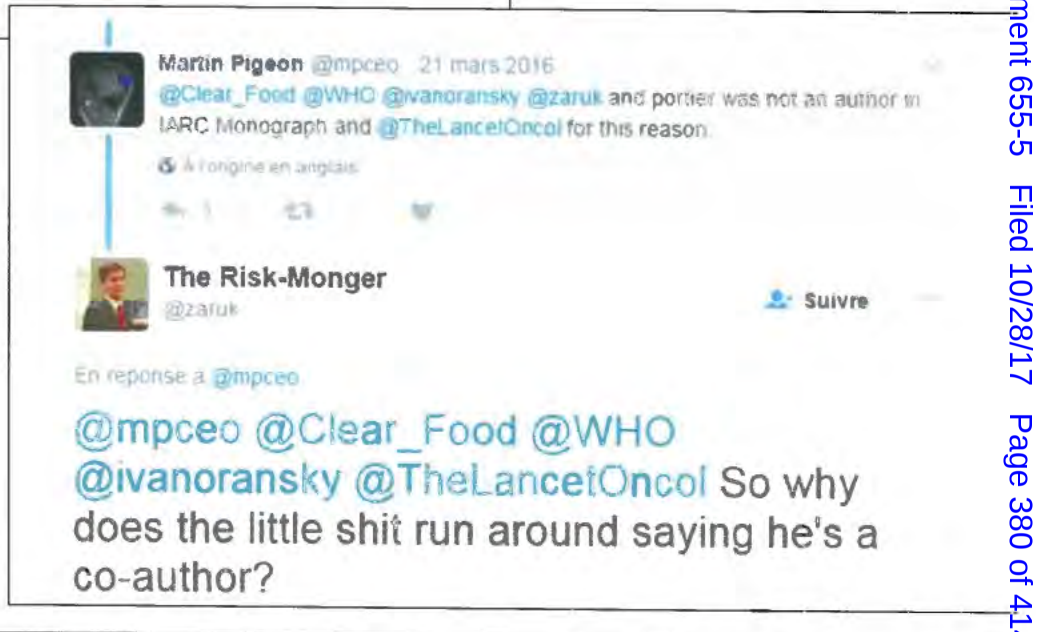
One activist scientist, Christopher Portier, squirreled his way onto an IARC Advisory Committee in 2014, which he then chaired and recommended an IARC study on glyphosate, and t
the technical adviser to that IARC Working Group
WG did what all IARC groups save one have done:
glyphosate was probably carcinogenic. All of this with IARC trying to hide that Portier was acting on behalf of the Washington-based anti-industry NGO – the Environmental Defense Fund.

LAWSUITS

Did Monsanto Hire Online Trolls to Attack Critics?

By Chris Crowley

EDF Official Position: "*Christopher Portier is a part time Senior Contributing Scientist with EDF. He also works on projects unrelated to the issues he works on for EDF. His work with EDF does not extend to glyphosate, and EDF's environmental health work does not focus on herbicides.*"



The Risk-Monger @zaruk · 8 févr.

How the hell did relentless little Chris Portier **worm** his way into ECHA's glyphosate consultation? youtube.com/watch?v=NBapbs... Worse than Waldo!

Questions you might ask

- What do the comments look like?

Experts' consultation 2.5 MSs to discuss the carcinogenicity of glyphosate. See reporting table public consultation 2(21)	**Background** **RAR:** **Vol. 3, B.6.5, Long term toxicity and carcinogenicity**, pp. 443-548 of the revised RAR **Vol. 1, 2.6.6 Summary of long term toxicity and carcinogenicity**, pp. 58-61 of the revised RAR – January 2015 Long-term toxicity and carcinogenicity of glyphosate were investigated in a large number of studies in rats and mice that were performed over the course of time on behalf of different notifiers. All studies previously evaluated in the EU were subject to rigorous re-evaluation for purposes of the RAR including an assessment of their quality and reliability according to current standards. For the new evaluation, five chronic or combined chronic toxicity/carcinogenicity studies in rats and three long-term studies in mice were additionally provided. There was no evidence of carcinogenicity of glyphosate in any of the rat studies. Chronic toxicity was confined to high dose levels in all the studies but remarkable differences became apparent in what was actually observed. In mice, the previously known studies did not provide evidence of carcinogenicity up to the high dose levels tested. The most recent 80-Week dietary mouse study conducted by [redacted] (2009, ASB2012-11492) can be considered very comprehensive with regard to histopathology. There were no adverse effects up to the highest dose level of 5000 ppm, that was equivalent to 810 or 1081 mg/kg bw per day in males and females, respectively. The carcinogenicity study in Swiss albino mice by [redacted] (2001, ASB2012-11491) revealed an increase in malignant lymphoma incidence (quite common in ageing mice) at the top dose level of around 1460 mg/kg bw per day. Malignant lymphoma accounted for 54.6 % of all tumours that were detected in all animals in the study by [redacted] (2001, ASB2012-11491). Malignant lymphoma incidence was significantly elevated as compared to the actual control groups in both sexes, was above the mean values of the (relatively small)	The experts (except BE expressing an uncertainty on this issue because of the lack of in-house HCD for the Wood study and exceedance of HCD in the [redacted] study) consider highly unlikely the carcinogenic potential of glyphosate. However, the background incidences of malignant lymphomas should be further elucidated for the Swiss albino mouse strain in a revised RAR. The reference values are considered to be protective with regard to the dose level where the malignant lymphomas occur. Open point: RMS to present the information available on the background incidences for the Swiss albino strain in a revised RAR.

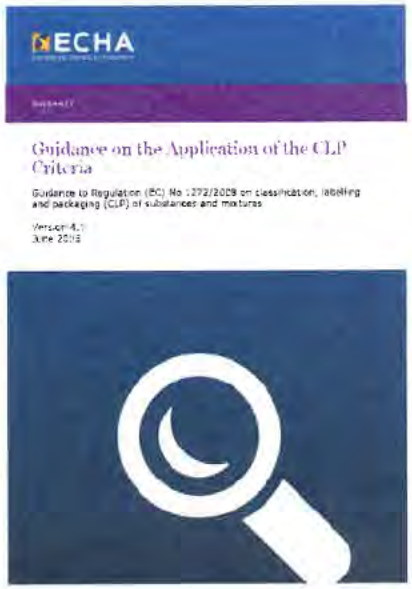
Comments of Norway

1. Cancer in experimental animals

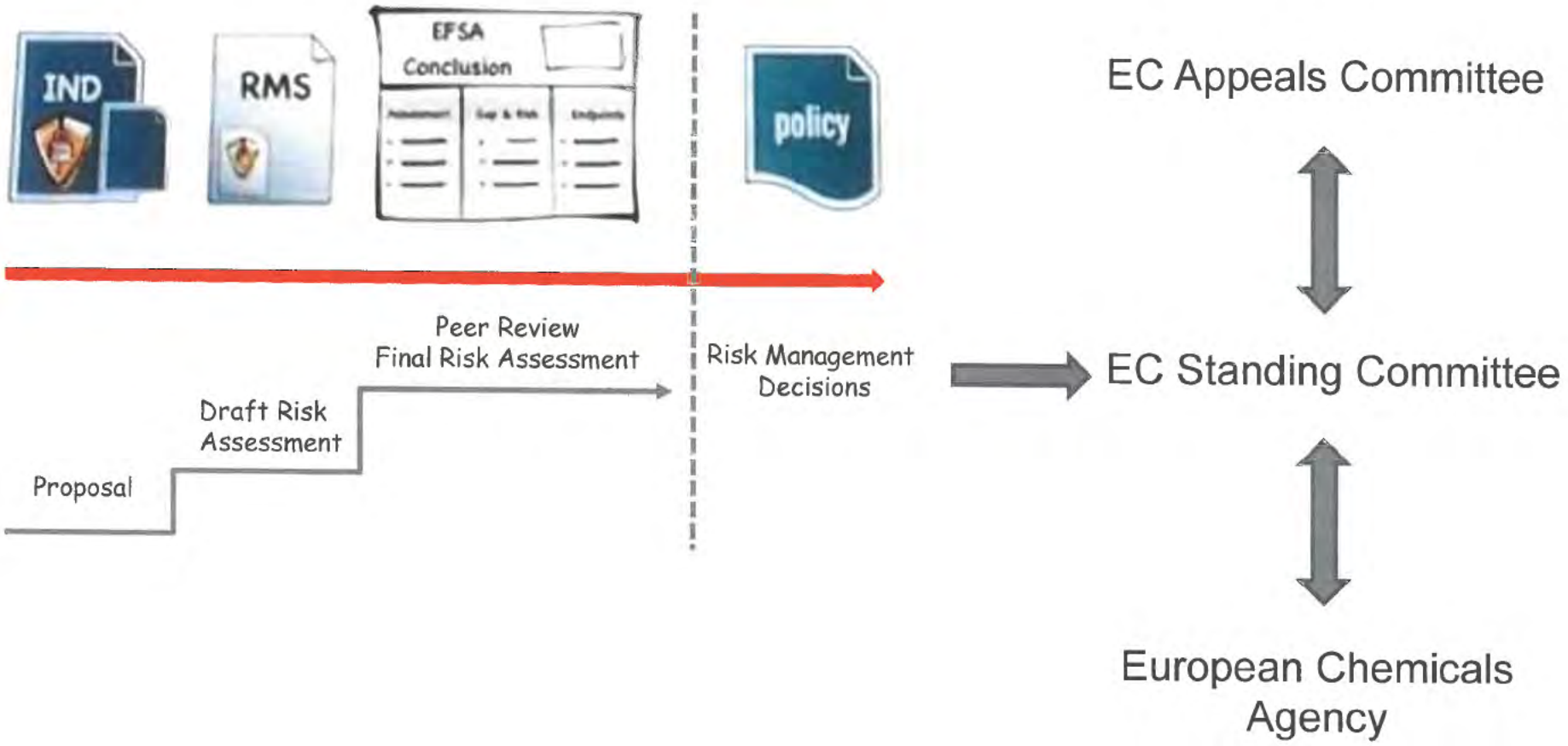
No.	Subject	Discussion Written Procedure	Conclusions Written Procedure
	Addendum 1 to RAR., Cancer in experimental animals, table 3-1	NO: Due to the application of different statistical approaches selected for the evaluation, IARC and RMS came to diverging conclusions. Why does the RMS consider the statistical evaluation provided with the study reports as more appropriate than the trend test used by IARC? According to the OECD guidance document on the conduct and design of chronic toxicity and carcinogenicity studies, significance in either kind of test is sufficient to reject the hypothesis that chance accounts for the result.	
	Addendum 1 to RAR., Cancer in experimental animals, point iii) differences in decision criteria, page 42	NO: It is stated on page 42 in the addendum that *"Since no consistent significant increase in any of the tumour types was originally reported in the available studies, the apparent effects were not considered sufficient for classification in the RAR."* However, we are of the opinion that effects do not necessarily have to appear in a consistent dose-dependent manner, in order to be considered as a treatment-related effect.	
	Addendum 1 to RAR., Cancer in experimental animals, point iii) differences in decision criteria, additional criteria CLP, page 43	NO: As stated in the addendum, the RMS has also taken into account additional criteria when evaluating the carcinogenic effects. To what extent should these additional criteria and the listed factors which may be taken into consideration, determine the conclusion with respect to a potential carcinogenic effect. In our opinion, too much weight is given to the factors "progression of lesions to malignancy" as well as "whether responses are in single or both sexes". This will for instance implicate that studies, in which a treatment-dependent increase in adenomas in male rats is demonstrated, will not be taken into consideration when evaluating the carcinogenic potential.	

Questions you might ask

- Why did the European Chemical Agency review glyphosate after EFSA?
  - EChA holds legal authority to classify products
  - EChA developed and maintains the guidelines used to evaluate data for carcinogenicity
  - Parliament asked for the review



Pesticide Peer Review in the EU



Glyphosate and Atrazine: EPA posts, then retracts, reports on top herbicide chemicals

Published time: 6 May, 2016 19:42

Get short URL

THE BLOG 05/02/2016 09:20 pm ET | Updated May 03, 2017

What Is Going On With Glyphosate? EPA's Odd Handling of Controversial Chemical

By Carey Gillam

EPA Magically Makes Glyphosate Safety Report Disappear

© Amr Abdallah Dalsh / Reuters

UNIT

95% CI=1.03–1.65). Given the limitations of the studies used and uncertainty in the analytical methods, the CARC concluded that a different weighting scheme could have resulted in a different meta risk ratio. Thus, while epidemiologic literature to date does not support a direct causal association, the CARC recommends that the literature should continue to be monitored for studies related to glyphosate and risk of NHL.

MEMORANDUM

DATE: **October 1, 2015**

SUBJECT: **GLYPHOSATE:** Report of the Cancer Assessment Review Committee

Overall, the CARC concluded that there was no evidence of carcinogenicity in the eleven carcinogenicity studies conducted in Sprague Dawley or Wistar rats and CD-1 mice. There were no treatment-related increases in the occurrence of any tumor type in either sex of either species.

FROM: Jess Rowland,
Deputy Division Director
Chair, Cancer Assessment Review Committee
And
Karlyn Middleton, Co-Chair
Cancer Assessment Review Committee
Health Effects Division (7509P)

TO: Charles Smith, Chief,
Risk Assessment Branch I

Kirkland (2013) were not considered by IARC. The CARC, based on a weight-of-evidence of the *in vitro* and *in vivo* studies, concluded that there is no concern for genotoxicity or mutagenicity. Glyphosate was no mutagenic in bacterial reversion (Ames) assays or *in vitro* mammalian gene mutation assays. There is no convincing evidence that glyphosate induces micronuclei formation or chromosomal aberrations *in vitro* or *in vivo*.

O
E
Glyphosate in accordance with the *EPA's Final Guidelines for Carcinogen Risk Assessment* (March, 2005). Attached please find the final Cancer Assessment Document.

Questions you might ask (continued)

and organ/brain weight ratios faile
e administration of Glyphosate.

CONTAINS TRADE SECRET OR CTHERWISE CONFIDENTIAL INFORMATION OF MONSANTO COMPANY

- Can I see the studies?
  - All epidemiology and journal-published peer-reviewed studies are accessible
  - Industry supported studies only available through petition to EFSA
    - Considered proprietary material
    - You can only have the data tables, NO MATERIALS, NO METHODS, NO ANALYSIS, NO DISUCSSION, NO CONCLUSIONS
    - You cannot share the material, but you can cite it
    - Required the threat of a lawsuit by the Green Party in the European Parliament

CLP Guidance on Carcinogenicity

- Category 1: Known or presumed human carcinogens
  - Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence
  - Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence

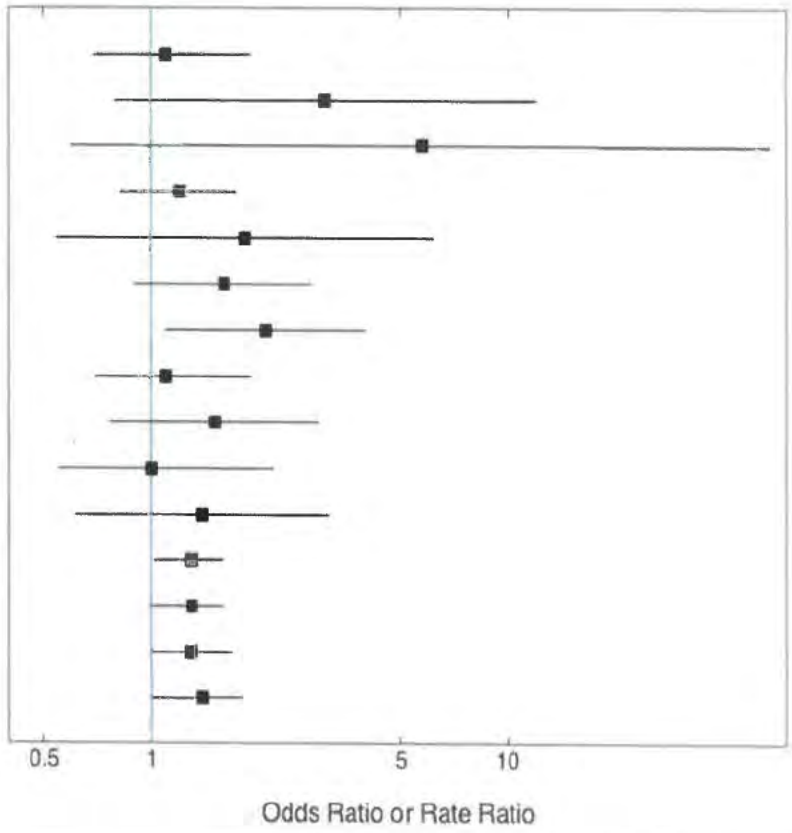
Guidance on the Application of the CLP Criteria, ECHA (2015)

CLP Guidance on Carcinogenicity
(continued)

- The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:
  - human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
  - animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).
- In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing **limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals**

Epidemiology Data – Non-Hodgkin Lymphoma

Study	RR	Lower	Upper	Weight (Model 1)
Cantor et al. (1992)	1.10	0.70	1.90	0.0
Nordstrom et al. (1998)	3.10	0.80	12.00	0.0
Hardell and Eriksson (1999)	5.80	0.60	54.00	0.0
McDuffie et al. (2001)	1.20	0.83	1.74	38.1
Hardell et al. (2002)	1.85	0.55	6.20	3.6
De Roos et al. (2003)	1.60	0.90	2.80	16.2
logistic regression	2.10	1.10	4.00	0.0
De Roos et al. (2005)	1.10	0.70	1.90	21.0
Eriksson et al., (2008)	1.51	0.77	2.94	11.6
Orsi et al. (2009)	1.00	0.55	2.20	3.6
Hohenadel et al. (2011)	1.40	0.62	3.15	0.0
Meta-Analysis: Model 1	1.30	1.03	1.60	
Meta-Analysis: Model 2	1.30	1.00	1.60	
Meta-Analysis: Model 3	1.30	1.00	1.70	
Meta-Analysis: Model 4	1.40	1.00	1.80	



Limited Evidence of Carcinogenicity

- ECHA: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.
- IARC: a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Human Data Conclusions

EFSA – very limited?

> From the wealth of epidemiological studies, the majority of experts concluded that there is very limited evidence for an association between glyphosate-based formulations and non-Hodgkin lymphoma, overall inconclusive for a causal or clear associative relationship between glyphosate and cancer in human studies. Minority views nevertheless were expressed that there was either inadequate or limited evidence of an association. No evidence of carcinogenicity was confirmed by the large

IARC Working Group – limited evidence

> There is *limited evidence* in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin lymphoma.

Major Tumors in CD-1 Mice

Summary of significance tests for 5 tumors from 4 studies in CD-1 Mice

Study	Months on Study	Neoplasm				
		Hemangio-sarcoma (male)	Hemangi-sarcoma (female)	Malignant Lymphoma (male)	Kidney Tumor (male)	Lung Adeno-carcinoma (male)
Sugimoto 1997	18	+/+++[1]	+++/+++	++/++	+/+++	-/-
Wood 2009	18	-/-	-/-	+++/+++	-/-	++/++
Sugimoto & Wood Pooled		++/+++	+++/+++	+++/+++	++/+++	-/-
Atkinson 1993	24	+++/+++	-/-	+/+	-/-	-/-
Knezevich 1983	24	-/-	NA	-/-	+/++	-/-
Atkinson & Knezevich Pooled		-/-	NA	-/-	++/+	-/-
All CD-1 Studies Pooled		++/++	+++/+++	+/+	+++/+++	-/-

[1]entries are p_{Trend}/p_{Hist} with values: – p>0.1, + 0.1≥p>0.05, ++ 0.05≥p>0.01, +++ p≤0.01

Major Tumors in Rats

Table 8: Summary of significance tests for 5 tumors from 7 studies in Rats

Study	Strain	Neoplasm						
		Liver Adenomas (males)	Mammary Gland Tumors (females)	Thyroid C-Cell Tumors (females)	Thyroid C-Cell Tumors (males)	Thyroid Follicular Cell Tumors (males)	Testis Interstitial Cell Tumors (male)	Kidney Adenomas (males)
Brammer (2001)	Wistar	+++[1]	-					
Wood (2009)		-	+++					
Suresh (1996)		-	-					
Pooled Wistar Rats		++	++					
Lankas (1981)	Sprague Dawley	-		+	-	-	++	-
Enemoto (1997)		-		-	-	-	-	+++
Atkinson et al. (1993)		-		+	-	++	-	-
Stout and Ruecker (1990)		++		-	+	-	-	-
Pooled Sprague-Dawley Rats		++		-	++	-	-	++

[1]entries are p_{Trend}/p_{Hist} with values: – p>0.1, + 0.1≥p>0.05, ++ 0.05≥p>0.01, +++ p≤0.01

Summary

- 18 statistically significant trend tests
  - 11 with $p<0.01$
- 9 positive findings in 4 studies in CD-1 mice
  - 3 tumors seen in more than 1 study
  - 6 tumors with $p<0.01$
- Formal use of historical controls
  - Did not reverse any positive findings against concurrent controls
  - Moved two marginal findings in rare tumors to statistically significant

Sufficient Evidence in Animals

- ECHA
  - a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) two or more independent studies in one species carried out at different times or in different laboratories or under different protocols. An increased incidence of tumours in both sexes of a single species in a well-conducted study, ideally conducted under Good Laboratory Practices, can also provide sufficient evidence. A single study in one species and sex might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites
- IARC – exactly the same

Limited Evidence in Animals

- ECHA
  - the data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies; (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential; or (d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.
- IARC – exactly the same

Conclusions

EFSA

or limited evidence of an association. No evidence of carcinogenicity was confirmed by the large majority of the experts (with the exception of one minority view) in either rats or mice due to a lack of statistical significance in pair-wise comparison tests, lack of consistency in multiple animal studies and slightly increased incidences only at dose levels at or above the limit dose/MTD, lack of pre-neoplastic lesions and/or being within historical control range. The statistical significance found in trend analysis (but not in pair-wise comparison) *per se* was balanced against the former considerations. During the teleconference 117, the experts also agreed to the conclusion of the RMS.

IARC Working Group

There is *sufficient evidence* in experimental animals for the carcinogenicity of glyphosate.

So, what is EFSA's criteria for a causal finding in animals?

- Both the trend test and the pair-wise tests significant
- All studies showing the same thing
- Positive results at doses below 1000 mg/kg/day
- Clear dose-response for pre-malignant lesions
- The response must be outside of the historical control range

Is this reasonable?

Use of Historical Controls

- IARC Recommendations
  - Use a formal statistical method
  - *"Generally not appropriate to discount a tumor response that is statistically significantly increased in comparison to concurrent controls by arguing it falls within the range of concurrent controls"*
  - Can be used for rare tumors

Using Historical Control Range

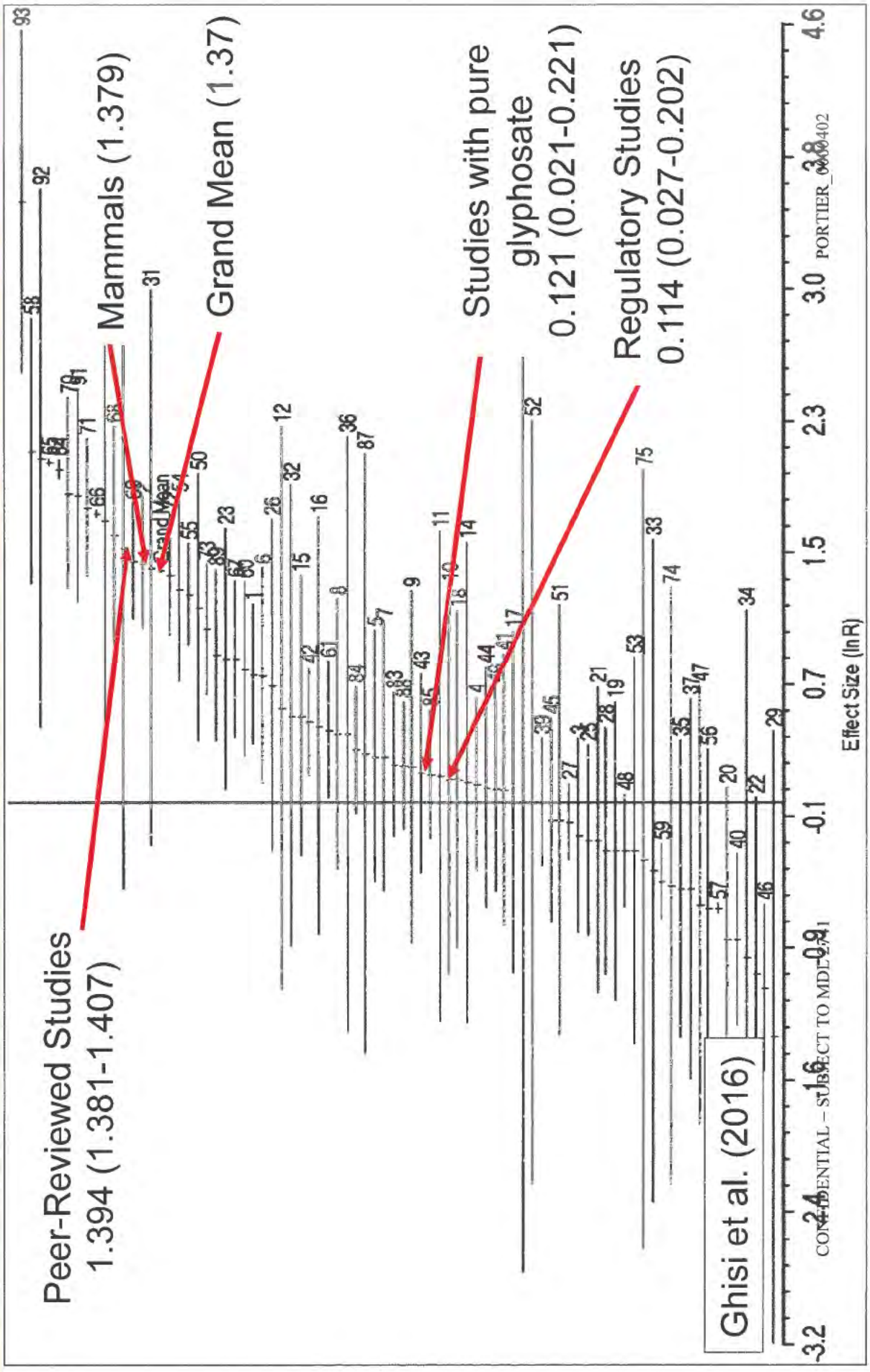
- Not a formal statistical test
- Range increases with number of historical control groups
- Animals in a cancer study are randomized to groups
  - Anything that would serve to alter concurrent control response also applies to treated groups

Summary of in vivo and in vitro genetox studies of glyphosate and glyphosate formulations in mammals[1]

In vivo or in vitro	Species	Cell type or tissue	Glyphosate[2]		Glyphosate Formulations	
			Number Positive	Number Negative	Number Positive	Number Negative
In vivo	Humans	Peripheral blood			2	1
in vitro	Humans	lymphocytes	5	2(1)	2	
		Hep 2	1			
		GM 38 HT1080	1			
		GM 5757	1			
		TR146	1		1	
In vivo	Swiss CD-1 Mouse	Liver/Kidney	1	1	2	
In vivo (micro-nucleus assay)	NMRI mouse	Erythrocytes		4(3)		2(1)
	Swiss CD-1 mouse		1		2	
	Balb C mouse		1			
	$B6C3F_1$ mouse			1		
	Swiss mouse		1(1)			3(2)
	CD-1 mouse		2(2)	1(1)	2 (2)	6 (6)
	Swiss albino mouse		1(1)	3(3)	1	
	C57BL mouse					1
	Mouse (not specified)				1	
	Rats (all)			2(1)		1(1)
In vitro	Mouse	L5178 lymphoma		2(2)		
	Chinese hamster	Lung		3(3)		
	Chinese hamster	ovary	1	1		
	Fischer rat	liver		1		
	Rat	Lymphocytes		1(1)		
	Bovine	Lymphocytes	1		2	

[1]each entry in the table corresponds to a single study where a study is positive if at least one valid positive finding emerged from the study $p<0.05$; entries in the table are only for studies where data was available to review including data from EFSA[88] and Kier and Kirkland (2000)[74]; [2]numbers are the total number of studies in this category, numbers in parentheses are the subset of studies that are regulatory studies

Forest Plot of Micronucleus Frequency



Green MEP: EFSA should release full glyphosate studies

By Nicole Sagener | EURACTIV.de | translated by Sam Morgan

May 2, 2017

Adverti

Is seeing the studies important?

Tumors with significant ($p<0.05$) trends in the carcinogenicity studies not cited in the EFSA and EChA Risk Assessments

Study (Species)	Tumor type Sex; Incidences	p-value (one-sided)	Test method
Sugimoto, 1997 (Mouse)	Total number of animals with malignant neoplasms	< 0.01	Pair-wise, Fisher's Exact Test (high dose)
	Males; 5/50, 5/50, 11/50, 16/50	0.004	Trend test
Wood et al., 2009 (Mouse)	Lung adenocarcinomas		
	Males; 5/51, 5/51, 7/51, 11/51	0.038	Trend test
Atkinson et al., 1993 (Rat)	Thyroid follicular cell adenomas and carcinomas	0.036	Trend test
	Males; 0/50, 0/21, 0/17, 2/21, 2/49		
Suresh, 1996 (Rat)	Thyroid c-cell Carcinomas		
	Females; 1/47, 0/49, 2/50, 6/47	0.003	Trend test
Enomoto, 1997 (Rat)	Kidney adenoma		
	Males; 0/50, 0/50, 0/50, 4/50	0.004	Trend test
Brammer, 2001 (Rat)	Hepatocellular Adenoma		
	Males; 0/52, 2/52, 0/52, 5/52	0.009	Trend test
Wood et al., 2009 (Rat)	Skin Keratocanthoma		
	Males; 2/51, 3/51, 0/51, 6/51	0.034	Trend test
Wood et al., 2009 (Rat)	Mammary gland adenocarcinomas		
	Males; 2/51, 3/51, 1/51, 6/51	0.046	Trend test

Current Events

Monsanto Weed Killer Roundup Faces New Doubts on Safety in Unsealed Documents

By DANNY HAKIM MARCH 14, 2017

The court documents included Monsanto's internal emails and email traffic between the company and federal regulators. The records suggested that Monsanto had ghostwritten research that was later attributed to academics and indicated that a senior official at the Environmental Protection Agency had worked to quash a review of Roundup's main ingredient, glyphosate, that was to have been conducted by the United States Department of Health and Human Services.

Go after the Funding

NIH needs public examination after giving millions to rogue UN agency

BY BRUCE M. CHASSY, CONTRIBUTOR - 10/24/16 12:32 PM EDT

POLITICS

Exclusive: U.S. lawmakers to investigate funding of WHO cancer agency

ACC begins campaign to change basis of UN cancer agency classifications

Current hazard-based approach 'misinforms policy making', says trade group

26 January 2017 / Toxicology, United States

The American Chemistry Council has launched a campaign aimed at reforming the monographs programme of the International Agency for Research on Cancer (Iarc) – a specialised agency of the World Health Organization.

International Agency for Research on Cancer

World Health Organization

The ACC describes its "campaign for accuracy in public health research" as "an initiative to promote credible, unbiased and transparent science as the basis of public policy decisions."

Take Home Messages

- Transparency is necessary
- Guidelines should be peer-reviewed and applied uniformly
- Proper statistical methods need to be applied and understood
- The format for the final evaluation needs better structure
- Data needs to be submitted electronically so re-analysis is possible
- Don't label me as a "Facebook Scientist" or a "little shit"

C. Portier Consultations

< 2015 >

Organisation not currently on the register; registration as it was on 21 Dec 2015

How to read and use (/how-to#data-cards) this data card.

This representative is currently not registered.

LOBBYING COSTS:

NO FIGURE AVAILABLE

Financial year: -

LOBBYISTS DECLARED:

0.25 FTE (1)

0.25

LOBBYISTS WITH EP ACCREDITATION: **0**

C. Portier Consultations

Registration on EU Transparency Register

346450820048-50 (http://ec.europa.eu/transparencyregister/public/consultation/displaylobby id=346450820048-50) (First registered: 21 Dec 2015)

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LobbyFacts is a joint project of Corporate Europe Observatory (http://www.corporateeurope.org) and LobbyControl (http://www.lobbycontrol.de).

Website development: nestor.coop (http://nestor.coop)

Growing Returns

A coalition of uncommon bedfellows is bringing sustainable agriculture to scale

By Suzy Friedman | Bio | Published: August 31, 2016

Today represents a huge advancement for sustainable agriculture, and a new era of food company collaboration. At the Farm Progress Show in Boone, Iowa, we are officially launching the Midwest Row Crop Collaborative (MRCC): a diverse coalition working to expand on-the-ground solutions to protect air and water quality, enhance soil health, and maintain high yields throughout the Upper Mississippi River Basin.

Founding members of the MRCC include Cargill, Environmental Defense Fund, General Mills, Kellogg Company, Monsanto, PepsiCo, The Nature Conservancy, Walmart, and World Wildlife Fund. The coalition will work directly with growers to help foster continuous improvement and implement conservation activities across three pilot states responsible for 44 percent of corn, soy, and wheat production in the United States: Illinois, Nebraska, and Iowa.

Clear goals and benefits

Along with a council of scientific and agronomic advisors, the MRCC has set the following goals:

- By 2025, 75 percent of row crop acres in the region will be engaged in sustainability measures that will advance Field to Market's Fieldprint Calculator analyses and improve soil health practices.
- By 2025, the region will reduce nutrient loading (primarily nitrogen and phosphorus) by 20 percent as a milestone to meet the Gulf of Mexico Hypoxia Task Force goal of a 45 percent reduction.
- By 2035, these three states will have met the 45 percent nutrient loss reduction goal and the Collaborative will be set up to expand across the Upper Mississippi River Basin.

Additionally, the MRCC will work to ensure that by 2025, 50 percent of all irrigation units used in Nebraska will maximize water conservation to reduce pressure on the Ogallala Aquifer.

Accomplishing these goals will result in clear environmental benefits: improved water quality, reduced eutrophication and greenhouse gas emissions, and restored groundwater in the Ogallala Aquifer, which provides water to about 20 percent of U.S. cattle, corn, cotton and wheat.

But the benefits expand to businesses and farmers, too, by improving yields, protecting against supply chain disruptions, and meeting consumer demand for sustainably grown ingredients.

Field to Market®
The Alliance for Sustainable Agriculture

Partnerships and measurements

Farmer organizations, environmental groups, food companies, state and local watershed organizations, and many others share these common goals – and much work is already underway to meet the MRCC's objectives.

That's why the Collaborative isn't reinventing any wheels. We're ramping up, leveraging and supporting the various technical and regional sustainability efforts already in place. Forging partnerships with farmers, who are at the core of MRCC, is absolutely essential to eliminate redundant efforts across various organizations and collaborators.

Some of the ongoing efforts to support farmers include:

- Collaborating with the National Corn Growers Association's Soil Health Partnership, which is identifying, testing and measuring farm management practices that improve soil health and benefit farmers.
- Establishing a Sustainable Agriculture Resource Center for farmers and trusted advisors that lays out the business advantages of sustainability – a key selling point for ag retailers, crop consultants, and farmers. Field to Market, The Alliance for Sustainable Agriculture, and the Agricultural Retailers Association will facilitate this initiative.
- Partnering with two existing Regional Conservation Partnership Program projects to improve the management of grower data and the metrics used to track environmental outcomes, as well as support conservation practices.

We're also applying the best available science and technologies to ensure that we're accurately measuring our on-the-ground environmental and yield benefits.

More work ahead

The MRCC is groundbreaking, since major companies have never before committed to ag sustainability at such a large scale. But it's also just a beginning. To keep momentum going for the MRCC and to make this effort a real success, we'll need many more partnerships with agribusinesses and trade groups, additional commitments from food companies, and we'll need every sector of the ag supply chain to get involved.

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