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

Job No: 128474

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:
Robyn D. Buck, Esq., Monsanto
Michael Baum, Esq. (By telephone)
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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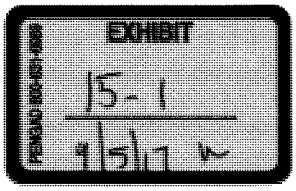
WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

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.

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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

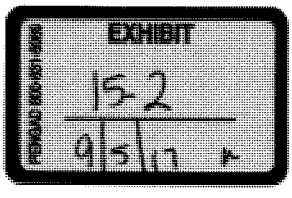
New text explains the difference between hazard and risk in the context of the risk assessment paradigm. The *Monographs* are described as an exercise in hazard identification. For several recent *Monographs*, however, the important public health questions have been both qualitative and quantitative. 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

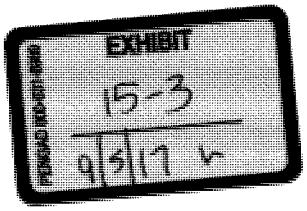
IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

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.

[4] Consultancies with L'Oréal, ECETOC, and Eurometaux, the European association of the metals industry. President of the Board of Directors of GreenFacts, a non-profit organization funded by corporations and other sources.

[5] Visiting Scientist at IARC, November 2005 to July 2006.

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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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[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:

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

144497

GEN
Birnbaum/orig
cc/
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 (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.

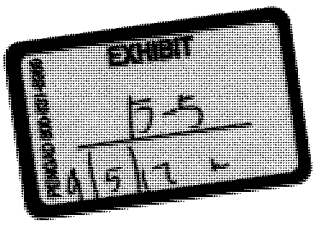
Harnessing a new technology to overcome an environmental health challenge

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

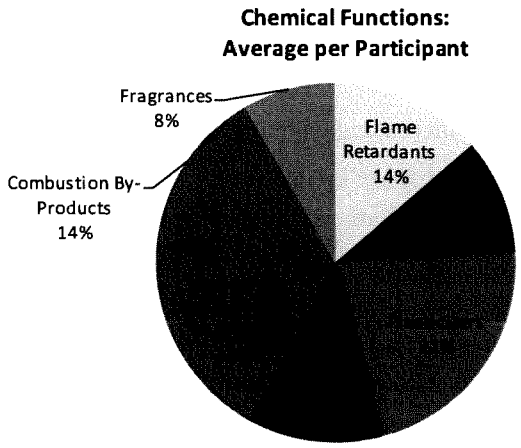
Summary Results

- **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

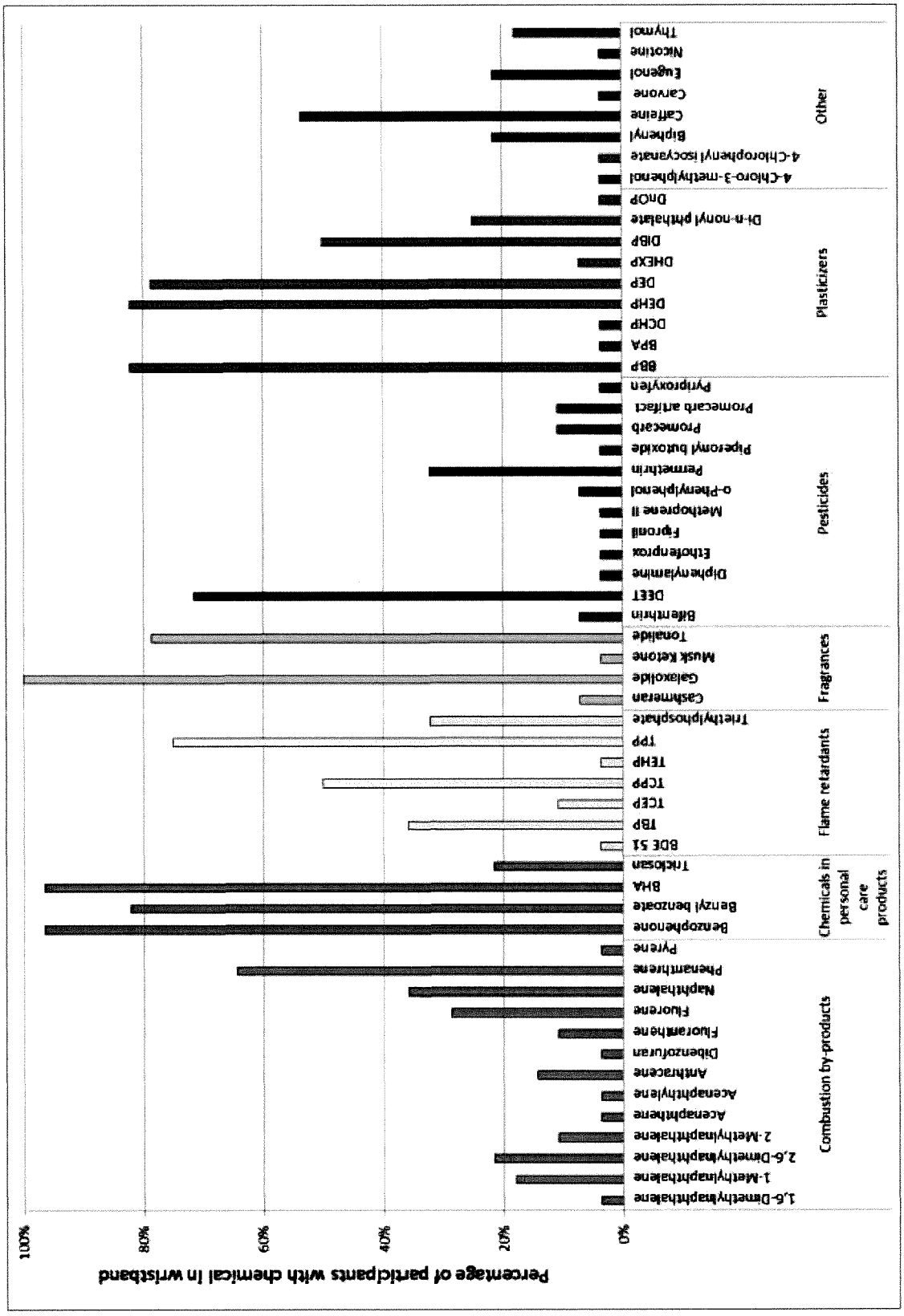


Are any of these chemicals hazardous**?

- 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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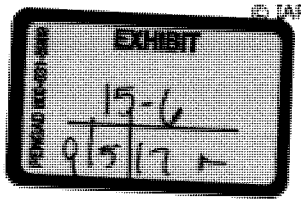

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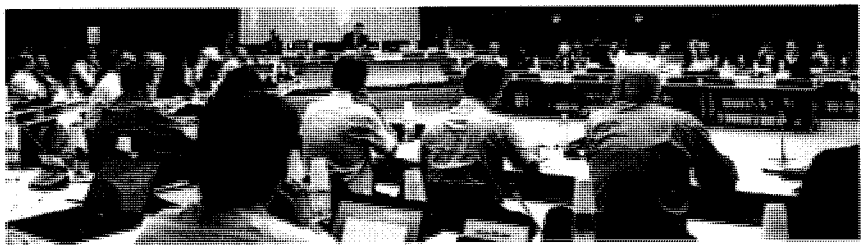

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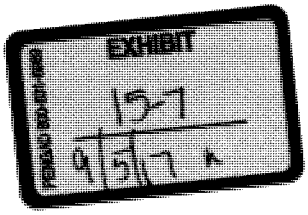

Meeting 112: Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos
(3-10 March 2015)

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

CONTENTS

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

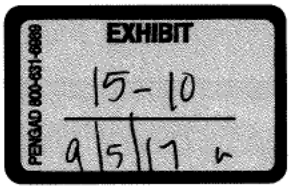
National Center for Computational Toxicology

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

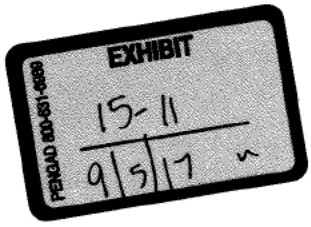
Dear all,

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

P118S2886_20150305115110_112-04-GLYP-Section_4-2-1-1stDraft-Tables_updatedFLC3.d
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-control
Midwest Canadian

Exposure Assessments

TCVP - Inadequate for carcinogenity

Parathion - excess risk for melanoma - limited
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,

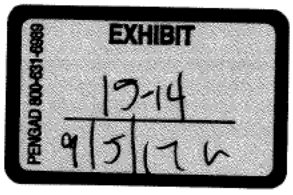
We thank you again for your outstanding contributions to the IARC Monograph volume 112 meeting!

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: -

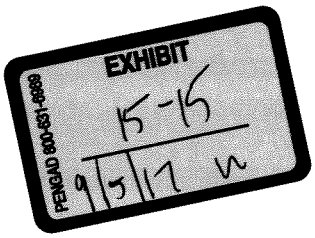
LOBBYISTS DECLARED: **0.25 FTE (1)**

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

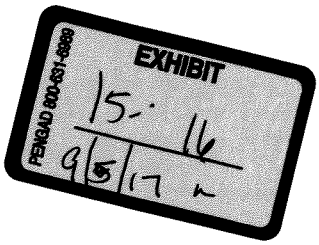
Address

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,

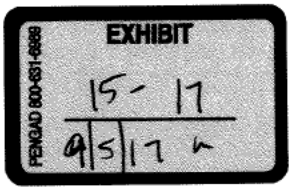
For IARC Monograph 112, 17 scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate. The Working Group concluded that glyphosate was a probable human carcinogen. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation 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

Privileged and Confidential
Attorney Client Privilege
Attorney Work Product

In re Glyphosate/Roundup Litigation

March 29, 2015

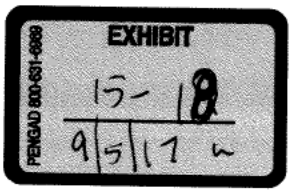
Hunter W. Lundy
LUNDY, LUNDY SOILEAU & SOUTH, LLP
501 Broad Street
Lake Charles, LA 70601
Email: hlundy@lundylawllp.com
Telephone: 337 439-0707 / Fax: 337 439-1029

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.



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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.

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

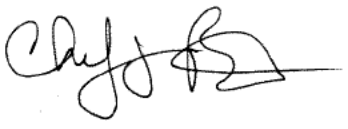
Reimbursement Information:

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

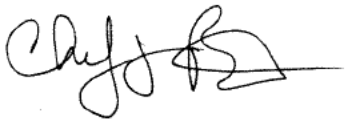
Reimbursement Information:

Name: Christopher Portier

[redacted]

[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

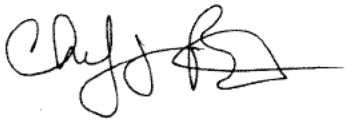
Reimbursement Information:

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

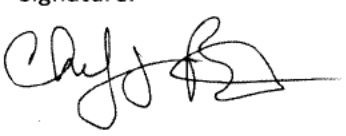
Reimbursement Information:

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

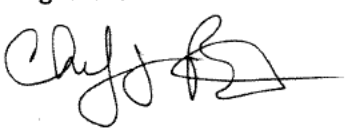
Reimbursement Information:

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

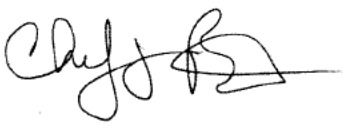
Reimbursement Information:

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

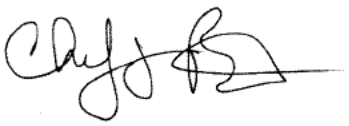
Reimbursement Information:

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

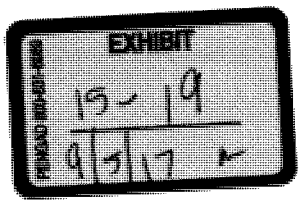
Cc: (email only)
Mr. Phil Hogan, European Commissioner for Agriculture and Human Development
Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety
Dr. Bernhard Url, Executive Director, EFSA
Dr. Giovanni La Via, Chair, ENVI Committee
EFSA Panel on Plant Protection Products and their Residues
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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