FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT

DOCKET NUMBER: EPA-HQ-OPP-2016-0385

FIFRA SAP WEBSITE http://www.epa.gov/sap

OPP Docket Telephone: (703) 305-5805

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

CONFERENCE CENTER LOBBY LEVEL

ONE POTOMAC YARD (SOUTH BUILDING)

2777 SOUTH CRYSTAL DRIVE

ARLINGTON, VIRGINIA 22202

DECEMBER 13 - 16, 2016

MR. STEVEN KNOTT: We're going to go ahead and get started. Good morning and welcome to this weeks' meeting of the FIFRA Scientific Advisory Panel to review EPA's evaluation of the carcinogenic potential of glyphosate. My name is Steve Knott and I will be serving as a Designated Federal Official to the FIFRA SAP for this meeting.

I'd like to thank Dr. James McManaman for serving as the chair of this session. I also want to thank both the members of the panel and the public for attending this important meeting. We appreciate everyone's time and effort and particularly preparing for these panel discussions, taking into account everyone's busy schedules. In addition, I want to thank the Office of Pesticide Programs and my colleagues on the FIFRA SAP staff for all of their work in preparing for this important review.

As additional background, the FIFRA SAP is a Federal Advisory Committee that provides independent scientific peer review regarding the impact of pesticides regulatory actions on human health and the environment. The FIFRA SAP provides advice and recommendations to the EPA. Decision making authority and implementation authority remains

with the agency. The panel's advice and recommendations are not final action.

The SAP consists of seven members. The expertise of these members is augmented through what is known as the Food Quality Protection Act Science Review Board. The Science Review Board members serve as ad hoc temporary participants in FIFRA SAP activities providing additional scientific expertise and assisting in reviews conducted by the panel.

As a DFO for this meeting, I serve as a liaison between the FIFRA SAP and the agency. And I'm also responsible for ensuring that the provisions of the Federal Advisory Committee Act are met.

The Federal Advisory Committee Act of 1972 established a system that governs the creation, operation and termination of Executive Branch Advisory Committees. The FIFRA SAP is subject to all of FACA's requirements and these include open meetings, timely public notice of meetings and document availability, which is provided through the Office of Pesticide Programs, public docket at www.regulations.gov.

As the designated federal official for this meeting, a critical responsibility is to work with appropriate agency officials to ensure that all

ethics regulations are satisfied. In that capacity, panel members received training on provisions of federal conflict of interest laws. In addition, each participant has filed a standard government financial disclosure report.

I, along with our Deputy Ethics Officer for the Office of Science Coordination and Policy, and in consultation with our Office of General Counsel, have reviewed these reports to ensure that all ethics requirements are met. And a sample copy of this form is available on the FIFRA SAP website. This website is noted on the meeting agenda.

The FIFRA SAP will review challenging scientific issues over the next four days. We have a very full agenda and the meeting times are approximate. Thus, we may not keep to the exact times as noted due to panel discussions and public comments.

I would ask that presenters, panel members and public commenters please identify yourselves when you present. And speak into the microphones provided since this meeting is being webcasted, transcribed and audio recorded.

Copies of all EPA presentation materials and written public comments are available in

the public docket at reglations.gov. And copies of the presentation materials submitted by public commenters during this week should be available within the next week.

For members of the public that have not preregistered for public comments, please notify either me or another member of the FIFRA SAP staff if you are interested in making a comment. At this time, the agenda is full. However, as we move through the proceedings, if time allows, we may be able to accommodate additional brief comments.

As I mentioned previously, there is a public docket for this meeting which is noted on the agenda. All of the background materials, the questions posed to the panel by the agency and other documents related to this meeting are available in the docket. Some of these documents are also available on the SAP website, which is also noted.

For members of the press, EPA media relations staff are available to answer your questions. You may contact me or another member of the SAP staff for further information.

At the conclusion of the meeting, the FIFRA SAP will prepare a report as a response to

questions posed by the agency, the background materials, the presentations and public comments. This report serves as the meeting minutes. We anticipate that these minutes will be completed approximately 90 days after the meeting.

So once again, I would like to thank the panel and the members of the public for being here today. I'm looking forward to a very interesting discussion over the next four days and at this time I would like to turn it over to our chair, Dr. McManaman. Thank you.

DR. JAMES MCMANAMAN: Good morning and welcome to this session. As Steve pointed out, we have a very full schedule and so I appreciate everybody's efforts to really be precise and very timely. For public presenters, if you're here, be ready to present your material.

I think that this is a very exciting topic and it's a very somewhat controversial topic so we'll try to stay on schedule so that we can accommodate everybody's availability to present about this and to elaborate on the importance of this topic.

With that, I'm going to ask the other panel members to introduce themselves but to begin,

I'm Jim McManaman. I'm a professor at the University of Colorado and I'm chairing this session.

DR. MARION EHRICH: I'm Marion Ehrich from Virginia Tech College of Veterinary Medicine in the College of Medicine and I'm a permanent panel member. I teach pharmacology and toxicology.

DR. DAVID JETT: Hello. I'm Dave Jett, I'm from the National Institutes of Health. I'm the Director of the Chemical Defense Program there and I'm also an adjunct Professor of Toxicology at the University of Maryland, School of Medicine.

DR. JOSEPH SHAW: I'm Joe Shaw. I'm a molecular toxicologist from Indiana University and I'm a permanent panel member.

DR. SONYA SOBRIAN: Good morning. I'm Sonya Sobrian. I'm a neuro-pharmacologist from the Howard University College of Medicine and I'm a permanent panel member.

DR. KENNY CRUMP: Good morning. My name is Kenny Crump. I'm a statistician. I'm partially retired at this time.

DR. LAURA GREEN: Good morning. I'm Laura Green. I'm a chemist and toxicologist.

DR. ERIC JOHNSON: Good morning. I'm Eric Johnson. I'm an epidemiologist from the University of Arkansas for Medical Sciences.

DR. BARBARA PARSONS: Good morning. I'm Barbara Parsons from US FDA's National Center for Toxicological Research where I work in the Division of Genetics and Molecular Toxicology.

DR. ARAMANDLA RAMESH: Good morning. My name is Aramandla Ramesh. I'm an Associate Professor of Biochemistry and Cancer Biology at Meharry Medical College and also Director of graduate studies in Pharmacology there.

DR. LUOPING ZHANG: I'm Luoping Zhang from School of Public Health, University of California at Berkeley, and I'm also a toxicologist.

DR. DAN ZELTERMAN: My name is Dan Zelterman. I am a biostatistician, Professor of Biostatistics at Yale University in New Haven, Connecticut.

DR. EMANUELA TAIOLI: Good morning. I'm Emanuela Taioli. I'm a cancer epidemiologist, Mount Sinai, School of Medicine in New York.

DR. LIANNE SHEPPARD: Hello. My name is Lianne Sheppard and I'm a biostatistician from the University of Washington in Seattle.

DR. JAMES MCMANAMAN: Okay. Thank you, panel members. With that I think that we'll go to the agency and have the first presentation. Dr. Housenger.

DR. JACK HOUSENGER: I guess that's me. Well, welcome everybody. Let me first apologize for the late time in the year that this has occurred. It seems like it's been forever coming but it's finally here. And I appreciate everybody's efforts and in advance I want to thank everybody for their careful deliberations on this.

Obviously, it's a controversial subject. It's one that's garnered a lot of public attention probably because two competing organizations have labeled glyphosate differently. We've looked at a lot of the studies that each of the organizations, over time, have evaluated in terms of carcinogenicity, put together a white paper and as you'll see there's a lot of information out there that I think we've done a good job of analyzing, doing a weight of evidence.

But now it's your turn to kind of tell us what you think of our analysis and hopefully put the subject to bed so we can move on. Glyphosate's a very important agricultural chemical. It's also used in the household so there's a lot of interest in what this panel has to say. There's also a lot of public comments that I know people have signed up for; probably more than I've seen in the past, which will probably push us into Friday, which usually doesn't happen.

I would just say to those people commenting, keep the comments short. Make your point because we do want this panel to deliberate and answer the charge questions and have enough time to do that.

Thank you very much and good luck. I'll see you around, I have to leave for another meeting.

DR. JAMES MCMANAMAN: Okay. Dana Vogel is up next.

DR. DANA VOGEL: Good morning. Yes, my name is Dana Vogel and I'm the Director of the Health Effects Division in the Pesticide Program. My presentation this morning is really going to be kind of short. I'll let you get to the meat of the

presentation. I'm just going to introduce the topics and what we're going to be discussing this week.

To begin, as Jack mentioned, glyphosate is registered for use for weed control in a variety of settings, both agricultural and nonagricultural and that's been the case since it was first registered in the 70s. In addition to the analyses -- the human health risk assessments that we complete prior to each new use of this chemical being registered -- there was a complete reevaluation done under the reregistration program in 1993. And currently glyphosate is undergoing registration review which is a program under the FIFRA Act where we reanalyze all pesticides every 15 years.

As you may know, the docket opening for registration review occurred in 2009, and at that time we published our Human Health Scoping document which kind of outlines the lay of the land for that chemical, what we know, what we don't know and our preliminary work plan. Kind of setting up what work we think we need to do and the general timeframe.

Moving on, I just thought I'd briefly touch on the previous carcinogenicity evaluations that we've done as an agency. In 1995, glyphosate was

categorized as a Group C possible human carcinogen based on the presence of kidney tumors in mice.

In 1996, we did bring the carcinogenic classification to FIFRA's Science Advisory Panel to get their feedback and determine whether the kidney tumors -- what their thought on that was and they were determined, at that point, to be equivocal. And the SAP recommended a Group D, not classifiable as to human carcinogenicity at that point; also, at that point, advised the agency to issue a data call-in, and asked for further studies concerning this question.

By 1991, we received two additional rat studies and that was the data that we had called in. And it was classified based on that new data as a Group E, evidence of non-carcinogenicity to humans.

Okay. As Jack mentioned in his presentation, and as you are probably aware, there are two different -- currently that have happened recently, evaluations of glyphosate that are not necessarily in agreement. The IRAC in 2005 classified glyphosate as a Group 2A, probable human carcinogen.

And as well as that, after the IRAC we also did, as an agency, a cancer assessment review and took it to our CARC committee. And at that point,

based on the evidence and the data that we had, we considered it, based on our guideline studies and the literature studies that were available, to be a not likely human carcinogen, which was in accordance with what we had previously considered and determined for glyphosate.

That brings us to why we're here today. Because of those differences in interpretation -- we are here today to give you what we decided to do as an agency, is comprehensively go back and look at all the available data that informed the carcinogenic potential that we could avail ourselves of. And we comprehensively analyzed that data to inform the carcinogenic potential of glyphosate. That includes epidemiological data, animal data, genotox data, as well as metabolism mechanistic data. That's the basis of this SAP and what we'll be discussing this week.

In conclusion, just quickly going through what you're going to be hearing about; an overview of the registration and carcinogenic potential, how we did our systematic review; that includes what data we collected, how we evaluated each of the different types of data that we had.

You'll hear about how we evaluated the epi data, how we evaluated the animal data, how we evaluated the genotoxic data. And finally, how we integrated all that data together and our weight of evidence across all those multiple lines of evidence in a systematic way. And I believe that's the end of my presentation.

DR. JAMES MCMANAMAN: Thank you. Any panel members have questions for Dr. Vogel?

DR. LIANNE SHEPPARD: Yes. This is Lianne Sheppard and my question is, can you give me a precise definition of carcinogenic potential?

DR. MONIQUE PERRON: So I wouldn't say there's an exact definition. Sorry, my name is Monique Perron in the Health Effects Division. Basically, we're looking at all the available data to see if there is any indication that this chemical has the potential to cause tumors in mammals; in particular, in humans, considering that we'll be using this information for human health risk assessment.

DR. ANNA LOWIT: Hi. My name is Anna Lowit. I'm a Senior Science Adviser here, in OPP. EPA uses the 2005 EPA Cancer Guidelines. And you'll hear in one of the presentations later of how the

glyphosate data fits within the guidelines. And so, we use the guidelines as the organizing principles for how we assess different lines of evidence as it relates to cancer potential.

DR. DANA VOGEL: And just one more thing I wanted to add. Part of the way we do our risk assessments is we're considering the doses at which we're trying to see whether or not it's relevant to humans at the doses we believe they'll be exposed to. And I think that that's an important part of our risk assessment.

DR. LIANNE SHEPPARD: So to clarify -- but this is not a risk assessment. This is evaluation of carcinogenic potential, correct?

DR. DANA VOGEL: Yes. This is the evaluation of the carcinogenic potential to humans. And in our minds, part of what we consider that is -- we make a consideration as to whether or not there's carcinogenic potential at doses that are relevant to humans based on how people are going to be exposed.

DR. LIANNE SHEPPARD: So based on your answer there is an element of considering human exposure in the carcinogenic potential?

DR. DANA VOGEL: Yes.

DR. LIANNE SHEPPARD: Because to me that comes in risk assessment.

DR. ANNA LOWIT: So EPA is a risk-assessment organization. We're not a hazard-based organization. Unlike IRAC, for example, that evaluates pure hazard. EPA is a risk-assessment based organization so exposure is important as we can think about the potential for humans to be exposed. And that's one of the big distinctions between how EPA assess cancer and IRAC does.

DR. JAMES MCMANAMAN: Okay, that was Dr. Sheppard and Dr. Lowit. All right, other questions? Okay, I think we'll move on then. Dr. Perron.

DR. MONIQUE PERRON: Thank you. My name is Monique Perron. I'm in the Health Effects Division of the Office of Pesticide Programs. I'm going to walk through an overview of the registration and carcinogenic potential; evaluations that have been done for glyphosate. I'll touch upon many of the points that Dana just went over and add a bit more information along the way.

Just a quick outline of what I'll be going over. As I mentioned, we'll talk about the

registration background of glyphosate as well as the exposure profile for glyphosate in the United States. And then again, walk through the previous evaluations that have been conducted by EPA of the carcinogenic potential.

Glyphosate was first registered in 1974, as a non-selective herbicide to control weeds in various agricultural and nonagricultural settings. It is currently undergoing registration review which is a program where all registered pesticides are reviewed at lease every 15 years to ensure chemicals continue to meet standards for registration. As part of this process, the hazard and exposure of glyphosate are reevaluated to determine its potential risk to human and environmental health.

It may be used on numerous food crops and also has labeled uses in nonagricultural setting such as aquatic and residential areas. Glyphosate is also registered for use on glyphosate resistant crops such as corn, soybean and cotton. Herbicide tolerant crops are engineered to have a tolerance to specific herbicides such that the herbicide kills the surrounding weeds while leaving the crop intact. And

these crop varieties were first introduced around 1996.

Following initial registration of glyphosate, total use was approximately 1.4 million pounds. By 1995 the use had increased to about 40 million. And by 2000, after the introduction of glyphosate tolerant crops, total use was about 280 to 290 million with agricultural use accounting for 90 percent of that.

This graphic is actually just the agricultural use and depicts moments in time when glyphosate resistant crops were introduced. Another thing to note is that in recent years you'll see the stabilization and that is primarily due to the increase in weed resistant species. And although there may be an increase in the number of farmers using glyphosate, the dramatic increase in use is more likely attributable to individuals who already used a pesticide, increasing their use and subsequent exposure.

The introduction of the glyphosate tolerant crops changed the use pattern for this chemical such that it shifted from pre-emergent use only to a combination of pre-and post-emergent use.

There was also an increase in the application rate and the number of applications that could be performed per year. Furthermore, individual farms also increased the acreage that they dedicated to these glyphosate tolerant crops; particularly since this coincided with the use of corn for ethanol production as well.

Here we have a map of the estimated agricultural use in the United States in 1994. This was generated by the US Geological Survey so this would have been prior to the introduction of glyphosate tolerant crops.

The same map generated for 2014 you see much higher use and you see also that the use is approximately all in the same areas that were depicted in the previous map. So again, for agricultural purposes the same areas are still being treated.

Based on its use pattern, there are several anticipated routes of exposure for humans. Glyphosate is used on agricultural crops for consumption and application may result in glyphosate reaching drinking water. As a result, exposure is expected via the dietary route.

Additionally, there are several products available for use in residential settings

where people may be exposed to glyphosate when they're applying the pesticide themselves or when they enter an area that has been treated previously. Workers may also be exposed while handling the pesticide prior to application, during application or when they are entering the treated sites.

Oral exposure is considered the primary route of concern for glyphosate. Metabolism studies have demonstrated relatively low absorption of the chemical with negligible accumulation in tissues and rapid excretion of the chemical primarily as unchanged parent. Due to its low vapor pressure, inhalation exposure is expected to be minimal and the dermal penetration information that we have via human skin has showed low dermal penetration indicating low dermal exposure is expected.

Furthermore, we have route-specific studies with glyphosate that show that no adverse effects were observed in either the inhalation or dermal toxicity studies. And all of this suggests that there is low potential for a sustainable biological dose following glyphosate exposure.

The agency has calculated high estimates of exposure based on the currently

registered uses of glyphosate. We use standard exposure assessment methodology, which are based on peer-reviewed and validated exposure data and models to obtain these estimates.

In residential or non-occupational settings, we expect children one to two to be the most highly exposed subpopulation, with oral exposure from dietary and incidental exposure, which would be a hand to mouth activity, for example, as well as dermal exposure from entering previously treated areas.

A high-end estimate for this subpopulation would be about 0.47 mg/kg/day. We would then expect adults to be even less than this. It should be noted that these estimates are based on maximum label rates that are applied to turf and assume that individuals are exposed every day to the residues on the day that you applied.

Also, these calculations assume that individuals are engaging in post-application activities on the turf for the maximum amount of time that children are considered to spend time outdoors. And in actuality, children do not spend all of their time on the turf. And as a result, these high-end estimates are considered conservative and very likely

that the true exposure would be less than these values.

For workers, there are several variables that may impact an individual's exposure. These include the formulation that's being used, the specific task, the rate of application and the number of acres being treated. And similar to residential assessment, the agency uses standard exposure assessment methodologies which have been peer reviewed and validated. And the exposure data and models have been validated to obtain the exposure estimates.

Assuming the maximum application rate for a high-acreage crop of 60 pounds per acre and assuming workers are not wearing any protective equipment, high-end estimates range from 0.03-7 mg/kg/day. And again, these values incorporate several conservative assumptions yielding values that are most likely overestimating true exposures.

As we discussed the numerous animal and genotoxicity studies later today, I would like you to keep these exposure estimates in mind. Administered doses in many of those studies went up to 1000 and in some cases 5000 mg/kg/day. And just to kind of put that into some perspective, we put together a few

calculations to determine how much an 80 kg or a 175-pound person would need to ingest to reach 1000 mg/kg/day.

And keep in mind that all pesticide products provide critical information on how to safely and legally handle and use pesticide products. Pesticide labels are legally enforceable and all carry the statement that it's a violation of federal law to use this product in a manner inconsistent with its labeling. In other words, the label is the law. One of the key functions is to manage the potential risk that people will endure from pesticide exposure.

Using currently registered use labels, the drinking water value at this time has been modeled at 0.159 ppm based on a direct application to water. And in order to get 1000 mg/kg/day a person would need to drink over 130 thousand gallons per day.

We can do a similar calculation for crops using tolerance levels which are the maximum amount of residue legally allowed in or on a crop commodity. Just for an example we chose carrots. And so, for carrots the tolerance level is 0.5 ppm. And assuming every carrot has this maximum amount of residue -- and in this case, we assumed a 70-gram

carrot just in case anybody wants to check the math -- a person would need to eat over 2 million carrots a day in order to achieve that dose.

So as Dana walked through earlier today there have been several evaluations of the carcinogenic potential of glyphosate. The first was in 1985 when it was classified as a Group C chemical based on the presence of kidney tumors in male mice. The subsequent SAP evaluation recommended a Group D chemical classification and advised the agency to issue a data call-in for additional studies.

With the submission of additional studies the agency then classified it, in 1991, as a Group E chemical, evidence of non-carcinogenicity for humans. And most recently, in September 2015, another review was performed by the Cancer Assessment Review Committee, or CARC, as part of a registration review. This evaluation considered relevant data available at the time, including studies submitted by the registrants as well as studies published in the open literature. And glyphosate was classified as not likely to be carcinogenic to humans.

In the current evaluation, a comprehensive analysis of the available data for

glyphosate was performed. The 2015 CARC evaluation served as an initial analysis. A systematic review of the open literature and toxicological databases was undertaken to identify relevant epidemiological animal carcinogenicity and genotoxicity studies. Metabolism and potential mechanistic studies were also considered. And all of the relevant data were then integrated and analyzed across multiple lines of evidence in a weight-of-evidence approach.

Before I conclude, I just want to note that for glyphosate human health risk assessment, both non-cancer and cancer effects are evaluated by the agency. However, the focus of this SAP will be on the human carcinogenic potential of glyphosate only.

And with that I will take any questions before moving on to the systematic review and data collection presentation.

DR. JAMES MCMANAMAN: Thank you. Dr. Green?

DR. LAURA GREEN: Thank you Dr. Perron for that very interesting presentation. I have a couple questions if I may, in no particular order. First, when you say absorption across the gut is relatively low -- I think you gave a number of 30

percent -- are you speaking of glyphosate acid or the glyphosate isopropylamine conjugate?

DR. MONIQUE PERRON: Most of the metabolism data that we have available have been on the acid and have indicated most of them are about 20 to 30 percent. We did have one study that indicated 40 percent is possible, but relatively comparable to other metabolism studies that we've seen on pesticides.

DR. LAURA GREEN: And do you have any absorption data at all on the glyphosate isopropylamine conjugate?

DR. MONIQUE PERRON: Not that we're aware of.

DR. LAURA GREEN: So a theme that I think is going to come up is -- and again excuse me because I'm a chemist so I see things through the lens of chemistry, I appreciate the agency's dilemma here -- the active ingredient is the glyphosate anion. However, there's a reason I expect that most of the commercial products are as the isopropylamine conjugate or another conjugate.

Those are expected to have very different properties in terms of water solubility and

obviously in terms of isoelectric point, and therefore presumably in terms of absorption across the gut. So I, at least, see an important data gap in that people in the real world, and of course crops in the real world, are not exposed to the unconjugated acid.

I don't know what your office's policy is with regards to how you separate out the chemistry of the anions from the chemistry of this (inaudible) anion in this case but I at least -- and I don't know about my other fellow panelists -- but I at least would urge you to think about those differences in chemistry which presumably translates into differences in -- well, certainly in terms of water solubility, in terms of isoelectric points, in terms of ability to be absorbed across the gut.

And I have one other question then I won't monopolize your time, I'm sorry. The data that you gave suggests that perhaps the epidemiologic studies are not actually looking at the most highly exposed groups. And Professor Sheppard and others, I'm sure, are going to weigh in on this later and I'm certainly not an epidemiologist. But if you're right that it's toddlers who are the most highly exposed group, and yet all of our epidemiologic evidence is on

farmers who presumably are grownups, I guess I wonder if you could comment on whether you think that's a data gap or not?

DR. JAMES MCMANAMAN: Okay before commenting, just want to remind everyone; the way this session is going to work is that during this period we're going to be asking clarification questions. And discussion of the approaches should be left until we address the charge questions.

And in order to make sure that this runs smoothly, I'd like everyone to adhere to that so that we can move through this as quickly as possible and really get at the issues as you brought up, Dr. Green, during the charge question discussion, because those are very important issues.

So just to remind everyone, this portion of the session is meant for clarification only. Okay? All right, other questions?

DR. DANA VOGEL: So can we just comment -- can we just respond to that one. Because I don't want there to be a misunderstanding. It's not that children aren't more highly exposed than workers. When we do our residential assessments, you know for the residential products because they are younger and

they exhibit hand to mouth exposure, they're exposed orally and they have that exposure. But workers are going to be exposed to a lot higher amount than anyone in the residential environment.

DR. JAMES MCMANAMAN: Okay. Thank you, Dr. Vogel. All right, Dr. Crump?

DR. KENNY CRUMP: In your review of the exposure information you didn't mention anything about exposures to production workers. Do you have any information on those kinds of exposures?

DR. DANA VOGEL: So production is kind of out of our scope of work. What we cover as the pesticide program are workers, mixer/loaders and applicators. As well as how people could be exposed in the occupational environment through handling, as well as post application, as well as residential. We don't do assessments for production workers. That's covered under a different area.

DR. JAMES MCMANAMAN: Dr. Taioli?

DR. EMANUELA TAIOLI: That exercise about the carrot and the water is actually very interesting. I'm wondering if you tried to build like a daily dietary pattern of how much would be in like a 2000 calorie diet of a person who is 80kg because

actually, that would be really a good understanding of how much is the exposure for a person who eats.

DR. MONIQUE PERRON: That was actually just for demonstration purposes. I didn't want to confuse by adding in tolerance levels for every crop that this is used. Actually, that is basically what our assessments do when we're doing risk assessments. In the case of glyphosate, we actually assume tolerance level for every crop commodity at this time to evaluate risk. It's actually quite unrefined.

In addition to that, we also assume that 100 percent of the crop has been treated which in most cases that's also not true. That was just for demonstration purposes for people to understand that those are very large doses that we'll be discussing throughout today and the rest of this week.

DR. JAMES MCMANAMAN: Thank you.

DR. DANA VOGEL: One more clarification on that. In addition to doing a dietary food exposure we add the drinking water into that as well as any potential residential exposure to do an aggregate exposure assessment. That's part of our risk assessment.

DR. JAMES MCMANAMAN: Okay. Yes, Dr. Sheppard?

DR. LIANNE SHEPPARD: So I wanted to just clarify. When you talked about routes of exposure you talked about dietary, residential and occupational. But with respect to residential and occupational, is it also dietary, or is it dermal, or is it inhalation, or what exactly is it?

DR. MONIQUE PERRON: For all of our assessments, we first do a dietary assessment on its own, which includes food and drinking water as Dana just mentioned. In addition, we will do in residential settings, for children, we do an incidental oral assessment. Hand to mouth, object to mouth as well as dermal exposures from going into treated areas.

Those are then aggregated with the dietary. Then you would also get a combined exposure as well at that point. It's all of those routes of exposures.

DR. DANA VOGEL: And worker inhalation and dermal.

DR. MONIQUE PERRON: Oh, yeah, sorry. And then in the occupational setting we also look at dermal and inhalation exposures as well.

DR. DANA VOGEL: And inhalation for residential.

DR. MONIQUE PERRON: Oh, I'm sorry. Did I miss inhalation? I should have just let Dana answer that one, sorry. So yes, I missed. We also do look at inhalation and dermal exposures for residential, people applying the chemical as well.

So again, for aggregate, I was focusing on children because they're the most highly exposed. But there are also the handlers, the adults who would be applying it, and also who could potentially at post application. Typically, the handlers will have higher exposures though. So again, we would aggregate the highest potential exposure with their dietary to get a worse-case estimate of their potential exposure.

DR. LIANNE SHEPPARD: Okay thank you. And maybe just to make sure I fully understand what's important with respect to exposure, you said the workers are the most highly exposed population. And that route of exposure is believed to be dermal? Oral?

DR. DANA VOGEL: We evaluate a couple different -- it could be different for different chemicals. Fumigants you might think inhalation would probably be more highly exposed. But we evaluate dermal and inhalation for people handling the pesticide, mixing/loading and applying. We also do post-application exposure assessments and that's mainly dermal. We also do spray drift assessments which have a component as well. We'll do drift to, you know, kind of offsite as well.

There's a lot of different pieces of it. It's kind of chemical specific. But a lot of times for this specific chemical -- I mean I think there's exposure that we evaluate because we're kind of trying to stay toward the cancer avenue here; we're talking about cancer. But at the same time, we'll look at the exposure that you get, inhalation and dermally, and use all that exposure together, if we were to calculate quantitatively a cancer risk estimate.

But by and large it's all potential routes that people could be exposed to through that occupational type of work, depending upon what their work is.

DR. LAURA GREEN: Excuse me, but I'm still confused.

DR. JAMES MCMANAMAN: Okay, one second. That was Dr. Perron, Vogel and Sheppard in that discussion. Okay, Dr. Green?

DR. LAURA GREEN: Dr. Perron can you please put back up your slide that showed the mg/kg/day estimates for exposure for the different groups. Yes, please. Okay, so as I read this, perhaps incorrectly, you have a half a mg/kg/day for toddlers, right? And you have that as a point estimate and it's a high-end estimate. Okay.

And then if you go to the second to bottom row and bottom row, you have a breathtakingly large range from not 0.03-7 mg/kg/day. And I assume that range is because there are many different ways of mixing and loading Roundup, right? But clearly what I took from this was that the reason your high-end estimate for your toddlers is high is because kids eat three times a day. And pesticide applicators do not apply Roundup three times a day.

And as I understand it, glyphosate is not very volatile and not very well absorbed across

the skin, but obviously, food is food. Am I missing something?

DR. JEFFREY DAWSON: Hello. I'm Jeff Dawson, I'm in the Health Effects Division and my background is exposure assessment. I'll try to answer what I think is the question.

When we look at the residential -- we do risk assessments and exposure component as Dr. Vogel said. We are looking at all different elements of how a chemical can potentially be used. And these estimates up here are just our view of the potential highest levels of exposure that could occur in different segments of the glyphosate market. If you'll look at it from that perspective.

And then with the first set of bullets up there, I believe that is looking at just the non-dietary exposure components.

DR. LAURA GREEN: It says oral exposure from dietary ingesting.

DR. JEFFREY DAWSON: Oh, okay. But when we do those calculations, typically the dermal and the hand to mouth component is usually a much greater contributor to that overall number. And we can find out exactly the specific contributors to

that. But I suspect that if you look at the dietary and the hand to mouth and the dermal piece that the dietary piece, which includes drinking water, would be a small contributor to the overall exposure.

And then the same is true for the occupational piece where that high-end estimate for mixers/loaders -- because glyphosate can be used in such a wide range of situations -- that's looking across the whole universe of how it could be legally used, which is dependent upon the crop and the cultural activities. And that's just the range of estimates.

DR. LAURA GREEN: I understand. But unless I'm misunderstanding, which I certainly could be, the fact is that the data on this slide seem to suggest that toddlers are, on the order, ten times or more highly exposed to glyphosate than your bottom row applicators. Am I right?

DR. JEFFREY DAWSON: Well, the mixers/loaders are 7 mg/kg.

DR. DANA VOGEL: Can I try? Sorry, just to kind of explain. Here's what we're trying to say here. If you look at all the different potential exposures you could have from an occupational use,

like you said, there's a wide variety of use that goes on agriculturally. And what we're trying to show in this slide is -- what we'll normally do is we'll do a calculation for mixers/loaders separately from applicators.

As you see on this slide for mixers/loaders the high end of that is 7 mg/kg/day. And if you go back up to the top part of the slide for one- to two-year-olds, and that's actually based on dermal and inhalation with dermal being the highest part of that exposure. Now if you go up to the top part with children one to two, you have a combination of things. This is just exposure. And what you're combining here is any potential dietary exposure which are not included at the bottom. There's no dietary component at the bottom.

What we've done at the top -- and we can give you an estimate of what it would be just for the residential portion of this -- is you're calculating a high-end dietary exposure based on tolerance level residual. You're adding into that how people will be exposed in the residential market or toddlers, and the potential for dermal exposure all thrown together which is still .47 compared to the

high end for workers for mixer/loader which would be 7.

And again, these are just ranges and that's the high end of the range. If you look at this all together and you think of all the different routes, the workers are -- especially considering how they're exposed, that they're mixing, they're right in there handling it -- they're definitely more highly exposed than children are. And the rates are higher and they're doing it more frequency.

DR. ANNA LOWIT: I'm going to add one little thing. I think it's important to understand the characterization of that top number. In our risk assessments, we have many hundreds of risk assessments that we have to do on an annual basis. What happens with our teams, is we use our resources efficiently and effectively.

In our food and drinking water assessments, we have a tiered system by which we start with very high-level screening assessments and move down into monitoring data and more sophisticated assessments. In the case of glyphosate, you've heard from both Monique and Dana that this represents what we call tolerance-level residues, which in our world

means extreme high end. These are not refined values. These are not monitoring values as I understand them.

In our workflow when a screening level assessment "passes" we just keep moving. The actual dietary exposure to glyphosate is far lower than would be represented had we done a full-blown assessment with a lot of monitoring data.

DR. LAURA GREEN: Perhaps I could suggest a way forward.

DR. MONIQUE PERRON: Well, if we're going to --

DR. LAURA GREEN: Or not, maybe later.

DR. JAMES MCMANAMAN: Okay. Yes, Dr. Dawson?

DR. JEFFREY DAWSON: One other thing that we haven't really talked about, and it's not really reflected well in that slide, is if you consider the temporal nature of exposures. In a residential setting -- and the way we're simulating exposure here is treating a yard, which remember glyphosate kills everything. And then putting a child out there and doing all this activity, that's like a single day. The next day your yard will be dead.

DR. LAURA GREEN: What's the --

DR. JEFFREY DAWSON: No, it kills everything. It kills everything. For occupational exposure remember the slide that Dr. Perron put up with the amount of poundage of glyphosate used. For example, with the GM crops and forth you get seasons of use for those who are involved in occupational activities associated with the use of glyphosate, particularly on the GM crop.

There's some areas of the country where this is obviously the major pesticide used and they use it across the -- you know, the entire beginning and middle parts of the growing season to get a mature crop. There's a lot higher frequencies of exposure as well that should be a consideration in the exposure context, which is not really reflected well in this slide.

DR. JAMES MCMANAMAN: Thank you. Dr. Johnson?

DR. ERIC JOHNSON: I have two questions which are interrelated. One, in your document you give a list of the search strings that were used to collect the literature/data. But I didn't see anything for the epidemiological studies. And I'm a little bit concerned about that because one, you just

mentioned that you are not concerned with the effect of glyphosate exposure among workers who are highly exposed during the manufacture of the compound. And not only that, these are the people who would more likely be exposed to the active ingredients also.

What I'm confused about is -- let's for the sake of argument say that the workers who produce glyphosate have high risk of cancer. If you say that you have no business with that group of data, why are we having this discussion here to determine whether this thing causes cancer or not?

DR. DANA VOGEL: Just to clarify. For the pesticides program, there's a different part. I think OSHA covers production workers. That's not under the purview of the Office of Pesticide Program. Our purview for human health risk assessments, under the EPA's Pesticide Program, covers all agricultural workers that could mix/handle, mix/load, apply, post application as well as nonagricultural settings as well.

We would do assessment. We do human health risk assessments for all types of workers that are using these pesticides products as well as any resident and how they might be exposed through use of

it or after. That's the purview and those are the risk assessments and the context for why we're asking about the carcinogenic potential for glyphosate, for use in our risk assessments.

DR. ERIC JOHNSON: I'm just concerned about this meeting and our roll in this meeting. Are we to confine ourselves to just applicators and spreaders or whatever, and forget about all of the information? Is that what you're asking? Because if there is evidence out there that this thing causes cancer in highly-exposed production workers, are we supposed to ignore that data and just look at what you're giving us here?

Because we have to make a decision whether this thing's potentially carcinogenic or not. That doesn't seem to me to be restricted to just whether it's just carcinogenic in applicators. It's just in general whether this thing is carcinogenic or not.

DR. ANNA LOWIT: So your question is about our systematic review and regarding our epidemiology, actually our next presentation is on our systematic review. And our paper included our search terms for both the epidemiology in animal and the gene

tox. And I believe our search terms for the epidemiology were general enough. They would have picked up production workers. And we're not aware that any such studies exist.

But in the context of this meeting, it's important to look at the context of this meeting as through the lens of the Environmental Protection Agency who works under the 2005 Cancer Guidelines, which I believe all of you were provided. And Section 6, I think, in our document puts the glyphosate epidemiology in animal and gene tox in the context of the 2005 Cancer Guidelines.

DR. ERIC JOHNSON: Right. But what I'm trying to get from you is that are we to concern ourselves when we make -- because the determination we have to make, we have about four or five different classifications of the potential of this thing to cause cancer. And we have to choose one of them. I mean, at least support one of them.

And my question is that, should we make a modification at the end of our conclusion to say that as far as the data concerns applicators, this thing is or it's not carcinogenic. She we make that

rider in there, because we do not have any data on other exposures.

DR. ANNA LOWIT: There are the epidemiology studies that exist that you'll hear about in detail later in the day, are on agricultural workers. Applicators would be included within that.

DR. ERIC JOHNSON: But what about production workers?

DR. ANNA LOWIT: So we'll get to the epidemiology review later. We're not aware that any such studies exist for production workers and that is outside the purview of EPA to regulate. The context of the review is through the lens of the EPA Cancer Guidelines under which we work. We can't characterize production workers for you and we're not aware of any data out there. Our purview is the food, the water, the residential use and the agricultural occupational work.

DR. JAMES MCMANAMAN: So perhaps this is an issue for the charge question and that may be a limitation in the charge. We can include that as part of the charge question discussion. That was Dr. Johnson, Dr. Lowit and Dr. Vogel. Other questions?

If not, then I think we'll move on to the next presentation.

DR. GREGORY AKERMAN: Good morning. I'm Greg Akerman of the Office of Pesticide Programs, Health Effects Division, and I will be presenting an overview of the systematic review and data collection process that we used in our evaluation of the carcinogenic potential of glyphosate.

In recent years, the National Academy's National Research Council has encouraged the agency to implement a systematic review process to enhance transparency of scientific literature review that support chemical-specific regulatory decisions. NRC defines systematic review as scientific investigation that focuses on a specific question and uses explicit pre-specified scientific methods to identify, select, assess and summarize the findings of similar but separate studies.

Consistent with the NRC recommendations, the Office of Chemical Safety and Pollution Prevention employs a fit-for-purpose systematic review which relies on standard methods for collecting, evaluating and integrating scientific data to support decisions.

The fit-for-purpose concept implies that a specific activity or method is suitable for its intended use, and allows for flexibility and is not a one size fits all type of review process. Systematic review begins with a problem formulation to determine the scope and the purpose of the search. Studies are considered on their relevance to answer specific questions and those studies that are deemed relevant are then further considered.

The fit-for-purpose systematic review allows for transparency in data collection, evaluation and integration. The agency strives to use high-quality studies when evaluating the hazard of pesticides and considers a broad set of data, including registrants' studies required under FIFRA, peer reviews, scientific journals and other sources from academia and government so that decisions are based on the best available science.

For the scope of the data collection it should be noted that glyphosate is primarily manufactured as various salts with cations, such as isopropylamine, ammonium and sodium. These salts are derivatives of the active substance glyphosate and increase solubility of technical glyphosate in water.

All these forms were considered in the current evaluation of glyphosate.

Data is collected by searching open literature and other publicly available sources which includes recent internal reviews and evaluations of other organizations. We also search internal databases for studies submitted to the agency that were conducted according to OECD or OSEP Harmonized Test Guidelines or other pesticide test guidelines.

The open literature search conducted used concepts consistent with fit-for-purpose systematic review, including detailed tracking of search terms and identification of articles that were included or excluded. The primary goal of the literature search was to identify relevant and appropriate open literature studies that had the potential to inform the agency on human carcinogenic potential of glyphosate.

OPP worked with EPA librarians to search three scientific search engines, PubMed, Web of Science and Science Direct. The search terms used are described in Section 2.1.1 of the issue paper. And since the focus of this review is the human carcinogenic potential of glyphosate, nonmammalian

studies were not considered with the exception of mutagenicity studies in bacteria.

The search results were cross referenced to eliminate duplicates. And one additional study that was not identified in the search was added for a total of 736 individual articles. The studies were then evaluated to determine if the studies were relevant for issue of concern which, again, was to human carcinogenic potential of glyphosate.

Of the 736 articles considered, 658 were determined to be not relevant to the scope of this search. An additional 27 articles were considered not appropriate due to the type of article. For example, if they were correspondence articles.

Fifty-one relevant articles were identified. Of these, 42 were considered in the current evaluation. And this included 31 genotoxicity studies, 9 epi studies and 2 animal carcinogenicity studies. Three articles described the use of glyphosate or its metabolites as a therapeutic drug for cancer treatment. And six others, upon further review, were not considered to be informative for the current evaluation.

The data collection also includes studies submitted to the agency under 40 CFR Part 158, Toxicology Data Requirements for Pesticide Registration. These data requirements provide information on a wide range of adverse health outcomes in the studies. Typically followed are harmonized OECD or OECS peak guidelines or OPP accepted protocols, which ease comparison across studies in chemicals.

The studies identified tested glyphosate and associated salts. All relevant animal genotoxicity metabolism studies from the toxicological database were collected for consideration.

A list of studies obtained from the toxicological database, the open literature search, were then cross referenced with recent internal review articles by the agency. The list also was cross referenced with review articles from the open literature.

We requested studies from registrants that were not previously available to EPA. And after the request, numerous studies were then subsequently submitted to the agency and reviewed. The study report for 1 animal carcinogenicity study and 17

genotoxicity studies were not available to the agency and were noted in the relevant section of the issue paper.

For these studies, data and study summaries provided, particularly in the Greim, Kier and Kirkland review articles, were relied upon for the current evaluation.

Studies submitted to the agency are evaluated based on OECD, OCSPP or OPP test guidelines requirements to determine whether the studies are acceptable for use in risk assessment. In the current evaluation, animal carcinogenicity studies, genotoxicity and metabolism studies located in our internal databases with access to the full study reports were evaluated in this manner. Those classified as unacceptable were noted and subsequently excluded from the current evaluation.

In order to evaluate open literature studies, criteria described in the Office of Pesticide Program guidance for considering and using open literature toxicity studies to support human health risk assessment was utilized. This guidance assists OPP scientists in their judgement of scientific quality of open literature publications.

And more specifically, the document discusses how to screen open literature studies for journal articles and publications that are relevant to risk assessment. How to review potential useful journal articles and categorize them into usefulness in risk assessment, and how the studies may be used in risk assessment. As with most studies, those deemed unacceptable were noted and subsequently excluded from our evaluation.

As mentioned in previous talks, a CARC evaluation of the carcinogenic potential was conducted in 2015. This table compares the number of studies considered for the 2015 CARC evaluation and the studies that are evaluated on fit-for-purpose systematic review.

As you can see in the table, the systematic review identified additional studies that were not included in the 2015 CARC evaluation. Also, the CARC relied more on data from published review articles for which the studies were not available to the agency, but have been subsequently submitted to EPA and the data were reviewed and included in this current systematic review.

In summary, the agency used a fit-for-purpose systematic review to identify and collect data for current evaluation. The review focused on studies that inform human carcinogenic potential of glyphosate and the studies were evaluated for acceptability. The process discussed in this presentation relates to charge question number one to the panel.

Thank you. At this time, I'll take any questions you may have.

DR. JAMES MCMANAMAN: Thank you Dr. Akerman. Dr. Green?

DR. LAURA GREEN: Thank you for that helpful presentation. Perhaps I missed it, but did you all limit your search to English language papers?

DR. GREGORY AKERMAN: Yes. We did.

DR. LAURA GREEN: Do you feel that might be a limitation? Let me just say I don't mean to be coy here. It is my understanding, perhaps incorrect, that there's more glyphosate made and used in China than in the US, and possibly the US and Europe combined. And I, at least, am wondering whether one of the important data gaps which is information of non-production workers and their health might be available in, let's say, the Chinese

literature and might be something that might be very much worth at least trying to find.

DR. MONIQUE PERRON: I should say that it wasn't necessarily that the search was limited. The search did not say not English. We did receive some that were not in English and those were subsequently excluded due to the fact that they were not in English. But I will say that I think that was only the case for maybe less than a handful of studies that came across.

I don't think it was a large limitation in the current search that we did. I understand what you're trying to get at though. But given the search engines that we looked at, and what we know is available out there, as well as we also looked at evaluations from Europe and across the world, and these are the studies that were identified. If we had found that there was one out there that was in another language that we thought was pertinent to the search, we would have included it. I'm not sure that I would say that was a strong limitation in the current search.

DR. LAURA GREEN: So if I understand then, just for the sake of discussion, if there was a

paper written in Chinese but in PubMed for example, and if there were the ability using Google translate or something to translate let's say the abstract from let's say Chinese to English, you would have read that?

DR. MONIQUE PERRON: At this time, if they were in the search and we actually -- if you look in the appendix there is one that I believe is in Russian. We did not try to translate it this time. There was quite an expedited timeline for this to make sure that we could get this SAP going. And again, I would say that's less than a handful of studies that came up in our search.

I would say though, if we had noticed that another agency or others out there were using a study that was in another language, we would have made more of an effort to go the extra mile to make sure that that was included, yes. But in this case that was not the case here.

DR. LAURA GREEN: Okay. I have just one more quick question. I noticed that in your exclusion terms you used the word water. In other words, you excluded papers that would have glyphosate and water in the title which I thought was odd. And

so I took it out, that is to say I excluded that exclusion term and I found lots of other papers on for example glyphosate and drinking water that you would have excluded a priori.

And while I appreciate that you're not interested for this purpose in aquatic toxicology, and therefore you used as exclusion terms aquatic and fish and that sort of thing, I'm perplexed as to why water was one of those terms. And wonder whether anyone has bothered to rerun the search including water and see what you get.

DR. MONIQUE PERRON: Yes. That was an attempt to try to limit the eco papers that we were receiving. Because as you can imagine when we first started this, we had quite a number of -- there are a lot of studies out there in the open literature. And we were attempting to work with our EPA librarian to constrain that as best as possible. And I believe that that's why we have a charge question for that and we will take any input on any of that information.

If you think that there were relevant studies that came up when you took out water that were relevant to the human carcinogenic potential of

glyphosate, then that is something that we want to know so we can incorporate those.

DR. JAMES MCMANAMAN: Dr. Jett?

DR. DAVID JETT: Just sort of a procedure question. For the study selection, did more than one person participate in that? Or was it just one person that did the selection?

DR. MONIQUE PERRON: Sorry, could you clarify? The study selection in terms of -- I'm sorry, I just want to make sure I answer your question. Do you mean which studies were considered relevant? Which ones were in the scope?

DR. DAVID JETT: Correct.

DR. MONIQUE PERRON: Okay.

DR. DAVID JETT: I think study selection was the term used, but yes.

DR. MONIQUE PERRON: Okay. I just wanted to make sure. That was conducted primarily by one person at first, yes. And then two other people on the team then also looked through that list as well to see if they thought any of those were relevant.

DR. DAVID JETT: So there wasn’t any parallel, you know, two people doing --

DR. MONIQUE PERRON: No. It was more conducted in this case for the ease of time. We had one person go through the full list all at once to try to categorize them at first. And then we had two subsequent people look at the list and see if they agreed with those.

DR. DAVID JETT: Okay. The other question was just a little clarification about -- so the latest influx of new studies, those were obtained from looking at reviews? And there wasn't an independent kind of a search or these just came directly from review articles?

DR. MONIQUE PERRON: Yes. We spoke with registrants and told them to please submit any of the studies that we knew were out there that were -- primarily it was the review article. I mean it really started by the Greim paper, where we knew that there were registrant-generated data in that paper. They then subsequently provided us with all but one unacceptable animal study, and all but 17 of the genotoxicity studies in that case.

DR. DAVID JETT: Got it. Last question. What happens with studies that were

submitted from registrants that weren't published? Were they included in this analysis?

DR. MONIQUE PERRON: Yes. The systematic review, as Greg walked through, not only was it open literature search, we looked through all of the toxicological databases for glyphosate and any of its associated acids. Our focus obviously was on any cancer studies, genotoxicity studies, but we also looked for any metabolism studies or mechanistic studies that might inform any of that additional information.

DR. DAVID JETT: Thanks.

DR. JAMES MCMANAMAN: Yes, Dr. Crump?

DR. KENNY CRUMP: Did the unpublished studies undergo any special review to determine their scientific validity?

DR. GREGORY AKERMAN: Yes. The unpublished studies went through our regular review where we have toxicologists that typically review studies that come in for registrants as part of the registration of a chemical. It went through the same process where we had a toxicologist review and then another toxicologist did a secondary review of those studies to make sure they were acceptable studies.

DR. ANNA LOWIT: Greg, tell me if I'm wrong, but our data evaluation records of the nonpublished studies are included in the package that all of you received. Each of you have seen our reviews of those unpublished studies.

DR. JAMES MCMANAMAN: Other questions? Dr. Johnson?

DR. ERIC JOHNSON: Just a slide clarification. The data you showed the first review picked up only nine epidemiological studies. And I would like to know how different is that review from the current review where we have 50 epidemiological studies? What was the timing and what's the difference? If you could just clarify that for us, please.

DR. MONIQUE PERRON: In the open literature search it picked up those nine studies. But we were also aware of other studies already during our 2014 and 2015 reviews of the epidemiological literature. And many of those were already actually part of those evaluations. The nine represents what was picked up by the search. There's actually 58 studies that were in total considered. That includes those nine studies plus all of the additional ones

that we identified in review articles or as part of those initial evaluations prior.

DR. ERIC JOHNSON: What was the most productive method where you got so many -- much more? Because on the first of which, the initial review, which we took only nine looked extensive to me. But to think that it missed almost 50 studies; could you just tell us what were the other methods which were so productive? Also, that even brings to mind why -- when you do review studies in occupational settings it's very difficult, I can you tell you that. You can miss a lot of studies. A lot of outcomes or exposure comes under the word occupation.

And it is when you read through the articles that individual cancers, you pick up. If we just relied on glyphosate on a search string, for example, we only pick up a handful of the 58 studies, epi studies; because glyphosate does not appear as a keyword or title in most of these 58 epi studies.

DR. MONIQUE PERRON: I cannot really speak toward why they were not picked up. We actually saw the same thing for the genotoxicity studies, and maybe it is part of the exclusion terms. That is something that we would love feedback from the panel

on if you think there are certain exclusion terms, as was already pointed out, that you think would increase our probability.

In a perfect world, we could search every search engine out there, but we can't. We are relying on all of the avenues that we can. We conducted a fairly broad search, actually. It really is glyphosate, plus cancer, minus environmental type terms to try to take out a lot of the eco type studies. This wasn't one where we really restricted the search very much.

Again, we would gladly take any suggestions on how to improve the search. As we said earlier, there is a charge question on that. But I would say that that is why we made sure to cross reference with review articles and other agencies reviews to make sure that we were being as comprehensive as possible in this case.

Again, I can't really speak towards why this search didn't pick up on every single one. And it could just be that the particular search engine didn't have the journal as part of their search. But that's why we tried to go across multiple search engines, to try to get at that issue.

DR. JAMES MCMANAMAN: Thank you Dr. Parron. Dr. Green?

DR. LAURA GREEN: I just have a practical question. What's the date after which studies won't be considered? In other words, time marches on. We were supposed to meet in October and here it is December. By the time we report back to you, it's going to be the spring of 2017, I guess. And I'm just wondering what the drop-dead date is since obviously, papers are published pretty regularly.

DR. MONIQUE PERRON: Sure. We'll continue to monitor the data as best we can. We put out a draft risk assessment first as part of registration review. And as part of that we receive public comment. People can send in papers at that time or say you should consider this paper at that time.

We have additional time during registration review where we can continue to incorporate any information that we think is pertinent. I wouldn't say there's necessarily a drop-dead date. Also, remember that we consistently are doing human health risk assessments. And often with

glyphosate, which is used fairly regularly, we pretty consistently over time have risk assessments every couple of years. And for each of those we always tried to include any relevant and pertinent information at that time as well.

There's always moments where we can start to incorporate new information. And we strive to use the best science out there when we are making those decisions.

DR. LAURA GREEN: Not to put you on the spot, but it's our understanding that our deliberations for all intents and purposes end this week. And the record that is established, is established this week. Let's say for sake of discussion, as we are preparing our report for you next month an interesting epidemiology study comes out, we obviously will not have had the opportunity to discuss that epidemiology study in your presence. What would you advise we do?

DR. ANNA LOWIT: Glyphosate is active in the open literature. Many scientists around the world are looking at many aspects of glyphosate. Everything from cancer to gene tox to eco tox, as you eluted to earlier. That will happen. It's more a

likely event than an unlikely event that a paper comes out on glyphosate after your report is done.

As Monique said, we maintain an active observation of the literature. This is a chemical that we maintain an active literature search on and we will incorporate it into our weight of evidence analysis to the best we can.

There is a large body of information here. The number of animal bioassays is very large. The number of gene tox studies is very large. And in the pesticide arena the number of epidemiology studies is also substantial, and particularly given those that have been studied in the Agricultural Health Study.

At some point, we expect our AHS colleagues at NCI to publish a second paper on glyphosate. That will happen, but we will do as we do with every other assessment. We will integrate that new information as best we can into our assessment. Keeping in mind the advice that we get from all of you during this week.

DR. JAMES MCMANAMAN: Thank you Dr. Lowit. Dr. Taioli?

DR. EMANUELA TAIOLI: When you treated the unpublished data that you used, did you try any

sensitivity analysis? Did you look at the data with and without the unpublished studies, and did you score the unpublished studies for some quality? Such as, it could be that they're not published because the funding is finished and the study was not completed, or not published because it doesn't reach the peer review process. Did you do any publication bias test because that's usually a problem?

DR. MONIQUE PERRON: So we did not do any analysis for publication bias or sensitivity analysis as you said. Just to sort of separate, when we did the searches, they were actually separate. The search string is for only the open literature.

The other half of the search for the review was in the tox databases which is going through our very old databases and trying to search for every possible study that we can find that could inform this. It wasn't necessarily that they were all searched together, just to be clear on that.

And I wouldn't say that we scored the unpublished data. We basically tried to categorize them to whether they were first of all relevant or within the scope of the issue of concern which is the human carcinogenic potential of humans. Often you

could figure that out either by the title or abstract. A lot of the time, especially with the term Roundup, things get a little bit more confusing. You don't realize how much that term comes up, so going through first to figure out whether they were even relevant to the issue of concern.

And then from there, of the relevant studies, whether they were acceptable or adequate for use in a quantitative or qualitative. I think Greg also mentioned in his presentation that we have guidance for evaluating open literature articles and that was basically how we reviewed that data.

DR. ANNA LOWIT: Just to add a little bit to that. Take a couple of steps back. Within the animal toxicology and the gene tox studies, it's important to remember that under FIFRA that this program has enormous data call in capacity. And in order to register a pesticide in the US, companies who want to do that have to develop large amounts of animal toxicology data.

The overwhelming majority of the bioassays that you have, come from chemical companies who have either registrations here in the US or abroad. And we have other studies, developmental tox,

dermal, inhalation, repro, the list goes on and on and on. And the overwhelming majority of that data is never published in the open literature.

This program has access to lots and lots of data for many pesticides, including glyphosate, that have never been published. And so that really represents, I think, the bulk of what all of you have as the registrant supported data.

And with respect to the grading of information, those studies are conducted under OECD guidelines. And Anwar and Greg will both explain how we look at a study done under the OECD guidelines and grade it for what we call acceptable or nonacceptable, or guideline/nonguideline.

It's not graded in the old hat point of view that you give a score of a 1, 2, 3, 4 or something like that. It's more through our lens from a regulatory point of view. Is it acceptable? I.E. did it meet the requirements in the OECD guidelines? Is it scientifically conducted?

We do score them in that way. And all of those would be in the data evaluation records or what we call the ERs that are in the package that you got.

DR. EMANUELA TAIOLI: I think a publication bias test would show that they all merge without difference and would give you a quantitative proof that what you're now saying in words is true. It would be a simple way.

DR. JAMES MCMANAMAN: Dr. Jett?

DR. DAVID JETT: One last question I forgot to ask and that was for the data streams, the streams of evidence that you used. You have human, you have, I guess, whole animal tumor studies and you've got genotoxicity; did you also consider basic mechanistic studies? You know, proteomics or what have you, or is that out of the fit-for-purpose approach that you took?

DR. MONIQUE PERRON: We did try to consider any mechanistic data out there, but there's actually quite a data gap on the mammalian mode of action of glyphosate. We had, I believe, one study that did have a proteomics component to it, but it was not found to be integral to the topic.

DR. JAMES MCMANAMAN: Dr. Crump?

DR. KENNY CRUMP: A question about data collection. When you identify the studies, did you actually collect the data from the studies? For

example, did you collect the raw data, in a sense, as you could do the same analysis that the study was done and maybe do additional analyses? And in particular, with the animal data, some of those studies are very old; and did you attempt to put the data in forums where it could be analyzed? And what's the status of those data.

DR. GREGORY AKERMAN: So the studies that were identified that were conducted by registrants, those study report contains the raw data so we could do an independent evaluation of those studies. It's only in a couple cases where we didn't actually get the full study report and we had to rely on some summary data that was available.

But as far as the unpublished data for literature studies, when we requested -- those studies that we identified, and we requested them and they came in, we did have the full study report where we could do an independent evaluation.

DR. KENNY CRUMP: Did you computerize those data or did you just have it in the raw paper forms; the data from the unpublished animal studies?

DR. MONIQUE PERRON: We have access to individual and summary tables that comes with those

study reports. When we receive study reports, they're just in a pdf or Word document format that we then go through. In the case of the animal studies that you're asking about, we identified the tumor types that we wanted to analyze in detail. And those were then put through statistical analyses from there. I'm not sure if that somewhat answers your question.

DR. KENNY CRUMP: I think so. It says that you did not really computerize all the data. You just look at the tables that were in the published report and picked out --

DR. MONIQUE PERRON: Right. We don't take all of the data and computerize it. It's just too large of an amount of time and resources that we don't have for every study that comes in. Especially for something like a carcinogenicity study. There's a lot of end points that are looked at, a lot of apical outcomes. We can't take the time to computerize all of that information, especially when we don't think all of them will even be fruitful in showing anything. We try to focus on where the information may lead to something that we need to investigate further.

DR. KENNY CRUMP: I would understand that a lot of those summary tables you don't have the

data for doing age-adjusted analyses so you were not able to do such analyses from the tables that were in the published report. Is that right?

DR. GREGORY AKERMAN: The published reports provide all the raw data. Sorry, the unpublished reports provide all the raw data, individual animal data. Any analysis could be performed because we have all the data for those studies.

DR. LAURA GREEN: If I could help. I think we just have one specific concern and maybe a practical suggestion. We do have a National Toxicology Program -- thank goodness -- and I know that you all are interacting with them.

Dr. Crump and I have been specifically wondering something. As you may know, the National Toxicology Program uses Poly-3 or other statistical tests looking at time to tumor -- you do not. That's fine that you do not, but many of us think that time to tumor could be a very informative exercise.

And so, our specific question is, if we were to recommend to you that you ask NTP to do time to tumor analyses, would that be a practical

suggestion or is that like, you know, a year's worth of work and totally off the table?

DR. JAMES MCMANAMAN: Well, I think we're getting into the charge question area again. It gets a little dicey here. We'll hold off -- in terms of at this point of clarification, we'll hold off on that question. Keep it in mind. Write it down because we'll come back to it when we come to the charge question.

Before we go on I think there was another couple of questions here. Before we go on that was Dr. Akerman, Dr. Perron, Dr. Crump and Dr. Green. That was that interaction. I think that Dr. Parsons had a question.

DR. BARBARA PARSONS: It's related. The unpublished literature, the study reports report the data in various format. My question is, were you able to go through all of those rodent carcinogenicity studies and collect the same data across studies for analysis? You're comparing apples to apples the whole time. And if so, what was the statistic that you used? Was it just terminal sack and more of them dead animals? Some of them are combined chronic exposure carcinogenicity studies.

And some of them, for example, combine data from all sacrifices. What was the method that you used; what was the specific data that was analyzed for statistics?

DR. GREGORY AKERMAN: I think that's probably a better question during the animal carcinogenicity studies that go over the bioassays and discuss the statistics that were used for that. That might be a better time to address that question.

DR. JAMES MCMANAMAN: That's fine. Okay, Dr. Zhang?

DR. LUOPING ZHANG: I just want to -- maybe I missed, but I'd like to confirm. You have a table to show all the different like epi study, animal and the genotoxicity. You have 2015 CARC evaluation and the current. First question is, is basically your current evaluation cover everything from the 2015, right?

DR. GREGORY AKERMAN: Yes.

DR. LUOPING ZHANG: I just want to confirm that. Second is, have you compared your EPA current evaluation, the paper selected, from IARC documents? What's the difference between your EPA document comparison with the IARC one? My guess here

is because IRAC only based it on the published papers; and here, EPA, you're including published or peer reviewed and unpublished or peer reviewed. Is that the case? I just want to confirm.

DR. GREGORY AKERMAN: That's true.

DR. LUOPING ZHANG: It's true? Okay. Then I also heard another question about if it's un-peer reviewed, have you looked into, peer reviewed and un-peer reviewed, the publication source or funding source, to analyze possible publication bias? Just looking into that.

DR. MONIQUE PERRON: Sure. And knowing the high profile of this chemical we did note, when we could, when the funding source was from a registrant or not, to speak a little bit toward that. But yes, we have done comparisons with IRAC. There are some fundamental differences in, like you said, they only use published literature. We have a very large, extensive database on our own that we can't ignore. We include those registrant studies as well.

And then there are also some other difference as well. They included data on plants and insects and other things like that that we did not believe would be informative for human carcinogenic

potential. There are some fundamental differences in how we approach the data, yes.

The ones that we thought would be informative for the purposes of this decision though, we made sure that we included. If we excluded it from our evaluation for some reason, we tried to note that in the white paper as well. Hopefully, along the way, people were able to have some indication of why we went a different route in particular instances like that.

In terms of any type of literature or abstracts that are out there that are un-peer reviewed, we would not consider. We feel that it needs to go through some sort of peer review before we're going to consider it. Because I know people have already identified some poster abstracts that are out there that people have already presented.

But again, without having access to the study report from the author to actually know what they did, how they did it, we don't feel it's appropriate at this time to incorporate it into our evaluation. We want to make sure that first of all it goes through some sort of peer review and then we can

evaluate it at that time when we have all of the information that we can get to consider.

DR. LUOPING ZHANG: All data included is peer reviewed? At least?

DR. MONIQUE PERRON: At this time, either the data has been reviewed internally -- because we have access to the full study report -- or it has been peer reviewed through a journal process and then included.

DR. LUOPING ZHANG: Okay.

DR. JAMES MCMANAMAN: That was Dr. Perron. Dr. Sheppard, you had a question?

DR. LIANNE SHEPPARD: Yes. I actually have a couple of questions. The first one's a clarifying question. You mentioned that all the data on the review we have access to. And I wanted to make sure I knew exactly what you meant by that. Are you referring to Appendix A of the issue paper? Or are you referring to something else that I should be paying attention to?

DR. MONIQUE PERRON: Can you remind me in what context I used it?

DR. LIANNE SHEPPARD: I don't remember exactly which --

DR. MONIQUE PERRON: Oh, the DERs. Okay, I'm sorry.

DR. LIANNE SHEPPARD: --which one, but it was without the review process and the judgements you made.

DR. MONIQUE PERRON: Yes. Sorry. When I was referring to access to, I meant that the whole study report has been submitted to the agency. We have access to all individual data as well as summary tables and information on the chemical composition and analyses and stability. We have a very thorough report of the study that's been submitted in that type of fashion.

DR. ANNA LOWIT: She wants to know where the DERs are.

DR. MONIQUE PERRON: Oh, where to find the DERs. Those are all included as part of the package that was supplied to the SAP. There are DERs generated for every study that was submitted to the agency that are considered -- what we keep on saying unpublished. Those are in the package as data evaluation records.

DR. ANNA LOWIT: Do those files have a common nomenclature? Because they receive many files. How would they know which ones were the DERs?

DR. DAVID AKERMAN: They should have MRIDs.

DR. MONIQUE PERRON: The file names are all numerical and end in .der. Any of those are .der records.

DR. LIANNE SHEPPARD: So just to clarify; I got the issue paper of course and there's all the materials that are in the docket, which are a little bit difficult to wade through, needless to say. And then I got a flash drive with FIFRA restricted documents. But what you're referring to is not clear to me I have.

DR. ANNA LOWIT: Maybe at the break we can talk to the SAP staff and find out where the files may have been posted.

MR. STEVEN KNOTT: They are in the docket and were linked for the panel members to access. It's all part of the background material that the panel did receive.

DR. JAMES MCMANAMAN: If they are .der maybe we can search for that and get that information to the panel members. Dr. Perron?

DR. MONIQUE PERRON: And actually you mentioned the FIFRA thumb drive, those are the actual studies. They're not the summary that we put together, those are the actual individual studies that have been submitted to the agency that are FIFRA protected.

DR. LIANNE SHEPPARD: So my next question was the evaluation of the FIFRA data that's not in the open literature for acceptability; if I understood you correctly, acceptability means that it meets guidelines. Is that correct? They're guideline studies? And there was no additional review done for acceptability other than they meet the guidelines?

DR. GREGORY AKERMAN: Yes. Correct. They were judged whether they were acceptable or unacceptable and if they were guideline. They could have still been non-guideline, you know, the data was of quality that we could use in the assessment.

DR. LIANNE SHEPPARD: Oh. It didn't have to meet the guidelines to be acceptable?

DR. GREGORY AKERMAN: Yes. That's correct.

DR. ANNA LOWIT: And one could conduct a study under the guideline and it still be unacceptable based on how it was conducted or problems that may have occurred in the laboratory. We used the guidelines as the structure and the framework, but the acceptable/nonacceptable is a statement of the science quality.

DR. LIANNE SHEPPARD: Thank you for that. I also had a question about Appendix A. The very last item in Appendix A is a retracted article by Seralini. What's the disposition of how that one was used?

DR. MONIQUE PERRON: Given that the article was retracted from the peer reviewed journal, we also excluded it from this.

DR. LIANNE SHEPPARD: Maybe you all are aware that it has since been republished in the peer review and so it's now in the peer reviewed literature, not retracted.

DR. MONIQUE PERRON: If that is the case, we have seen that study prior. And we had already identified issues with that study. In

particular, especially the number of animals that was used. There was only, I believe, ten per dose which is not enough for a cancer bioassay. In addition to many other issues that we identified in that study, prior to it being retracted, so prior to much of this process even.

And I will note that other agencies out there have not included the Seralini paper in their review as well. I think at this time there's just too much stigma around it. Again, you can suggest to us the reasons why we should reconsider it, but at this time it has been excluded from the current evaluation.

DR. JAMES MCMANAMAN: Yes. We can ask that that be read during the discussion of the charge questions. If you want to include that, please feel free to do so.

DR. LIANNE SHEPPARD: Thank you. And I had one final question and that was on page 22 of the document. For the 18 studies that weren't available to the agency you used summaries provided by other authors. I just wanted to have a little clarification of exactly what you meant. Because somebody else's interpretation of the data as opposed to actually

reviewing the raw data, you know, that's just a lot further removed.

DR. GREGORY AKERMAN: Yes. We recognized that for those particular studies in the review articles they did provide additional summary tables that were available online. And we did not include that, but we actually noted where we used that in the white paper. For those particular studies, we didn't have the actual individual data for those studies.

DR. JAMES MCMANAMAN: Dr. Taioli?

DR. EMANUELA TAIOLI: So for the unpublished studies, if somebody else wants to reproduce your process, how would they be able to come to your conclusion if those studies are not available? Is there a way for a scientist to get that kind of data in some format?

DR. DANA VOGEL: Yes. You can look at our data evaluation records at any time. However, if you want to get -- as you guys got on a thumb drive, anyone can make a FOIA request for that data should they want.

DR. JAMES MCMANAMAN: All right. Well, this has been a very good discussion. And we are a

little past the time for a break. Before we leave, we have an announcement about the microphones.

MR. STEVEN KNOTT: Yes. Just a brief announcement. We're getting some noise and feedback on the microphones. My understand is these are new microphones so there seems to be an optimal distance to be away from it to speak. If you're too close, it buzzes. But you have to be close enough to be heard; for the presenters and the panel, please remember that.

Something else that may help as well is just to make sure that your microphone is turned off when you're not speaking. And hopefully that will help get rid of some of the distortion.

DR. JAMES MCMANAMAN: So let's be back at ten after.

[WHEREUPON A BREAK WAS TAKEN]

MR. STEVEN KNOTT: Okay. I just wanted to welcome everyone back from the break. And there's a couple of things, one clarification I'd like to provide. This is Steve Knott, DFO for the meeting. Earlier there was some questions about these studies that are submitted that they include all the raw data, also referred to as 10G studies that are protected

from disclosure to foreign and multi-national pesticide producers under FIFRA 10G.

And just one clarification I wanted to provide for the public, those studies, since they were given to the panel do not have to be requested through FOIA. You can gain access to them by contacting the docket. You will still be required to file what's called an affirmation of non-multi-national status or something like that. You'll still have to file that form, but you just contact the docket, file that form and they'll be able to provide that information for you. You do not have to file a formal FOIA request.

Because those studies were provided to a federal advisory committee, this panel. I just wanted to provide that clarification on the process. And again, those 10G studies that the panel received are the raw data studies. That's why they're protected, that were submitted to the agency.

One additional question has come up for those who have the panel list. There's an additional panelist a Dr. Kenneth Portier -- I'm sure you seen on the panel list. A question was asked about where he is this morning. There's actually a conflicting meeting of the Science Advisory Board, one of their

committees, so Dr. Portier will be joining us tomorrow afternoon to participate in these proceedings.

DR. JAMES MCMANAMAN: Okay, with that welcome back, next presentation is, I think, Dr. Perron and so the floor is yours.

DR. MONIQUE PERRON: Thank you again, this is Monique Perron from the Health Effects Division of Office of Pesticides Programs. And I'm going to give a walk-through of our data evaluation of the epidemiological studies. A quick outline, I'm going through a quick introduction, walk through some of the study quality evaluation considerations.

Also, review the results of that quality evaluation and our determination of relevance to the current analysis. Go through a summary of solid and non-solid tumor cancer studies. And then some overall findings.

As many of you know, epidemiological studies may provide direct evidence on whether human exposure to a chemical may cause cancer. An initial evaluation of epidemiological literature was performed by the agency in 2014 as part of the registration review. A subsequent evaluation of the available epidemiological data was performed as part of the 2015

CARC evaluation, which added an additional three studies to those identified in the 2014 evaluation. Both the 2014 and 2015 evaluations considered design and overall quality of the studies. However, formal study quality evaluations and rankings were not conducted.

A total of 58 studies were considered in the current evaluation. This included all of the studies in the 2015 CARC evaluation and any additional studies identified as part of the systematic review. The analysis focused on primary literature and any associated meta-analysis that evaluated the association between Glyphosate exposure and cancer outcomes.

As such, reviews were used to identify potentially relevant studies. Studies with the most complete analysis, utilizing the greatest number of cases in controls, were evaluated for ranking. And all relevant studies were subjected to formal study quality evaluation.

This flow chart outlines the study evaluation process. This process aided in identifying studies that were relevant for the evaluation of the human carcinogenic potential of glyphosate. And those

studies that require detailed evaluation to assign a quality ranking.

Some of the points I just discussed are towards the top of this flow chart. And as you move down the flow chart, there are some additional questions regarding the collection of glyphosate-specific exposure information. And whether a quantitative measure of an association was reported for glyphosate.

Key considerations for evaluating studies included study design, exposure assessment, outcome assessment, confounding control, statistical analysis and risk of bias. It should be noted that these study quality considerations were specific to the issue of concern. As such these considerations are considered fit for purpose, and could differ in other regulatory or scientific context.

Although the basic concepts apply broadly, the study quality considerations have been tailored specifically to the studies investigating the association between glyphosate exposure and cancer outcomes. Table 3.1 of the white paper provides a matrix of the study quality considerations.

In a typical cohort study, individuals are classified according to exposure status and then followed overtime to quantify and compare the development of the health outcome of interest by an exposure group. In a prospective study, subjects are enrolled prior to developing a health outcome. While in a retrospective study subjects have already developed the outcome of concern.

The chief advantage of the cohort study design is that it affords the investigators the opportunity to avoid and/or adjust for potential biases. They also allow for discernment of the chronological relationship between exposure and outcome.

The primary disadvantage of a cohort study is the logistical inefficiency with respect to the necessary time, expense and other resources needed to conduct them.

In some instances, case control studies may be nested within a cohort study. And as a result, those studies may share many of the attributes of the cohort study. In a typical case control study, individuals are classified according to their outcome

status and exposure information is collected, as well as for additional risk factors.

Cases are those who have developed the outcome of interest and controls are selected that represent the population from which the cases arise. The relative odds of exposure are then compared to between cases and controls. The primary advantage of these types of studies is the logistical efficiency relative to the cohort studies. Often being conducted at a fraction of the cost then fraction of the time as the corresponding cohort study.

Cross sectional studies are used to evaluate associations between exposure and outcome prevalence in a population at a single time point or period in time. They're relatively quick and inexpensive to conduct as a long period of follow up is not required and exposure and outcome assessments occur simultaneously. It may be difficult to discern temporal relationships in these studies though, and prevalence rather than incidents of the outcome are often estimated.

Ecological studies are used to evaluate associations between exposure and outcomes using population level rather than individual level data.

The primary advantage of these studies are related to the logistical efficiencies since they often rely on pre-existing data sources, and don't require individual level of exposure, outcome or covariate assessment.

Although these are advantages, the lack of individual data may lead to inappropriate extrapolation of association observed on the aggregate level to associations on the individual level. These studies are also more susceptible to confounding.

In all of the studies, exposure information was collected from the subjects and/or proxy individuals using questionnaires and/or interviews. These exposure assessments typically include questions to determine the amount of direct to pesticide use or to collect information on behaviors and conditions associated with the pesticide use.

Studies that exclusively use subjects rather than including proxy individuals were considered more reliable since subjects would have a more accurate recollection of their own exposure. All except one study utilize state or national cancer registries, physicians and/or special surveillance programs to determine the outcome status.

In several studies cases were also verified by histopathological evaluation. Overall the outcome measures were relatively consistent across the studies and are likely to have minimum errors. The remaining study evaluated in detail Koureas et al. (2014). Utilized a low specificity enzyme amino acid to assess oxidative DNA damage rather than an association with a cancer type.

It was noted that there are more sensitive quantitative methods available for evaluating the same outcome as this study did. This will be discussed a little bit further in this presentation.

Confounding control varied across the available studies. Standard variables such as age and sex were adjusted for analytically or by matching. Some studies collected information on potential confounders. However, not all of these variables were evaluated or the results of the evaluations were not reported in the study.

The direction and magnitude for confounders are, in general, difficult to determine because they are depended on the relationship of each

factor with glyphosate and the type of cancer under investigation.

Given most people in the studies, who used pesticides occupationally, will be exposed to multiple pesticides and in some instances, those other pesticides are risk factors to the same cancer under investigation, it's a particularly important concern to address either the study design or statistical analysis. Across numerous studies co-exposure to other pesticides was found to be positively correlated with exposure to glyphosate, and exposures to those other pesticides appear to increase the risk of some cancers.

For example, Eriksson, et al. (2008) reported an unadjusted affect estimate for non-Hodgkin lymphoma, or NHL, that was 70 percent higher on a natural log scale than the adjusted estimate. As a result, effect estimates were expected to be inflated in the absence of statistical control. Besides co-exposure to other pesticides there are other potential confounders. For example, in the case of NHL, occupational exposures to diesel exhaust fumes, solvents and UV radiation are likely confounders that were adjusted for in any of the available studies.

In terms of statistical analysis, considerations or whether the statistical analysis was appropriate, whether there was a sufficient sample size. Evaluating some of the analytical decisions. For example, were any of the subjects left out of an analysis for one reason or another. And how well the statistical analysis was reported.

The internal validity of the studies reviewed was judged by noting the design strategies and analytical methods used in each study to constrain or eliminate selection bias and information bias.

Selection bias can occur when the sampling of the population by the investigator yield the study population that's not representative of the exposure and outcome distributions in the population sampled.

Put simply, selection bias occurs if selection of the study sample yields a different estimate of the measure of an association than that which would be obtained had the entire target population been evaluated. Selection bias in the currently reviewed studies may have been induced by a low participation rates, lost to follow up or selection methods of controls in case control studies.

Information bias arises when study participants are incorrectly characterized with respect to their exposure or outcome status. In the currently reviewed studies, misclassification may be due to recall bias from subjects or proxy respondents, an interviewer or observer bias.

The results of our quality analysis yielded three high quality studies. One was a cohort study utilizing the Agricultural Health Study in two case controls. The first De Roos et al. (2005) was the only available cohort study identified for evaluation.

As part of the Agricultural Health Study over 54,000 private and commercial applicators and their spouses were recruited as subjects. The publication evaluated the association of glyphosate and numerous cancer outcomes including solid and non-solid tumor types.

As part of this study, exposure information was collected at enrollment from subjects for glyphosate as well as other pesticides. In addition to covariates and other potential risk factors. There were three exposure metrics utilized, ever/never use, cumulative lifetime exposure and

intensity-weighted cumulative exposure. There were numerous factors adjusted and/or considered and this included co-exposure to other pesticides.

The second study, Koutros et al. (2013) is a nested case control study within the age as cohort that evaluated the association between pesticide use and prostate cancer. Exposure and other covariant information was collected again at the time of enrollment from the subjects.

From enrollment, the follow-up time was approximately ten plus years. In addition to reporting effect estimates using cumulative exposure and intensity-weighted cumulative exposures metrics, unlagged and 15-year lagged analysis were conducted as part of the study.

The last high quality study was Eriksson et al. (2008), which is a population based case control study from Sweden. In this study physicians treating lymphoma within specified health service areas identified cases and exposure information was then collected from the subjects. An effect estimate was reported for ever/never use with multivariate analysis that adjusted for co-exposure to particular pesticides, including glyphosate. There

was also a latency analysis performed, however the sample size and covariant adjustments were not specified for that analysis.

Twenty-one studies were assigned a moderate quality ranking. All of these were case control studies and shared many design characteristics. Exposure information was collected from subjects and or proxies. The study populations were from several countries and the sample size varied across these studies.

However, all of them utilize state or national registries or surveillance programs for outcome assessment. It was noted that none of them accounted for exposure to other pesticides.

Seven case control studies and twenty-seven descriptive studies were ranked as low quality. All except two were not subjected to detail evaluations since most reported based on a total pesticide exposure. In many instances glyphosate exposure was assumed and no glyphosate specific information was collected.

There were also studies that did not evaluate a cancer outcome. Cocco et al. (2013) was one of the two studies that received detailed

evaluation. Although, the study was included in the IARC and 2015 CARC evaluations, there was very low study power with only four cases and two controls. There was also inconsistent control selection with a mix of hospital and population based controls. A difference in overall participation rates was noted. Such that population base participation was lower.

And lastly, the study only reported ever/never use without accounting for confounders including exposures to other pesticides. The other study evaluated in detail that received a ranking of low was Koureas et al. (2014). It was a cross-sectional study performance with 80 pesticide sprayers in Greece.

As I mentioned earlier, this study evaluated oxidative DNA damage rather than a tumor type. And it reported a non-statistically significant affect estimate for glyphosate. However, there was no adjustment for standard covariates or potential confounders and there was questionable study power given the number exposed to glyphosate was not reported.

The immunoassay used for outcome assessment has low specificity and there are other

analytical methods available that are more sensitive. Such as HPLC with electric chemical detection or GCMS.

Lastly, it was noted that the study evaluated primary DNA damage, but does not measure the consequence of that genetic damage. An increase in oxidative damage may lead to cell death or initiate DNA repair rather than lead to a mutation.

All of the high and moderate quality studies were considered relevant to inform human and carcinogenic potential of glyphosate. Studies assigned a low ranking were not considered reliable to evaluate the association between glyphosate exposure and cancer outcomes due to limitations identified.

With respect to meta-analysis, caution should be taken when interpreting the results. Meta-analysis is a systematic way to combine data from several studies to estimate a summary affect for meaningful results, careful consideration of whether studies are similar and should be combined in the analysis. Furthermore, the bias and confounding issues inherent for each individual study are carried over into those meta-analyses.

I'm going to hopefully, briefly go through each of the studies; as many of you know there

are quite a few. First starting with the solid tumor types. As I mentioned many of the studies utilized the Agricultural Health Study cohort. And in De Roos 2005 it evaluated numerous solid tumors, which included all cancers and specific anatomical sites.

Additionally, there were nested case control studies that evaluate specific anatomical sites as well. No association was observed with glyphosate exposure utilizing any of the exposure metrics, ever/never used cumulative life time exposure and intensity-weighted cumulative exposure for all of the types of cancer listed there. I won't run through all of them.

For prostate cancer, there were two studies that utilized subjects from the age as cohort. Neither found an association between glyphosate exposure and prostate cancer. It was noted that both of these identified cases during the prostate specific antigen or (PSA) area, which means that the cases were typical identified at an earlier stage in progression of the disease.

A case control study in Canada was also available that evaluated the association between glyphosate exposure and prostate cancer. The study

was conducted prior to the (PSA) area so it included more advance tumors before diagnosis. A non-statistically significant effect estimate was observed. It was noted that there was no adjustment for exposure to other pesticides in this study. And as I mentioned, in many of studies we noticed that when adjustment was not made for other pesticides, there was inflation of effect estimates.

For brain cancer, two case controls studies were available. The first reported a non-statistically significant effect estimate of 1.5. There was no adjustment for exposure to other pesticides and it was noted the results differed when using subjects who self-reported their exposures as compared to the proxy respondents.

In the other study, Yiin et al. (2012), there was no association observed for home and garden use or non-farm jobs. After adjusting for age, education, sex and use of other pesticides.

There was only one study available each for evaluating stomach cancer, esophageal cancer, and soft tissue carcinomas. No associations were observed with these tumor types despite a lack adjustment for exposure to other pesticides. Control selection

issues were noted however in the soft tissue carcinoma study.

Lastly, total childhood cancer was evaluated in Flower et al. (2004), which is a nested case control study in the Agricultural Health Study. There was no association observed between maternal or paternal exposure to glyphosate.

So overall, with respect to solid tumors, no evidence of an association between glyphosate exposure and any solid tumor types was observed. Many of these, though, were limited to one or two studies and most studies did not adjust for co-exposure to other pesticides. In some cases, there was low or questionable power in the case control studies.

So now moving on into the non-solid tumors. There were two studies considered relevant for evaluating leukemia. In the cohort study De Roos et al. (2005) there were no statistically significant effect estimates observed using any of the exposure metrics. And no trend with increasing exposure.

In Brown et al. (1990) there was no association observed however, it was noted that there was a relatively low number of cases exposed to

glyphosate. In addition, there was no adjustment for co-exposure to other pesticides. Chang and Delzel recently conducted a meta-analysis for leukemia using these two studies as well as one that we ranked as low. The meta-risk ratio was equal to the null.

For Hodgkin lymphoma, there were also two case control studies available. Karunanayake et al. (2012) found no association following adjustment for age, Canadian province of residence and certain medical history variables. There was no adjustment for exposure to other pesticides.

In Orsi et al. (2009) a non-statistically significant affect estimate of 1.7 was observed. However, there was a low number of glyphosate exposed cases in this study. Which yielded a wider confidence interval for the estimate. Again, no adjustment was made for exposure to other pesticides. Chang and Delzel, also did a meta-analysis using these two studies and the ratio came out to 1.1.

For Leukemia and Hodgkin lymphoma there was no evidence of an association with glyphosate exposure. Both were limited to two studies for each cancer type. In almost all cases there was no

adjustment for exposure to other pesticides and in some instances, there was some questionable power issues.

For multiple myeloma, there were five studies available which included the cohort study and four case control studies. The ever/never affect estimates ranged from 1.19 to 2.6; all of these, though, were non-statistically significant. The only study to adjust for exposure to other pesticides was the cohort study De Roos et al. (2005). However, it was noted that a restricted dataset was used for its fully adjusted model.

Two studies evaluated the exposure response relationship. In the cohort study, there were non-statistically significant trend and risk ratios reported when stratified by tertile. A statistically significant trend and risk ratio was reported when stratified by quartiles. However, the cases were sparsely distributed with the additional stratification. And this also yielded particularly wide confidence intervals.

Kachuri et al. (2013) stratified subjects into light and heavy users. There was a non-

statistically significant increased odds ratio reported for heavy users.

However, there was a low number of cases in controls exposed to glyphosate in the study. And again, there was no adjustment for co-exposure to other pesticides.

As I mentioned there was a note that the De Roos et al. cohort study used a restricted dataset. Sorahan (2015) reanalyzed the full dataset using Poisson regression. And compared the results to the restricted dataset. An ever/never estimate of 1.12 was obtained and the author concluded that the restricted dataset might not be representative of the cohort population in that case.

And lastly, a study by Landgren et al. (2009) was also available that looked at pre-clinical marker of multiple myeloma. The study found no association between glyphosate exposure and MGUS.

In a meta-analysis, Chang and Delzel produced meta-risk ratios using four independent study populations. Using those they consider prioritize studies a non-statistically significant meta-risk ratio of 1.4 was obtained.

When using alternative estimates for a study population, for example, substituting the data for De Roos et al. for Sorahan, relatively no impact was seen on the meta-risk ratio.

At this time, the agency does not believe that the epidemiological evidence for glyphosate is adequate for multiple myeloma. The data are limited due to potential confounding concerns. There are concerns with the restricted dataset and there are small sample sizes.

Additionally, there was a limited observation of a possible exposure response relationship in a single case control study, but this observation was not seen in the cohort study and was most likely limited by sample size.

For non-Hodgkin lymphoma or NHL, there were six studies available, one cohort study and five case control studies. Effect estimates using ever/never use as an exposure metric range from 1.0 to 1.85. Although these estimates were non-statistically significant, two of the studies did not adjust for other pesticides and the small sample sizes were noted in several case control studies. Meta-risk ratios have been calculated by several researchers and have

ranged from 1.3 to 1.5, which were primarily non-statistically significant.

Three studies evaluated the exposure response relationship between glyphosate exposure and NHL. In the cohort study, De Roos et al. reported effect estimates less than one for cumulative and intensity-weighted cumulative exposure metrics. And this was the only study that adjusted for exposure to other pesticides in this case.

In Eriksson et al. (2008), non-statistically significant effect estimates were reported when stratifying by days per year of use. A statistically significant odds ratio was reported for those with greater than ten years of use; however, there was questionable power and a relatively wide confidence interval. Furthermore, this estimate was likely inflated given there was adjustment for exposure to other pesticides.

Lastly, McDuffie et al (2001) reported a statistically significant odds ratio for subjects with more than two days of use per year. Again, this is mostly likely inflated since there was no adjustment for exposure to other pesticides. And it should be noted that it's difficult to make

conclusions regarding dose response with only two exposure categories as was used in the two case controlled studies, Eriksson and McDuffie.

Across the six studies evaluating NHL, several issues and concerns were discussed in the white paper. As I have mentioned already there were limited sample sizes in several of the case control studies. In most instances, there was no control for potential confounders such as exposure to other pesticides as well as diesel exhaust fumes, solvents and UV radiation.

Recall bias and missing data are also limitations. The quality of the exposure assessment is a major concern since the validity of the evaluations depends, in large part, on the ability to correctly quantify and classify an individual's exposure.

The use of proxy respondents has the potential to increase recall bias and thus may increase exposure misclassification, especially for those proxies that are not directly involved in pesticide application and farming operations. They may be more prone to inaccurate responses.

It was noted that higher effect estimates were reported in studies during a period of relatively low use of glyphosate. As I discussed earlier today in the overview, glyphosate use has dramatically increased following the introduction of glyphosate tolerant crops.

If a true association exist, prevalence alone would not be expected to result in corresponding increase. However, the use pattern has changed since the introduction of these crops; such that individuals that were already using glyphosate are increasing their exposure.

As a result, if a true association exist between glyphosate exposure and NHL, then higher effect estimates would be expected in more recent studies. However, this trend was not displayed.

Some have argued that the follow-up period in the cohort study is not sufficiently long to account for the latency of non-Hodgkin lymphoma. However, we have noted that the latency of NHL is relatively unknown. Also, the current evaluation was restricted to total NHLs since the sample sizes were too small for those instances when subtypes were evaluated.

There are approximately 60 subtypes of NHL classified by WHO and there may be etiological differences between them. Further analysis is really needed to determine the latency time of NHL and NHL subtypes.

In summary for NHL, the ever/never effect estimates were relatively small in magnitude ranging from 1 to 1.8 and were all non-statistically significant.

There are conflicting exposure response results between the cohort and case control studies. There were several limitations and concerns identified for these studies and at this time chance and/or bias cannot be excluded as an explanation for any observed associations.

And just mentioned, as part of question 2d, we specifically ask about our evaluation of the NHL studies. Wrapping up, in this evaluation of the available epidemiological studies, 58 individual literature studies were considered; 24 of these were ranked high or moderate and were used to inform the carcinogenic potential of glyphosate. These studies covered a range of solid and non-solid tumor types and

were mostly case control studies conducted in the United States or Canada.

There was no evidence of an association between glyphosate exposure and any solid tumor types, leukemia or Hodgkin lymphoma. At this time, the data are inadequate to evaluate the association between glyphosate exposure and multiple myeloma, and for NHL a conclusion could not be determine based on the available data. At this time, I'm glad to answer any questions before we would move on to the animal bioassays.

DR. JAMES MCMANAMAN: Thank you Dr. Perron. Dr. Johnson.

DR. ERIC JOHNSON: I'm not sure that I'm missing something, but the three high quality studies, you said there was one cohort and two case control studies. But I think the Koutros et al. 2013 is a cohort study. They measure the rate ratio and Poisson regression, so I don't see how it's classified as a case control study unless I'm missing something. Unless that's for the same reference.

DR. MONIQUE PERRON: Sorry, you're asking about Koutros?

DR. ERIC JOHNSON: Yes, 2013.

DR. MONIQUE PERRON: That was a nested case control study within the cohort. We spoke to someone at AHS and they said that was a nested case control study within it.

DR. ERIC JOHNSON: In the statistical analysis in the paper, if you look at it, it's rate ratios that they measured. And they did Poisson regression. I didn't see anything about odds ratio there on that paper. Unless it's the wrong reference.

DR. MONIQUE PERRON: I'm sorry this is Monique Perron --

DR. ERIC JOHNSON: Maybe if you look at the abstract it says that it was rate ratios that they measure.

DR. MONIQUE PERRON: Okay. We can go back in and look. I believe though, again, I spoke with people at AHS and they classified it as a nested case control study.

DR. ERIC JOHNSON: No. No.

DR. MONIQUE PERRON: As I mentioned earlier, many nested case control studies share many of the attributes of the cohort study they're in. So -- but that's fine we can reclassify it as a cohort study if that’s more appropriate.

DR. ERIC JOHNSON: I think it's a cohort study. Yes. It's a full cohort study.

DR. MONIQUE PERRON: Okay.

DR. JAMES MCMANAMAN: Other questions. Dr. Green.

DR. LAURA GREEN: Hi, thank you. I think we all stand in awe of the amount of work you had to do. We're very mindful of the fact that there's a heck of a lot of stuff to go through. Any questions we have, I hope you appreciate come from respect but also humility. We're not sure we could have done all that work.

Having said that, I'd be curious to know, within your health effects division, when you look at other materials that you have to register or reregister. I assume much of the time you have actual exposure data which, to my mind, mean something, at least, semi-quantitative or more precisely actually quantitative; i.e., milligrams per kilogram per day or levels in blood or levels in urine or something.

I don't know if that's true but I'd be interested to know. It seems to me, unless I'm missing something, that for glyphosate -- and I'm wondering whether this is unique or kind of the usual

problem for you all. That when you say exposure here, with regard to the epidemiologic studies, I didn't see, even within the Agricultural Health Study, a single number. Is that unusual or is that kind of what you have to deal with all the time?

MS. DANA VOGEL: This is Dana Vogel, I'm going to try not to speak too close to the mic.

DR. LAURA GREEN: Oh, I'm sorry, was I?

MS. DANA VOGEL: No, no, no. I been doing that. If we talk about true exposure, a lot of what we do -- there is a little bit of biomonitoring data and Anna will explain the kind of biomonitoring data that we get. But what we usually do, and the context of our risk assessments, is there's a lot of data submitted that's hazard data. There is not a lot of data -- actual data -- that's submitted from the registrant that's exposure data.

A lot of what we do, we get data from other places. We rely upon other sources, especially for dietary, we rely upon other sources. And a lot of what we do, especially when we're talking about occupational and residential exposure, is we have policies and procedures that have been vetted where we estimate exposure; so based on what we know about how

people are exposed, the label and how -- like for instance the application rate and what we know about -- if we're talking about agriculturally -- how people would apply a pesticide, the different kind of activities that might happen for a given crop.

As a handler, mixer/loader, post application, we use all of that information to come up with an exposure estimate for the different potential scenarios of how people might be exposed, occupationally, residentially, through the diet.

That's the majority of the data that we have. Would like add anything? He's making faces, he's the exposure expert. If I miss anything he's going to come up and tell me. That's the majority of what we do, but there's a lot of data that supports those assessments. There are data that we have that support how people are exposed through different post application activities that they might conduct.

There are data that help us understand how someone might be exposed given a certain kind of application for a mixer/loader. There are data that we've looked at to develop residential scenarios of how different populations, given how pesticides is

applied, how people may be exposed, whether they're applying it or whether it's post application.

We look at all the different routes for a given scenario, but a lot of that work is based on data that we have and our policies on how we put all that data together to come up with an exposure estimate.

MR. JEFF DAWSON: Sorry, Jeff Dawson, Health Effects Division. The only thing I would add is within, for example, the Agricultural Health Study, the exposure metrics that are used as predictors, are part of the same information that Director Vogel was discussing, has been used in the development of pieces of those exposure metrics as well. That's one thing to think about.

DR. ANNA LOWIT: So this is Anna Lowit, to add on to that. Based on what Dana and Jeff both explained, our program has a very long history of doing exposure assessment for both workers and residential. All of our approaches have been heavily peer reviewed by different parts of the SAP over the last ten to fifteen years. Our exposure approaches are heavily vetted and strongly supported.

Around the 2010 timeframe, we actually brought to the SAP some case studies that we were doing at that time, looking at the Agricultural Health Study, and trying to do some comparison of their binning of their exposures and how they match to our exposure equations for workers in particular.

And it actually turns out that when AHS was originally developing their exposure algorithm, they came to us, to our program. And so there's actually a strong correlation between their exposure binning and our exposure assessments.

And there is a case study -- I think it's a SAP from 2010, where we actually do some analysis in the context of Atrazine. We actually went through the Atrazine Agricultural Health Study and compared it to how we had done some of our work. And there's actually a really nice comparison there. They don't provide numbers per se, but we have confidence that they're able to accurately bend them.

DR. LAURA GREEN: So if I understand, which perhaps I do not, the De Roos et al. (2005) paper that you went over, contains zero quantitative exposure assessment, right? There's no number. But you separately have -- within your group -- so for

example they say high cumulative, you know, medium cumulative, low cumulative, but there's no number.

What I'm asking is can we as a panel get from you all, or get from the document, any numeric matching so that when we look at the De Roos et al. high cumulative exposure group, we can say to ourselves, okay so that appears to be equal to XPPM years or something like that. Or is that information not available? Do you see what I'm asking?

DR. MONIQUE PERRON: So you are correct. There's no quantitative exposure information integrated in that study, as well as across any of the studies. None of them do; they all do the same type of questionnaire based information type of retrieval for exposure information.

I think the one unique thing that Anna just pointed out though, is that we have a lot of confidence in the Agricultural Health Study because we've actually worked with them and they've actually utilized our exposure algorithm as part of their binning of exposure.

In that case, we do have a little bit more confidence in that type of metric. We can't really speak towards the other ones. None of them

provided any of that type of information across any of the studies. Whether it was solid or non-solid tumors.

DR. ANNA LOWIT: So if it's okay to the panel if our technical team -- most of the exposure people are not here in the room -- we can speak over lunch or may be to the afternoon on what could be provided relatively quickly. If we would just have you keep in mind that we're in the middle of doing our risk assessment for registration review. It would not certainly be complete and it would be some preliminary things to give you a sense of the ballpark. But we would have to get together as team and it certainly wouldn't come today, tomorrow at the earliest.

DR. LAURA GREEN: Friday's fine.

MS. DANA VOGEL: And again, just recognizing that it is an exposure estimate based on our policies and procedure and how that compares to what was actually happening. You know, it's just back to what Anna said about what we know in our dealings with AHS.

DR. ANNA LOWIT: And it might be informative, if we can -- because SAP staff can help you find the link to the SAP where we looked at the

occupational assessment where we've done some cross validation with my biomonitoring studies to show how our occupational assessments match the biomonitoring. And I'm looking at Jeff because he did that work. That may also help you ground truth sort of some of where --

DR. ANNA LOWIT: Great. Thank you very much.

DR. JAMES MCMANAMAN: Okay. We had Dr. Crump over here had a question.

DR. KENNY CRUMP: I noticed that with the animal data that EPA did a lot of analysis of the data and published your own analysis. I wonder if there was any attempt to do the same with the epidemiological data. I know that, I think, at least some of these studies were paid for by federal funds so the data should have been available.

And one reason that I'm interested is that there were several studies where I wondered why they did the analysis this way. And I wondered what they would have gotten if they had done the analysis another way. And I would be interested in an answer to that question. I just wonder if you ever retrieved any of the data, or tried to retrieve any of the data,

from any of these studies to do your own analysis of them?

DR. MONIQUE PERRON: At this time, we do not have access to any of the data for any of these studies. I don't know of anybody else have anything to --

DR. ANNA LOWIT: With respect to the Agricultural Health Study, we could put in a request if -- let's say for one of the AHS studies, whether it's the De Roos cohort or one of the nested case controls, if there was an initial analysis that one of panel members thought would be useful, there are processes by which we can request and receive those data. In fact, we've done some collaborative analysis with them and our preference would be, I think, to work with the NCI staff to do that.

But it's certainly within your purview to recommend some of those suggestions. But all federally funded studies we don't necessarily have access to it. It depends on which ones.

DR. KENNY CRUMP: Well, I think the reanalysis of De Roos study that was published gave some useful additional information to help interpret

that study. I think that might be true of other studies as well if we could get the data.

DR. JAMES MCMANAMAN: Okay that was Dr. Lowit. Dr. Taioli.

DR. EMANUELA TAIOLI: So my general question as an epidemiologist, we are used to looking at several other pieces to come to conclusions. We think about looking at levels of the compound in the body or, in this case will be urine because I understand it's excreted. How much is, you know, in a sample of people, we're interested in looking at the environmental exposure, in this case diet, and then we look at the occupational exposures.

Now here you have a lot. You have some data on occupational exposure, but where are the other pieces? I can't believe that with all the cohort studies that are available, here and in Europe, nobody has taken the time to look at the urinary levels necessary with cancer, which is a very straightforward piece of information, because this is very lacking. There is a lot missing here.

DR. MONIQUE PERRON: Yeah, you're correct. As of right now we are not aware of any studies that utilized biomonitoring exposure for their

exposure estimate and correlated it with a cancer outcome. There are some studies available that have just looked at urine levels in particularly farm workers and not surprisingly.

I think the interesting thing there is that the urinary values didn't necessarily always correlate with their exposure level. You might see a low urinary value for somebody who is binned into the high category. I think this goes back to some of the issues I kind of brought up earlier today, where this chemical is not very well absorbed and there's not a very long -- there's not a high prediction of whether it will sustain a biological dose.

There may be issues with it. That might be why people have not gone that route. I'm not sure, I can't really speak towards that. But at this time, we don't have any epidemiological studies that looked at the data that way.

DR. ANNA LOWIT: This is Anna Lowit. I will add one thing to that. With respect to interpreting urinary biomarkers for glyphosate, first it's poorly absorbed; that which gets absorbed is quickly released from the body. Within 24 hours an exposure is likely to be gone from the body.

An epidemiology study that would use that urinary biomarker would be heavily controlled. Because you'd have to match the taking of the urine with the applications. The note that Monique said about the biomonitoring data we do have, they don't necessarily match to -- application time and the amount in the urine don't match because of that rapid excretion.

DR. JAMES MCMANAMAN: Thank you Dr. Lowit. Other questions, David.

DR. DAVID JETT: So the only thing I was thinking -- the general question is maybe a yes or no answer. But for me, you know, the issue of multiple exposures -- exposures to other pesticides is huge in way I'm thinking about this. I mean, you know, we heard this a lot with a lot of the studies that this was one thing that sort of reduced the level of confidence. Is there a standard way that EPA tries to adjust for multiple exposures? Can it even be done?

DR. MONIQUE PERRON: We didn't conduct any of these studies, first of all. In our evaluation, typically multivariant analysis are the primary way that they adjusted for the co-exposure to

other pesticides. In a simpler term, you may include it in your regression model as a covariate.

I think that's all a part of what I was talking about and one of the study quality considerations is, you know, how are you adjusting for different covariates and confounders, and do you think that's appropriate. That's primarily what we're looking at because, as I said, we are not conducting the studies and we don't have access to the data typically, almost all the time.

If we did, we could evaluate what we think would be the most appropriate, depending on the study, but as a long-winded answer, no we don't have an exact way that we do it since we're not actually --

DR. DAVID JETT: Wouldn't you need to know about the carcinogenic potentials of these other pesticides as well? And that's sort of the limiting factor -- well, one of the limiting factors, I think.

DR. MONIQUE PERRON: Sure. For it to be considered a confounder it needs to have some association with glyphosate as well as the cancer outcome of concern. In that case, you would consider it a confounder, but then also things like age and sex

are covariates. Maybe it might just be an important covariate that needs to be adjusted for.

It may not be necessarily causing the cancers, but you may need to adjust for it to make sure that you are getting an accurate effect estimate.

DR. ANNA LOWIT: This is Anna Lowit. I want to add one quick thing to that. I think the question about being able to control for other pesticides highlights the power of the Agricultural Health Study; that they're looking at the -- at least at the time they started -- the fifty most heavily used pesticides here in the U.S.

And so that at least for those they're able to -- because the individual growers reported what they had been using, so they can do appropriate matching of an individual and what they may be using at the same time or across the same years. I think it really highlights the value of the AHS.

DR. JAMES MCMANAMAN: Dr. Green.

DR. LAURA GREEN: This is Laura Green. To Dr. Jett's point, as Professor Johnson mentioned earlier this morning, absent any epidemiologic or clinical study of men and women who make glyphosate, I think we're all at a bit of a loss. Clearly, if we

had data on glyphosate manufacturers, and that's all they make, well that obviates the confounding issue. And I would argue, and I'm surprised that the draft document does not discuss this more broadly, as I'm sure you all know because you work with farmers a lot, for many decades NHL has appeared to be at slight excess among farmers.

There are many hypothesis as to why this is. Some of them revolve around herbicides, fungicides, rodenticides and other insecticides, other pesticides. Some revolve around antigenic stimuli that are present on farms and not in urban settings, for example.

And this is another reason, I think, that all the money being spent on the Agricultural Health Study might perhaps be better spent if you were in a position to ask your registrants to look at their workers; and maybe not in the U.S. where industrial hygiene is good, but maybe again in China -- not to pick on China.

But, if you had the power to ask your registrants to look at their own workers, even if it were only to, let's say, look for chromosomal abnormalities and circulating lymphocytes, right.

I mean there's lots of ways to do this, you don't have to wait for fraying cancers, although that would be nice. It just strikes me as very odd that the entire draft document is in sort of three pieces.

There's the very high dose rodent data on, as I've said before, I believe, the wrong molecule because it's not the isopropylamine, but that's another issue. Then there's this epidemiologic data which Dr. Perron and her colleagues have very carefully shown is --

DR. JAMES MCMANAMAN: Dr. Green, is there a question here? Is this clarification or is there a comment?

DR. LAURA GREEN: **--** All right, I'll stop. But I'm trying to --

DR. JAMES MCMANAMAN: -- I think it's an important comment but --

DR. LAURA GREEN: -- I'm trying to help you get what I think would be reliable scientific data that wouldn't be plague by confounders.

DR. JAMES MCMANAMAN: But I think that for the end of the charge question more appropriately.

I think it's a good question but just in a little while. Over here.

DR. ARAMANDLA RAMESH This is Ramesh. If occupational exposure to glyphosate comes under the purview of OSHA but not EPA, how come occupational exposure to diesel exhaust fumes was viewed as a confounder for non-Hodgkin lymphoma?

DR. MONIQUE PERRON: So just to clarify manufacturing and production of glyphosate is not under our purview. Occupational applications, mixing/loading or even workers who go into a treated field after it's been treated with glyphosate, those are under our purview, just to clarify. It's not all occupational that's under our purview. There are certain aspects such as production and manufacturing that is not under the purview of OPP.

DR. JAMES MCMANAMAN: Okay Dr. Zhang had a question.

DR. MONIQUE PERRON: This is Monique Perron, again I keep on forgetting

DR. JAMES MCMANAMAN: Dr. Perron.

DR. MONIQUE PERRON: I keep on forgetting. Just on the occupational diesel exhaust fumes side, that is considering diesel exhaust fumes

while they are applying or mixing or loading anything, that type of exposure. It is applicable for the current evaluation that we're discussing.

DR. JAMES MCMANAMAN: Dr. Zhang.

DR. LUOPING ZHANG: Hi, this Luoping Zhang from Berkley. Just want to cover one practical question and just to try save our time. I noticed you have three categories, high, medium and low; and you include the three highs in the 21 medium, right, so total is 24 studies. But in your documents and in our charge question there's only 23 studies. Last night I reviewed the reports again, one sentence just says, okay 23 of the 24, but didn't say which one dropped and also why you dropped that one. It's definitely from medium, so this is question number one.

DR. MONIQUE PERRON: Sure, I apologize. Sorry, I apologize. That would be a typo. All of the studies that were high or moderate were included. All of them. If they were high or moderate, they were included.

DR. LUOPING ZHANG: So then that's 24, but our charge question is 23.

DR. MONIQUE PERRON: Exactly, it was a typo. I apologize.

DR. LUOPING ZHANG: There is a sentence to say 23 or the 24.

DR. MONIQUE PERRON: Yes, I apologize for that.

DR. LUOPING ZHANG: So I couldn't find it anywhere.

DR. MONIQUE PERRON: There were a lot of moving parts during this process.

DR. LUOPING ZHANG: Okay. This is my question number one. Can I ask a next question?

I also noticed from your presentation, from all the low-quality group, all except the two, not subject to detailed evaluation, which of course you went through the cohort 2013 and 2014. I'm just curious, you know, since it's the low, I didn't really pay attention to look the original.

But I just wondered, thinking you may already know, what's like Cocco 2013, what's their findings just roughly. Definitely, they did a cancer outcome. And then you list all the reason why you excluded, because is the one IARC included in this study and also your 2013, CARC evaluation was included.

So back to my earlier question, I thought from the earlier data one, everything included in 2015 CARC evaluation is included in the current, but here in Cocco 2013, it's not.

DR. MONIQUE PERRON: So this is Monique Perron. I will remember one of these times. As we discussed during the systematic review, it was covered in the evaluation, but we went to quality evaluations at that point afterwards to determine which ones are relevant and could inform the human carcinogenic potential of glyphosate.

In the case of the study you're talking about Cocco, it was only four cases and two controls. I don't necessarily remember exactly what the effect estimate came out to be for that study, but regardless, we did not think that the study was robust enough to be included. It was put into the low category at that point. I don't know if that clarifies it a little bit more for you.

All of the studies in the 2015 evaluation were considered as part of this evaluation. That's what we meant, was that all of them were considered. And then going through the study quality evaluations, they were then binned into whether they

were considered high, moderate or low at that point. And if they were low, we then determined that those studies would not be informative for our issue of concern.

DR. ANNA LOWIT: So this is Anna Lowit. I'm going to add some big picture thought to what Monique said. I think to some degree the difference between what you see in the CARC and what you see in the white paper, that you're to review, is an evolution that's occurring within our office as we bring in systematic review.

In 2015, we had a smaller number of epidemiology studies, we had a smaller number of gene toxin and animal studies. We had some had awareness that that was not a complete set of the information. The other thing is as we -- so we've done the systematic review with the literature search, but what we've also done is a more transparent objective look at those studies and how we grade them and how we weight them.

If you go back to the CARC, it's a little bit unclear how those studies were graded and how they were weighted in the analysis. Whereas, in the new paper it should be more clear how we evaluated

them and how we've weighted them. We've made that evolution, which we think is an improvement to our analysis.

DR. JAMES MCMANAMAN: Dr. Sheppard.

DR. LIANNE SHEPPARD: I wanted to make sure that there's a correction registered in the record. You mentioned both in your presentation and just now, the Cocco paper, it's four cases and two controls, they're exposed. The study's actually much larger than that. Several places in the document the word exposed is left out. And it becomes, I think, quite misleading when you leave that word out.

DR. MONIQUE PERRON: Yes, thank you for that clarification. When we're discussing the low sample sizes we're referring to the glyphosate exposed cases on the glyphosate exposed controls in that case. We apologize for that oversight.

DR. LIANNE SHEPPARD: Yeah. Another thing in your presentation, you said the Agricultural Health Study was spouses and applicators, but in fact, the De Roos paper is only applicators. And there's very, very few women, implying also that there are no spouses.

I know there are some of the data analysis of the Agricultural Health Study that includes spouses, but most of them appear to me to not include spouses.

DR. MONIQUE PERRON: Yeah. Your correct, sorry. When I was discussing the Agricultural Health Study I was speaking towards it broadly at that point because it did enroll both subjects and their spouses. But for De Roos, yes, it was only the subjects.

DR. LIANNE SHEPPARD: To maybe get more into the decision making you all made, can you help me think about the relative weight of the ranking of all the criteria that you used? Like was there something that trumped everything else in terms of up or down weighting it?

DR. MONIQUE PERRON: I would say that the co-exposure to other pesticides, we tended to focus on greatly. Overall, we tried to look across all of the aspects, the key considerations, to see where we thought that they would be appropriately ranked.

We tried to capture that in table 3.1 in the study matrix that goes to those key

considerations. I think the only thing that maybe you can say is what you put it is trumping maybe -- I wouldn't say trumping; I would say that it was heavily weighted.

Yeah. It was heavily weighted whether or not that adjustment was weighed because we noticed across many of the studies how much that impacted the effect estimates. I'm not sure if that answers your question or not.

DR. LIANNE SHEPPARD: Yeah. And how did you weight the power considerations?

DR. MONIQUE PERRON: So typically, if they were what we -- because there's not bright line on what is considered low, very low, and not adequate. We had some discussions about how some people do try to have their bright line, but that varies across different people. Some people think it's ten; some people think it's twenty.

If it was less than ten, we definitely thought that that was very low for the study power. In the tens to twenties, you know, we said questionable in many of those cases. Then past that, a lot of time we didn't really note it as being low or moderate at that point.

DR. LIANNE SHEPPARD: So by ten you mean exposed cases and controls or you mean something else?

DR. MONIQUE PERRON: Yes, ten, like in terms of the exposed cases, because -- typically with the case control studies considering there's only one cohort here or two. So yes. We're talking about the exposed cases and the exposed controls that I'm speaking towards, thank you.

DR. LIANNE SHEPPARD: Yeah, and so just as a -- and we'll get this later, but I would probably refrain from talking about it as power. Because once a study's done, the effect estimate and the confidence interval will give you all the information you'll actually need. A better way to frame it would be just, you know, low numbers as opposed to power. Because that implies you can do power calculations after a study's done and really the study results contain everything you need.

DR. JAMES MCMANAMAN: Dr. Taioli.

DR. EMANUELA TAIOLI: Yes, Emanuela Taioli. I have one point about your presentation as well. You have in the text as well, when you talk about the Eriksson as in the example that by adjusting

the odds ratio you go down 40 percent adjusting. I went back and looked at the paper, it's not adjusted for the other pesticides; it's adjusted for age, gender and personal variables.

It is not a good example to bring to your point because the -- I went back and look at the paper before leaving and it's basically the same odds ratio, but adjusted for covariate. Your example was about adjusting for other pesticides. That's what you wanted to portray.

DR. MONIQUE PERRON: So Eriksson performed -- sorry this is Monique Perron -- Eriksson did perform a multivariate analysis, which included other pesticides and that was what we were comparing to the unadjusted at that point.

DR. EMANUELA TAIOLI: Go back and look at the numbers. Maybe the numbers that were extracted are not appropriate for your point.

DR. MONIQUE PERRON: Okay, we'll go back and check. Thank you.

DR. JAMES MCMANAMAN: Dr. Zhang.

DR. LUOPING ZHANG: This is Luoping Zhang. Could you put back to your slide number four, number four and five? I just have -- current review.

DR. MONIQUE PERRON: This one?

DR. LUOPING ZHANG: Yes. You have the one -- from the bottom number two, studies with the most complete analysis utilizing the greatest number of cases and the controls evaluate for ranking.

From the back slide, I think that that's also on the third one. If you go next slides. My understanding -- it's like the third bar, right. That's how you evaluate. Is that how you compare it if the papers study from the same. It's from the same. Then you are picking up a one, which you use most -- you know, most subjects you include in most of the cases. So not from different studies, is that correct?

DR. MONIQUE PERRON: Right. This is Monique Perron. Those are primarily regarding pooled analysis. In the paper, it discusses how the same study population was looked at and then what happened was another study came along and pooled the analysis from those.

If you actually look in the back -- I don't remember which appendix. But there are actually little family trees to show you how the different studies are related. In one case, it's the same exact

study except that they, you know, did a follow up a few years later on the same exact study population.

In other cases, it was maybe three different studies that were pooled together to make the number of exposed cases and controls, in that case. That's what those are referring to. If you look at that appendix, I think, it might be clearer how those studies relate to one another.

And then in one of the tables that goes through the different studies, we note, you know, this study did not get a detailed evaluation because it was included as part of another study. And it usually says what that study was. I believe that is all noted fairly well along the way in the white paper.

DR. LUOPING ZHANG: Okay. For that you use data from the same source.

DR. MONIQUE PERRON: You're using the one that is the most, yeah, the most complete analysis.

DR. LUOPING ZHANG: Just for clarifying, you mean the pool analysis, but you don't really mean meta-analysis in this case.

DR. MONIQUE PERRON: Correct, this is not meta-analyses, no.

DR. LUOPING ZHANG: My next question is for the non-Hodgkin lymphoma, they are three recent meta-analyses and it could have been the only meta-analyses. You show, from your presentation, they all consistently show the positive association. I'm just wondering how, out the end -- how your conclusion come.

I mean, for any of these epidemiological studies, there's always some uncertainty for most of the human studies, right. So now meta-analyses are the one to sort of help us to see difference between studies. And it was three independent meta-analyses consistently show some association. So how could, you know, your documents come up with that? Just help me to understand the conclusion.

DR. MONIQUE PERRON: Sure. This is Monique Perron, when you're referring to three meta-analyses, I should say that one of them was an update after the Sorahan re-analysis of the De Ross. It's actually the same meta-analyses, just including some of the more up to date data.

I think they also did a -- but it's actually the same studies. In many of these cases

with the meta-analyses across those, it was all the same studies, just small tweaks here and there. Which is why you're finding them all to come out about the same.

There are not strong differences between those meta-analyses to act like those are, you know, three independent type of things. Just to clarify they are strongly related, each of them, in their base. But as I mentioned earlier, I think that caution has to be taken when you do meta-analyses and interpret them.

First of all, you're combining cohort study with case control studies. Your taking some that adjusted for co-exposure to pesticides where some didn't. You have all the limitations that you have noted along the way in those individual studies, and carrying them over into your meta-analyses, including several that the sample sizes were quite small and resulted in wide confidence intervals; which the meta-analyses were typically non-statistically significant.

When they were, it was because it was -- 1.03 was the lower bound of the confidence interval. We're talking very borderline here. Not that, you know, it's 1.2 to 1.5, you know, around it.

None of them were really what I would consider statistically significant in my mind. As much as we looked at the meta-analyses, I think the evaluation of the individual studies is a better analysis. I don't really put a lot of weight onto meta-analyses. I think they're an indication that they are showing that there's a relatively small magnitude seen, actually, in the increase of the risk estimate. Your 1.3 to 1.5, you're not very far from the null and they're all non-statistically significant. It's not just the number by itself. We have to consider all of the information that goes into that one number.

DR. LUOPING ZHANG: You said that in your mind if it's significant or not, I think, the data itself would say if it was significant, if 95 percent confidence interval, it's over, yeah.

DR. EMANUELA TAIOLI: I think we need to be a little careful. I don't want to go into discussion for the charge. First of all, meta-analyses are one of the methods to look at a situation like this when you don't have enough data.

We don't want to be discount, with all the limitation, because the epidemiologist is science

of limitations, but that's what you have. The other thing is that, all the book says, when you have one that's you are significant, one is one.

There is another example where you have for multiple myeloma is 1.4 and the confidence interval is 1.0, and you said non-significant; that's significant for all of us. We have to be careful with that. And the other thing is that one of the meta-analyses has done a lot of sensitivity analyses, taking out of the cohort study.

Taking out the one -- adjusting -- and the odds ratio fluctuates between 1.3 and 1.7. It has a little variation, but it's always constantly with 1 as a low confidence interval, so we need to describe this in an objective way, in an appropriate way.

DR. JAMES MCMANAMAN: Dr. Taioli, can you include those during your --

DR. EMANUELA TAIOLI: It is. It is. I don’t want to go into the afternoon discussion, but.

DR. JAMES MCMANAMAN: Yeah, this is not -- yeah, we're not. It's becoming a discussion.

DR. MONIQUE PERRON: I’d appreciate any of those comments to characterize it more accurately.

DR. EMANUELA TAIOLI: Yeah.

DR. MONIQUE PERRON: I will again say, though, that I think that there has to be some caution in the meta-analyses and you can't just disregard the limitations of individual studies when you look at a meta-analysis.

I understand what you're saying, but at the same time I think it's one part of the story. And actually, in some ways it also shows the small magnitude of the change. That even when you group all of those together, you're not, you know, all of a sudden up in the threes or fours or anything like that.

Just remembering that it was considered as part of the full evaluation, it wasn't necessary just discounted. We just took a lot of caution; especially considering a lot of these meta-analyses when it was two studies, three studies. Even in the case of NHL, we only have six studies. Meta-analyses are generally more robust when there are, you know, when they looked at some of the genotoxicity where there's like two hundred.

I think that we also have to remember that we're just in a limited space here,

unfortunately, when it comes to epidemiological data. Thank you, though, for the comments.

DR. JAMES MCMANAMAN: All right Dr. Johnson.

DR. ERIC JOHNSON: I agree that the issue of exposure to all the pesticides are one of the most important consideration which you've addressed. And I think that Dr. Jett has also pointed that that is one of the most important consideration interpreting this data. But another factor is the issue of farmers being exposed to oncogenic viruses. Many people may not know this, but excess risk of hematopoietic lymphatic cancers have been observed in farmers way back in the 1930s, before the introduction of pesticides.

And it's frustrating for me personally that you look at all -- we spend so much money on all these pesticide studies and people have not collected data on exposure to animals and oncogenic viruses. I think the Heidel (sic) study and one other study, which looked at animals, they found significant risk for exposure to animals. That's an issue which we have to consider. These studies are deficient.

DR. JAMES MCMANAMAN: All right thank you. Okay. I think we've trumped this issue long enough. It's 12:30 and I think it's time to break for lunch for an hour. We'll meet back at 1:30.

[WHEREAS A LUNCH BREAK WAS TAKEN]

DR. JAMES MCMANAMAN: Is the agency ready to go? I think it's you. All right. I just checked with the audio person, just to remind you, I guess I'm about at the right distance right now.

Carlos? Good? Okay.

This is about where you should be when you speak into the microphone, otherwise it gets kind of garbled back there if you're too close or too far away. With that, let's get started.

DR. ANWAR DUNBAR: Good Afternoon. My name is Anwar Dunbar and I'm going to discuss the data evaluation of Animal Carcinogenicity Studies of the issue paper.

Okay. I'll start again. Good afternoon. My name is Anwar Dunbar and I will be discussing the data evaluation of Animal Carcinogenicity Studies for the white paper.

My talk is going to follow this outline. I'm going to give an introduction discussing the significance and purpose for the rodent carcinogenicity studies, our determination of study quality for analysis, our identification of studies for analysis and our considerations for determining a chemical's carcinogenicity coming from our 2005 guidelines for carcinogen risk assessment. I will then discuss the rat carcinogenicity data from our analysis, the mouse carcinogenicity data analysis and then I'll talk about what's known about glyphosates ADME profile and then I'll conclude.

Under the CFR, carcinogenicity studies are required in two separate species for food uses or for pesticides that are likely to result in repeated human exposure or a considerable portion of the human life span. Cancer bioassays in animals historically are the primary studies available to evaluate cancer hazard in humans along with genotoxicity assays. And as I will describe, these studies are evaluated in the context of our 2005 Cancer Guidelines.

In terms of study quality, study quality is determined using EPA's Test Guidelines, Studies 4200 and 4300. In these studies, pesticides

are typically administered the oral route. The test article, the pesticide is administered via the feed for 18 to 24 months in mice and 24 months in rats, typically with groups for interim sacrifice and a minimum of 50 animals per sex, per dose are used.

The highest dose level should elicit signs of toxicity without altering the normal lifespan of the animal due to effects other than tumors or without inducing inappropriate toxicokinetics, which I'll discuss later on. Also, the high dose need not exceed 1000 mg or kg per day, which I will refer to throughout my talk as the limit dose.

In terms of identification of the studies, using a systematic review, 20 rodent studies were evaluated. Five of those studies were deemed inadequate. Of the 15 remaining acceptable studies, 9 rat studies were identified and 6 mouse studies were identified.

The acceptable studies had a strong adherence to our guidelines described in the previous slide. Once again, these studies and this data were evaluated using our 2005 Cancer Guidelines. These five studies had numerous inadequacies which are

listed here, and which led to our not being able to use them in our analyses.

In terms of interpretation of the data, several factors are considered when interpreting results which are described in our 2005 Guidelines for Carcinogen Risk Assessment. Keep in mind that the guidelines are not designed to be a black and white checkbox approach, but more of a weight of evidence approach, pulling together multiple lines of evidence. And the evaluation of data includes consideration of both biological and statistical significance.

In terms of dose selection, doses tested should be selected based upon relevant toxicological information. The highest level should illicit signs of toxicity without substantially altering the normal lifespan of the animal due to effects other than tumors, also without inducing inappropriate toxicokinetics or overwhelming absorption or detoxification mechanisms.

It is highly recommended that the highest dose not exceed 1000 mg per kg per day and the doses should provide relevant dose-response data for human hazard for human health risk assessment.

And it's important to note here that one of the challenges with glyphosate is that it's understood to be a very non-toxic chemical, setting the maximum or the highest dose in many of these studies has been a challenge.

Statistical analyses help us determine whether exposure to a test agent is associated with an increase in tumor development rather than due to chance alone, and they should be performed for each tumor type separately. Given that the statistical evaluations were performed at different times for each study, all statistical analyses were reanalyzed for the current evaluation and they were conducted by our statistician here in HED, James Nguyen.

Our two key tests are the Cochran-Armitage Test for trend and the Fisher Exact Test for pairwise significance amongst the dose groups. The 2005 EPA Guidelines for Carcinogenic Risk Assessment state that considerations of multiple comparisons should also be taken into account. Utilizing multiple comparison methods reduces the probability of a type 1 error, what many may call a false positive. In the current evaluation, a Sidak correction method was used to adjust for multiple comparisons.

In terms of historical control data, the Guidelines state that treatment related effects should be compared to the concurrent control first and foremost. Additional insight however can come from historical control data. If historical control data can add to insight, particularly by identifying uncommon tumor types, or a high spontaneous incidence of a tumor in an animal strain, generally, statistically increased incidences of tumors in the treated groups should not be discarded solely because they are in the historical control range or because the incidences in the concurrent control are somewhat lower than average.

On the other hand, when concurrent controls are unusually low, compared to previously reported rates for a tumor type, these are noted and considered as part of the weight of evidence.

Carcinogenicity Rodent studies are designed to also examine preneoplastic lesions and other indications of chronic toxicity that may provide evidence of treatment related effects and insights into the way the test agent produces tumors. Presence or lack of supporting preneoplastic or other related non-neoplastic changes are noted in the current

evaluation of each study and considered in the weight of evidence. And these are additional considerations and they strengthen or lessen the significance of potential tumor findings.

That concludes my introduction. And I'm now going to walk you through the data sets in both rats and mice using the just described weight of evidence from our 2005 Cancer Guidelines.

This table depicts the nine studies that were analyzed, the nine rat studies analyzed. The doses used in those studies are depicted in the center column, the next column over to the right are the multiple strains used and the tumors identified for further analysis are in the far-right column, and I'm going to walk specifically through those studies where the Xs are located.

Each of the datasets I'm going to show you are going to utilize this format. The doses are listed followed by the incidences and the corresponding percentages. Each of the dose groups except for the control results of the pairwise comparisons are presented as raw p-values followed by Sidak p-values, which account for multiple

comparisons. In the control column, results of the trend test are presented.

In the study, Lankas, testicular tumors were observed. They tested up to 31 mg per kg per day. And there was a statistically significant trend with the p-value of .009 though there was no monotonic dose response. There was also a pairwise significance for the raw and adjusted p-values and for multiple comparisons. Just one quick note, the double star designates p-value of less than .01 while the single star represents a p-value of less than .05.

There was an unusually low incidence in the concurrent controls. There were no corroborating histopathological lesions, such as interstitial cell hyperplasia, which we'd expect to see, and taking these lines of evidence together these tumors were not considered treatment related.

In Stout and Ruecker, numerous tumor types were identified for analysis. I'll start with the pancreatic tumors in males first. In this study, as you can see, they tested up close to the limit dose, going as high as 940 mg per kg per day. There was no trend for any of the groups listed. Pairwise significances were observed at the low and high doses,

but there was no monotonic dose response for adenomas. There was no significance when adjusted for multiple comparisons.

In addition, there was an unusually low incidence in the concurrent controls. There was no progression of adenomas to carcinomas, and there were no corroborating preneoplastic lesions. And taking these lines of evidence together, these tumors were considered not treatment related.

In the same study, hepatocellular tumors were identified for further analysis in males. Once again, they tested close to the limit dose and there was a statistically significant trend only for adenomas with a p-value of .022. But there was no pairwise significance of any kind. There was no progression of adenomas to carcinomas. And there were also no corroborating histopathological lesions. And taking these lines of evidence together, these tumors were considered not treatment related.

C-Cell tumors were identified for further analysis in this study as well in both sexes. I'll start with the males first. For males, again they tested up close to the limit dose. And there was no trend or pairwise significance for any tumor type.

In females, C-Cell tumors were also identified for further analysis. And as you can see they tested just above the limit dose. For adenomas, there was a trend with a p-value of .04 but no pairwise significance at any of the doses tested. For the combined tumors, there was a trend with a p-value of .042, but no pairwise significance at any of the doses tested. There was no progression from adenomas to carcinomas. The non-neoplastic lesions showed no monotonic dose response for incidences or severity. And taking these lines of evidence together it was concluded that these tumors were not treatment related.

In Brammer, hepatocellular tumors were identified for further analysis. They tested just above the limit dose. A statistically significant trend with a p-value of .008 was observed and a pairwise significance at the high dose was observed for the unadjusted but not for the multiple comparisons. It was noted that there was a higher survival rate at the highest dose and there were no corroborating histopathological lesions. Taking these lines of evidence together, these tumors were not considered treatment related.

In Wood, mammary gland tumors were identified for further analysis. And as you see, they tested just above the limit dose. A statistically significant trend for adenocarcinomas with a p-value of .042 was observed, but there was no monotonic dose response. There was no pairwise significance for any of the dose groups either. For the combined incidences, there was a statistically significant trend with a p-value of .007, but there was no monotonic dose response.

There was a pairwise significance at the high doses for the unadjusted p-values but not for multiple comparisons. There were also no histopathological observations and taking these lines of evidence together these tumors were concluded to be not treatment related.

In summary of the rat data, nine studies were evaluated in the rat. In five out of the nine studies, no tumors were identified for detailed evaluation. In the remaining studies, statistically significant trends were observed for tumor incidences in the testes, the pancreas, the liver, the thyroid or the mammary gland. However, none of these tumors were considered treatment related based on the weight of

evidence for each study. In general, many of the tumors lacked monotonic dose response. Tumor findings were typically seen at or above 1000 mg per kg per day, and lacks statistical significance when adjusting for multiple comparisons.

In addition, there was a lack of support for biological significance in the limited cases we noted unusually low incidences in the concurrent controls.

I will now walk you through the mouse data. And similar to the rat, the studies analyzed are listed out on this table, listing out the doses and the various strains and the studies that were identified for further analysis are in the far-right column and I'll walk you through those.

I will start with Knezevich and Hogan. In Knezevich and Hogan, renal tumors were identified for further analysis. They tested up to five times the limit dose, even the mid dose was approaching 1000 mg per kg per day. There was no trend or pairwise significance for any tumor type.

It's important to note that these renal tumors are considered a rare tumor type and however, again, there was no statistical significant trend for

pairwise comparisons. Furthermore, there were no corroborating histopathological lesions. And taking these lines of evidence together, it was concluded that these tumors were not treatment related.

In Atkinson, hemangiomas were identified for further analysis. They tested up to the limit dose. There was a statistically significant trend with a p-value of .003, but no pairwise significance of any kind. It's worth noting that hemangiomas are considered to be a commonly seen tumor type in mice. And there was only an increased incidence at the highest dose tested. And taking these lines of evidence together, it was concluded that these tumors were not treatment related.

In Wood, lung tumors were identified for further analysis. They tested close to the limit dose. The statistically significant trend for lung adenocarcinomas with a p-value of .028 was observed but there was no pairwise significance of any kind observed. Furthermore, there was no progression of adenomas to carcinomas. There were no preneoplastic related non-neoplastic lesions. And taking these lines of evidence together, it was concluded that these tumors were not treatment related.

Also in Wood, malignant lymphomas were identified for further analysis. And they tested up to close to the limit dose once again. There was a statistically significant trend with a p-value of .007. And pairwise significance at the highest dose tested for the unadjusted p-values was observed but not for the multiple comparisons. Also, the incidences in control were low. Taking these lines of evidence together, these tumors were considered not treatment related.

In Sugimoto, hemangiomas were identified for further analysis. They tested up to four times the limit dose. And once again, the mid dose was close to the limit dose as well. A statistically significant trend with a p-value of .002 was observed. Also for the raw unadjusted p-values of the high dose but not for adjustment for multiple comparisons. And taking these lines of evidence together, these tumors were considered not treatment related.

In summary in the mouse, six studies were evaluated. No tumors were identified for detailed evaluation in two of the six mouse carcinogenicity studies. In the remaining four

studies, three observed a statistically significant trend in tumor incidences in hemangiosarcomas, lung adenomas, malignant lymphomas or hemangiomas. However, none of these tumors were considered treatment related based on the weight of evidence of each study. In general, many of the tumors lacked a monotonic dose response. Tumor findings were typically seen only at or above 1000 mg per kg per day and lacked statistical significance when adjusting for multiple comparisons.

In addition, there was a lack of support for biological significance and in limited cases we noted unusually low incidences in the concurrent controls.

I'm going to switch gears here because the 2005 Cancer Guidelines permit the use of other key data that may be appropriated into this analysis.

In our current evaluation, we had over 20 studies that helped inform the absorption, distribution and metabolism and excretion profile for glyphosate. The ADME data information can aid in understanding a chemical's mechanism of toxicity and/or potential for accumulation and biotransformation. Overt toxicity or qualitatively-

altered toxicokinetics due to excessively high doses may result in tumor effects that are secondary to the toxicity rather than directly attributable to the agent.

In recent years, EPA and other international agencies have used toxicokinetic data to inform dose, selection and avoid nonlinearity. For example, some of the test guidelines that are out there are listed on this slide. These measurements are highly weighted in other groups besides EPA.

As mentioned, we had over 20 studies available. And based upon those studies we found that from 5 to 400 mg per kg, glyphosate was not well absorbed from the GI tract. On average, it was absorbed 20 to 30 percent. The maximum amount in any study was 40 percent. Glyphosate was mostly eliminated through the feces. It was clear from the body, within one day, it did not accumulate in any tissue. Also apparent, glyphosate was not significantly metabolized.

There were conflicting results regarding linearity of absorption. EPA and OECD guideline, ADME studies, are designed for a different purpose and do not provide the information needed to

adequately determine whether linear kinetics are still occurring at the high doses for glyphosate. These studies are often limited to one or two doses and do not include time course data. A well-conducted pharmacokinetic study, testing multiple doses, is needed to conclusively make this determination.

Earlier I walked through the weight of evidence for each study and we concluded that none of the tumor findings were treatment related. Looking across all the animal bioassays, we also noted that none of the tumor types were reproduced, even in the same strain at similar or higher doses.

In today's introduction, Monique discussed that our high-end estimates of exposure to glyphosate -- she discussed our high-end estimates of glyphosate based upon the registered use patterns. Putting these into the context of the animal bioassays, we see that they are approximately 140 to 2000-fold lower than where we are seeing increased tumor incidences. Thus, even if tumor findings at the highest doses tested were considered treatment related, findings at these doses are not considered relevant for human health risk assessment.

In conclusion, a total of 15 rodent carcinogenicity studies were considered adequate to inform the human carcinogenic potential of glyphosate. Nine of those studies were using the rats, six were using the mouse. And based upon a weight of evidence none of the tumor findings were considered treatment related. The tumor findings were not reproduced including studies in the same animal strain at similar or higher doses. And even if the high dose tumors were considered treatment related, findings at these doses are not considered relevant for human health risk assessment.

And that concludes my part of the talk.

DR. JAMES MCMANAMAN: Thank you Dr. Dunbar. This is now open for questions and I'll start with a couple of questions. In the studies that you evaluated, was there any consideration given to the appropriateness of the strain of rodent for the type of test that was being conducted? It's well known, at least for mice, that certain tumors develop better in some strains than in others. I just wondered if that had been considered?

DR. ANWAR DUNBAR: No, we did not consider a specific strain.

DR. JAMES MCMANAMAN: Okay. The second question.

DR. GREG ACKERMAN: They are all performed in strains that we accepted according to our guidelines.

DR. JAMES MCMANAMAN: Those strains are established to develop these kinds of tumors in other models?

DR. GREG ACKERMAN: Right. I mean, those strains are acceptable for us for conducting carcinogenicity bioassays.

DR. JAMES MCMANAMAN: Okay. In your evaluation of the data did you consider, not tumor initiation, but did you consider the potential effects of glyphosate on tumor promotion? Did any of the studies evaluate the effects of glyphosate on promoting tumors initiated by another agent?

DR. ANWAR DUNBAR: So are you asking did we look for a precursor molecular event such as --

DR. JAMES MCMANAMAN: No, in the female for instance, there are lots of ways in inducing a tumor in animal model. I'm asking did you consider, or did you run across any data addressing the role of

glyphosate in promoting tumors initiated by another agent?

DR. ANWAR DUNBAR: No.

DR. JAMES MCMANAMAN: Okay. I would think that that might be a consideration in terms of -- because an agent may not be a tumor initiator, but it may be a tumor promoter so it might be an issue that should be considered at some point.

DR. ANWAR DUNBAR: No, we specifically focused on --

DR. JAMES MCMANAMAN: Okay.

DR. ANWAR DUNBAR: -- glyphosate.

DR. JAMES MCMANAMAN: All right.

Yes.

DR. DANIEL ZELTERMAN: Dan Zelterman. If you could go to slide number 15 on the Lankas, my question concerns the multiple comparisons. In this example, there were animals exposed to four different doses and there's the raw p-values using the Fisher Exact Test and the Sidak p-value adjustment for multiple comparisons. This would be back a little more, number 15. Yeah. This is the simplest example. The Sidak correction requires that the p-values be independent. And in this example, notice that each of

the doses above the control is compared to the same control. All of the tests are dependent in some kind of funny way because they're all compared to the same control.

But I have a much bigger problem than that. If you look at the Lankas paper, they highlight the testicular cancers, but they also examined dozens of other cancers as well of which this is the most extreme. When you correct for multiple comparisons, how many comparisons were actually done? Not these four, but I will guess, well over a hundred. Many of them being dependent on each other.

DR. MONIQUE PERRON: Yes, I'm wondering, is your question are the p-values representing the full study itself or just this tumor type? Is that your question?

DR. DANIEL ZELTERMAN: My question is mostly pointing out that these p-values don't represent what you think they represent. The correction is wrong because first of all the tests are dependent. And second of all, of all the cancers that were tested, you need to correct for all of the tests. That's what they mean by multiple comparisons, that a

great many hypothesis tests were performed before we got to this table.

DR. MONIQUE PERRON: I understand your concern. I would say that in terms of statistically analyzed, this was the only analysis done though. That's why only the three hypotheses being tested simultaneously here are being adjusted. That's what the p-values are representing, are for that tumor type. This was the only tumor type analyzed statistically. There were no statistical analyses performed by us on any of the other tumor types in the study.

DR. DAN ZELTERMAN: No, but Lankas did. And then you got the introduction --

DR. MONIQUE PERRON: Yes, Lankas did, but what we are showing here is our analysis of the data -- I guess I can only clarify what we're showing.

DR. DAN ZELTERMAN: Thank you.

DR. JAMES MCMANAMAN: Dr. Crump.

DR. KENNY CRUMP: Kenny Crump. I have two or three questions. You said these were the tumors identified for further analysis. I didn’t see anywhere in the document where that was defined. How did you identify tumors for further analysis?

DR. ANWAR DUNBAR: Okay, well some of these tumor types were previously analyzed several times, years ago. And then for the studies that we got in from the systematic review we did an exhaustive -- I wouldn't say an exhaustive -- but a search of the pathology reports to see if there was anything in there that warranted a further look.

DR. KENNY CRUMP: What was your criteria for deciding if it required further analysis?

DR. ANWAR DUNBAR: Looking for potential dose response.

DR. KENNY CRUMP: Okay.

DR. ANWAR DUNBAR: Also statistical significance where there was a potential dose response.

DR. KENNY CRUMP: Yeah. Well I wasn't sure how you decided -- I kind of -- I didn't look clearly for the data, but I did identify a couple of cases where there were things that were significant at .05 that were not analyzed. And your point about monotone dose responses, I've never seen that used as a criteria before. Maybe I've missed it, but I didn't see it in the EPA Guidelines and I sort of wondered

where that criteria came from and how much it was weighted.

DR. GREGORY ACKERMAN: It was just used as one of the lines of evidence, not the sole line of evidence for those. We expect in increasing dose that you would see an increase of instances of the tumor. That when we did see that, we used it as one line of evidence to support or not support the particular tumor finding.

DR. KENNY CRUMP: But when you were deciding which tumors to analyze, did you ever rule any out for analyzing because the dose response wasn't monotonic?

DR. MONIQUE PERRON: I can't speak towards all of the studies, but I'm sure there were instances where you may have seen quite a bouncing around of the tumors, especially when they're common, where we probably would not have analyzed them due to that instance. I mean it really -- in many ways, it is a professional judgement at that time when we're going through the data.

There are a lot of different anatomical sites looked at in these studies, and we do go through a thorough evaluation of all of the individual data

during our evaluations to determine which ones we believe need to get further statistical analyses beyond what we're seeing in the individual raw data.

DR. KENNY CRUMP: Did you ever consider doing some sort of analysis to -- assume you do have a monotonic dose response, look at them, how frequently do you get a non-monotonic-observed dose response?

DR. MONIQUE PERRON: I don't think -- no we haven't done that analysis.

DR. KENNY CRUMP: Okay. One other question, none of these analyses are controlled for longevity. Did you consider doing like a Poly-3 test like NTP does to correct for longevity; or did you consider that that might not be necessary in this case, for example?

DR. MONIQUE PERRON: In terms of the studies available here, we did not see any differences in survival. We do do a different analysis when we see survival differences. But in the case of glyphosate, all of these studies did not have that difference so we did not think it was appropriate to do any adjustment. Some people have actually looked at this data using the Poly-3 which really, if you do that for a 24-month study, it's not actually doing

anything in the case of glyphosate because there's no survival differences.

In terms of the mouse studies that were 18 months, you're basically extrapolating out to 24 months if you do that adjustment. But you're also assuming that all of those tumor free animals have survived to 24 months and there are some underlying faults in doing that. In the case of the studies that we had available, we did not think it was appropriate to do that adjustment.

DR. KENNY CRUMP: Okay. Thank you very much.

DR. JAMES MCMANAMAN: That was Dr. Perron. Dr. Green?

DR. LAURA GREEN: Thank you. A number of us have noticed that the document maybe does itself a disservice by saying that it follows the Carcinogen Assessment Guidelines but in fact it doesn't. And it's a little confusing to us.

We wonder why, for example, you picked this so called limiting dose of a gram per kilogram when the Guidelines A say that the tester need not exceed that; but certainly, the Guidelines do not say

the tester should not exceed that. At a minimum, we suggest you maybe clean up that language.

Number 2; as you correctly mention, since glyphosate is so nontoxic, you have an inherent difficulty finding a maximally tolerated dose. And testing at a maximally tolerated dose under a gram per kilo, when in fact, this stuff is really nontoxic. We don't really understand why you are alluding to guidelines you're not really using. I mean it's okay that you're not using them, but you shouldn't have it both ways, it seems to us. Are we missing something here?

DR. ANNA LOWIT: I guess maybe a little bit of clarification is may be what's the question is there. I guess we would disagree we're not following the Cancer Guidelines. I think we've actually tried very hard to keep strictly to the guidelines. And if you look at the language in the paper, we've actually extracted sections from the guidelines to make sure that we didn't misstate certain areas. I'd like to get some clarification where you think that we have not, and where that language may be in your view, inappropriate.

DR. LAURA GREEN: Yeah, it's very simple. As I tried to say, your guidelines say when a bioassay's being conducted, the experimenter need not test at doses greater than a gram per kilo. But it doesn't say they don't have -- it doesn't say -- I'm sorry. It does not limit the tester to a gram per kilo. It limits the tester to a, I think it's 7 percent in the diet, is that right? Five percent in the diet. Which is a lot more. And it specifically says, as you know, and is important, when at all possible the highest dose should be maximally tolerated. And that's not the case here.

And even in your slide show -- early in your slides you said the dose “need not” exceed a gram per kilo, and then later in your slides, it says the dose “should not” exceed a gram per kilo. Well, those are two very different statements and our reading -- my reading at least, and I speak for several of us -- of the Cancer Guidelines is pretty clear on that and you seem to say both things at once and it's a little odd to us.

DR. ANNA LOWIT: So if there's some --

DR. JAMES MCMANAMAN: Let me interject here. Are you asking what is the rationale for not

exceeding the mg per kg since they didn't do that or are you asking why they're not exceeding that?

DR. LAURA GREEN: No. I'm saying very simply, obviously, a lot of these bioassays have three, four grams per kilo as the high dose. And obviously, that's the case because those, in fact, are within the maximally tolerated dose range.

DR. JAMES MCMANAMAN: You're asking why they didn't go higher.

DR. LAURA GREEN: No.

DR. JAMES MCMANAMAN: Okay.

DR. LAURA GREEN: I'm saying that in your assessment, your draft document says we are ignoring doses above a gram per kilo because the Carcinogen Assessment guidance of 2005 says to do that. And we don't see that in the guidance. It's pretty simple.

DR. ANNA LOWIT: I'm confident that our document doesn't say ignore doses above 1000.

DR. LAURA GREEN: It does.

DR. ANNA LOWIT: I think we have accurately pointed out throughout the document and also the presentation where those doses come close to or exceed. But as you can even tell from each of the

slides, we have not ignored any data available to us at any dose.

I would ask, again, if there's specific areas of the document that have language that you don't view are in accordance with the guidelines. We would appreciate that feedback in your comments. But to be clear, we have not ignored or eliminated any study at any dose.

Our view is that those results approaching or exceeding 1000 milligrams per kilogram per day have questionable relevance as it relates to risk assessment. And when we get later on, to the evaluation of the cancer category, that evaluation of doses and the context of those doses become important as we think about the different descriptors. I'm using the wrong word.

DR. JAMES MCMANAMAN: Okay. Sonya?

DR. SONYA SOBRIAN: Sobrian. I want to ask you about your slide 40 which is your ADME profile which is new data. It wasn't in the original white paper. It's nice to see. I have two questions. Is there any data on absorption over 400 milligrams per kilogram? A lot of the studies went above that. Slide 40, sorry.

DR. ANWAR DUNBAR: Yeah. Yes, there is data above 500.

DR. SONYA SOBRIAN: Okay. Now given your last sentence which says it's not linear. When you don't know what the pharmacokinetics are, and you're suggesting that they may or may not be linear, what does that do to your eliminating findings when you don't have a significant trend?

DR. ANWAR DUNBAR: Our position is that it's not clear. There's conflicting data. It's not clear what's happening at those higher doses.

DR. SONYA SOBRIAN: But then I still ask you, given that it's not clear, how probable is it that you can then stand by your suggestion that when you don't see a linear trend in a dose response, that it's not a significant effect?

DR. ANNA LOWIT: I feel like maybe you're mixing the issues. The issue with the absorption, the ADME profile, if we could go way back a few slides to the comments, the bullets that Anwar had from the OECD Guidance and other guidance from other -- that one. It's only one slide, thank God.

That the EU and the OECD have guidance that suggest that if dosing is in the nonlinear range

that that would be a way to define a toxicokinetic MTD, whereas we've already concurred that from a toxicological point of view, since it's considered fairly non-toxic, you can't define an MTD in the classical way based on body weight or clinical signs.

That if we were able to understand the absorption kinetics and the pharmacokinetic profile, that we could better understand if we've actually exceeded a pharmacokinetic MTD as it relates to the dosing at these really high dose studies. And that's the point on Anwar's -- the next slide about whether or not it's linear kinetics or non-linear kinetics.

DR. SONYA SOBRIAN: Okay. There were some studies in the -- I think it was in the rat studies -- where you see changes from the control at the low and the medium doses, which are at or near the 1000 milligrams per kilograms, but you don't at the high dose. And so you reject a possible linear trend but now you're telling -- now this says that you don't have -- you're not sure about the absorption at that high dose or it may be completely -- the pharmacokinetics may be different. It's just a suggestion that you're always looking for linear trend

and that is in your guidelines. It's right before it says 50 rats per sex. It's in your guidelines.

But the suggestion is should you maybe look at something else and not stick with just something that gives dose response as a linear trend? Because there are other possible trends that you're missing. Especially when you don't have the information about absorption or toxicokinetics at really high doses.

I have, if you don't want to answer that one, I have another question. We were asked to determine the adequacy of non-neoplastic findings and preneoplastic findings and they're not defined easily. And given the 4000 pages for one or two studies, it's really hard to know, there's just tons and tons of data. Could you just give us some guidelines on what you were looking for?

DR. CHARLES WOOD: So this is Charles Wood from EPA Office of Research and Development. So typically, at least for non-mutagenic carcinogens -- not always -- but for many outcomes you would want to see some sort of a precursor effect. Whether it be something like hyperplasia, if you have a mitogen, or something like necrosis if you have a cytotoxic agent.

And so that's why that appears as one of the factors in the weight of evidence.

For example, with the renal tumors, it would be very difficult -- I can't think of a precedent where you would have renal carcinogen for a chemical and not see some sort of preneoplastic or non-neoplastic effect. Does that help answer your question? It could be anything that indicates that there is a target toxicity at that site.

DR. SONYA SOBRIAN: Because there's so much data in these files that we got, I mean, you can go through pages and pages and you see lots of different things. It would have been nice to have some, you know, examples of what you look -- I look for hyperplasia, but I may have missed some things. And you say that there weren't any in your presentation, that there weren't any preneoplastic -- there is for one and it's in my write up, but I don't know what you based your saying you didn't find anything. Because I don't know what you were looking for to begin with. And I think that might have been helpful in your charge, giving us some idea of what we should look for when you're going through 2000 pages of data.

DR. CHARLES WOOD: So for many different target sites you could have 25 different non-neoplastic changes. It would be completely overwhelming to try to bring in all of that data in a way that was useful or informative.

I think the point was that there were no non-neoplastic lesions flagged for the sites, at which these different tumor outcomes were noted, that would suggest that organ as a site for some sort of chemical effect.

DR. SONYA SOBRIAN: There is one study in which there is, but I have to go through my notes to find it.

DR. JAMES MCMANAMAN: So I think Dr. Johnson was next.

DR. ERIC JOHNSON: So I just want you to go back to the slide with Woods on the mouse carcinogenic test. Wood. Right. That's the one. I mean, it seems to me the dose response was fairly contained --

DR. JAMES MCMANAMAN: Dr. Johnson, could you speak into the microphone?

DR. ERIC JOHNSON: Yeah. It seems to me that the dose response was fairly consistent, 1 of

51, 2 out of 51 and then 5, no, no. That's not the one. There was one that was 5 out of -- oh, that's 51, not 5 out of 5. I'm sorry. Still, it's 5 out of 51, it's fairly consistent. And now I'm wondering why this study was just ruled out that it's not of any significance.

DR. CHARLES WOOD: So one of the factors for this particular study was this strain; I don't have it in front of me exactly what it was. If I recall, there was not historical control data provided from the lab that ran this study. But in a review of multiple other studies reporting historical control data, in this particular strain, none of them had a control instance of zero. And so the interpretation was that the control values here were below what you would normally expect in this strain.

DR. LUOPING ZHANG: Could I add the -- just following up study on this one?

DR. JAMES MCMANAMAN: Okay. So -- Dr. Zhang?

DR. LUOPING ZHANG: Okay. Luoping Zhang. Okay. Just is there any p trend test passed down from this Wood study?

DR. CHARLES WOOD: Was it exact --

DR. LUOPING ZHANG: Trend test, trend test.

DR. CHARLES WOOD: The trend test was it exact or approximate, is that the question?

DR. LUOPING ZHANG: Mm-hmm.

DR. CHARLES WOOD: It's my understanding that all of these were exact.

MR. BAYAZID SARKER: Yeah. This is Bayazid Sarker from EPA. These are all exact tests. The Trend test and the Fisher Exact are the exact one-sided test.

DR. LUOPING ZHANG: But you show here it is only for each dose compared with controls. Here you didn't show any trend test.

MR. BAYAZID SARKER: Yeah, so the raw p-value, if you look at .007 that was the trend test.

DR. LUOPING ZHANG: Yeah, that's my question. Okay. See, that's not very clear. That's my guess.

MR. BAYAZID SARKER: Okay, okay. Yeah. Sorry.

DR. JAMES MCMANAMAN: Okay.

DR. ERIC JOHNSON: So back to my question.

DR. JAMES MCMANAMAN: Okay. Sorry. Lost you. All right. Back to your question.

DR. ERIC JOHNSON: Yeah. I still just don't understand the criteria in which you're basing your results on historical controls; when on this particular study we have enough evidence. Even if the tumor incidence is lower than expected, zero to five, but it's consistent for all the other doses. At least that's consistency within this study.

I would trust that more. That whatever strain of mouse you used, it's consistent for this experiment, rather than relying on historical data which might be another different strain of mice or whatever.

DR. CHARLES WOOD: I think in some cases like this example, the negative evidence from other studies in the same strain, in some cases, at higher doses was also an important factor. If you weren't sure about this study and you redid it and did not find this, you know, would that influence your interpretation?

DR. ERIC JOHNSON: Well, I would look for a reason why. I mean, why should the incidences be consistently low in this experiment? Are there

other deficiencies within this study, that's why incidence is low consistently over all the doses? Even though we have a dose response. I mean, if the issue's just the baseline -- that the incidences -- the outcome background levels are lower than expected, I mean, it's still a control within its own experiment that is consistent across all.

It's telling you something specific about this particular experiment. And to compare with other experiments you need to just see other conditions in which these experiments were conducted under.

DR. MONIQUE PERRON: This is Monique Perron. I just wanted to say that remember that we are doing a weight of evidence evaluation of each of these studies. It's not necessarily just one statistical result that then trumps everything else and then we go down that path, we're trying to look at all of the lines of evidence and integrate them together for that study. And one of the lines of evidence that we had available was historical control data. And in this instance, especially when it was zero, I see what you mean, our statistical analyses

are always done with the concurrent controls. I see your point there.

But also, recognizing that there is additional information available that could explain why we're seeing a pairwise significance in the raw p-value. But again, we didn't see one in the multiple comparisons and that was also part of our weight of evidence. There were multiple lines of evidence integrated and that was one of them. But the concurrent controls were considered as part of the statistical analyses as well. They were not just disregarded; it was just that they were all considered together at once.

DR. ERIC JOHNSON: I just wish that a small note could be made that these types of observations were seen, although overall, we did not think it was. Because the message I came away with was that all of these animal experiments were negative. And that's the message I got.

DR. JAMES MCMANAMAN: Just a minute, Dr. Green. Dr. Ramesh?

DR. ARAMANDLA RAMESH: This is Ramesh. One reason for those, some studies the lack of difference could be due to the fact when doses are 5

to 400 milligrams per kilogram only resulted in 20 to 30 percent absorption of glyphosate. At 1000 milligram per kilogram it would not have made a big deal of difference anyway. And in that context, EPA may want to revise their language which it says that the high dose should not compromise the outcome of the study by inducing inappropriate characteristics.

Already at such a high dose the metabolic machinery is saturated. It would not make any big difference. There is no difference, but at 1000, at 2000 or 3000, because at such a high dose the metabolism is saturated, we might see a little bit increase in tumors, but not higher than the background noise.

DR. JAMES MCMANAMAN: Thank you. We encourage the panel to ask questions, that was a very important point. But can you -- I feel like a judge -- can you ask that in a question.

DR. ARAMANDLA RAMESH: Sorry. We will incorporate it our charge responses.

DR. JAMES MCMANAMAN: Dr. Green, a question.

DR. LAURA GREEN: Okay. I'll phrase it as a question. First, is there a reason you did not

show the female mouse data for malignant lymphoma for this study? This is only the male response.

DR. MONIQUE PERRON: Correct. For each of the types of tumors identified for evaluation, we only presented the data if they were flagged for analysis. If you did not see any data for the other sex, then that was because we didn't flag that data for analysis.

DR. LAURA GREEN: So not to state the obvious, and try to ask it as a question, would it not be helpful for those of us struggling with whether these are bona fide results, to see whether the same strain but the opposite sex -- if we're still allowed to say opposite sex -- whether the results are coherent or not? Would that not be a helpful thing?

DR. MONIQUE PERRON: We have the data available. We can show that data as well, and to show that you would hopefully come to the same conclusion as us that it was only seen in one sex in that study, yes.

DR. JAMES MCMANAMAN: Okay. Can you provide that data then? Is it easily -- Anna's saying, what, wait, wait, wait.

DR. ANNA LOWIT: So this is Anna Lowit. You have that data and, as been said, you probably have thousands of pages. And in fact, you have our data evaluation records, which is the shorter summaries, and hopefully Steve Knott has helped the members of the panel find those data evaluation records because they would have that. They would have more details on the difference between sexes across these tumor types. Keep in mind that we're limited to a part of the day to give a presentation on, you know, what amounts to an enormous amount of data. We appreciate that you understand that we've shown pieces of a very big picture.

DR. JAMES MCMANAMAN: Okay. That was Anna Lowit. Dr. Parsons, I think has had her hand up for a while.

DR. BARBARA PARSONS: I'd like to follow up on Dr. Sobrian's questions about preneoplastic lesions. She asked what ones you were considering. And maybe a clearer way to get at this point would be if you could explain to us how you surveyed the primary documents and reached this conclusion that there are no preneoplastic lesions? What was that process?

DR. CHARLES WOOD: So again, this is Charles Wood from Research and Development of EPA. I mean, the short answer to the previous question was of which lesions were looked for, it would be any and all. Anything that was flagged as a potential treatment-related response. And that process typically takes place in the conversion of the original pathology report which might be 800 pages long into the data evaluation record. Okay.

DR. BARBARA PARSONS: So then you really did no primary analysis of any preneoplastic lesions. You went based on the summary reports of what was flagged?

DR. CHARLES WOOD: The original reports are available if needed, to go back and look at context.

DR. BARBARA PARSONS: I know. I'm asking what was done.

DR. MONIQUE PERRON: So this is Monique Perron. Maybe a little bit more clarification about our processes might help. In addition to all of these cancer studies, we also get a whole battery of other studies that I'll go through a similar evaluation where we look at all of the available data in a study

report. In a study report we'll have a, you know, a quick summary typically of what they saw in the study. They'll go through all their methods, everything like that. They'll usually summarize the data. But then they also provide to us all of the individual data.

When those come in, we go through all of that individual raw data to evaluate whether we think -- and not just for cancer, you know, are we seeing any other adverse effects in the study, whether it's body weight, whether it -- even if it -- you know, anything at all.

We want to be very thorough in our evaluation so, as Dr. Wood mentioned, there are histopath reports typically included in that that can -- in the case of carcinogenicity studies are often 800 pages. We go through all of that individual data, as well, to try to see if there are any effects being seen. We do try to see where are we seeing adverse effects if any or are there any effects that we need to look at in more detail and discuss.

DR. BARBARA PARSONS: How do you do that?

DR. MONIQUE PERRON: In many ways. You look at, you know, do you see an increased incidence?

Do you see that incidence increasing across dose? Is it, you know, something that, you know -- are you seeing it in the controls as well as all of the other ones at a similar rate? That type of information.

Typically, it's mostly incidence. We also consider severity. Depending on the study and how well they define the severity, we can often determine where there's actually a functional impairment from what they're seeing. We tried to incorporate all of that information and so when those studies come in and toxicologists in our division will then summarize all of that information into a data evaluation record which is what you keep hearing about these DERs. Those are our summary after many, many hours of combing through the data to see if there's anything there that's even worth discussion.

Sometimes we even include stuff that we don't think necessarily is going to be adverse, but we want to explain that we saw something and we don't think it's adverse. There is quite a spectrum. We do look across all of the anatomical sites, all of the available data. And in the case of many of these tumors, for instance, with the kidney tumors we look specifically at the kidney data. Did we see any

lesions that would corroborate those kidney tumors? I don't know, maybe that helps a little bit more in explaining how we determine that, but it really is a very long and comprehensive evaluation of the available data.

DR. BARBARA PARSONS: Can I ask one more question? Using this as an example, 0 out of 51 animals, what is in the denominator? What animals are in the denominator? And was this the same for all studies?

DR. ANWAR DUNBAR: So you're asking about the incidences? Those are like the total number of animals per sex for that dose.

DR. BARBARA PARSONS: So terminal sacrifice and more have been found dead are always? Was that always?

And I noticed some of your tables for instance, they said it had a footnote, only animals that survived past 55 weeks. Other tables don't have that. I'm trying to get a sense of how variable this was across studies or was it always the same groups of animals selected and presented?

DR. CHARLES WOOD: So again, this is Charles Wood, EPA, Research and Development. The

standard approach is that for early deaths prior to the occurrence of the first tumor of the type that you're interested in are not included. And that's why you'll see these shifts across groups. After the first tumor of that particular type is diagnosed, at that point all early deaths, whether they be moribund or actual deaths, if there is available sample to be read out by a pathologist, they're included. And that's, I believe, the standard approach taken by EPA and other organizations.

DR. BARBARA PARSONS: So there were some combined chronic exposure carcinogenicity studies where there were interim sac; were those included in the data that was analyzed, those interim sac?

DR. CHARLES WOOD: In some cases they could be broken down in different ways. But again, it would go back to whether or not that particular tumor was diagnosed prior to the interim sacrifice. But if you included -- maybe this will help -- if you included all the interim sacrifices in some ways you would dilute your effect if it was a later in life effect. And I don't think that is standard protocol if it comes before the observation of the first tumor.

DR. BARBARA PARSONS: Okay. I think what I'm hearing you say is that no matter how they reported out the results in the primary document, EPA went back and reanalyzed the data in this consistent way that you just described?

DR. CHARLES WOOD: For the studies that were submitted to EPA, that had comprehensive data, that allowed that sort of analysis, yes.

DR. BARBARA PARSONS: Okay. Thank you.

DR. GREGORY ACKERMAN: And this is Greg Ackerman. Just one clarification. The studies that are combined chronic, there's additional animals added to those studies. There's more than 50, so it's 70 so we wouldn't include -- that denominator would be -- typically it’s a tumor.

DR. JAMES MCMANAMAN: Dr. Crump?

DR. KENNY CRUMP: My first question has been answered, I think along the way. But I do have a -- just brought up another question. I think most of these studies, the denominators are all the total animals in the group. Does that mean that no animal had cancer until the final sacrifice or does it mean you just didn’t have the data to do the breakdown you were talking about?

DR. CHARLES WOOD: Charles Wood. I can't speak to individual study without really looking at the original pathology report, but again, typically, if an animal dies early, and that whatever you're looking for -- and the samples are valid to be read out by a pathologist, then they would be included. So long as it's after the observation of the first tumor type.

DR. KENNY CRUMP: So we can assume on this study, all the animals that had the tumor were found at the final site because they're all included?

DR. CHARLES WOOD: You know, just looking at this, yes.

DR. JAMES MCMANAMAN: Okay. I have a -- Jim McManaman. I have a question. The question relates to the use of the historical data. And Dr. Wood made the statement that all the strains of mice that were included in their evaluation, the historical data were made on the same strain. Is that known for a fact, or is that just an assumption?

DR. CHARLES WOOD: No. When it was -- ideally, the historical control data would come from that particular vendor, or whoever ran the study, the contractor if it be. If those data were not

available, at that point, you know, I think in this case, we had to look through the literature, through other databases to try to come up with something to gauge whether or not, you know, 0 out of 51 is reasonable for that particular strain. And of course, there's going to be genetic differences.

DR. JAMES MCMANAMAN: Right. That was my question. These were all CD1 mice, I think all the studies that you quoted were CD1s. So just to verify that all the animals that were used in the historical data were also CD1 and they had -- okay. Great.

DR. CHARLES WOOD: Right. We -- right. We didn’t go across strains.

DR. JAMES MCMANAMAN: Okay. Great. Thank you.

DR. LUOPING ZHANG: Quick question. Besides Wood 2009 study for the lymphoma, were there any other animal studies that also show the lymphoma outcome? My understanding, seem there are two more studies. I just wondered if you only pick up this as an example or that's the only one animal study to show lymphoma results.

DR. MONIQUE PERRON: So in our evaluation of the data, lymphoma was only flagged for

detailed evaluation in this study. We did not look at detail in any of the other studies because it didn't have increased incidences or increasing incidence with increasing dose. It wasn't flagged for evaluation. This type was only seen here and was not seen in any other mouse study including those that were also in the CD1 mice at similar or higher doses.

DR. LUOPING ZHANG: I see.

Something else I read, it seems like for my information there are three animal studies, you know, had lymphoma outcome. But I didn't know the detail so that's why I'm asking if you have seen.

DR. JAMES MCMANAMAN: That was Dr. Perron. Did we have another question? Yes, Dr. Sheppard?

DR. LIANNE SHEPPARD: Yeah, I wanted to follow up on the historical control question. Specifically, with respect to Wood, which was done in 2009, how appropriate is it to use historical controls that were collected from 1987 up to 2002 for a study that was done in 2009?

DR. CHARLES WOOD: Charles Wood. I think the standard is you do your best to get within a

five to ten-year range. But a lot of time that's simply not available.

DR. SONYA SOBRIAN: Can I just answer that by saying your guidelines say two to three years either way? Because that's what's in your guidelines.

DR. CHARLES WOOD: Ideally, yes. I mean, ideally --

DR. SONYA SOBRIAN: I mean, I think earlier someone said that you had broken some of the rules of your own guidelines, that's one of them that I found too. The question is what do you do with that? And how do you justify doing that?

DR. JAMES MCMANAMAN: That was Dr. Sobrian.

DR. CHARLES WOOD: Charles. I would say it weighs into the uncertainty. Especially if you don't have control data from that particular lab.

DR. MONIQUE PERRON: This is Dr. Perron. Also, just to clarify, 2009 is when the study report is dated, that does not mean that the study was conducted in 2009. It would have been conducted prior to that. Just as a small clarification.

DR. SONYA SOBRIAN: Well your document, which is what I'm basing it on, says, "conducted in"

in doesn't say published in. It says, "conducted in" so that was my interpretation of what conducted meant.

DR. MONIQUE PERRON: Okay. I apologize for the oversight. No. The study reports that we receive are dated for when the study report comes in. They would be after it had been conducted, all of the data has been analyzed by the registrant and pulled together for the report. So just to clarify on that point. I apologize for the oversight in the paper.

DR. JAMES MCMANAMAN: That was Dr. Perron and Dr. Sobrian. Dr. Green?

DR. LAURA GREEN: Yeah, I want to make a couple of practical suggestions, but also note something. I think this panel, although there are many smart people around this table, all of them smarter than I, none of us are a pathologist. Which I think is a significant problem here. Unless I'm missing something. Dr. Ehrich, maybe you are. Are you a pathologist?

DR. MARION EHRICH: I work with a pathologist.

DR. LAURA GREEN: Oh, so maybe I should just ask you then.

DR. JAMES MCMANAMAN: Is this is a clarification question?

DR. LAURA GREEN: Sorry, sorry. Here's my question to you all.

DR. JAMES MCMANAMAN: I really want to get to these charge questions but we've got to ask these --

DR. LAURA GREEN: Sorry. Would you not benefit from -- since obviously lymphoma's kind of an important issue here, right, we haven't even gotten really to the epi. Would you not benefit from a more detailed discussion in your white paper, whatever this is called, about lymphoma in mice? As Dr. McManaman has mentioned, there's a lot of data from the CD1 mouse. My friends who are pathologists, and apparently, I have one here or close to it, have told me that first of all, there are a very diverse group of cancer. Second of all, a lot of pathologists don't agree among themselves as to what kind of malignant lymphoma they're talking about.

My understanding is that the historic ranges range from like 1 percent in aged rat to like 25 percent in aged rats. I think there's -- my superficial understanding is that there's so much

interesting detail here from the pathology that I think you would maybe do yourselves a favor if you would consult with some pathologists in the agency or others because I think this is going to be a really important thing to talk about.

And let me just also say, looking at my statistics friends, as far as I can tell, since there are 15 valid bioassays here, this means you have 13 -- I'm sorry, you have 30 experiments where the question has been asked is lymphoma dose related to glyphosate or not. And I think a lot of us might benefit from a more holistic discussion of all 30 tests of the same hypothesis.

DR. JAMES MCMANAMAN: I think we'll do that during the charge question discussion. Okay.

DR. CHARLES WOOD: Very quickly. Charles Wood, and I am a pathologist. And I take your point that more discussion could be built up around the variability that is seen across colonies, across strains, and even across specific laboratories, mainly due to endogenous and exogenous retroviruses.

DR. JAMES MCMANAMAN: All right. Dr. Sheppard? Okay. Wait a minute. All right. Dr. Sheppard first and then Dr. Johnson.

DR. LIANNE SHEPPARD: One of the things that I struggled with in reading this whole section was thinking about how animal studies are designed and then thinking about how you weighted the evidence. Animal studies are designed to detect on the order of 10 percent excess cancers or whatever events. Whereas for human health, we care about things that happen on the order of one in a million or less.

That's one of the reasons why we study such high doses, right? Is to understand what might happen at the high doses in order for, in risk assessment, to extrapolate down to the lower dose.

And that's in fact, I think, why your guidelines say you need at least 50 animals per group and why you need to have a sufficiently high dose; and why you have to have at least four doses and they have to be at a range that captures the range. Given that, I'd like a little bit more comment from EPA about why is it appropriate to discount the highest dose in these studies in your evaluation? In many of the studies they were discounted because they were at or above the limit dose which we've already established is sort of an arbitrary number.

DR. MONIQUE PERRON: First of all, I would say that we aren't discounting because they were seen at that dose; we were discounting based on the weight of evidence analysis for each of those individual studies. In addition to that, we have also noted that none of the tumor types were reproduced in the same species at similar or higher doses and beyond that. Even if you did consider those tumor findings at the highest doses to be treatment related, we don't believe they would be considered relevant for human health risk assessment and that goes back to some of our discussion earlier today that you're at a dose well above.

They weren't discounted because of it, there was just additional characterization put into the paper to say that even if you considered these treatment related, they wouldn't be relevant for human health risk assessment because 1000 milligrams per kilogram per day remember, the label is the law. It is used to manage your exposure to pesticides. In order to get that type of dose is just almost implausible. That's where that argument comes in.

Again, we're not discounting the findings because they're at the high dose, but we are

characterizing that there has been some disagreement about whether those are treatment related. And even if you did, they are not considered relevant for human health risk assessment.

DR. LIANNE SHEPPARD: But there's a lot more that's done in human health risk assessment that has to do with extrapolation and species and so on. I mean, by down weighting those high doses, that's where the evidence is because that's how the studies were designed. That basically is saying that we're not going to consider animal studies is what I think it says.

DR. JAMES MCMANAMAN: Wait, I think we're getting into an area that we don't want to get into right at this point. I don't think that further discussion is going to make much difference about this. We can discuss this; we can talk about it during the charge question discussion. Dr. Johnson?

DR. ERIC JOHNSON: Just a general question. My question is in all the studies you've done, all the reviews you've done, did you see any gender differences in how this compound is handled at all?

DR. MONIQUE PERRON: I think we touched upon this a little bit with somebody else's question. If we didn't show the data for the other sex that meant, we didn't see it. Actually, I think there's only one tumor type that we saw in one study where you saw it in both sexes. Typically, we would only see it in one sex, actually.

DR. ERIC JOHNSON: I'm not referring to the tumor -- any outcome -- I'm just saying how this compound is handled biologically by the different sexes.

DR. ANWAR DUNBAR: This is Anwar Dunbar. No. No. In all the guideline studies, no.

DR. JAMES MCMANAMAN: All right. This has been a very thorough discussion. I think that we could maybe move onto the next presentation, Genetic Toxicity. Dr. Ackerman?

DR. GREGORY ACKERMAN: This is Greg Ackerman, the Health Effects Division again. Stephanie and I will discuss the data evaluation of the genetic toxicity findings.

This slide shows the outline of the presentation where I will first provide some background information on genotoxicity and then

describe the source of the data used in our evaluation. And then I will describe the three main types of genotoxicity to analyze which will include the gene mutation studies, in vitro and in vivo studies evaluating chromosomal abnormalities and then assays evaluating primary DNA damage.

Now I'll next describe the assessment of data and how we used the weight of evidence approach to make our conclusions.

I think the battery's dead on this.

DR. JAMES MCMANAMAN: Are we having technical difficulties?

DR. GREGORY ACKERMAN: Yeah, the battery's not working. It keeps -- it turns on and then back right off again.

DR. JAMES MCMANAMAN: Okay. The computer's behaving like glyphosate. It's just kind of random. Well, while we're tracking down batteries, we'll take a break. Be back at 3:00.

[WHEREUPON A BREAK WAS TAKEN

DR. JAMES MCMANAMAN: Okay. A couple of announcements. One is try to not lean in too far to the microphones. But lean in far enough that you be heard because it does get garbled. And we're

trying to get a transcript of this, so it's important that they can hear what we're saying.

Secondly, as we're running late, we have two public presenters that we would like to get in today, so the question is to those presenters. Are you going to be around? Because we're going to be probably an hour late or so, so we may be running up against 7:00 this evening before we complete. If there's an issue, you should let us know, and we'll try to reschedule.

But those are the two things. It looks like we're running late, and so we're going to try to get this part of the docket done today. With that, Dr. Akerman's going to put on his best Brooklyn accent and rush right through this.

DR. GREGORY AKERMAN: All right. Thank you. Again, this is Greg Akerman. And when I left off, I had just presented my outline and my presentation so I'll move forward.

Genotoxicity is a broad term used to describe damage to genetic material. This damage can be transient or permanent. Transient damage is unintended modification of structure of DNA. This type of damage is repairable and may or may not

undergo successful repair. Whereas, permanent DNA damage refers to heritable changes in DNA sequence, better known as mutations. Such changes in a single base pair or a single or multiple genes or chromosomes, and this include chromosomal breaks leading to deletions, duplications, rearrangements of chromosome segments, and mitotic recombinations.

The consequences of genotoxicity may lead to cancer if mutations occur within regulatory genes such as (inaudible) genes or tumor suppressed genes, and may also signal a cell to undergo apoptosis in which case the damage is not fixed and passed along to daughter cells.

Battery in genotoxicity, the chemical involves a weight-of-evidence approach that considers various types of genetic damage that can occur. No single genotoxicity assay evaluates the many types of potential genetic alterations that may be induced by a chemical. The Agency employs a battery of genotoxicity tests to adequately evaluate the genetic endpoints important for regulatory decision-making. EPA considers genotoxicity as part of the weight of evidence when determining the human carcinogenic potential of a chemical.

This slide shows the mutagenicity testing required for pesticide registration. Mutagenicity testing is required for all food use and non-food use pesticides. The current battery includes a bacterial reverse mutation test, which is also known as the Ames assay. And as well as an in vitro forward mutation and in vitro mammalian cell chromosomal aberration test and an in vivo test for either a micronucleus induction or chromosomal aberrations, the source of genotoxicity data for fit-for-purpose systematic review identified data from both regulatory studies and the published literature.

Since the purpose of this review is to determine the carcinogenic potential of glyphosate in humans, for our evaluation, we limited the studies to mammalian based assays and conventional mutagenicity assay in bacteria. For example, the Ames assay. The search identified studies for both glyphosate-technical and glyphosate-based formulations. The search also identified regulatory studies that were not previously available to the Agency.

Next, we cross-referenced studies identified from the search with published review articles on glyphosate as well as recent international

evaluations of glyphosate. This includes 17 genotoxicity studies to the active ingredient glyphosate that were evaluated in the 2013th year in Kirkland review article. But these studies were not available to the Agency. However, summary data files for these studies are available online by the journal. And we noted in the White Paper where we used summary data from these studies.

In considering the quality of the data, both from published studies and unpublished or regulatory studies, we considered the study design, how the data were reported, and how well the study was conducted. We also considered critical elements such as test conditions such as pH, solubility, and cytotoxicity, and elements of the study design such as number of test organisms, doses tested, and use of controls and whether or not there was blinded evaluation, for example. This was applied to the evaluation of both published and non-published data.

In cases where they determined that the testing conditions or study designs were inappropriate and clearly had an impact on the outcome, for example with improper pH conditions were tested in in vitro

study, then those studies were excluded from our analysis.

The assays included in our evaluation that detect gene mutations included bacterial mutagenicity tests and in vitro mammalian cell gene mutation tests. And assays that detect chromosomal damage included in vitro and in vivo chromosomal aberration tests and micronucleus tests. And finally, genotoxicity tests, they'd also include assays that detect primary DNA damage, which included the Comet assay and Unscheduled DNA synthesis assays.

As I mentioned earlier, we used the weight-of-evidence approach to evaluate the genotoxicity data. Different factors influenced how much weight we gave to the genotoxicity findings. For example, permanent DNA damage was given more weight than findings of transient DNA damage. Evidence of chromosomal damage, for example, was given more weight than evidence of primary DNA damage. In vivo findings were given more weight than in vitro findings. And the routes and administered doses were considered for the relevance in human health risk assessment.

In the studies that evaluated gene mutations, 27 studies or assays were identified that

evaluated glyphosate technical. All 27 were found to be negative for the induction of mutations, both in the presence and absence of metabolic activation. Four studies were identified that measured gene mutations in mammalian cells in vitro. And one assay was conduct in CHO cells and three were conducted in mouse lymphoma assays. All four were negative in the presence and the absence of S9 activation for metabolic activation.

In vitro studies evaluating chromosomal abnormalities, there were eight in vitro studies that looked at chromosomal aberrations. Six of the eight were negative. All three that were conduct in cell line CHO or CHL cell lines were negative. There were two studies using lymphocytes that were positive for chromosomal aberration induction, both in the same laboratory. One used human lymphocytes and one used bovine lymphocytes.

However, there were three other studies using lymphocytes that reported negative findings, one in bovine and two in human lymphocytes, which were tested up to much higher concentrations, over a 100-fold higher in bovine cells and over 800-fold higher in human cells that were negative.

Looking at the in vitro micronucleus tests, there were six identified from the published literature, four of the six showed positive results and two showed equivocal results. Of the positive responses, three required metabolic activation and two were conducted using human lymphocytes, and one was conducted in CHO cells.

Positive response was also reported in a cell line, TR146 cells, which is a tumor cell line derived from human buccal mucosa. Which had not been previously used at that time for genotoxicity testing.

As mentioned previously, glyphosate was also negative in the three mouse lymphoma assays. Which, in addition to detecting gene mutations, it can also detective chromosomal damage.

Next, we looked at the in vivo tests for chromosomal abnormalities. These included three in vivo mammalian bone marrow chromosomal aberration assays. All three of these were negative. It included two studies conducted in the rat, one by i.p. injection up to 1,000 mg/kg and one by oral gavage with glyphosate trimesium salt. There was also one study that was conducted in a mouse up to 5,000 mg/kg/day.

In addition, there were two in vivo rodent dominant lethal tests, which evaluates the potential of a chemical to induce mutations in germ tissue. These were negative. One was conducted in a mouse, and one was conducted in a rat.

A systematic review identified a large number of in vivo mammalian micronucleus assays that were conducted with glyphosate. There were 19 studies in total. It includes studies conducted for regulatory purposes and studies that were published in the open literature and one study that was conducted by NTP.

Of these studies, nine studies were conducted by the i.p. route. They were all conducted in the mice. And ten studies were conducted by the oral route. Of the oral route studies, eight were performed in mice by oral gavage and one, the NTP study, was conducted by dietary administration. And there was one study in the rat that was by oral gavage, so the NTP studies, and the one by dietary administration.

This slide shows the results from the in vivo micronucleus studies that were conducted by i.p. administration. Seven out of nine studies were

negative, which tested up to approximately 2,000 mg/kg, either a single or double dose administration. The two positives were identified from the open literature.

One study, Bolognesi, reported positive findings in male mice at a dose of 300 mg/kg and that was administered at half-doses that were 24 hours apart. And the Manas et al. reported positive findings in both male and female mice administered two doses of 200 mg/kg per day 24 hours apart. Again, these are by i.p. administration.

There were seven other studies that were performed by using i.p. administration, and they were tested up to much higher doses. And those showed no significant induction of micronuclei.

Moving on to the in vivo micronuclei studies that were administered by oral gavage, eight of the nine studies in the mice were negative up to 5,000 mg/kg/day glyphosate. The only positive finding was seen in female mice treated with two doses of 5,000 mg/kg, and they were seen at 24 hours after dosing. It should be noted that the male mice in the study were negative for micronuclei induction up to the same dose of 5,000 mg/kg/day.

Finally, in the NTP study with dietary administration of rats, there was no significant induction of micronuclei following 13 weeks of dietary administration up to 3,000 mg/kg/day of glyphosate.

Next, we looked at studies that evaluated primary DNA damage. The systematic review identified a number of genotoxicity assays that evaluate primary DNA damage. Again, these are studies that measured genetic damage but not the consequence of genetic damage, so not the mutation or the chromosomal damage. The endpoints measured in primary DNA damage tests include DNA adduct formation, DNA migration and comet assays, unscheduled DNA synthesis, all of which may lead to cell death or may initiate DNA repair rather than a mutation.

Glyphosate was negative in the only study identified that evaluated the potential for glyphosate to form DNA adducts in mice. Again, Bolognesi et al. did report evidence of oxidative damage using a biomarker 8-hydroxydeoxyguanosine in the liver. It was not seen in the kidney in mice, and this was following an i.p. injection of 300 mg/kg/day.

It is noted that some have reported LD50 glyphosate in the range of 134 to 545 mg/kg/day.

But in our review, the validity was not an issue in this dose range in the majority of the i.p. studies we reviewed.

Glyphosate was evaluated in two unscheduled DNA synthesis assays using rat primary hepatocytes. There was no significant increase in unscheduled DNA synthesis in either of the studies. It was also negative in a DNA repair test using the Rec-A test in bacteria.

Bolognesi reported an increase in single-strand breaks in the liver and kidney in mice four hours after an i.p. injection of 300 mg/kg. This was using an alkaline elution assay. However, they noted that after 24 hours, the elution rate returned back to normal levels.

In five studies that were identified that used a comet assay to detect primary DNA damage, all five reported positive findings. However, there were some issues or some uncertainties with how studies were conducted or how the data reported that identified during our review of the studies, which may limit the impact of the findings. There were two studies that were conducted using tumor cell lines.

One in HEp-2 cells, which is a HeLA derived cell line. And again, the TR146 human derived buccal cell line.

Two comet studies were conducted in human lymphocytes. One reported only an increase in tail length in the comet assay, and the other one reported an increase in tail intensity. And there was a 14-day drinking study by Manas et al. that reported positive comet findings in blood and liver cells in mice dosed with 40 and 400 mg/kg/day. There were a number of limitations identified in this study as well as questionable biological significance and based on just the magnitude of the changes that got reported.

There was also a number of sister chromatid exchange assays that were identified during our systematic review. These were conducted either in bovine or human lymphocytes. This particular assay has sort of fallen out of favor in the regulatory arena because the mechanism of action for the induction of sister chromatid exchange is unclear. And in fact, OECD no longer has an active guideline for this particular assay.

Glyphosate was also evaluated in a cell transformation assay. Although mechanisms other than genotoxicity can result in positive response in this

assay, glyphosate was negative in the cell transformation assay.

In summary, the systematic review identified an expansive collection of genotoxicity studies evaluating glyphosate using a variety of test systems and genetic endpoints. A weight-of-evidence approach was used to evaluate the genotoxicity data. This involved integrating in vitro and in vivo results as well as an overall evaluation of the quality, consistency, reproducibility, magnitude of response, dose-response, and relevance of the findings.

Genetic endpoints of gene mutation in chromosomal alterations were given more weight than endpoints reflecting the primary DNA damage that could be transient or reversible.

In vivo mammalian studies were given the greatest weight. And more weight was given to doses and routes of administration that were considered to be relevant for evaluating genotoxic risk based on human exposure to glyphosate.

Glyphosate technical is not considered to be electrophilic and did not induce DNA adducts in the liver or kidney. Evidence of DNA strand breaks were reported in a number of mammalian studies that

used the comet assay. Additionally, transient increases in alkali labile sites in the liver in mice were reported.

However, due to some of the technical limitations identified in a number of these studies -- for example, the use of cancer cell lines that have not been well-characterized or atypical exposure protocols. Also, in some cases there was a lack of indication whether the study was conducted blinded treatment. We determined that caution should be exercised when interpreting some of these results.

There's no evidence of gene mutations in vitro in mammalian cells or in bacteria. And while there were mixed results of studies evaluating chromosomal alterations in vitro, all three of the in vivo chromosomal aberration studies were negative. And glyphosate was also negative in the rodent dominant lethal test.

Glyphosate was negative in 16 of the 19 in vivo bone marrow micronucleus studies. Two that were positive were conducted by i.p. routes, and one was positive at oral route at 5,000 mg/kg. The positive findings were not seen at other micronucleus

studies testing at similar or higher doses for these routes of administration.

Overall, the weight of evidence indicates there was no convincing evidence that glyphosate induces mutations in vivo via the oral route. When administered by i.p. injection, the micronucleus studies were predominantly negative. There was limited evidence of genotoxic effects in some of the in vitro experiments, but the in vivo effects were given more weight than in vitro effects, particularly when the same genetic endpoint was evaluated.

The only positive finding reported in vivo were seen at relatively high doses that were not relevant for human risk assessment. And the information provided in this presentation is related to charge question number four to the panel.

And at this time, I'll take any questions.

DR. JAMES MCMANAMAN: All right. Any questions from the panel for Dr. Akerman or about this presentation?

What? Oh, Dr. Green. Of course.

DR. LAURA GREEN: Sorry.

DR. JAMES MCMANAMAN: That's all right. I was worried that we had fallen asleep or something.

DR. LAURA GREEN: I'm wondering the raison d'etre for what you looked at and didn't, and here's what I have in mind. Those of us, as I'm sure we all are, interested in mode of action as sort of an approach to whether something has carcinogenic potential and how you can think about it. Obviously, a key mode of action for stressors that increased risk of lymphoma is immunotoxicity.

And I'm not sure I saw in the draft document -- nor did I see in your presentation or anyone else's presentation -- whether you all had included or excluded immunotoxic assays or endpoints in what you've been looking at. I mean, clearly, genotoxicity is a way to cancer, but it's not the only way to cancer, nor is ordinary old cytotoxicity. I guess I'm wondering whether that was in or out or how we should think about it.

.

DR. GREGORY AKERMAN: We didn't include immunotoxicity as one of --

DR. LAURA GREEN: I'm sorry. Did or not?

DR. GREGORY AKERMAN: Did not include immunotoxicity as one of the search terms for it. But we have -- okay. I'm sorry. Go ahead.

DR. ANWAR DUNBAR: We do have an immunotoxicity study, but it's negative.

DR. LAURA GREEN: Can you elaborate?

DR. ANWAR DUNBAR: There was no -- the sheet, the red blood cell assay, it's not in the White paper. No. But we could add that in, though.

DR. LAURA GREEN: Thank you.

DR. JAMES MCMANAMAN: Okay. That was Dr. Akerman and Dr. Dunbar. Other questions? Yeah. Dr. Zhang.

DR. LUOPING ZHANG: Luoping Zhang. I thought maybe they are very limited studies, really, testing for immunotoxicity. That's number one. I think from some of your report, only one thing mentioned the immunoassay. Actually, I think I saw that. I don't know if that's what you mentioned. Oh, unless you think that you already see quite a lot of immunotoxicity data.

DR. MONIQUE PERRON: So in the current paper that was provided to you, there was not information on immunotoxicity provided. What Dr.

Dunbar just mentioned is that we have another study available as part of our battery of tests that are required as part of registration that looks specifically at immunotoxic effects. And in that study, there were no adverse effects seen. And we can provide that information to you.

DR. LUOPING ZHANG: Yeah. That paper.

DR. MONIQUE PERRON: So you don't have it at this moment, but we can provide that. Sorry. This is Monique Perron.

DR. LUOPING ZHANG: That's definitely helpful.

DR. MONIQUE PERRON: Sure. No problem.

DR. JAMES MCMANAMAN: Other questions? Yes. Dr. Taioli.

DR. EMANUELA TAIOLI: Emanuela Taioli. Some of the slides had the references. Some didn't. Is that because you used the same criteria we talked about this morning that some are unpublished material and some are published? Or just there were no references because it had no space or something?

DR. MONIQUE PERRON: This is Monique Perron. in terms of the slides, it just happened to be like that. But if you look at the tables in the

paper, all of them are cited by the author names. They were all treated equally whether they were published or unpublished.

Much of the data, actually, is both. Some of it has been provided to us by registrants, but they've also published that data, as well, so also noting that. And altogether really across published or unpublished we saw pretty much the same results, you know, except for the few instances that Dr. Akerman pointed out.

DR. EMANUELA TAIOLI: This is definitely not my area of expertise because I'm an epidemiologist. But 29 studies and like everything negative in a sense that they all look the same because that never happens to us to see 30 things, they are the same. So just statistically there's always something that looks different. I'm just wondering if that's common in this area?

DR. GREGORY AKERMAN: This is Greg Akerman. If you look across genotoxicity assays, you always see positives pop up. But I think that way you're talking about the Ames assay? That one's probably not so unusual to get negative response in that. We still have criteria of what a response is so

it's not like it was not just an increase. We have certain levels where we consider it to be a positive response or not.

DR. JAMES MCMANAMAN: Yes? Dr. Jett.

DR. DAVID JETT: This is Dave Jett. I was not going to ask this, but we're talking about the number of studies. The comet assay studies, how many were there? I can't recall the slide, but there was more than one, right?

DR. GREGORY AKERMAN: Right. And they're all from the published literature. Yes.

DR. DAVID JETT: Okay. Was it five, ten, or? Yeah. And I guess so the question I actually have is it correct to assume that all of those were problematic and that's why it, sort of, downgraded their significance? Because they were positive, if I recall, right?

DR. GREGORY AKERMAN: Right. Their issue is with some of them because some people would call a positive response, and it was just an increase in tail length where under OECD guidelines, we only look at tail intensity as a better parameter of a measure. In that case, that would limit some of them.

There are still some positive responses, but we looked at in the weight of evidence looking at, as I mentioned before, putting more weight on endpoints that were chromosomal damage or mutations and in vivo versus in vitro effects, as well.

DR. DAVID JETT: Okay.

DR. JAMES MCMANAMAN: Dr. Zhang.

DR. LUOPING ZHANG: Okay. Luoping Zhang. I have a specific question just to try to clarify, but if you don't remember it you can get me back later. For the human monitoring study, the Bolognesi -- I don't know how to -- Bolognesi -- si, Italiano -- 2009, micronuclei, is this study included in your evaluation as a human monitoring study or not? And if no, what's the reason that one wasn't tested.

DR. MONIQUE PERRON: So we decided to include the human biomonitoring as part of the epi analysis. Those were all studies that were considered low in terms of being able to provide information with respect specifically to glyphosate and whether there was an outcome of concern there.

DR. LUOPING ZHANG: So you include it or not include it? Not include it because you can see that it's low?

DR. MONIQUE PERRON: Right.

DR. LUOPING ZHANG: Why? Why is it low, the human monitoring --

DR. MONIQUE PERRON: So going back to that flowchart from earlier today, it didn't meet some of the criteria there. It didn't get a detailed evaluation for those reasons. For many of them, they assumed glyphosate exposure, but really, they had no glyphosate-specific information. They just had total pesticide use as their exposure metric. We were looking for glyphosate-specific studies that would inform whether we think glyphosate would cause a carcinogenic effect.

DR. LUOPING ZHANG: That brings me to my second question. You're saying from that flowchart anything scored low quality in there is not included? Not only because it's from the human study, even though from the genotoxicity data, like biomonitoring, you took it out. Because I remember, you know, two off of the lows, you know, they have a specific -- besides Cocco 2013, Koureas.

DR. MONIQUE PERRON: Koureas? Yes.

DR. LUOPING ZHANG: Yeah. That's actually measure the DNA damage so that's part of genotoxicity.

DR. MONIQUE PERRON: Yes. As we walked through earlier today -- sorry. Again, this is Monique Perron. That study used an outcome assessment that wasn't very specific for the outcome. There are other more specific ways to measure the outcome such as HPLC or GC-MS. We just didn't think that the data would be robust enough to rely on at that point. When we looked across all the key considerations, we put that into the low category. It was not considered reliable to inform the carcinogenic potential of glyphosate.

DR. JAMES MCMANAMAN: Other questions? Yes. Dr. Shaw.

DR. JOSEPH SHAW: So you mentioned that you defined mutation as including insertions, deletions, as well as rearrangements. Which assays give a measurement of insertion, deletion, or rearrangements?

DR. GREGORY AKERMAN: So if it was an assay that caused chromosomal damage, we would assume that it could cause that. It was not one that

actually measured those. But I was just giving examples of what, in general, are considered mutations if it's assumed, if it caused damage to the chromosome, that you can end up with a mutation.

DR. JOSEPH SHAW: Okay.

DR. JAMES MCMANAMAN: Other questions?

(Whereupon, there was no response.)

DR. JAMES MCMANAMAN: Okay. Hearing none, we'll move on to the next presentation.

DR. MONIQUE PERRON: So this is Monique Perron. I'm going to be presenting the last presentation, which is data integration and weight-of-evidence analysis across multiple lines of evidence.

In 2010, OPP developed a draft "Framework for Incorporating Human Epidemiological and Incident Data in Human Health Risk Assessment," which provides the foundation for evaluating multiple lines of scientific evidence. This framework is consistent with the World Health Organization's mode of action/human relevance frameworks, and highlights the need to integrate information at different levels of biological organization.

The conclusions and observations from the epidemiological animal carcinogenicity, and

genotoxicity studies were evaluated in the context of the modified Bradford Hill Criteria. Additional information, such as metabolism and potential mechanistic information, was also considered.

Starting with dose-response and temporal concordance. Given the lack of consistent positive findings, particularly at doses of less than 1,000 mg/kg/day across the lines of evidence, the lack of mechanistic understanding of glyphosate, and lack of biological activity in mammalian systems to glyphosate, there are few data to assess key events in the biological pathway and the associated temporal or dose concordance.

However, with respect to the epidemiological studies, the prospective cohort study is designed to collect exposure information prior to the development of a cancer. In De Roos et al., there was no association found between glyphosate exposure and numerous cancer subtypes. There was also no increase in effect estimates with increasing exposure for almost all of the cancer types.

In the case-control studies that divided cases and controls into two exposure categories, greater effect estimates were obtained for

the highest exposure categories in both instances. However, there was no adjustment for exposure to other pesticides in these studies, and the stratification reduced the power or the number of exposed cases and controls since the studies were already limited by the number of exposed cases and controls overall.

So there seems to be conflicting results with response to dose-response relationships between the cohort and case-control studies. It also should be noted that these analyses again, they combine all NHL subtypes, which may have etiological differences. Although some studies did provide effect estimates for subtypes, there were not considered in the current evaluation due to limited sample sizes. At this time, there are no data available to evaluate dose-response for NHL subtypes

Furthermore, a dose-response relationship was not observed following the dramatic increase in glyphosate use due to the introduction of glyphosate-tolerant crops in 1996.

Due to the change in the use pattern from introducing these crops, if a true association exists between glyphosate exposure and non-Hodgkin lymphoma, the large increase in use would be expected

to result in a corresponding increase in the risk of NHL associated with glyphosate. Therefore, higher effect estimates would be expected in more recent studies. However, some of the highest adjusted risk measures for NHL were reported prior to 1996.

Similarly, if a true association exists, it would be expected that higher effect estimates would be reported in countries with higher use of glyphosate and/or that use glyphosate-tolerant crops such as the United States and Canada as compared to countries that exhibit less use. Once again, this trend was not observed, such that effect estimates in Sweden were similar or higher than those reported in the United States and Canada.

With respect to the animal bioassays, key events in the mode of action or adverse outcome pathway are evaluated to confirm that they precede tumor appearance. This temporal concordance evaluation cannot be conduct for glyphosate since a mode of action has not been established for mammals. It was noted, though, however, that there were no preneoplastic or related non-neoplastic lesions reported in any of the studies to support any of the observed tumors.

Additionally, there was no support of a direct mutagenic mode of action in genotoxicity studies and only limited evidence of genotoxicity in vitro studies that was not supported by the in vivo findings.

Strength, consistency, and specificity. A large database is available for evaluating the human carcinogenic potential of glyphosate. For epidemiological studies, only one or two studies were available for almost all the cancers investigated. However, no evidence of an association was observed with solid tumors, leukemia, or Hodgkin's lymphoma. The data were considered inadequate for multiple myeloma at this time. The largest number of studies was available for NHL, for which a conclusion at this time could not be supported.

With respect to NHL, the magnitude of the ever/never effect estimates were relatively small ranging from 1.00 to 1.85. The widest confidence interval was observed with the highest estimate, indicating less reliability in that estimate. All of these estimates were non-statistically significant with half of the estimates approximately equal to the null and the other half clustered from 1.5 to 1.8. As

a result, studies of at least equal quality are providing conflicting results.

Again, we also want to recognize that the many limitations and concerns that were identified for these studies and discussed earlier today such as confounding and sample sizes.

There were also conflicting exposure-response results. All of the effect estimates reported in the prospective cohort study were below 1. While higher effect estimates were reported in the case-control studies when stratified into two exposure categories. There are differences in confounding and covariant controls as well as the study design. There were also concerns identified in terms of sample sizes and potentially short follow-up time.

Oh, I'm sorry. Oh, there it is. Sorry.

Over 80 genotoxicity studies with the active ingredient glyphosate were analyzed in the current evaluation. And there's no convincing evidence that glyphosate is genotoxic in vivo via the oral route. Studies that administered glyphosate by i.p. injection were predominantly negative. There were two cases with increased micronuclei, but the

results were not reproduced at similar or higher doses.

Glyphosate was negative in all gene mutation assays. Although there is limited evidence of positive findings for primary DNA damage, the endpoints measured in these assays are less specific in regards to detecting permanent DNA changes and can be attributed to other factors such as cytotoxicity or cell culture conditions.

There were some positive findings reported for chromosomal alterations in vitro. However, these findings were limited to a few studies, and they were not supported by the in vivo studies that are more relevant for the human health risk assessment.

Biological plausibility and coherence. The genotoxicity studies demonstrate that glyphosate is not directly mutagenic or genotoxic in vivo. The available data regarding non-cancer endpoints also do not provide any support for carcinogenic process for glyphosate and have shown glyphosate to have relatively low toxicity.

In general, laboratory animals display non-specific effects such as clinical signs and

reduced body weight following glyphosate exposure at relatively high doses. And there were no observations of lesions to corroborate any of the observed tumors in the carcinogenicity studies.

As discussed earlier today, metabolism studies demonstrate that glyphosate has low oral absorption and it's rapidly excreted. The available data, however, are not sufficient to determine whether linear kinetics is occurring at the high doses where some of the tumor findings were observed. I just want to also note that there's a lack of mechanistic understanding of glyphosate toxicity in mammals. Although, the pesticidal mode of action is well understood, it's not relevant for mammalian systems.

Overall, tumor incidences were only increased at doses of approximately 1,000 or higher in the animal bioassays. Human exposures to these high doses is considered almost implausible based on the currently registered use pattern. During the overview this morning, I discussed how pesticide labels are legally enforceable and function to manage the potential risk from pesticides.

Based on the currently registered uses for glyphosate, high-end estimates of potential

exposure ranged from 0.02 to 7. As a result, even if the tumors seen at excessively high doses were considered treatment related, they are not relevant for human health risk assessment.

When evaluating a database, it's also important to assess the uncertainties associated with that available data. When the uncertainty is high, there is less confidence in the exposure and effect estimates. And therefore, informs in the reliability of the reliability of the results. Understanding the sources of uncertainty within a database can help characterize observed results and aid in developing new research that will have reduced uncertainty.

In some instances, the Agency did not have access to all of the data underlying the studies analyzed in the current evaluation. This included all of the epidemiological studies, one animal carcinogenicity study that was considered unacceptable, and 17 genotoxicity studies. As a result, the Agency had to rely upon information reported by the study authors and without the raw data, statistical analysis could not be replicated or recalculated.

As mentioned earlier, there are numerous metabolism studies available for glyphosate. However, the data are not sufficient to determine whether linear kinetics is occurring at high doses where tumor findings were observed in the animal bioassays. With respect to the epidemiological data, the database is limited for each investigated cancer with only typically one or two studies available.

Even in the case where six studies were used for NHL, the results were constrained by limitations of the individual studies such as small sample size, missing data, and control selection issues. More recent studies will help further elucidate the association between glyphosate exposure and cancer outcomes given the dramatic increase in glyphosate use and the changing use pattern after the introduction of glyphosate-tolerant crops.

Some have noted that the median follow-up time for the Agricultural Health Study was about seven years. A longer follow-up would be beneficial to better understand whether there is an association glyphosate and NHL given the latency of NHL and NHL subtypes is relatively.

Another consideration is that farmers and other applicators apply formulations, not the active ingredient alone. It's possible that different formulations were used across and/or within the different epidemiological studies. There are studies that have been conducted on numerous formulations that contain glyphosate.

However, there are relatively few research projects that have attempted to systematically compare glyphosate and the formulations in the same experimental design. Furthermore, there are even less instances of studies comparing toxicity across the formulations. Despite these uncertainties, the available data are considered more than adequate for evaluating the human carcinogenic potential of glyphosate in order to determine a cancer classification using the 2005 Guidelines.

There are five classification descriptors in the 2005 Guidelines for carcinogen risk assessment. When assigning a descriptor, all of the available data from multiple lines of evidence are used. The guidelines emphasize that choosing a descriptor is a matter of judgment and cannot be reduced to a formula. And that rather than focusing

simply on the descriptor, the entire range of information included in the weight of evidence should be considered.

The descriptor "carcinogenic to humans" is appropriate when there is convincing epidemiological evidence of a causal association between human exposure and cancer. The descriptor "likely to be carcinogenic to humans" is appropriate when the weight of evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor "carcinogenic to humans."

Excuse me. The Agency does not believe these two descriptors are supported by the weight of evidence. There was no evidence of an association between glyphosate exposure and solid tumors, leukemia, and Hodgkin's lymphoma. The data were considered inadequate for multiple myeloma at this time. And a conclusion could not be supported for NHL at this time.

None of the observed tumors were considered treatment related. Even if they were, the doses are not considered relevant for human health risk assessment. Furthermore, the tumor findings were

not reproduced in other studies using the same strain at similar or higher doses. And lastly, there was no direct evidence of a mutagenic mode of action for glyphosate.

The descriptor "inadequate information to assess carcinogenic potential" is used when available data are judged inadequate for applying one of the other descriptors. Again, the Agency does not believe that this descriptor is supported. There's an extensive database available for glyphosate with well-designed and well-conducted studies.

There is limited epidemiological data. However, these data are not available for most pesticides. Typically, two animal bioassays and a battery of genotoxicity studies are the only data available. And the Agency routinely evaluates human carcinogenic potential using these smaller datasets.

The descriptor "suggestive evidence of carcinogenic potential" is appropriate when a concern for potential carcinogenic effects in humans is raised but the data are judged not sufficient for a stronger conclusion. It covers a spectrum of evidence associated with varying levels of concern for carcinogenicity.

The evidence to support this descriptor are listed above. I will note that the first bullet should actually say, "Non-statistically significant effect estimates greater than the null for NHL and meta-analysis based on ever/never use ranged from 1.3 to 1.5." I apologize for the typo.

In addition to that, there was limited evidence of a possible exposure response relationship in two case control studies. Statistically significant trend results were observed in some of the animal carcinogenicity studies. And in some instances, statistically significant pair-wise comparisons were seen when looking at unadjusted p-values.

And there were some limited positive responses in genotoxicity assays evaluating chromosomal and primary DNA damage. However, the guidelines state that rather than focusing simply on the descriptor, the entire range of information included in the weight-of-evidence narrative should be considered. Therefore, it's not appropriate to view these findings only in isolation.

The 2005 Guidelines also state that positive findings should not be contradicted by

studies of equal or higher quality in the same population group or experimental system. For the epidemiological studies, half of the estimates were approximately equal to the null. And there were conflicting exposure response results between the cohort and case control studies.

In the animal bioassays, statistically significant tumor findings were not reproduced in other studies, including those in the same strain at similar or higher doses. And following the weight-of-evidence evaluation, none of the tumor findings were considered treatment related. And in seven of those studies, there were no tumors identified for detailed evaluation.

Lastly, the positive responses in genotoxicity assays were not reproduced such that in vitro results were not supported by positive responses in vivo. And the endpoints evaluated in primary DNA damage assays, which are less specific with respect to permanent DNA changes. And these changes can also be attributed to other factors such as cytotoxicity or cell culture conditions.

The evidence to support the remaining descriptor "not likely to be carcinogenic" includes no

evidence of an association in the epidemiological studies. There were no tumors identified for evaluation in 7 out of the 15 animal studies. And the tumor findings were not considered treatment related based on the weight-of-evidence evaluation. And the tumor findings in those individual studies were not reproduced in the same strain at similar or higher doses.

All of the in vitro gene mutation assays were negative, and positive in vitro findings were not supported by in vivo results. And lastly, there was no convincing evidence that glyphosate was genotoxic in vivo.

For this descriptor, the guidelines also state that you can consider whether there's convincing evidence that a carcinogenic effect is not likely below a defined dose range. It was noted that even though tumor findings were not considered treatment related, the tumor incidences were primarily only increased at doses of approximately 1,000 or higher. Incidences were not increased at dose levels of 500 or less, except for the testicular tumors seen in a single study.

And genotoxicity assays via oral administration were negative except in one study at 5,000 mg/kg/day. Based on these oral studies, it could be concluded that effects are not likely below 500 mg/kg/day.

The guidelines also state that weighing of the evidence includes addressing not only the likelihood of human carcinogenic effects of the agent, but also the conditions under which such effects may be expressed. As I just mentioned, increased tumor incidences were primarily seen at doses of 1,000 or higher. The only positive finding in an oral in vivo genotoxicity assay was at a dose of 5,000 mg/kg/day. And other positive in vivo findings were only observed via i.p. injection.

As I discussed earlier today, high-end estimates of potential exposure are well below these administered doses. And as a result, these high doses would not be considered relevant for human health risk assessment.

After walking through all of the cancer classification descriptors and considering the entire range of information in the weight of evidence, the data do not support the "carcinogenic to humans" or

"likely to be carcinogenic to human" descriptors. Given the extensive database available for glyphosate, the descriptor for "inadequate information to assess carcinogenic potential" is also not supported.

There isn't strong support for "suggestive evidence of carcinogenic potential," especially since positive findings are contradicted by studies of equal or higher quality. The strongest support at this time is for "not likely to be carcinogenic to humans" at doses relevant to human health risk assessment. On all of the information that I just went over, we have drafted charge questions under charge question five.

DR. JAMES MCMANAMAN: Okay. Questions from the panel?

Yes. Dr. Sheppard.

DR. LIANNE SHEPPARD: So this is Dr. Sheppard. I have to ask some questions about this idea that the Epi study results for non-Hodgkin lymphoma are conflicting. And I want to understand exactly what the criterion is for determining conflicting. I saw what I read in the document, which was there was this post-hoc division of studies into ones that had bigger estimates and ones that had had

smaller estimates. Is that your criterion, or is there something else?

DR. MONIQUE PERRON: No. I think when we looked across those six studies we just saw that there seemed to be this clustering of three studies that were right around the null. And then another three that clustered around 1.5 to 1.8. But it wasn't just that where there was where we would say conflicting results. I mean I think that's just part of the picture.

I think also in terms of the exposure response relationships and that analysis, we definitely see that in the cohort study, you have risk estimates that are coming out below 1. And then in these case control studies that did evaluate it in different ways; they were finding a different result. It's not just that. But I think we saw it as a little bit more of across all these studies we're not exactly seeing a consistent yes, we think definitely something's going on.

DR. LIANNE SHEPPARD: Okay. Because we're not deliberating, I'll set aside the dose-response because that requires a longer conversation. But I want to get at this idea that, as in this figure

you helpfully provided and had in your slides, we have six estimates and confidence intervals that completely overlap with each other.

And we have meta-analysis which are an accepted way for combining evidence from epidemiology that provide estimates on the order of 1.3 to 1.5. All of which the bottom end of the confidence interval is at or slightly above 1.01. And in fact, the I-squared statistic for that said there was no residual heterogeneity in those studies. So where is the evidence of conflict in those estimates?

DR. MONIQUE PERRON: Sure. I guess in many ways, we did characterize this to show that information because a lot of people are putting weight on those higher estimates. Even though all of them, like you said, are overlapping, they were all non-statistically significant. I mean I will go back, again, on the meta-analysis that although it is an accepted way to look at it, again, there should be caution taken when looking at that data, especially when there are not many studies available to include in that meta-analysis.

But I think there is consistency in the database. We just wanted to recognize that even if

you focus on those very high estimates, then you're ignoring the fact that you have three studies that were resulting in effect estimates approximately equal to the null.

DR. LIANNE SHEPPARD: But the meta-analysis uses all of those. And so that's a not post-hoc way of using all of that evidence. But sort of post-hoc saying, oh, there's three that are big and there's three that are small, that's not a statistically valid way to do -- that's not evidence of conflict. I mean I guess what I'm trying to sort out -- we don't want to be deliberating. But what I'm trying to sort out is when you are using statistical evidence and when you are using some other evidence.

DR. MONIQUE PERRON: So this is Monique Perron again. So again, I think we were trying to show the data in a different light. If you really wanted the bottom line of how we looked at the data, it was all of these are non-statistically significant. They were consistently of small magnitude. And even with a slightly significant meta-analysis where the confidence limit was 1.03 or something like that -- again, the meta-analysis, which again I do feel that caution should be taken with those.

I get what you're trying to say. But you're also carrying over all of the limitations and concerns that you have in individual studies every time you do those meta-analyses. I will say that, again, I think that, again, you are seeing a very small magnitude, even in the meta-analyses. And in many instances, actually they were non-statistically significant.

DR. LIANNE SHEPPARD: Yeah. Not statistically significant is different from conflicting, right? Do you agree with that?

DR. MONIQUE PERRON: So and that's what I mean. So back to my first statement that we were trying to characterize it a little bit differently so people could see more than just the bottom line. And maybe that got lost in what you're trying to say. And we can take that back in our characterization and improve it in that way.

DR. LUOPING ZHANG: Luoping Zhang. If I remember correctly actually, EPA yourself, you come back to the meta-analysis, as well. And it has come out positive and statistically significant, as well.

DR. MONIQUE PERRON: So we have not conducted the meta-analyses for these. No.

DR. LUOPING ZHANG: I thought I read somewhere --

DR. MONIQUE PERRON: No.

DR. LUOPING ZHANG: Just that, you know, in-house analysis or --

DR. MONIQUE PERRON: No. We don't have access to any of the data. Oh, the meta-analyses. Yes.

DR. LUOPING ZHANG: Yeah. Meta-analysis. Yeah.

DR. MONIQUE PERRON: And we could reproduce probably using the effect estimates. Yes, the meta-analyses. But I don't believe we actually included them in the paper. I think that that figure only shows the effect estimates. We could do it. Yes. And it would probably come out exactly the same as some of the ones that you've already seen. In particular, if you look at Chang and Delzel. I think we talked about earlier where they replace effect estimates depending on the study, and they all kind of come out about the same regardless of the study.

DR. LUOPING ZHANG: Also, I feel when you are saying the few like six original studies included for non-Hodgkin lymphoma analysis, so a lot

of them is not significant. But when we looked at the data actually, quite a lot of them seems are statistically significant from the data.

DR. MONIQUE PERRON: So this is Monique --

DR. LUOPING ZHANG: Even from the number four presentation, you know, you have statistically significant data.

DR. MONIQUE PERRON: This is Monique Perron. And --

DR. LUOPING ZHANG: So I just feel what I was --

DR. MONIQUE PERRON: -- the majority of the results were non-statistically significant. At least in terms of the ever/never effect estimate.

DR. ERIC JOHNSON: I think one of the areas of confusion is what are we calling cohort studies? How many cohort studies are there? Because from my counting, there's only one cohort study which was repeated twice, I mean, in terms of looking at the high-quality study. I brought it up this morning that Koutros, an Agricultural Health Study, and that was a cohort study analysis, not a case-controlled study.

When you say up there that they have conflicting results between cohort and case-controlled studies, if it's only one or two cohort studies, I think it's best if you just state that, so people know that it's only one of two cohort studies.

DR. MONIQUE PERRON: Okay.

DR. ERIC JOHNSON: Rather than saying that -- say if we have a really strong body of evidential cohort study and a strong body of case-controlled study, then that is a conflict.

DR. MONIQUE PERRON: So this is Monique Perron. In terms of this slide presentation, we were focusing on the non-Hodgkin lymphoma. The other study that we spoke about earlier today, Koutros, that was for prostate cancer. That's why we are only talking about one cohort study here. Because it was just the one De Roos paper and then five case-controlled for NHL.

DR. JAMES MCMANAMAN: Thank you.

Dr. Taioli.

DR. EMANUELA TAIOLI: So I have two points. One is what other light -- you have numbers, so you have a summary estimate, it's over 1. You have no heterogeneity, which is that I-square and the Q-

square are the lowest I've seen in my life. And fortunately, I've seen a lot. That's the numbers. What other light you can look at? That's one question. Then I have a question about the increased use, your slides with the map.

DR. MONIQUE PERRON: So statistically, I know what you're talking about. The I-square values came out very low. Yes. But as we noted earlier today, there are distinct differences that were highlighted in some of those studies. Some adjusted for co-exposure to pesticides. Some didn't.

You have the difference of cohort versus case-control study. You have these things that may not possibly be picked up by a heterogeneity analysis. And once again, I mean, I appreciate the utility of meta-analyses. But they are the most robust when you have many more studies than six or less.

DR. EMANUELA TAIOLI: Sorry. The other point is that 1.4, 1.5 for epidemiologist is a big number. It's not a small association. When there are risk factors that are scored as sure risk factors with values that are even less than that. Those are numbers that are not irrelevant for us, in general.

DR. MONIQUE PERRON: I see what you mean. Again, in terms of magnitude, I mean, there are different definitions depending on the epidemiologist. I mean there is no definitive --

DR. JAMES MCMANAMAN: I think we're veering off into charge questions issues.

DR. MONIQUE PERRON: Anyways.

DR. EMANUELA TAIOLI: Now in terms of your math, I read it on the description and on the paper, as well. I'm not sure where you're getting that with increased use. Because if there is increased used, you would you see increased incidence. But you are not really in a position of measuring incidences because you don't have a cohort study that shows, unless you have a follow up of that cohort.

In terms of increased exposed amount, the cases, you would see increased exposure among the controls, as well. If both increase of 10 percent, let's say, the odds ratio becomes the same. You would not see changes of odd ratio all the time. I'm not sure where you getting with that concept. If I understand it correctly, I don't think you can get to that statement with the data that you have. But maybe I didn't get the point you guys wanted to make.

DR. MONIQUE PERRON: Right. The point that we're trying to make that following the introduction of the glyphosate-tolerant crops, the use pattern changed. So how people were using it previously, it changed in terms of the number of applications they could use, the number of acres they're treating because some of the farmers switched over their acreage. Also, there was a shift from smaller farms to more corporate farms.

There was just a large increase in the use of glyphosate as well as this change in use pattern. We do think that individuals that were already using glyphosate have increased their use significantly based on that change in use pattern.

DR. EMANUELA TAIOLI: Then you would see a change in the dose-response, which you haven't really -- you don't have a lot of data to look at that.

DR. MONIQUE PERRON: Right. We don't have a lot of data. And --

DR. EMANUELA TAIOLI: Yes or no would not change. The dichotomous association would not change because the number of people who are exposed --

DR. MONIQUE PERRON: Yes.

DR. EMANUELA TAIOLI: -- are either the same or increased both among cases and controls. You would not see a difference, I think.

DR. MONIQUE PERRON: Okay.

DR. JAMES MCMANAMAN: That was Dr. Perron and Dr. Taioli.

Dr. Johnson.

DR. ERIC JOHNSON: Yes. When I look at your presentation on the genotoxicity test -- and I'm not very familiar with all those studies at all. But just listening to what you said, and also reading the issued document, one comes away with the fact that yes, there is clear evidence that the heterogeneity test shows no evidence at all, or very little evidence of anything at all.

But for some of the other ones like some of the mammalian in vivo tests, I come away with that there's something there, but every time there's something, you're saying that well, there's something deficient about it because of so, so, so, so. And then you went further towards the end of your summary and you said, you're ignoring certain in vitro tests because they were not consistent with in vivo tests, meaning in vivo tests being all negative. When,

really, some of them were substantial evidence of something going on.

I just come away with the fact that you are downplaying some of the genotoxicity tests, especially the in vivo ones. I think it was the micronuclei one or whatever. But I think they were quite substantial. And every time there was something positive there you said there's something wrong with this study. I mean that's what I came away with. I'm not very familiar with --

DR. GREGORY AKERMAN: I'm sorry. Excuse me. This is Greg Akerman.

DR. JAMES MCMANAMAN: I think this may be an issue again, where it's a charge question. It's a limitation. It's a perfectly valid point, but there is not a clarification question in that. It's more of a comment than a question, and I think we should just stick with the question trying to get clarification. Since it's getting late in the day, and we've got more to do.

DR. LIANNE SHEPPARD: Yeah.

DR. JAMES MCMANAMAN: Dr. Sheppard.

DR. LIANNE SHEPPARD: I wanted to address two things in addition to my previous comment.

One is getting back to this expected higher effect estimates. On slide five it says, "Expected higher effect estimates in countries with higher use of glyphosate and/or using glyphosate-tolerant crops." And it seems to me, again, you're comparing the relative risk or odds ratio estimates without taking into account the confidence intervals. Is that a fair assessment of what you meant in that statement?

DR. MONIQUE PERRON: Yes.

DR. LIANNE SHEPPARD: Okay. Thank you. And the second one was, I actually spent some time reading that 2010 document about use of epidemiologic studies that was chaired by Steve Heeringa. And one of the things that they talked about with was concern about statistical bias, particularly when you have too many parameters in a model. And I haven't heard and I didn't read anything in the issue paper about that. And I was wondering how you all thought about that issue.

DR. MONIQUE PERRON: Sorry. Can you repeat that question? I was writing it down but it wasn't all --

DR. LIANNE SHEPPARD: Yeah. Okay. I'd be happy to. It's a pretty subtle one. But it's very

clearly stated in the 2010 document that one of the things to pay attention to is statistical bias, which basically comes about when you overfit models, when you put too many parameters in a model. And I just didn't see any attention paid to that at all in this issue paper. I was wondering how much that factored into any of the work that you all did.

DR. MONIQUE PERRON: Yeah. In the current evaluation, we didn't factor that part in. But that could be something that could be integrated later.

DR. LIANNE SHEPPARD: Okay. That's probably important to then maybe try to drill down a little bit more carefully in what aspects of the 2010 document were addressed, you know, and how. I guess maybe that's work for us to do as a panel. But yeah, because you say you did use that assessment or that evaluation. I wanted to be clear on that.

DR. JAMES MCMANAMAN: Other questions? Okay. Then I think we'll -- oh, sorry.

Dr. Lowit.

DR. ANNA LOWIT: Just a point of clarification because I've heard a little bit of this from a few people today. Both the Cancer Guidelines

and the 2010 draft epi framework are not recipe books per se. They are guidances and frameworks to guide the Agency on evaluating multiple lines of evidence.

Although it's fair to go through and say where we may be consistent, there are areas where we can improve our language or increase our characterization. I wouldn't want to grade the assessments on that recipe book per se that the analysis is intended to be a weight of evidence across multiple lines and data using as much information as available, being accurate about the characterization of that information.

It's not about following those frameworks and the guidelines as if I'm going to make cookies next week as if I was going to bake cookies. Because if I left out the salt or I didn't put enough butter, something bad would happen, right. But in the case of this kind of analysis, we can't hold up these as recipe books that we just check off.

DR. JAMES MCMANAMAN: Okay. Dr. Green.

DR. LAURA GREEN: Yeah. I have a question for you all and possibly for you. It strikes a number of us that one of the problems, which we all face, is that there may be a square peg/round hole

issue here. By which I mean are you constrained -- well, let me say it in the affirmative and then ask the question. You seem to be constrained to have to decide at the end of the day to put glyphosate in one of five categories.

And I'm wondering if you are allowed to come up with a sixth category. And what I have in mind is that as a toxicologist, I'm aware that NTP, for example, a long time ago came up with a descriptor called "equivocal." And they do that for a reason, right. NPT, a federal agency, specifically says data shall be considered equivocal under certain conditions. I'm wondering do you have the freedom to do that or are you constrained to, at the end of the day, choose one of these five?

DR. GREGORY AKERMAN: This is Greg Akerman. We have to classify it in one of those five, but we can add qualifying statements to that. If it happens below a certain dose or something like that, we could say that. Or a certain dose range or whatever, we can add a qualifying statement. But at the end of the day, we have to put it one of those classification descriptors.

DR. ANNA LOWIT: So this is Anna Lowit. To add to that, to the extent that if the panel, let's say you're using the word "equivocal," I think what would be important is that you would describe the science, what equivocal means from a scientific point of view. At the end of the day, the cancer classification is really a policy call, which is the agency's purview to make those policy calls.

What we're looking for, from all of you, is to help us improve our science analysis that gets us to that policy call. But also, helps us understand where the characterization across the spectrum of information. If, let's say, you like the word "equivocal," it would be important that you explain the science that underlines that equivocal call. And then we could then think about how that fits into the Cancer Guidelines or something else, right.

DR. JAMES MCMANAMAN: Other comments or questions?

Yes. Dr. Parsons.

DR. BARBARA PARSONS: This may be out of right field, but in terms of uncertainties, I think you've said a few times today that there is no

evidence of bioaccumulation. And I was just wondering what the nature and strength of the evidence was. You know, how long were animals exposed to understand whether or not glyphosate bioaccumulated?

DR. MONIQUE PERRON: This is Monique Perron. That information is primarily based on the metabolism studies. And as Anwar walked through earlier, we have over 20 studies available there. And what they do is they evaluate the tissues in the individual animals to see how much is ending up in the different tissues. And in the case of glyphosate, predominantly almost all of it ends up in the urine and excreta and ends up being sent out as parent compound. That's why you'll often see us say that it's not bioaccumulated or biotransformed, as well.

DR. ANWAR DUNBAR: This is Anwar Dunbar. Also, in some of those designs, you're also looking at repeated exposures over 14 days.

DR. BARBARA PARSONS: So 14 days is the extent to which that was studied. Okay. Thank you.

DR. JAMES MCMANAMAN: Okay. We move on to the next -- was that your final one? Or it looks like you had another one.

DR. MONIQUE PERRON: That was the final one.

DR. JAMES MCMANAMAN: That was it?

DR. MONIQUE PERRON: That was it. I'm not sure where the other one on the agenda came from. (Applause)

DR. MONIQUE PERRON: We just wanted to make sure you stayed on schedule.

DR. JAMES MCMANAMAN: Yeah. All right. In order to save time, unless anybody needs a bile break, I think we'll move on to the public commenters.

I have it as Daniele Court-Marques. Welcome, Daniele.

For other public commenters who are here -- since we have a full load of public commenters tomorrow. You know your roughly scheduled time so try to sit close so that there is not so much time going back and forth between your seat and the desk up here.

We'll hear about the European view.

DR. LARS NIEMANN: Lars Niemann. Since Daniele will present the European view, I will try to provide the German view. Perhaps to avoid redundancies and to speed up the process, sir, if you don't mind, I would suggest that we will give our

presentations one after the other. And then answer the questions together. Is that possible?

DR. JAMES MCMANAMAN: That sounds wonderful.

DR. LARS NIEMANN: Fine. Thanks.

DR. JAMES MCMANAMAN: Is there anyone here with a Brexit point of view?

MR. STEVEN KNOTT: Can I just ask a clarification very quickly? We received a new thumb drive but that is not a different presentation than what was emailed previously, correct?

MS. DANIELE COURT-MARQUES: Sorry. I didn't hear well.

MR. STEVEN KNOTT: The presentations that were emailed previously is the current --

MS. DANIELE COURT-MARQUES: Yes.

MR. STEVEN KNOTT: -- presentation, right?

MS. DANIELE COURT-MARQUES: Yes.

MR. STEVEN KNOTT: Okay. Thank you.

MS. DANIELE COURT-MARQUES: Yes. That I sent to you end of last week, yes?

MR. STEVEN KNOTT: Great.

MS. DANIELE COURT-MARQUES: Yes.

DR. JAMES MCMANAMAN: All right. Daniele, do you want to begin?

MS. DANIELE COURT-MARQUES: Okay. Thank you very much, Mr. Chairman.

I'm Daniele Court-Marques, and I am a toxicologist working in the Pesticide Unit in EFSA, the European Food Safety Authority. So --

DR. JAMES MCMANAMAN: Daniele, put your microphone a little closer. There you go.

MS. DANIELE COURT-MARQUES: Okay. So before presenting the conclusions of the Pesticides Peer Review in Europe, I would like to shortly explain the pesticide peer review concept and how the glyphosate assessment was conducted. I will shortly -- oh, sorry. Yeah. I would like to shortly go through the glyphosate toxicokinetics and toxicodynamics before then going into a bit more details into the genotoxicity assessment, carcinogenicity data that includes animal data and epidemiology.

How was the peer review conducted in Europe? I think it's an important point to clarify that one basis of the legislation in Europe is a complete separation between risk assessment and risk

management. And that the risk assessment is here on the left-hand side. The concept is that industry or applicants provide a dossier to a designated Rapporteur Member State, in this case, Germany here on my left side.

And then the Rapporteur Member States produce an assessment report that is then sent to EFSA and all other Member States who then conduct a peer review. Meaning that there's a commenting period. Or maybe we can just go to the end and it results in the EFSA conclusion that includes a scientific assessment after the peer review, a list of endpoint, in data gaps and areas of concern.

And then this conclusion is sent to policy managers who take the decision of the approval of the active substance on the European market. Then it's the responsibility of each Member State to assess each formulation by itself. That will be authorized in their own territory based on this approved active substance.

Regarding the timelines of glyphosate peer review, so it begins in the 2012, 2013 when the Rapporteur Member States produced the first assessment of what is called a renewal assessment report in this

case, because glyphosate is not a new active substance in the market. And then it was sent to EFSA late 2013. Then the peer review itself began when Member States were called for comments on this renewal assessment report. And the public consultation was launched on the renewal assessment report.

Then early 2015, as a result of this commenting period, the Rapporteur Member States produced a first revision of the renewal assessment report. And also, the applicants were given the opportunity to give more information when there were some doubts about or need for further information. And then the experts' consultation was conducted in different areas for glyphosate, meaning mammalian toxicology residues, environmental fate, and ecotoxicology.

The outcome of this expert consultation was taken into consideration by the Rapporteur Member States who produced a second revision of the renewal assessment report. At that stage, it was when we were made aware by the Lancet publication of the conclusion of the IARC assessment of carcinogenicity. And on this basis, EFSA received a mandate from the European Commission to review the IARC on carcinogenicity.

And therefore, we then waited for the IARC Monograph to be published, which happened in August. And the rapporteur Member States produced an addendum to the renewal assessment report so that it could be, again, considered by all Member States. And then so in August and September, there was a new expert consultation that was dedicated to carcinogenicity. That in October 2015, there was a final consultation with Member States and the adoption of the EFSA conclusion.

To make hopefully a bit clearer what are the documents that were produced during the peer review and the basis for the assessment. First of all, the applicants sent the dossiers that consist of the mandatory, regulatory studies according to the data requirements that are here meant by regulation of 2011. Then the applicants are also required to do a search for the scientific peer review literature according also to EFSA Guidelines to comment on how to perform such search and eventually, other evaluations.

Then we go to the documents here on the right-hand side that consist of the Rapporteur Member State evaluation and respective updates that are

highlighted in different colors depending on the different updates.

And then the peer review report of glyphosate that consists of all the comments that were received during the public consultation and by Member States. The response to these comments or how they were handled. The meeting reports with Member States experts and Member States' views. And then what actually is the EFSA conclusions. That is a short summary finally on the scientific assessment and highlights the critical concerns, data gaps, and validated agreed endpoints.

Glyphosate, as we already heard today, has an exceptionally rich dossier. And only in the mammalian toxicology section more than 700 studies and reference were considered in the renewal assessment report revised twice, again, by the Rapporteur Member States.

This includes 20 long-term carcinogenicity studies in rats and mice, more than 100 genotoxicity studies, and around 30 epidemiological studies. To note that when the IARC Monograph was published, the Rapporteur Member States

still added a few additional studies that were mentioned in the IARC Monograph.

I like to give a very short overview of the toxicokinetics of glyphosate. That was found to be rapidly but fully absorbed. It's considered that 20 percent would be systematically available. And this is because we also considered worst case. For us, its worst case is 20 percent systematically available. Then it's very poorly metabolized, very widely distributed. However, a certain affinity for bones was observed. Then it was mostly eliminated unchanged via feces with the absorbed dose recovered in urine. And again, no evidence for accumulation was observed.

An overview of the toxicodynamics. We all know that glyphosate show a very low acute toxicity whatever the root of exposure. It was severely irritant to eyes and mucosa in the acid form. And interestingly, glyphosate showed a very inconsistent pattern of toxicity over the overall package. However, intestinal tracts, including salivary glands, were considered as target organs of glyphosate, which can be expected considering the toxicokinetics and acid properties of the substance.

Also, I think it's interesting to show that the overall short-term NOAEL was between 300 and 500 mg/kg/day depending on the specie considered. And the overall long-term NOAEL was 100 mg/kg/day in rats and 150 in mice. This is considering the overall values considering all studies together.

However, the most critical NOAEL came from the developmental toxicity studies in rabbits where post-implantation losses, reduced fetal weight, and ossification were observed at (inaudible) doses. This NOAEL of 50 mg/kg weight led the overall risk assessment.

Going now to what interests us today regarding the genotoxicity assessment would like to go through the in vitro studies and the in vivo studies to get to a weight of evidence. Regarding the genotoxicity assessment as for other endpoints of the dossier, we had high numbers of studies in the dossier, either from the industry or from the open literature. In each case, they were assessed for their acceptability and reliability.

And I think this is important to mention that studies conducted with the formulations were excluded from this analysis to avoid bias derived

from the toxicity of co-formulants. It is also essential that well-defined test material is known to avoid bias from potentially genotoxic impurities.

And the study design was also carefully checked to be fit for purpose for the genotoxicity assessment such as the use of concurrent negative and positive controls or pre-test determination of cytotoxicity or toxicity to target cells and as well as whether the concentration and dose levels were appropriate. And overall, it was also considered that mammalian systems are more representative for human health.

Regarding gene mutation, as was already mentioned today, either bacterial assays or gene mutation test in mammalian cells were consistently negative results. Even considering studies that were less acceptable, overall, they were all negative.

Regarding chromosome aberration, three fully acceptable studies gave also negative results up to dose level of 1,250 mg/ml. However, in contrast, two non-guideline studies at much lower concentrations gave positive results.

Going now to indicator tests, they are considered indicators because they are not designed to

detect direct mutagenicity, but rather, primary DNA damage.

Mixed outcome was seen in these tests such as negative in vitro UDS tests, unscheduled DNA synthesis tests, positive sister chromatid exchange tests that are given usually of a low weight into the overall genotoxicity assessment. And then positive results for induction of DNA strand breaks or in vitro or also in vivo with high intraperitoneal dosing above the intraperitoneal lethal dose 50 or even repeated dosing also some methodological deficiencies were observed.

In vivo studies are usually used to clarify and possibly contravene positive outcomes that are observed in vitro. As long as the same endpoint is considered and tissue exposure has been demonstrated. Regarding in vivo studies, seven in eight fully acceptable micronucleus or chromosome aberration studies in rats and mice treated by the overall dose, up to twice 5,000 mg/kg weight, gave consistently negative results.

Also, six further studies conducted by the intraperitoneal route at high-dose levels above the maximum tolerated dose also gave negative results,

except two studies where methodological deficiencies were observed. And again, as was already mentioned, there were two negative germ cells mutagenicity tests, one in rats and one in mice.

Regarding the weight of evidence for genotoxicity, in summary, we found one weak positive response in eight studies using the oral route. This weak positive response was observed at high-dose level in females only and was a high standard deviation. Also, two in six intraperitoneal studies gave positive response at doses exceeding the intraperitoneal LD50.

And in studies presenting methodological drawbacks such as low number of animals only one dose level used. It was unclear when the controls were sacrificed questioning the statistical comparison. Also, independent coding of the slide was not reported.

In the second study, bigger major drawback was seen as the scoring for total erythrocyte was done instead of immature polychromatic erythrocyte for micronucleus which we found not appropriate. Then the DNA damage observed at high or toxic dose was considered to be due rather to cytotoxicity rather than DNA interaction. So overall, considering all

this data, glyphosate is considered unlikely to be genotoxic.

Going now to the animal data on carcinogenicity, I would like also first, before going into the detailed assessment of carcinogenicity, to clarify, in general, how the carcinogenicity assessment is performed. Also, because we have studies from different quality and this has all to be weighted. The design and conduct of the report of the study is very important to define which studies were acceptable or considered only supplementary as well as to have a well-defined test material.

Then regarding the interpretation of the study results, we take into consideration the dose-response curve, the weight of the trend analysis versus pair-wise comparison for possibly adjustment to other variables. Very importantly that the appropriate historical data are considered, such as they have to be of the same strain, similar performing laboratory and contemporaneous to the study itself.

We considered usually around five years around the study conduct. And then also consideration of a plausible mode of action where there was reduced latency or progression to malignancy of the tumors.

Also, an important factor is whether there was concomitant toxicity, whether the maximum tolerated dose was achieved.

Overall, in long-term rat studies, we had 12 studies. Six of these studies were considered acceptable. Then two studies were considered supplementary. One because it was conducted with too low dose levels, no toxicity at all was observed in this Lankas 1981 study. And the other study was of too short duration. It was actually a toxicity study, not really a carcinogenicity study.

Then four studies were considered inadequate for assessment of carcinogenicity potential of glyphosate. Also, because these studies were performed with too low dose levels, there were study design and reporting deficiencies, sometimes undefined test material, and/or a low number of animals undergoing histopathology or the use of formulation. Or one study that was considered to have a protocol that was inadequate for a carcinogenicity study.

Going into more details on the tumors that observed in the rats. From six acceptable studies, we found that five did not present treatment-related increase of tumor incidents. However, here we

can see that in the Lankas studies, what was considered a supplementary study, there was an increased incidence of pancreatic islet cell adenomas in a pair-wise comparison at the low-dose level. Also, testicular interstitial cell tumors were increased also in a pair-wise comparison at the high-dose level.

Then in the oldest of the acceptable studies, which is the Stout & Ruecker from 1990, there was, again, pancreatic islet cell adenomas found also in a statistically significant pair-wise comparison at the low and high-dose levels. And there were two trends of hepatocellular adenomas in males and Thyroid C-cell adenomas in females at the high-dose levels.

Just to mention that also this older study regarding the acceptable study. There was a low survival overall in all groups meaning that mortality was higher than 50 percent at the end of the study, which for us give a lower weight to this study in comparison to others.

What was the weight of evidence regarding these tumors? Again, the tumors were limited to a supplementary study and the oldest study in six acceptable studies. Regarding the pancreatic

islet cell adenomas in males that were found in two studies, one of which is supplementary, there was no dose-response in a statistical significant increase in a pair-wise comparison.

Regarding the testicular interstitial cell tumors, they were found in these supplementary studies. It was the highest dose level of the study but which was still a low-dose level of 13 mg/kg/day, and it was not reproduced in six long-term studies using much higher dose levels.

Since the statistically significant trends for hepatocellular adenomas in males and Thyroid C-cell adenomas in females corresponded to marginal trends in benign tumors limited to one sex and not reproduced among five long-term studies. And they were not confirmed by a statistical analysis in a pair-wise comparison.

The pancreas, testis, and the thyroid were not target organs of glyphosate. And the liver toxicity was quite limited. We didn't find any pre-neoplastic lesions and no progression to malignancy. On this basis, the peer review concluded that there was no evidence for a carcinogenic effect in the rats treated with glyphosate.

Going now to the mouse studies that were much more complicated for us and which gave much more discussion in the peer review. We had eight studies in mice. Four of these studies were considered acceptable. One study was considered of doubted reliability after further consideration by the peer review. And three studies were considered inadequate.

The studies were inadequate because, for instance, they used low number of animals, only two dose levels were used, there were sometimes a low number or examinations. Also, the test substance was not well defined or even there was a use of formulation in the case of the George 2010 study.

Regarding the study of doubted reliability, it was after checking with the U.S. EPA, actually, that we found that they considered that study was bias with a viral infection. This was not very clear from the study report, so it remains in this class, if you like, of doubted reliability. However, it's true that we found that the animals were translocated in the middle of the study from one room to another and that the initial room was fumigated so, really, this may show that something happened with

these animals and they were then translocated back to the initial room to continue the study.

Malignant lymphomas were actually, the tumors that gave most discussion in the peer review. Of note is that in the oldest study of Knezevich & Hogan malignant lymphomas were not mentioned. However, in this case, we report some lymphoreticular neoplasms that we found should correspond to the current terminology of malignant lymphomas.

Of note is that malignant lymphoma is one of the most common neoplasms in CD-1 mice, females being more prone to two more types than males. In the first two studies, there were no increased incidents of malignant lymphomas, either in males or females. Then an increased incidence of malignant lymphomas was statistically significant in a pair-wise comparison in this study of doubtful reliability.

Also, above the historical control data for these studies. Which in this case, were another strain of mice, the Swiss albino mice. And then we had two trends that were reported in males for the Sugimoto and Wood study at the high-dose level.

What was the weight of evidence in conclusion of the expert judgment in the peer review?

Is that considering that malignant lymphomas are one of the most common neoplasms in CD-1 mice? And that is one instance statistical significance, according to a pairwise comparison, and outside historical control data, was recorded in a high-dose level, and in a study probably affected with virus.

And considering the inconsistency in results among five studies in particular, when comparing similar dose levels, this finding was not affecting the animal survival and there was no change in tumor latency. Overall, the incidences are within historical control data even at the highest dose tested level. Also, one study, lack of valid historical control data.

Sorry. Maybe I'll go back just in an instant, because I didn't mention that in the Sugimoto study the highest incidence that was found of 12 percent was within the historical control data, although it was above the average of the historical control data.

Then in the Wood study below, although the incidences were lower, there was no valid historical control data. That's why we, again, concluded that the overall incidences were always in

the historical control data, even at the highest dose tested. Although acknowledging that in one study we lack this valid historical control data.

But again, there was a minority view in the peer review that considered that based on these findings glyphosate may require classification as carcinogenicity category 2. That would mean suspected of causing cancer, according to the GHS classification criteria. But the majority of the experts consider that there was insufficient evidence to classify glyphosate as a carcinogen based on this data.

Now reviewing the renal tubular tumors in mice. First, it was found difficult to differentiate between adenomas and carcinomas because also there was a review of the same data showing different outcomes. It was considered certainly appropriate to consider adenomas and carcinomas combined in this case.

Renal tumors are rare in mice, at least in CD-1 mice, as is shown here in this slide. However, the data also shows that renal tumors spontaneously occur in control animals as low incidences. In this case, again, there were statistically significant trends that were observed in

two studies at the high-dose level. In this case, the high-dose level was above 4,000 mg/kg/day where the maximum tolerated dose was achieved or even exceeded.

At the end of the presentation, I just left for you a background document, an overview of the toxicity data on these studies where the description of the toxicity occurring at this high-dose level is described. In this case, we considered that we could not also exclude that the carcinogenic effect could be biased by the toxicity data, as well. In none of these studies there was a statistically significant increase of tumors according to a pair-wise comparison.

The weight of evidence for renal tumors in mice was that they were mostly observed above 4,000 mg/kg weight which is above the maximum tolerated dose and at the same incidences as observed in controls in other studies. As I just said, there was no statistical significance in a pair-wise comparison. That allows to adjust for other variables in the study such as happen, for example, in one study where we found higher survival of the high-dose group.

The adenomas were not associated with preneoplastic changes, as we would expect tubular

hypoplasia if it would be treatment related. Of note, there was still some chronic interstitial nephritis observed at the high dose in this study. However, it was considered natural event for tubular neoplasms.

Now going to the hemangiosarcomas. Here I made a differentiation between A, B, and C because hemangiosarcomas could be found in different organs. The ones that interest us is in the Atkinson and Sugimoto studies where hemangiosarcomas were observed in the vascular system. And here also, there were two statistically significant trends in these two studies. Just to note that in the first studies, Knezevich & Hogan, hemangiosarcomas happened in the spleen without a dose-response.

And in the Wood study, these hemangiosarcomas were observed in liver and/or kidneys. Also, they occurred without a dose-response. And now also left the Kumar study, as it was again found as of doubted reliability.

Here again, is the highest incidence occurred in the Atkinson study where at an incidence it was within historical control data. While in the Sugimoto study where no historical control data were available, the incidences at a much higher dose level

was still lower than the one within historical control data.

What was the conclusion of the weight of evidence and expert judgment regarding these hemangiosarcomas? They were considered not toxicologically relevant because they were observed the highest incidences were within historical control data. And the highest dose level without historical control data showed lower incidences. Then there was no statistical significance in the pair-wise comparison. Also, circumstantial, there was no blood and/or endothelial toxicity observed with glyphosate.

Considering this data, the majority of the experts considered that glyphosate was unlikely to pose a carcinogenic hazard in both rats and mice.

Regarding the epidemiological studies, overall, we had more than 30 epidemiological studies that were considered together between the cohort and case-control studies. As was today, again, already mentioned, the cohort studies, that is currently the largest study available, the Agricultural Health Study did not show any -- glyphosate did not cause or increase a risk of all cancers, although the interpretation of multiple myelomas is limited.

And then in contrast, a reduced number of case-control studies concluded elevated odd ratios for an association between glyphosate and non-Hodgkin lymphomas. The weight of evidence that was concluded by the peer review, it's considering the lack of consistency in the results with a few cases and the limited increases in odd ratios and/or odd ratios not statistically significant, considering, also, the lack of positive association in the cohort studies and many of the limitations inherent to the epidemiological studies, such as the confounders, including co-formulants or multiple exposure to different pesticides and other risk factors, the exposures that is difficult to measure and the classification of cancer that it may change over time.

It was concluded that there is very limited of evidence of an association between glyphosate-based formulations and non-Hodgkin lymphomas. Although, evidence was inconclusive for a causal link or otherwise convincing associative relationship between glyphosate and cancer in human studies when we consider, also, the lack of response in animal studies. This means that, of course, it

could not be excluded, that there could be an association but overall it was very limited.

This leads us to the conclusion of that hazard characterization of glyphosate. Said glyphosate is unlikely to be genotoxic, neurotoxic, or toxic for reproduction or development and is unlikely to pose a carcinogenic hazard to humans.

And that the reference values for acceptable daily intake, the acute reference dose, and the acceptable operator exposure levels were all based on the developmental toxicity studies in rabbits. As I already told you, with an over NOAEL of 50 mg/kg/day and using an uncertainty factor of 100.

Just to mention that EFSA recommended still that the toxicity of each formulation should be taken with particular care, even the genotoxicity potential to be further considered and addressed by Member States because it was found that formulations and also due to one formulant that is known to be often used in glyphosate formulation was of higher toxicity. Either the formulation or this co-formulant were found to be of higher toxicity than glyphosate itself.

And finally, I would like to just mention that was is the current E.U. status of glyphosate. The Standing Committee on Plants, Animals, and Food and Feed, that is the body deciding on the approval of glyphosate, in June 2016 decided to postpone its decision regarding the renewal of approval of glyphosate awaiting the conclusion of the Risk Assessment Committee at the European Chemical Agency who is responsible for the harmonize classification and labeling of chemicals in Europe.

So therefore, the current approval was extended until December next year to see what will be the final decision of the ECHA, the chemical agency.

And with that, I thank you very much for your attention.

DR. JAMES MCMANAMAN: Thank you. We're going to move into the next presenter, Lars.

DR. LARS NIEMANN: Okay. Thank you very much. Good afternoon. My name is Lars Niemann. I'm working in the German Federal Institute for Risk Assessment as a veterinarian and toxicologist. And I'm very glad about the opportunity to provide you the German view on the carcinogenicity -- or our Institute's view of the carcinogenicity of glyphosate

here. Here you can see what I'm planning to present. And I promise that I will try to keep it short or most to keep short, but I will go into the details of some points here only.

The next picture might be familiar to you because you've just seen a very similar one. Here are the two processes described or depicted which glyphosate is just undergoing in the European Union. In the middle or in the lower half you can see the way of the intended for the approval of glyphosate as an active ingredient in plant protection product in the E.U.

For this process, Germany was the Rapporteur Member State and produced a very comprehensive review report to which our Institute contributed the toxicological part, the residue part, and the part on residue analytics. And this report was then heavily discussed in the E.U. Underwent public consultation, was revised and modified, and the results have really been just described and reported to you by Daniele. And the process is now more or less finalized. But the final decision is pending, as you have just heard.

In the upper part of this slide, you can see another process depicted. And this is the evaluation of glyphosate for classification and labeling for which the European's Chemicals Agency is responsible, the ECHA. And the decision to provide a dossier on classification and labeling off glyphosate has been taken in Germany independent from any EFSA or European decision.

It was a political decision in Germany just to do that. That means the Member State, here Germany, has to provide a so-called Registry of Intentions and then to provide such a dossier. I have it here with me. And this dossier is about all the toxicological endpoints and include also environmental hazards.

This process has been initiated this year, yeah, in spring. The dossier underwent public consultation, as well. And the decision of the ECHA is pending, and I don't dare to predict anything about ECHA's decision with regard to the classification. And the point of most concern is, again, carcinogenicity.

You see, again, our contribution to the two processes. First, for the intended renewal of the

approval of glyphosate. And this process is mainly on risk assessment. In contrast, the process for which the ECHA is responsible is hazard assessment. And human exposure is not taken into consideration here but only the properties.

This second process, there's one for classification and labeling, has a strong impact on the first one because if a substance is classified as a carcinogenicity, mutagenicity, or reproductive toxicity, including developmental toxicity compound of the categories 1-A or 1-B for the so-called CMR properties, it will be, in principle, not feasible to use this compound in plant protection in Germany and in Europe.

And even if the compound would be classified as a carcinogen of the category 2, there might be strong restriction on its use, in particular with regard to who will be allowed to apply such a compound in plant protection products. There's a strong impact of the decision of the ECHA. And that's why the final decision on approval in Europe has been postponed.

So now I will focus on carcinogenicity. Usually, as you know, epidemiological studies may

provide evidence that the compound was carcinogenic. We can take evidence of carcinogenicity from long-term studies in rodents. The genotoxicity studies may give a hint or more than a hint.

And we should also take into account mechanistic considerations. But I think only if there are positive findings, either in the genotoxicity studies or in the carcinogenicity studies or in the epidemiological studies that should be somehow explained. The evidence of a certain mechanism alone without hard facts from all the other studies would be not sufficient for classification and labeling.

Okay. With regard to the epidemiology, we have seen no association between an exposure to glyphosate or better to say glyphosate-containing herbicides and a number of different cancers which are listed here. Even, too, I have my doubts whether this is, in fact, comprehensive. But we have heard very comprehensive evaluations on the epidemiology before today.

Of course, we had also our biggest concern was regard to non-Hodgkin lymphoma. And we have one big cohort study that is the Agricultural Health Study. And there are different publications in

which part of the Agricultural Health Studies have been reported. But with regard to NHL, the De Roos publication is the most important.

And as we have seen before, the outcome of the Agricultural Health Study seems partly contradictory to the case-controlled studies or part of the case-controlled studies. However, even in case-controlled studies which provided odds ratios in the mean higher than 1, the magnitude of these increases is quite low and the confidence intervals are quite wide.

And according to the meta-analysis I wouldn't say that it's convincing evidence of a real association between glyphosate exposure and non-Hodgkin lymphoma. And as you have discussed broadly today, there are many general problems with the interpretation of epidemiological studies and they all apply for the possible association between glyphosate and NHL too.

And to me, the strongest problems have to do with multiple exposure to different pesticides, not only to glyphosate-containing herbicides and to the exposure in general. In principle, we don't know the actual exposure of the people who have been

enrolled for the epidemiological studies. That's the main problem here.

When we go to the animal studies, we have first to take into account that the toxicological database for glyphosate is extremely huge here. I think it's larger than for any other pesticide. We had to evaluate glyphosate for the first time for the E.U. in the 1990s. And even at that time we had a large number of studies on all of the toxicological endpoints. Even, too, in the 1990s, at least in Europe, nobody cared, really, about glyphosate. But there were many applicants already at that time.

And now for the renewal of glyphosate in the E.U. there are much more applicants than there were before. And that's the reason for submitting more studies. Actually, we were surprised when we got, in 2012, more than 150 new toxicological studies, including many long-term studies, repro studies, developmental studies, and so on. We didn't expect it, actually.

And what we had to do was first to reevaluate all the old studies and reevaluation meant here in this context that we had to downgrade many of them from acceptable to not acceptable or at least to

supplementary. And we had to evaluate all the new studies.

If I say "new studies" that not necessarily means that they are actually new, let's say produced after 2000. Some of these studies were from the 1990s but submitted now by companies which have not been the applicants in Europe for the first evaluation. Perhaps that explains the great number also of new studies.

And then we had the huge amount of published information. When you see here more than 900 publications, that means at the beginning of our process, so in 2012. Meanwhile, we have much more, and it's really difficult to define a deadline for publications to be taken into account.

Okay. Only to give you an idea what we have here, I've selected a few endpoints here, only. And in the third column you can see what is normally required according to European legislation for the different endpoints and what we normally have for other pesticides, other than glyphosate. And in the fourth column you can see the rabbit studies that we had available for the different endpoints.

And this is only a selection in principle. I could do the same for eye irritation or developmental toxicity and the rats and all the genotoxic endpoints and so on. Yeah.

Okay. With regard to carcinogenicity, we have direct studies and the studies in the mouse and sent to EFSA and to Daniele. You've got all of the incidences, for all the tumor types, I will speak about now in the two species. With regard to the long-term studies in rats, I've compiled here seven studies.

On the former slide, you can see six valid studies. I have included study eight. It's the Lankas study from 1981. According to today's view, the study is not acceptable anymore because the highest dose level of about 31 mg/kg was much, much too low for glyphosate. In principle, we could not take the study into account. However, because it was always discussed with regards to carcinogenicity, I've included it here in this slide.

You will see there was evidence of carcinogenicity in the two oldest of the studies here, Lankas and Stout & Ruecker. We have the same organ, the pancreas, even in two studies. However, in the

Lankas study there was a higher incidence of pancreatic islet cell adenoma only at the lowest dose level, so clearly no dose-response.

And with regard to the study by Stout & Ruecker, there was no dose-response because the incidences were nearly the same in all treated groups. Also, it was higher in all treated groups than in the control. And the pancreatic tumors and increase in pancreatic tumors was not seen in any other study.

And that leads me to, I think, a general consideration here. If you have that many studies on all the toxicological endpoints, you cannot rely only on a so-called "key study." If you have that many valid studies, you have to put them together. And this is for also the weight of evidence. And so if you have higher tumor incidences as compared to the concurrent control in the same study, but you don't see an increase in any other of the studies at comparable or even at higher dose levels, you have seriously to put the one isolated finding into question.

And this is what happened with the liver tumors in the Stout & Ruecker and also with the thyroid studies, also in the same study by Stout &

Ruecker. And you have seen the incidences in Daniele's presentation. And the increase in the testicular tumors in the Lankas study, okay, it was at the highest dose level. It was statistically significant, but at the dose level that was the highest in that study but, as compared to all the other studies, was extremely low.

That's why we came to the conclusion that the weight of evidence suggests that the findings in the rats were not treatment related. The mouse is, of course, of much higher concern. And that's why under much more scientific and non-scientific debate.

And before I go into the detail of the mouse studies, I would like to tell you one thing. In the beginning, I told you that we provided the draft for the European Renewal Assessment Report and that this draft was then discussed, modified, revised during the discussions with the Member States and with EFSA. And now you can find the final European report. Everything is published. It's not that reader friendly because it's more than 6,000 pages, yeah, but all the studies are described there in detail, at least.

Okay. We had to perform a second task. The second task we got after the IARC evaluation was released in March 2015. And the task was to provide a draft addendum under the IARC Monograph. We had to reevaluate all the cancer studies. And after it was clear that EFSA got the mandate to provide an independent evaluation of the IARC Monograph and that Germany was responsible to provide the first draft for that, or the basis, then it was decided in our Institute immediately that other people should do that than those who did the first evaluation.

I was involved in the evaluation of all the long-term studies for the first round. But I didn't take part, for example, in the reevaluation after the IARC Monograph was released. This was done by other people. Also by people who were, I think, more familiar with all the statistical issues.

And there I would like to explain you our statistical approach. In the first round, we more or less, relied on the statistics that was provided with the original reports. We, of course, checked whether the statistical method used in the original report was appropriate, was in line with the OECD

Guideline requirements for the time when the study was performed.

But after the IARC evaluation had been released, all of the statistical evaluations were repeated. And now we have performed also trend tests and different pair-wise comparison for all the tumor types that had been put by IARC into question. That's why now the statistical evaluation is different than in the first report. And what you can see now is mainly based on this second, on this reevaluation.

Okay. If you have here the studies, according to our evaluation, we have five valid studies in mice, four in CD-1 mice and one, this Kumar study in Swiss mice. What we have seen in the first evaluation is now in brackets here. That was the first increase in any tumor incidences that became apparent in our first evaluation because there was an increase in malignant lymphoma in the Swiss mice.

And the malignant lymphoma in the Swiss mice are different from all the other tumor types you can see here in the following slide because here, we have a frequent tumor. All the other tumors are rare. But here in the Swiss mice, we had a high background incidence, around 20 percent, also in the control

animals. And indeed, the Swiss mouse is prone to develop malignant lymphoma.

And this is unique also in that way that we had here, I think, is the only tumor in mice, also an increase in female mice here. The lymphoma in female mice were also increased. And we had a statistically significant difference to the control groups in a pairwise comparison in the set test.

However, when we reevaluated all the tumors, we did also (inaudible) test, and the statistical significant disappeared. Then we performed the trend test of which the IARC was very much in favor. And here, we didn't find any statistically significance. I think this is because of the high background incidences in the strain here.

And of course, we cannot be sure which contribution might have a possible viral infection for which we don't have real proof, but which we cannot exclude. There's a long story of possible contribution of oncogenic murine viruses and cancer in mice here. That's why we have put it here in brackets.

But the evidence of a higher incidence of malignant lymphoma in Swiss mice, we saw it in a

more thorough look at the malignant lymphoma incidences in CD-1 mice. And actually, there are two studies in CD-1 mice with a higher lymphoma evidence. And I think we had the question in the afternoon here about the number of studies with the higher evidence here. These are the studies by Sugimoto and the Wood study in CD-1 mice with a higher number of malignant lymphoma.

However, when we looked at the historical control data we found good historical control data, at least from the Sugimoto study from the same lab, showing that the number of tumors was well within the historical control data. By the way, for the Swiss mice, at least for the females, it was also inside the historical control data. And for the Wood study, we found also at least good historical control data from the literature.

What we have on the malignant lymphoma, then we have the kidney tumors and we have thee hemangiosarcoma. The problem is we didn't consistently see such an increase in all the studies. In some studies, we had, for example with regard to the kidney tumors, even a decrease in renal tumors.

We came to the conclusion that we have seen statistically significant increases for different tumor types in the trend test, so for like hemangiosarcoma and for the malignant lymphoma in CD-1 mice and for kidney tumors in CD-1 mice, but never in pairwise comparisons. We had for all of these tumors only low incidences, even at excessive doses. I will show that later. They were all within the historical control data range.

And we had no consistency among all the studies. And there was no evidence of supporting pre-neoplastic lesions for any of these tumor types. That's why our weight-of-evidence evaluation that also the tumor findings in the mice were not treatment related despite the increases at the top dose levels in certain tumor types here.

To go more into the details, here you can see the malignant lymphoma in the male CD-1 mice. In the CD-1 mice, in contrast to the Swiss mice, only the males were of concerns. It's a rare tumor in CD-1 mice. All the tumors at all dose levels in all four studies in CD-1 mice were below the maximum of the historical control dose, historical control range.

And we have seen that even in the control rates, in the untreated controls or at the low-dose levels or the mid-dose levels we had sometimes evidence of a higher tumor incidence but not necessarily at the high-dose levels even though exaggerated dose levels were used at least in the studies by Knezevich & Hogan that one on the right, and by Sugimoto.

Same pattern you can see with regard to the hemangiosarcoma. Here, we had the highest numerical incidence in the study by Atkinson et al. However, all through this incidence is covered by the historical control range. And at much higher dose levels, we had lower incidences of hemangiosarcoma. Again, there is no consistency.

With regard to the kidney tumors, the pattern is similar. Only with the difference here that at the highest dose level that was employed in any of the studies, the incidence was three kidney tumors in 50 male animals here, was at the upper edge of the historical control range but still within. That's why we think that even the tumors in mice are not related to glyphosate.

With regard to genotoxicity, I can only confirm the evaluation that was presented here today by the EPA colleagues. Glyphosate proved negative in the vast majority, if not in all, genotoxicity studies in which the usual genotoxic endpoints such, in mutations and bacteria or in mammalian cells, chromosome aberrations were investigated.

But we had some evidence of induction of sister chromatid exchange of interaction with the DNA in so-called indicator tests from of which we don't know if the indicate real genotoxicity or might lead to apoptosis, cell death, and so on or will be repaired by the organism.

Even if glyphosate might induce such DNA strand breaks, for example, it seems based on the negative in vivo studies in the standards tests that the organism can cope with it. So again, the weight of evidence suggests that glyphosate as the active substance does not induce mutations.

I wouldn't be that sure with regard to all the formulations that are on the market. And here we have frequently the problem that positive evidence was found in publications in which studies are described which were performed with formulations and

not with the glyphosate itself. Sometimes, a title or an abstract made be misleading because the test item for the formulation are not the active ingredient.

At least our doubts were strong enough for the formulations that we have required for the so called representative formulation in the E.U., genotoxicity assays and that we would strongly recommend a Member State level to ask for genotoxicity studies with formulations. We know that in other parts of the world, for example in Brazil, it is usual to provide also for formulations genotoxicity tests.

DR. JAMES MCMANAMAN: Dr. Niemann, we're running a little over on time here.

DR. LARS NIEMANN: Yes, sir. Okay. This is the weight-of-evidence considerations. Principle, it's the same as what you have seen from the EPA presentations here. And the result with our weight-of-evidence approach was then that we think that glyphosate is unlikely to pose a carcinogenic risk to humans. And that's why we hadn't proposed it as a classification in the ECHA process, as well.

And I think we don't stand alone with that evaluation since it is more or less the same as it was reached by many international organizations.

Of course, the IARC evaluation is in contrast to that but we should emphasize that IARC had to rely on summaries of industry studies only and irrelevant publications.

Thank you very much.

DR. JAMES MCMANAMAN: Thank you to both of you.

Are there any questions for these two presenters, commenters?

Dr. Crump.

DR. KENNY CRUMP: Could we go back to the first presentation and look at the slide that had hemangiosarcomas in mice? Yeah. I just want to point out that I think in the Atkinson study, at least when I look at those data, I got the same numbers of tumors that you have, 0004, but it looked to me like they examined far fewer than 50 animals in each group.

I got they only examined five, six, three, and nine. But the same thing was in the EPA study, and I think it was also in the IARC study. If I'm right, all of these have got the wrong denominators. And result is still statistically significant with those numbers. But it's not as significant as it was with the 50s up there.

MS. DANIELE COURT-MARQUES: And which study is that? I'm sorry.

DR. KENNY CRUMP: That's Atkinson, male CD-1 mice, males and females both. The denominator, I think, are wrong in both the males and females. You may want to check that.

MS. DANIELE COURT-MARQUES: Yeah. It's possible.

DR. KENNY CRUMP: Just check it. You'll see. Make sure you got it right.

MS. DANIELE COURT-MARQUES: Thank you. Yes.

DR. KENNY CRUMP: And the same goes for the EPA. They have the same numbers, I think, that you all have.

DR. JAMES MCMANAMAN: Other questions? Yes. Dr. Taioli.

DR. EMANUELA TAIOLI: Emanuela Taioli. For the E.U. evaluation, is there a public site where we can see who are the people -- did you have like people invited to do the evaluation or was it an internal evaluation of the document?

MS. DANIELE COURT-MARQUES: Yes. Actually, there were also, I must say, a polemic

around this because the peer review -- well, first we take into consideration all public comments. And this is all reported and all published in these 6,000 pages, I'm afraid, of report that are published together with EFSA conclusion. The EFSA conclusion is very succinct. It's just a report, a short summary, let's say, of the overall evaluation. Because it's all in detail to the (inaudible) first that is also published, and then the report of the peer review.

Now the peer review is done with Member State experts. And according to the EFSA rules, the Member State experts are nominated by their own Member State. It's not under EFSA's, let's say, legislation. And they are not obliged to declare or publish their name, if you like, because they are public servants usually in the respective Member States. And yes, it's true that there was some polemic about this because not all of these experts agreed to have their name published on the EFSA website.

DR. LARS NIEMANN: What you can see on this report is, for example, the following. You will find there on one side a description of all the individual studies. For each study, you will find -- at least for the new studies here. For the old it's

more an overview. But the new studies you will find the description of the studies. Then you will find a conclusion.

And in the conclusion of the Rapporteur Member State here of our Institute you will also find if the same conclusion has been reached by the applicants or by the study director. And if not, what are the reasons for the different conclusions. And then if the same conclusion was then amended later on because of comments from the Member States or from EFSA, this is also mentioned.

For example, if an NOAEL is changed or, for example, there was the acute reference had not been regionally proposed by Germany, but was introduced after the expert meeting. And everything can be found in the report, but it's 6,000 pages, unfortunately.

DR. EMANUELA TAIOLI: Emanuela Taioli. The idea is that the IARC and the EPA committee have a process for choosing the experts, and the experts are public. And I wanted to know if that was the same. You're saying that it's not, according to what you said, more or less.

MS. DANIELE COURT-MARQUES: Part of the experts agreed and their declaration of interest are also published on the EFSA website.

DR. JAMES MCMANAMAN: Yes. Dr. Sheppard.

DR. LIANNE SHEPPARD: So I wanted to ask questions about guideline studies and studies that were considered with nephrological deficiencies. Because there's been some things in the literature to say that guideline studies, well, they're in place for a good reason because there was a lot of problems back in, I can't remember if it was the '70s or the '80s so they instituted guidelines. But they're not necessarily using assays that are as sensitive as peer-reviewed papers or studies in the peer review literature.

I wanted to just get a sense from both of you about how you all looked at the -- because, for instance, Daniele, in your document it says a couple of them weren't guideline studies as though that's a problem with them. And I guess I wanted to get a better sense from you about the role of guideline studies in the work that you all do.

MS. DANIELE COURT-MARQUES: Well, also we should make also the distinction between GLP studies and guideline studies. Because on one hand, GLP were, let's say, put in place mainly for the industry. Because, of course, there are conflict of interests, and this was a way to guarantee, I would say, that the studies were performed according to -- and could be then checked afterwards that they were conducted properly and there was no cheating, let's say, as because there were also some cases that were reported.

This is, I think, the main purpose of GLP studies. And this GLP one, for us, are mandatory when they are nonpublished industry studies so that it's, let's say, a guarantee that all right, we can go back to the study report, if necessary or to the raw data, if necessary. And this has been done from time to time with checking or validation of study when there could be some doubts on the results that are presented.

Now the guidelines are more related to the results themselves. How can we see, for instance, the dose-response or can we have test materials that is well defined that, in this case, can be quite

important. This is more regarding to the results themselves that we would like to see the guidelines. And this would apply most to industry or also public literature.

DR. LARS NIEMANN: I'd like to amend that, even too, it is sometimes claimed I don't believe that the guideline studies themselves are insensitive. All the tumor findings we have shown here and discussed here have been found in guideline studies, for example, yeah. But I think the point is it's the legal basis. We have, as well as you have in the U.S., in Europe we have also the legal data requirement. It is clear which endpoints have to be addressed by the applicants. And that is not unique for glyphosate, so for all the pesticides.

And it is also required by law that they have to perform the studies in a certain way. And that means in accordance to the OECD test guidelines, so for this endpoint OECD guidelines are available. These guidelines are also under revision. And what we have to do is to compare whether the study design, the methods they used, are in compliance with the guideline requirements, if all the parameters have

been measured. And so of course, they can go in excess of the guideline requirement.

The problem are not the guideline studies. The problem -- even so, we have also downgraded guideline studies or considered them not acceptable. Even if it was claimed I have followed this or that guideline, some of them we have downgraded.

But the problem I think it's more to take into account better the published data. And I think EFSA, for example, made considerable efforts in the past to include published data better. And that's the problem, I think. We should not, let's say, leave the guideline studies aside. We should better include in addition, more of the published information.

DR. JAMES MCMANAMAN: All right. I think we can call this a day. I think it's getting late. And I thank the folks from Europe very much for their nice presentations.

(WHEREAS THE MEETING WAS ADJOURNED FOR THE DAY)

DAY 2

MR. STEVEN KNOTT: Well good morning everyone. We're going to go ahead and get started. Welcome back to the second day of the meeting of the FIFRA Scientific Advisory Panel regarding EPA's evaluation of the carcinogenic potential of Glyphosate. Once again, I'd like to thank the panel members and the member of the public for attending today's session.

Dr. McManaman, our Chair, is going to be joining us shortly. Dr. Ehrich has agreed to fill in as Chair for the first few minutes until Dr. McManaman arrives because we would like to go ahead and get started with today's public comment session. There's a large number of public comments to move through today so we want to go ahead and get started with the first presentation. At this point I'll turn it over to Dr. Ehrich. Thank you.

DR. MARION EHRICH: Okay. Because we have so many public comments, those of you who are making them, get up to the microphones and not spend a lot of time back and forth. Also, you need to speak close enough to the microphone so it can be heard and

recorded but not so close that it's garbled. Please, people making public comments, keep that in mind.

Now I'd like to go around and introduce the panel that's reviewing this document. I'm Marion Ehrich, I'm from Virginia Tech. I'm a pharmacology and toxicology teacher at their veterinary school and at their medical school.

DR. DAVID JETT: Hi. I'm Dave Jett. I'm a permanent member of the FIFRA. I'm Director of the Chemical Defense program at the National Institutes of Health, also adjunct professor at the School of Medicine, University of Maryland.

DR. JOSEPH SHAW: Hello. I'm Joe Shaw. I'm a permanent member. I'm an environmental toxicologist at Indiana University.

DR. KENNY CRUMP: I'm Kenny Crump. I'm a semi-retired statistician.

DR. LAURA GREEN: Good Morning. I'm Laura Green. I'm a chemist and toxicologist with Green Toxicology.

DR. ERIC JOHNSON: Good morning. I'm Eric Johnson. I'm a professor in the Department of Epidemiology at the University of Arkansas for Medical Sciences.

DR. BARBARA PARSONS: Good morning. I'm Barbara Parsons from FDAs National Center for Toxicological Research.

DR. ARAMANDLA RAMESH: Good morning. My name is Aramandla Ramesh. I am Associate Professor at Meharry Medical College. My research interests are environmental toxicology and chemical carcinogenesis.

DR. LUOPING ZHANG: Good Morning. I'm Luoping Zhang from University of California, Berkeley, and my research focuses on the chemical exposure associated cancer, particularly leukemia and lymphoma.

DR. DANIEL ZELTERMAN: Good morning. I'm Dan Zelterman. I'm a Professor of Biostatistics at Yale. I design and analyze clinical data for cancer studies.

DR. EMANUELA TAIOLI: Good morning. I'm Emanuela Taioli. I'm a professor at Mount Sinai School of Medicine and I'm a cancer epidemiologist.

DR. LIANNE SHEPPARD: Hello. My name is Lianne Sheppard. I'm a biostatistician at the University of Washington and also in the Department of Environmental and Occupational Health Sciences. And my work focuses mostly on health effects of environmental and occupational exposures.

DR. MARION EHRICH: Okay. Our first public comments this morning are from Monsanto Company. Would you please get yourself ready at the microphones. We have Donna Farmer, Caroline Harris, John Acquavella, Jim Bus, Joel Haseman, David Kirkland, and Rick Reiss.

And the panel has the opportunity to ask you questions, so they will raise their hand if such occurs during the presentation. But we want to keep this on time so we want you to be ready and move this forward. Dr. Farmer are you the first speaker?

DR. DONNA FARMER: Yes, I am. Good morning. My name is Donna Farmer. Let me say on behalf of the Monsanto Company we would like to thank the EPA and the members of the Scientific Advisory Panel for giving us this opportunity to speak to you today.

The order of the presenters today will be as follows: I will make some opening remarks. I am a Senior Toxicologist in Monsanto's Regulatory Product Safety Center. And I will be followed by a group of distinguished experts that have been invited to review and address EPA's charge questions.

The first to speak will be Dr. Caroline Harris, Corporate Vice President, Center Director, and Principal Scientist with Exponent, and she will discuss dietary exposure. Dr. Harris will be followed by Dr. John Acquavella, Professor, Department of Clinical Epidemiology at Aarhus University in Denmark. He is also retired from Monsanto. And Dr. Acquavella will address epidemiology charge question number two. Dr. James Bus, Senior Managing Scientist with Exponent, retired from Dow, will address animal bioassay charge question number three.

Dr. Joseph Haseman, President, J.K. Haseman Consulting will discuss biostatistics. He will be followed by Dr. David Kirkland, Honorary Professor, University of Swansea, UK. He is a genetic toxicology consultant with Kirkland Consulting and will address gene toxicity charge question number four.

Our last presenter will be Dr. Rick Reiss, group Vice President and Principal Scientist with Exponent. And he will address carcinogenicity classification, charge question number five and provide closing remarks.

I also want to point out that doctors Acquavella and Kirkland were members of the expert panel, convened by a scientific consulting firm and sponsored by Monsanto that reviewed Glyphosate epidemiology, animal bioassays, gene toxicology, and exposure. The four publications from that review were published in Critical Reviews of Toxicology in Volume 46 in 2016.

In addition, Dr. Harris published a paper on chronic dietary exposure in food chem toxicology in 2016. And that was sponsored by the European Glyphosate Task Force. Before you are binders that have our presentations and our bios for you.

Glyphosate is a versatile herbicide that has been used for over 40 years by farmers, land managers, gardeners, and others to simply, safely, and effectively control unwanted vegetation. Since their introduction in 1974 Glyphosate-based products have become the most commonly used herbicides in the world. The wise-spread adoption of this herbicide is based on three key factors: Glyphosate's ability to control a wide spectrum of weeds, its extensive economic and environmental benefits, and its strong safety profile.

Indeed, when it comes to safety assessments no other pesticide has been more extensively tested and evaluated than Glyphosate. In an evaluation spanning four decades the overwhelming consensus of regulatory experts worldwide including those you have head from this past day, the EPA, the BfR, and EFSA has been that Glyphosate does not present a carcinogenic hazard to humans. And was said the label is the law, and it can be used safely according to label directions.

While Glyphosate contains a carbon and a phosphorus it is not an organophosphate and does not inhibit cholinesterase activity. Glyphosate works by inhibiting enzyme in a process present in plants that as you heard yesterday people and animals do not have. Glyphosate when applied to a plant is absorbed and travels to the roots where it blocks the specific plant enzyme. Without that enzyme the plant can't make the building blocks it needs to grow and the entire plant withers to the ground.

Any remaining Glyphosate in the environment binds tightly to soil, degrades over time into naturally occurring substances such as carbon dioxide, nitrogen, and phosphate. In the 1990s,

combining Glyphosate with crops that could withstand applications of this herbicide transformed agriculture and modern agricultural biotechnology began. Labor and machinery requirements declined and adoption of this technology is associated with increased off farm income because of savings.

Glyphosate tolerant crop varieties greatly simplified weed control for corn, cotton, and soy bean farmers. It also allowed sugar bean farmers to increase their yields by both eliminating weed competition and reliance on other herbicides that can cause crop damage. Addition of Glyphosate tolerant crops is also associated with an increased likelihood of adopting conservation tillage or not plowing the soil. Conservation tillage is defined as a system that leaves enough crop residue.

And you can see that the base of the cornstalks down there on the soil surface after planning provide 30 percent soil cover, the amount needed to significantly reduce soil erosion. Conservation tillage systems offer numerous benefits that conventional tillage can't match. Reduced soil erosion, improve soil and water quality, fewer tractor trips across the field, saving, for example, 1,700

gallons of fuel on a 500-acre farm, and lower carbon dioxide emissions.

In 2014 alone, the reduction of carbon dioxide emissions was equivalent to removing 4.6 million kg of carbon dioxide from the atmosphere or equal to removing 1.9 million cars from the road for one year. Although Glyphosate resistant weeds have evolved Glyphosate based herbicides are still very important tools in a farmer's toolbox and it is possible to effectively manage this issue by adopting and developing diversified weed management plans.

Today, Glyphosate tolerant crops form the backbone of many U.S. major crop-pro businesses and accounted for over 33 billion of annual exports. In agricultural systems where Glyphosate tolerant crops are not available Glyphosate based herbicides still provide significant benefits by simplifying weed management and reducing the need for conventional mechanical tillage. For orchards and vineyards effective weed control is necessary to ensure productivity. In these settings Glyphosate is an essential tool for controlling vegetation beneath the trees or the vines.

In wheat, Glyphosate has allowed farmers to adopt no till practices that help them to conserve soil moisture, thus enabling rotation with more profitable crops. In sugar cane Glyphosate improves harvest quality in addition to controlling weeds. Glyphosate also enables the adopt of cover crops by providing a simple and effective means to eliminate the cover crop prior to planting a cash crop without raising concerns about plant back restrictions.

Cover crops, you can see up there, like rye, field peas, and clover are key components of a strategy to reinvigorate and protect the soil between rotations of cash crops. In non-agricultural settings Glyphosate provides cost effective weed control along highways, railways, and other rights-of-way. In an economic analysis of highway median weed control, for example, Glyphosate was 275 percent less expensive that alternative methods that included multiple mowing events and alternative herbicides. Glyphosate-based herbicides have also delivered significant benefits for invasive weed management.

National parks have relied on Glyphosate to decisively manage non-native vegetation

in aquatic settings, as you can see up there. It has been used to replace mechanical weed removal to enable navigation of waterways, maintain water flow in drainage ditches, irrigation canals, and eliminate weeds that crowd out native wildlife. All of us at Monsanto are consumers who are committed to developing a broad range of products that contribute to safe and nutritious food choices and effective control of unwanted vegetation for everyone including our own families, neighbors, and friends.

Safety is our top priority and my job as a scientist at Monsanto is to ensure our products are safe for you, for your families, and for mine. I have spent 25 years looking at the safety of herbicides, specifically Glyphosate for 25 years and I am fully confident in the safety of Glyphosate. Glyphosate-based herbicides have a history of more than 40 years of safe use around the world. And as you heard yesterday it is supported by one of the most extensive worldwide human health and environmental effects databases ever compiled for a pesticide including seven complete regulatory data packages.

These data packages have been developed by different registrants in different testing

facilities in different geographies over the decades. And that's the data that you heard the EPA, EFSA, and EFR look at yesterday. Comprehensive toxicological, ecotoxicological and environmental fate studies conducted over the last 40 years have time and time again demonstrated the strong safety profile of this widely used herbicide.

Over the past 40 years, as we've talked about, Glyphosate has been reviewed and re-reviewed by regulatory agencies, scientific bodies, and independent experts around the world. As I just mentioned there are multiple registrants and seven complete regulatory data packages.

The consensus of this comprehensive set of toxicology studies as you heard yesterday have been consistent and demonstrated that Glyphosate has low oral, dermal, and inhalation toxicity, it shows no evidence of genotoxicity, neurotoxicity, immunotoxicity, disrupting the endocrine system, reproductive or developmental toxicity, and it does not produce malformations.

Regarding carcinogenicity, regulatory agencies whose job it is to prove and regulate pesticides as well as scientific bodies and other

independent scientists have reviewed and re-reviewed over the past 40 years the rat and mouse carcinogenicity studies and have consistently concluded on a weight of evidence analysis all of the data that Glyphosate does not pose a carcinogenic hazard to humans. Monsanto takes great pride in the science behind the safety of our products.

We believe conclusions about a matter as important as human and environmental safety must be nonbiased, thorough, and based on sound science that adheres to internationally recognized standards. We support the rigorous process used by regulatory authorities to use all available data, published and unpublished, in a weight of evidence evaluation. And we would like to thank and commend the U.S. EPA on its comprehensive and science-based critical review of Glyphosate.

To be clear, no regulatory agency in the world considers Glyphosate to be a human carcinogen. Similar to the slide that we saw presented by Dr. Niemann from BfR; on this slide on these reviews from 2015 forward, from regulatory agencies around the world, as he mentioned, Australia, New Zealand, Japan, JNPR, the European Union, and

Canada. The conclusions of these agencies reviews are consistent with the recent and previous conclusions of the U.S. EPA as well as those regulatory authorities and international bodies around the world over the 40-year history of Glyphosate.

Based on the overwhelming weight of evidence the Monsanto Company strongly agrees the classification the EPA has proposed in this issue paper that Glyphosate is not likely to be carcinogenic to humans. Maintaining access to Glyphosate is critical to maintaining environmental and economic sustainability to agriculture. Its versatility, effectiveness and safety have transformed vegetation control across a wide range of environments around the world.

Glyphosate-based herbicides ability to effectively control unwanted vegetation, provide benefits that extend from individual farms, to global trade, to national parks, to golf courses, to local governments and gardeners. For all of these reasons, Glyphosate was called a once in a century herbicide by Dr. Stephen Duke, research leader at the United States Department of Agriculture. Continued access to this important technology is essential. And again, on

behalf of Monsanto we would like to thank EPA and all of you, SAP panel, the opportunity to speak to you today. And I would like to introduce the next speaker, Dr. Caroline Harris.

DR. CAROLINE HARRIS: Thank you. Well good morning. I'd like to speak to you this morning about dietary risk assessment and Glyphosate residues. It's not a charge question per se but it does help put some of the studies into context that's been carried out. When we talk about exposure of the general population to Glyphosate dietary exposure is a principal way through which they are exposed.

The EPA in their charge paper presented an unrefined dietary risk assessment. And what I'd like to share with you today is a publication from Europe this year by myself and my colleague, Claire Stephenson, which is an assessment from Europe that shows the possibilities to refine this intake assessment. Part of explaining the dietary exposure is to also put into context the basis to which the general population are exposed compared to the levels which are used in the carcinogenicity testing. I'm not going to speak about operator exposure at all. Dr. Acquavella will cover that later on this morning.

Going back to basics, the risk assessment paradigm is very simple, you identify the hazard, you determine the exposure, and the risk is a function of the hazard and the exposure. And this is used everywhere in the world for assessing risk not just for agrichemicals but virtually every chemical. And when you carry out these assessments, generally, regulatory authorities don't use any more effort than they need to to demonstrate a suitable margin of safety.

You start with very conservative assumptions. And when I say conservative I mean that you default to safety and you over estimate exposure rather than doing anything that would under estimate exposure. But you can apply refinements and these refinements are dependent on a number of things but primarily the data you have available and how far you need to refine that exposure. And please don't take these comments as a criticism of the EPA's issues paper. They have done their dietary risk assessment in the same way as virtually every other regulatory authority around the world.

And I think this was highlighted by Dr. Perron from the EPA yesterday. They've used as much

effort as necessary to show suitable margins of safety for consumers. And they've not put in additional resources to show that there are even larger margins of safety that can be obtained. If we look at Glyphosate, a few interesting points about absorption et cetera, et cetera. Generally, the dietary exposure is low and absorption through the GI tract is low. Numbers have been quoted over the last two days of around about 20 to 30 percent.

Although not relevant to consumers, actually the dermal exposure or dermal absorption is also very low, it's less than one percent. And those residues of Glyphosate that are absorbed are virtually all excreted by urine. And interestingly, when you look at the publications on Glyphosate residues in breast milk virtually every study around the world shows the same thing, that there were no detectable levels of residues found. And in a number of cases the limited quantitation that was used with these methods of analysis was incredibly low.

There was one publication which did show detectible residues but this had used an ELISA method which wasn't validated for use in breast milk. And when you make a back calculation it's difficult to

show that those levels are actually biologically plausible. What was presented in the EPA issues paper? Well it was a calculation carried out using a D-model using a very conservative approach. And this is equivalent to the Theoretical Maximum Daily Intake or TMDI which I'll talk about later on.

And default adjustment factors were used in that assessment and that would take account of any potential increases in residues that might occur as a result of processing. Looking at the various levels of refinement that could have been used and starting with the TMDI, why I feel this is conservative is because the assumption you make is all feeds that could contain Glyphosate residues do contain Glyphosate residues and these occur at the maximum residue limit or tolerance which is the maximum legal limit.

Now clearly over a lifetime that's not going to happen. And internationally it's considered that the median residue gives a much better estimate of the likely exposure in chronic assessments. And therefore, you refine your TMDI to a national estimate of dietary intake or a NEDI. But you can also go on and refine that even further while using actual data

on the changes in residue that occur in the processing or using data that are found in monitoring. These are not residue levels that you're using based on controlled residue studies. They're actually what is in the population or the food that the population is consuming.

And in the example, I'll present to you I've also done some additional refinements for the Irish and the German diet taking account of cereals and citrus processing. Particularly for cereals for humans, they don't eat raw wheat or raw barley. They eat breakfast cereals, the eat bread, they drink citrus juice. And therefore, those refinements should be taken into account in the assessment. This is a diagram that's taken from the publication.

And if you look at the top part of this diagram and the large blue column this is the theoretical maximum daily intake. The very conservative approach. And there are three models I've used here. The UK toddler is defined as a child between one and a half and four and a half in the UK, German children and an Irish adult. But in the top diagram it's not very easy to see the effects of the refinement. We've truncated the columns in the lower

diagram to a maximum of 15 percent. This is just to show how the refinements have been applied.

And the differences that you see here with the TMDIs are just a function of the different consumption patterns that are used in those countries. But you can see the massive reduction that you get in exposure when you refine to the NEDI that's using the median residues. And that's the red column. And then even further when you take account of processing changes or monitoring changes. And those are the green and the purple columns.

You can see the big reduction in exposure that can be demonstrated, this is theoretical exposure, when you make those refinements using actual real world data. We've gone from a worse-case scenario of 80 percent of the reference dose then to something in the order of two or three percent. And this is just the actual values of the consumer intake, just to express that conservatism. And I've put these numbers in a stepwise order starting with the values that were quoted in the EPA issues paper. The equivalent value that was calculated in Europe PRIMo just refers to the model that's used, the Pesticide Residue Intake Model.

And then progressively how you apply the different steps to reduce that exposure using real life data. And you see that from the top European exposure at .4 milligrams per kilogram body weight per day. You actually refine down to a fraction of that when you applied processing data to .01 milligrams per kilogram body weight per day. And I've actually included there some information from the public domain on biomonitoring as well. And that just gives you an idea of the actual real life exposure that takes place for consumers.

Keith Solomon from Canada also did something very similar to this. It's quite a complicated diagram but he's tried to get all exposures on the same normal distribution here. The red stars indicate the various chronic reference datas or ADIs that have been used and the green bars show the modeled exposures versus the measured general population exposure or all biomonitoring. And you can see the range of differences that are here.

What refinements could the EPA have made to their assessment? Well they could have adjusted for the percentage of crop treated. As I've mentioned before, the model that was used, it seems

that all crops that are eaten would have been treated with Glyphosate and all will contain residues at the maximum permitted limit. And that is really an incredibly unrealistic conservative approach which is not realistic for assessing lifetime exposure. But it's a very good way of making an assessment using the right amount of resources to show appropriate margins of safety.

When you've made all of these calculations you then compare these with the reference dose. And the reference dose that the EPA has in place at the moment is 1.75 milligrams per kilogram body weight per day which would equate to an exposure for consumers of between approximately three and 13 percent of this value. And what you were trying to use or trying to demonstrate to show safety is that your consumer exposure will not exceed 100 percent of the reference dose.

And here with this model which is defaulted to conservatism and used over estimates we can clearly demonstrate large margins of safety for consumers. Thank you.

DR. MARION EHRICH: Any questions from the panel for this speaker?

DR. JAMES MCMANAMAN: I think we'll hold questions until the end if we can for the entire presentation.

DR. CAROLINE HARRIS: I'd like to hand over to Dr. Acquavella who will address the epidemiology charge question number two.

DR. JOHN ACQUAVELLA: Thank you. What I hope to do today is use my experience researching Glyphosate and other pesticides to address some of the issues that I think might be helpful for the agency and hopefully for the panel members to interpret the Glyphosate epidemiology literature.

I'm just going to start by saying that my review of the agency's epidemiology section was that I thought it was an excellent review. Having just been the first author of an expert panel review of Glyphosate I thought the agency was painstaking in reviewing the pluses and minuses of all the available studies.

I thought it was appropriate to weight studies on the basis of quality criteria and to base conclusions on the most reliable studies. I agreed with their overall conclusion. The one area where I would quibble with the agency would be whether or not

any of the case control studies could be considered on a par with the Agricultural Health Study. As I go through my presentation I'll explain some reasons why that's the case.

I'm going to talk first about Glyphosate biomonitoring and the implications of that for epidemiology research. And then I'm going to talk about exposure. Both the way it was collected and the absolute amount of exposure that's represented in the Agricultural Health Study versus the case control studies. And then I'm going to talk about some analytic issues that perhaps aren't apparent to people who haven't had a lot of experience or haven't necessarily worked with these studies over a long period of time that I hope will be helpful in interpreting some of the things that were discussed yesterday.

I think we discussed this in several of the presentations, Glyphosate has low vapor pressure and dermal penetrability. It's excreted virtually unchanged that's apparent in urine. And if you collect urine at the appropriate time you can provide a reliable measure of the amount of pesticide that actually gets into the body. And I'll go through some

explanations of how we did that both in terms of urinary concentration and the milligram per kilogram dose.

The most comprehensive study done to date is an industry sponsored study done in collaboration with the University of Minnesota called The Farm Family Exposure Study. And this was a biomonitoring study of farmers and their families in South Carolina and Minnesota and the field work was done in the years 2000 and 2001 and in this study, we had three pesticides. We had 48 farmers who applied Glyphosate. We have data on those farmers and their spouses and their children. I'll run through that data mostly focusing on farmers.

And we had 32 farmers who applied 2,4-D Chlorpyrifos and this was an extensive urine collection protocol. What we did was we collected 24 hour urines the day before, the day of, and for three days after the application. And we used the terminology day minus one for the day before and day zero for the day of application. And for the applicators we had very high compliance. If you want to evaluate that you can go and read Beth Baker's paper that was published in 2005 where she goes into

the reasons why I say there was high compliance with the urinary collection.

The Glyphosate applications were substantial. Twenty-two of our 48 applications were 100 acres or more. We also had the farmer fill out a questionnaire about the application practices. We used the Ag held study questionnaire with some additional questions that we thought might be helpful in understanding the values we saw in farmers. And we also had trained field observers who recorded what actually happened in the field from an objective standpoint as somebody who was observing. And I've given two publications there that you can go to for more detail if you'd like. I'm going to cover it at a very high level.

This graph shows our geometric mean values for the day before the application, the day of, and for three days after for our 48 farmers. Our method had a one part per billion limit of detection and quantification. Our geometric mean value for Glyphosate was three parts per billion in the 24-hour period after the application and then the values dropped rapidly from there. For Glyphosate but not for the other pesticides 40 percent of the farmers had

values that were below our limit of detection and we included them in the calculation at one-half the limited protection or .5 parts per billion.

And interesting to me in just looking through the data that eight of the 18 farmers who had Glyphosate below the limit of detection had applied Glyphosate to more than 100 acres. It wasn't just that the people who were doing the smaller applications in the study, a number of them had values below the limit of detection, it was also farmers who had done very substantial applications. We had one farmer who had a value of 200 and 33 parts per billion I think that is, 23, sorry. My vision is changing and it's hard sometimes to see something in the distance.

Anyway, based on the field notes for this farmer he had a very eventful day with his equipment and he had to repair his boom sprayer many times in the field. And he wasn't always careful to use gloves as he was preparing his boom sprayer. He was also smoking cigarettes when he was repairing his boom sprayer in the field and he ate in the field, obviously, without gloves on. A lot of these distributions of exposure have a positive skew, you know, they're skewed to the right. And he was our

outlier, our next highest value was about 40 percent of his value. And he did everything you shouldn't do if you're trying to limit your exposure.

On the other hand, it means that this farm family study has the highest exposure that's ever been collected to date. It does give you more of a robust sense of the range of values that are possible for Glyphosate than if you didn't have some people who weren't doing things maybe the way you should or didn't have eventful days in the field.

Before I move on, I just wanted to say the panel asked yesterday about spouses and children. We had 48 spouses in the study that we biomonitored for Glyphosate using the same protocol. Two of the 48 had at least one day where they had a value above our limit of detection and their highest value was two parts per billion. We had one who had one point something parts per billion and one who had two. Otherwise all the other spouses were below the limit of detection.

We had 78 children who were biomonitored for Glyphosate. Nine of them had at least one day where they were above the limit of detection. The highest value was 29 parts per

billion. It was the son of the farmer who had the 223 parts per billion and who was helping his father with the application. And it's interesting, one of the things we did with this data was create informational booklets that the Ag Extension Service uses about how to prevent kids from getting exposure.

Both this farmer and his son were very important in the kind of learnings about how to minimize exposure for children who aren't necessarily the primary applicator in the study. Let's move on. If you look at the Glyphosate data exclusively you get one picture about the exposure properties of Glyphosate that comports well with the physical chemical properties but we had two other chemicals in this study. And this just gives you an idea about the exposure potential of Glyphosate compared with these two other pesticides. The orange line is the primary metabolite of Chlorpyrifos and the blue line is so 2,4-D.

And you can see the importance of an appropriately timed sample when you're doing biomonitoring. Had you only biomonitored on the day of application you would have missed the peaks both for Chlorpyrifos and for 2,4-D. The geometric mean

for 2,4-D was 64 compared with the three for Glyphosate and it was 18 for Chlorpyrifos. And you can also see the elimination patterns are also different for those two chemicals compared with Glyphosate. The agency and the toxicology studies tend to express the values of interest in terms of milligrams per kilogram.

Because we have the urinary values over five days and because we had information about each of the participants in the study, we could take the amount of Glyphosate in their urine and calculate a systemic dose in terms of milligrams per kilogram. And so what I've got on this slide if you look at the Y-axis, is just the cumulative proportion or the cumulative percentile organizing the values from lower to highest. And the green is the Glyphosate values and the orange is Chlorpyrifos. The blue is 2,4-D.

And the geometric mean value for Glyphosate was 0001. milligram per kilogram and the ninetieth percentile value was .001 milligram per kilogram. It doesn't show up on a chart that scaled so that you can see all the values. But here you get a sense on a milligram per kilogram basis that maybe it takes 20 or 30 days of Glyphosate application to

get the same milligrams per kilogram that you would get from the average exposure to 2,4-D or the average exposure to Chlorpyrifos.

Epidemiology studies tend to use this metric of days of use as though a day of use for one chemical is equal to a day of use for another chemical is equal to a day of use for another chemical. But really the exposure property of chemicals varies greatly in terms of how much get in your body and this is just one illustration. And you see the Glyphosate distribution barely overlaps the other distribution even in the high end for that fellow who had the most eventful day.

In previous publications in thinking about the exposure assessment and prioritizing chemicals for valuation I've advocated thinking a little bit about the exposure properties of the chemicals. And to put some weighting in studies and weighting in the exposure assessments that reflects how much chemical actually gets into your body. Now this is a cleaned-up version of the slide that was shown that included dietary exposure, just taken all that out.

And on this log scale then I've indicated in the box and whisker plot the range of biomonitoring values in terms of milligrams per kilogram for Glyphosate. As I mentioned before, the geometric mean 10 to the minus four milligrams per kilogram, the ninetieth percentile value is 10 to the minus three milligrams per kilogram. The regulatory guidelines average about a one times 10 to zero milligrams per kilogram and the toxicology studies go up to 10 to the third milligram per kilogram.

You can see the order of magnitude differences between the amount of exposure that you're likely to see from Glyphosate application, which happens a few times a year versus what are daily regulatory limits and versus what are daily doses in toxicology studies. Depending on how you think about it, it spans seven orders of magnitude or six orders of magnitude.

DR. KENNETH CRUMP: Kenny Crump. I just wanted to know if the biomonitoring data are for a day that they used, they were exposed, or is it averaged over like a year?

DR. JOHN ACQUAVELLA: No. It's not an average over the year. The day minus one would be the

day before the application. What we were trying to accommodate, because you know if you measure Glyphosate in urine you're measuring Glyphosate from all sources, dietary, occupational, whatever. And we were trying to parse out what the contribution of the application is above and beyond the background level. These milligram per kilogram doses are expressed relative to the application but taking into account all the Glyphosate measurements that happened over the five days on study.

DR. KENNETH CRUMP: Okay. Thank you.

DR. JOHN ACQUAVELLA: So before I leave the issue of exposure, panelists asked yesterday about production workers and if you go in the literature there are few production worker studies. I published one in about 2000 on Alachlor production workers looking at the experience, looking at cancer incidents from the 30 years of our time that had elapsed since the plant started through I think it was 1999. We did that in collaboration with Iowa Cancer Registry.

There were 2,4-D production worker studies in the literature but the thing of it is in doing those studies, my cohort has 1,000 people in it and 1,000 people were enough people to make enough

Alachlor for hundreds of thousands of farmers to do it. And in our study, we had an expected lymphopoietic cancer of, I think, one or two. So, you know, it's very problematic to accumulate enough production workers that you can look at rare cancers. And so forward a little bit.

As part of corporate due diligence, when I worked for Monsanto we did go to the Glyphosate production facility. And we did walk with the engineers and the industrial hygienists to try to understand areas where exposure might happen. Glyphosate becomes Glyphosate very late in the process. It's an enclosed process and then that goes to a canning line. And it involves very few workers to make very large quantities of Glyphosate.

And the opportunity for exposure potential and the limited number of workers involved led us to believe the study was not feasible. We did do an overall mortality study of the plant population that looked at workers who had been employee from the time Glyphosate started, through the 1990s, or something like that. The mortality profile was very good. They had very few cancers compared to what would be expected, based on Louisiana rates, which is

where the plant is conducted. But you just can't really assemble a production worker cohort that would be very informative.

Really, most of the exposure is in the end users and we weren't able to shed any light on that work for Glyphosate.

DR. ERIC JOHNSON: Could you just clarify --

DR. JAMES MCMANAMAN: Excuse me, Dr. Johnson. I think we'll hold the questions until the end of the presentation. We can come back. Write it down and we will keep the continuity going.

DR. JOHN ACQUAVELLA: Yes. Thank you. Hopefully I can keep my train of thought so let's move on. I want to talk a little bit about exposure in epidemiologic studies. Everybody knows that there's one cohort study. The other studies that assess exposure use case control design. I've included in this graph or in this chart Cocco et al., which the agency didn't include further. But it doesn't really affect what I'm going to say or the conclusions that the agency reached whether you include it or not because of the content of the study.

But in our review article we did include Cocco et al. I'll talk about six case control studies and one cohort study. And if you look at the exposure information from other case control studies, four of them based their analysis on even one day of use in a lifetime. And I think it would be helpful for the agency to try to get a little bit more detail about what that means. You know, one day of use in a lifetime can mean, you know, that there are a fair number people who have one or two or three days of use in a lifetime and maybe one or two people who have 10 days or 20 days.

But, you know, when I look at one day of use of Glyphosate, five days of use of Glyphosate knowing how little gets into the body and knowing that usually in chemical carcinogenesis we talk about people who have had years of exposure? I mean it's hard for me to believe that just a couple of days of use in somebody's life versus all the other exposures they have daily, versus working with other pesticides that have much greater exposure potential can be a valid indicator of the risks for Glyphosate exposure.

I think the agency would do everybody a service if you just ask them to talk about what the

interquartile range is or the range just so we know if we're looking at a study like Hardell or are we talking about cases and controls where the maximum exposure if four or five days. That would be more informative than just an any use analysis. There are two studies that do talk a little bit about use. The McDuffie study is an interesting one. You know, if you look at the exposure metric it's not really a cumulative exposure metric, it's average days of use per year but you don't know how many years.

There's a greater than two days of use per year and there's a one or two days of use per year. But from a cumulative exposure standpoint if you have five years at two days of use, and two days at three years of use, you know, you've got a people with more cumulative exposure in the lower exposure category than the high exposure category. I'd also ask McDuffie, et. al., what kind of overlap do you have in those exposure categories you're using in terms of cumulative use? Because my chemistry professor used to tell me, pay attention to the units when you're trying to solve problems.

And here the units are days per year which isn't a cumulative exposure, it's an average

without the requisite information you need on how much exposure there is. And then of course the Ericsson study has greater than 10 days as the highest exposure category. And again, it would be useful to know, these distributions tend to skew positive, whether most of the values are near 10 or whether there are some extensive values. Because as I mentioned, it's a rule in chemical carcinogenesis that you focus on people who have a lot of exposure, extended exposure, as opposed to intermittent exposure.

I'll just give you an example, a recent publication from The National Cancer Institute, Martha Linet, who has been studying the cohort of Benzene workers in China -- I know, Dr. Crump, you have great interest in this study. You probably know it better than I do. But in her methods section, they excluded anybody who had less than six months' exposure to Benzene because there's so much about their history that you don't know, other exposures. Just intermittent workers, you know, aren't usually the focus of a chemical carcinogenesis study.

Usually you like to focus on workers who have more exposure for lots of different reasons. Let's move on to the Agricultural Health Study. I

thought the agency was right to say that the Agricultural Health Study is a different animal than the case control studies. I thought maybe I could explain why that's the case. I was around when the Agricultural Health Study started. They were kind enough to invite me to their advisory committee meetings to present on the farm family exposure study.

The rationale for the Agricultural Health Study was that there were some unfixable issues in the case control studies, mainly recall bias. Any of you who know somebody who has cancer know it affects the way they think about everything. I have a relative who is about my age, he has advanced prostate cancer. We sit together a lot. And he thinks a lot about what might have caused his cancer. I could imagine him being the case and I would be a control and my context is very much different for answering those questions than his would be.

He’s been spending a lot of time thinking about why do I have cancer, you know? What did I do in my life? So, you know, I’ve spent a lot of time working in pharmacoepidemiology. This is equivalent to being unblinded in some ways. It’s something that you can’t fix, you can only say that

it’s a bias, you don’t know how important it is. Basically, the Ag Health Study was set up to deal with this issue of recall bias. It's a very significant research issue. But they also did some other things that are important. They focused on frequent pesticide users.

They recruited these people after they had finished their pesticide training for the year so they're knowledgeable reporters which is also important, and there were no proxy respondents. The Agricultural Health Study isn’t just a study, it’s a program. They have three agencies working on it, they’ve spent tens of millions of dollars, they’ve published hundreds of papers. They've given incredible consideration to how you go about doing exposure assessment and the like. This is like a second-generation epidemiology study of pesticides. I think it probably didn't get its due yesterday in some of the discussions.

But anyway, if we look at the De Roos paper on Glyphosate, the ever/never analysis reflects the fact that about three-quarters of the analysis cohort and three-quarters of the non-Hodgkin lymphoma cases had reported a history of Glyphosate use. But

they also did some analyses that look at the number of days that people have used Glyphosate. And they have a category of 21 to 56 days and they have a category 57.

I don't think anybody in their study has 2,600 days but they have a category of 57 to, you know, several hundred, who knows, I don't know what's in that category. I'd ask the agency to perhaps get some more information on what's in that category. But this is selected from the people who have complete covariate data which is about 36,000 people in the study. And so, you can see by looking at the proportion of cases and what the odds ratio is for some of those different categories there's probably 10,000 or 12,000 people in the cohort who have 21 to 56 days of use and 57 to, who knows, several hundred days of use.

The amount of exposure that's considered in the Ag Health Study is really important. And when you make judgments perhaps based on a meta-analysis of ever/never use and you don't give more weight to an analysis where there are possibly hundreds of days of use I think you can miss the big picture about what's going on. We usually focus on

the highest exposed people as being the most informative. And so anyway I'm not sure the exposure differences were apparent to everybody based on the discussion yesterday so I thought it might be helpful to highlight that a bit.

Okay. So now a couple of analytic issues that you see in the studies. And again, you have to tease them out but I hope I've teased them out sufficiently to explain them to epidemiologists and non-epidemiologists alike. The first one has to do with the things you do in the analysis creating a bias. Let's start with epidemiology 101, you know, case control and cohort designs are related. And every case control study can be conceptualized within a cohort study, a hypothetical cohort.

I'm going to talk a little bit not to illustrate what I'm trying to say looking a multiple myeloma study that was done in Iowa as a case control study. You go to the Iowa Cancer Registry, you identify all the multiple myeloma cases who have occurred. And hypothetical cohort there is the person time experience in Iowa. Because it's too rigorous to enroll everybody in Iowa, you sample. And so, you

sample from the population in Iowa just controlling for age and sex and all that stuff.

What you're trying to do is get a population that is representative of the population that gave rise to the cases. And the controls in this context are supposed to provide an estimate of the exposure prevalence in the population that gave rise to the cases. If you've done this correctly the ratio of exposure odds for cases and controls estimates what you would get from a cohort study like the Ag Health Study where you compare the ratio of disease incidence for the exposed participants versus the unexposed participants.

The two Swedish case control studies, in their analysis, they defined unexposed as no exposure to Glyphosate or any other pesticides. But the population that gave rise to the cases included those with exposure to other pesticides. What does this do? I wasn't able to trace all the numbers in Ericsson, I wasn't able to trace all the numbers in Hardell, but I was able to trace all the numbers in Brown, et. al., which is one of the studies that the agency considered for multiple myeloma. And so, this is the hypothetical cohort I was talking about.

The multiple myeloma cases were identified from the cancer registry and the controls were randomly selected from the Iowa population to have the age and sex distribution from the cases. And so, if you just take the populations as selected and you look at the proportion who had exposure to Glyphosate you get six percent of the cases were exposed and six percent of the controls were exposed, odds ratio of one. But when they actually did their chemical specific analysis they defined unexposed as non-farmers which I'm using as kind of analogous to using unexposed as no pesticide experience.

And you can see by doing that they excluded 58 percent of the cases and 52 percent of the controls. That changes the exposure prevalence's that you sampled already and now the exposure prevalence is higher for the cases for Glyphosate than it is for controls. And because you've taken all these other exposures out the analysis you can't control for other farm exposures. And you can introduce confounding by comparing people who are primarily working and living on farms with people who aren't working and living on farms to generalize that to the cohort context.

It's hard to know in Ericsson because he does say there's one analysis that's multivariate the other ones are considered to be univariate controlling, I think, for sex and for age or for year that the case was detected. It's hard to know whether their multivariate analysis included all the exposures or just modeled the exposures in this limited population where you've excluded everybody who didn't have exposure. I think it would be worthwhile to inquire from Dr. Ericsson how that was done.

But in any event, this practice of excluding of from the unexposed group people who don't have exposure to other pesticides can create a bias in the analysis. We call that selection bias in the analysis and it's illustrated, again, in our article that appeared in 2016. Okay. Want to talk a little bit about latency. There's been some talk about the Ag Health Study not having long enough follow-up compared to the case control studies and I just want to be clear about the terminology.

Epidemiologists divide the period from first exposure until disease detection into two separate periods. The first one is the induction period, that's the period of causal action of the

chemical exposure. The latent period is the period from when it's caused until it's detected. Typically, it's hard to know where one begins and the other starts. But typically, in chemical carcinogenesis studies you see 20 years or so for many exposures. And there the term is being used loosely, latency is being used to mean induction and latency. This is a chart that I took from the OPP website and included in an article I wrote in a 2003 and I can't read it. I'm sure you can't read it either.

But it just shows the progression of different pesticides in terms of their rank in terms of pounds applied. And Glyphosate was approved in 1974, it cracked the top 20 of pesticides in 1987, and then it became one of the top five pesticides of 1997. But there were periods after initial registration where it wasn't widely used. And I think the agency said yesterday, you know, the epidemiology studies will become more informative as you get into periods where Glyphosate use is a little bit more frequent and the people who use it have ore days of use, et. cetera.

But you really can't tell in any of the studies how long it's been for the cases or how long

it's been for cohort members from first exposure until when their follow-up has been completed. I tried to put all the studies on the same basis. The only thing I could think of that would put all the studies on the same basis is just to say when the cases were detected and then to calculate the year since Glyphosate approval. And that would be the maximum amount of time that could have a passed that would be represented in the data that's included in that analysis.

And so, the study that sticks out first of all is that De Roos 2003 pooled case control study which was a very sophisticated analysis. But 83 percent of the cases in that analysis were diagnosed between 1979 and 1983. And I don't know when their first exposure was but their maximum time since first exposure could have been nine years. But it's unlikely that all of those cases ran right out when Glyphosate was approved and applied it then. It's probably some number that's much less than that. The De Roos et al. study sticks out in terms of a short time from potential follow up or short latency as people are saying.

That study gets 16 percent of '08 in the meta-analysis. And looking at just how soon those cases were detected after Glyphosate was on the market it's hard to imagine that it's informative with respect to Glyphosate. You can see the two other studies that were relatively early on in terms of the case detection have a maximum of about 17 to 20 years or 13 to 16 years or 13 to 18 years. But in terms of the potential maximum amount of time that's elapsed for people who are in the cohorts or in the case control studies you can see that the Agricultural Health Study spans from 19 to 27 years which isn't that different than the other studies.

In pharmacoepidemiology we often use a new user design, and in that case if you only had eight years of follow-up you would only have eight years of follow-up. But the Agricultural Health Study kind of intercepts farmers in the middle of their lives. They've all had histories. And I know from our farm family exposure study, our average farmer age was 45 and they average 24 years of pesticide application as of age 45. I think this issue of how short the follow-up is in the Ag Health Study misses

the amount of exposure experience and time since first exposure that's in the Ag Health Study.

And at least on this basis it seems to comport pretty well with the longest of the case control studies. Okay. The last thing I want to talk about was meta-analysis and what it means to use a random effects model and what the implications are for interpreting the p-value. There was a lot of discussion yesterday and there's been some comments to the docket about whether or not a meta-analysis was statistically significant. I thought this might be helpful. All students in epidemiology who take advanced methods train with a textbook like *Modern Epidemiology* which Ken Rothman and Sander Greenland wrote.

And when I teach pharmacoepidemiology, I actually use Greenland's original paper on this. Greenland here is trying to explain the difference between interpreting a p-value in a randomized study and in an observational study. If you're doing clinical trials you're randomizing patients to a treatment or a control in an attempt to have the prognosis be the same in both groups. Because if the prognosis wasn't the same you couldn't assess the

effect of the drug adequately. But as Greenland points out in this article because it's random the prognosis isn't always going to be the same.

You could have studies where the group that gets treatment has the worst prognosis going into the study or the group that gets the placebo has the worst prognosis going into the study. But because it's random if you repeat the studies many, many, times these things will average out. And as Greenland shows in his paper with mathematical proof, also, a logical proof, you will center on the right value. And in that case the p-value has it's intended meaning which is the frequency of seeing results as extreme or more extreme than those observed if the known hypothesis is true.

That's the definition of a p-value that that you learn early on. However, Greenland goes on it to say that that's not the same thing as looking at a p-value in observational studies where you could have recall bias, you could have uncontrolled confounding, you could have selection bias. And he says interpreting those p-values at face value can be very misleading. So, just thing that’s important when we think about the meta-analysis that's been done. If

you look at the studies and their characteristics which I think the agency detailed very well, the case control studies all have the potential for a recall bias but the Ag Health Study doesn't.

There is selection bias in the Ag Health Study and also in the case control studies. No proxy respondents in the Ag Health Study but three of the six case control studies have an appreciable number of proxy respondents and the confounding control was very extensive in the Ag Health Study. But it was poor in the five to six case control studies. The only case control study that my expert panel thought was a good extensive confounding control was De Roos. So, you know, De Roos is a very skilled data analyst.

She brought the same really advanced thinking in terms of analysis to both of those studies. All the meta-analysis, which again focused on ever/never use which is probably not the most informative analysis that's been done in any of the studies used a random effects model. And if you read Greenland's chapter on meta-analysis he says, "When differences between studies are likely due to systematic factors, the assumptions underlying random

effects model are violated." And so, we can use the same example he used in his paper about randomization, if things are random they equalize with time.

But you have six studies that have the potential for recall bias, you have one study that doesn't. That would be like combining clinical trials that are double blind with double blind with clinical trials that aren't blinded. The probability model you need to evaluate that is not a random effects model. Greenland advocates things like it using external factors to adjust and to try to get the systematic error out of the studies you're using. He also says that these heterogeneity tests aren't very powerful for picking up systematic differences of this type in epidemiology studies.

He says kind of a common-sense approach, if you've can see the studies are different, frankly different, then you have to question whether you're going to combine them regardless of what the heterogeneity test tells you because the heterogeneity test is insensitive to these kinds of things. Okay. So just to conclude. I've rambled on a little bit about a few topics but I hope they're helpful. I thought the agency identified all of the relevant

studies. I thought it's good to try to figure out what the highest quality information is.

And, you know, if you think about the agency contrasting Ericsson with the Ag Health Study that's like a meta-analysis of two studies that you've considered to be a high quality. And I guess that was the basis for the agency saying the two highest quality inputs that we had conflicted and that's why we think you can't make a conclusion. But in any event, I thought that what the agency said in terms of their conclusions was appropriate given the data. And I thought their review was very good. It was certainly at least as good as my expert panel did. Thank you.

DR. JAMES MCMANAMAN: Okay. I think that the past two presentations are kind of grouped broadly in topic. I think we can open it up to questions to the previous two presenters if there are any from the panel. Yes. Dr. Johnson?

DR. ERIC JOHNSON: So in the past year in many of these industries which manufacture chemicals the earlier days most of the processes were open processes. I think you mentioned that in the case of Glyphosate you actually went to the factory

and it was a closed process. I would like to know whether it has been a closed process right from the very start or did it initially was an open process and then later converted to closed process?

DR. JOHN ACQUAVELLA: Well, the production of commercial volumes was always a closed process. I'm not an engineer but I've walked through plants enough to know that often times before you scale up a process to produce commercial quantities you'll have a pilot operation. It is possible that that was done for Glyphosate to develop all the information needed to scale up for commercial production but that would have involved very few workers. And I don't remember during our assessment whether we did identify that there was a pilot operation.

Sometimes those aren't closed. But it would involve very few workers and it would have been for a very short period of time.

DR. ERIC JOHNSON: Well, I mean, I don't quite agree with you that it's only for the pilot project that were only open processes. Because I remember for the Dioxin herbicides I also visited some of these companies. They were open processes in

which people were actually going to open vats to do cleaning and all that. There were a lot of open processes I observed. It was later on that they converted to really closed system in which exposure was really low and only few workers involved. I think it's critical for us to know whether Glyphosate manufacture was closed throughout the manufacturing stage.

DR. JOHN ACQUAVELLA: Yeah. I'm almost certain it was. And like is said, it becomes Glyphosate at the end of this process, right. There are other parts of the process where chemicals are being mixed, all sort of stuff, and the chemical engineering is taking hold. And as I said my recollection, I didn't know we were going to be asked this question so I'm just operating on memory. It's been a closed process, and that the number of workers who would have worked on the part of the process where it was Glyphosate was few.

There was a canning operation. And probably if you were thinking about where the most exposure was it would probably be in canning; because sometimes you have to get in there and it's spilling out of a can or whatever you're doing there could be

something. But with time that's become more and more automated as well. I just don't think that there are that many workers who have had the chance to have that much contact with Glyphosate.

DR. ERIC JOHNSON: Could you clarify for me whether the people who are involved in the manufacture of Glyphosate were actually studied in a cohort study at Monsanto. Do you know of anywhere else, in other companies where workers who are manufacturing Glyphosate were studied in a cohort study?

DR. JOHN ACQUAVELLA: Yeah. Well, I mean our mortality study included some people who had worked in the process. But for a lot of our, I say our, I haven't worked for Monsanto for 15 years.

But for a lot of studies that have been done of Monsanto work forces, you know, you use Social Security tax records to make sure you've enumerated everybody from the start of the plant. There have been studies where we've gone back into the 1920s, and the 1930s and enumerated everybody using the Social Security 941 forms to make sure that nobody has been missed. And then we followed them for a lot of years.

In this case, because we didn't see that there was any Glyphosate exposure, I think we used the convention of taking all employees who were employed as of 1980. The process started in '74 and we followed them I think it was through 1996. We could conceivably have missed. We didn't have complete enumeration of everybody who has always worked at the plant. And like I said, our exposure assessment and feasibility didn't lead us to believe that we could actually do a study of Glyphosate. We did it more because there's a lot of due diligence that goes on and a lot of interest in the plant populations about how their health is.

And it was more for our internal purposes to make sure that there wasn't anything going on that maybe you miss by just walking around the plant and trying to decide what's going on. And it's information that we shared with the workers and with the community. The community also had a lot of interest in the experience of workers.

DR. ERIC JOHNSON: That was a published study?

DR. JOHN ACQUAVELLA: No. A cohort study of 600 people who have overall mortality that's

50 percent of the general population and where you have 10 cancers expected but you only saw five, that's not the kind of an epidemiology study that you could get into a journal. And it really wasn't done to be a publishable study.

DR. ERIC JOHNSON: Right. And that was the complete workforce who were involved in the manufacture?

DR. JOHN ACQUAVELLA: This is all from memory, I haven't read the report in many years. Anyone who was employed I'd say 1980 followed through I think 1996.

DR. ERIC JOHNSON: Okay. 1980? Thank you.

DR. JAMES MCMANAMAN: Okay. Any other questions? All right. Thank you very much. We'll move on to the next presenter.

DR. JAMES BUS: Good morning. My name is Jim Bus and it's a pleasure here again to be this morning making this presentation. The focus of my presentation this morning will be addressing the set of sub questions that are associated with charge question three which is how basically EPA handled the treatment of the animal carcinogenicity studies. And

the sub questions I'll touch on each individually throughout my presentation. And the first of those of course is EPAs overall review and evaluation of the relevant laboratory and animal carcinogenicity studies.

Number one, it was an appropriate treatment of the nine rat and six mouse cancer bioassays for consideration for the weight of evidence analysis that was used. However, we should note to the Science Advisory Panel that one of the studies, the earliest one, Barnett in rats, published in the 1970s was indeed conducted with a Glyphosate contaminant and not Glyphosate. We would just remind that that particular study was not a Glyphosate bioassay. The EPA did take an appropriate and use an appropriate reliance on its guidelines for carcinogen and risk assessment.

And the appropriate carcinogenicity test guidelines found in test methods for conducting animal bioassays. And overall there were appropriate weight of evidence conclusions that Glyphosate is not a carcinogen in any individual rat or mouse study or an animal carcinogen in an integrated weight of evidence analysis of all the studies. And of course,

the use of a weight of evidence approach is one that is openly prescribed in the EPA's 2005 cancer risk assessment guidelines.

And those weight of evidence evaluations certainly call for the integration of a variety of different sets of data sets in order to assess the overall potential for carcinogenicity in animals. Those considerations certainly include the appropriateness of dose selection to real world exposures that happen in humans, the occurrence of or evidence of pre-neoplastic or non-neoplastic lesions to support those tumor findings if they indeed are observed, the evidence of potential progression to malignancy across the tumors that are reported and analyzed.

Most importantly of course, the ability, if you have a data rich set such as Glyphosate the potential for reproducibility of those tumor findings across studies. And lastly of course is the consideration relative to the actual interpretations of the study per se are relative to the use of historical controls and how that might further inform the significance of those tumors. And closely related to that of course is the statistical

evidence associated for dose response or the overall on tumor incidents.

Taking a look at the animal studies that the agency has identified for review for animal carcinogenicity, as you heard yesterday and we're discussing actively, there are nine rat studies and six mouse studies. As I've just reminded you the first study, Barnett, is not one of a Glyphosate bioassay. All of these studies were done using Glyphosate acid. The reason for that is it's well recognized that salts of agricultural chemicals including the one that you were discussing yesterday, the Isopropylamine Salt.

Once they are introduced into a biological environment they immediately dissociate into the parent compound under those physiological conditions. That type of dissociation is readily apparent from toxicokinetic studies that have been conducted with Glyphosate and biomonitoring studies in the human population, which primarily indicate the only material detected in blood or in urine is Glyphosate acid. Turning to the first key issue that is obviously of consideration relative to the overall

weight of evidence evaluations of the carcinogenicity studies.

And that is that the evaluation of dose selection in the studies and was it appropriate for interpretation of potential carcinogenicity. The key question of course which was under discussion yesterday and which I'll reiterate here is did these studies indeed use adequately high dosing. And the answer as you can see from this table surrounded by the red boxed colors, the answer is yes for 11 of the 15 studies. But despite such high dosing, acceptable dosing, there were no statistical significance by pair-wise comparison to any of those high doses observed and reported in these studies.

The question of course that is key to any cancer bioassay evaluation is did the top dose indeed meet or exceed the limit dose of 1,000 milligrams per kilogram per day. And again, you can readily see that the answer is yes for 10 of those 15 studies. The EPA throughout its evaluation generally gave less weight to tumor findings that were observed at or significantly above that limit dose. Particularly when doses are well separated from human exposure.

There has been some comment to the docket, as well as what was discussed here yesterday, that EPA might have deviated from its own guidance relative to the use of 1,000 milligrams per kilogram limit dose. In fact, there is very specific guidance prescribed in the animal testing guidelines for carcinogenicity which specify the selection of 1,000 milligrams per kilogram per day limit dose as it relates to human risk assessment. The first bullet that I have up there describes the guidance found in the EPA chronic toxicity and carcinogenicity test guidance which sets the dose of 1,000 milligrams per kilogram per day; and I emphasize here, “unless there is expected human exposure”, may indicate the need for a higher dose level.

That same position is mirrored in the OECD guidance for testing of chronic toxicity and carcinogenicity studies in rodents which is the OECD 453 guidelines. And that explicitly states a limit of lot 1,000 milligrams per kilogram body weight per day may apply except when human exposure indicates the need for a higher dose level to be used. Now, as Dr. Acquavella just mentioned we do have available to the

scientific community and the agency as well a number of human exposure studies conducted by biomonitoring.

These are high quality studies and they provide a very accurate estimate of what the potential daily exposure to Glyphosate might be under a variety of different exposure conditions. But the average real world human external dose, if you look across all these biomonitoring studies, translates to a general does that is less than .0005 milligrams per kilogram per day. And of course, you can readily do the arithmetic given that scenario that the human exposure then across these biomonitoring studies is more than two million-fold lower than a 1,000 milligram per kilogram limit dose used in the Rhoden bioassays.

Certainly, this human exposure information provides key data that suggests that the 1,000 milligrams per kilogram per day limit dose was indeed appropriate when considered in the context to demonstrated human exposures.

Let’s turn to another sub question that the panel was charged with addressing and that is EPA's conclusions regarding the absence of preneoplastic or related nonneoplastic lesions and a lack of progression to malignancy. If you look at the

animal bioassays you find that the terminal sacrifice data in both rats and mice do not show any evidence of tumor promotion.

But more importantly, particularly in the rat studies, most of them in fact all of them had interim sacrifice data that allowed further exploration of potential preneoplastic lesion. And none of those types of lesions such as cell proliferation of evidence of cytotoxicity were apparent in those interim sacrifice animals. And then ultimately if you both the terminal sacrifice data with the interim sacrifice data you can see that the combination of those two comparisons lead clearly to the conclusion that there is little evidence, if any, of malignant progression to tumors.

Based on these criteria in part, EPA found no evidence of carcinogenicity in any study. Turning to another sub question as part of the review, and that is EPAs interpretation of conflicting evidence and reproducibility across the multiple bioassays that are available for Glyphosate. And this particular comparison and consideration is very important for Glyphosate because it's very unusual in the world chemical testing whether it's pesticides or

chemicals in general. And then Glyphosate is an extremely data rich compound with respect to obviously carcinogens bioassays being available for it.

There is that opportunity to again examine very closely for evidence of reproducibility. EPA correctly looked across the studies to evaluate for both consistency and coherence. And when those data are evaluated in totality there's no consistent findings across the studies. By way of example there is differing or a total absence of tumors in multiple differing studies. Obviously providing clear evidence of a lack of replicability. There was also no coherence as the tumors were often observed only in one sex or in one species.

And then lastly, and of course importantly, the lack of statistical significance when adjusted for multiple comparisons. And as I'll address here in just a few moments additional consideration of whether the tumor findings indeed represent rare or common tumors in the rodent studies that were conducted. I'm going to speak briefly with respect to the EPA's methodology regarding its interpretation and use of statistical analyses. The

EPA did indeed appropriately calculate all statistics based upon the data they had available to them.

And the absence of statistical significance is further evidenced by the impact when you bring in considerations of rare versus common tumors on the ultimate pair-wise and trend tests that were conducted for these bioassays. Let me provide a particular piece of information which I think is important for interpretation of animal bioassays. It's recognized that obviously, these bioassays can be subject to excessive false positives. Particularly that can be an issue when you have common tumors in this strain of animal that you might be examining.

As a consequence of that, as early as 1983, Dr. Haseman, when he was at the National Toxicology Program and later in the FDA in 2001, developed a series of decision rules modeled to help facilitate interpretation of animal bioassay data. Based upon whether the tumors that were observed in the animals are either rare in terms of their incidence in background animals. And that’s defined as a rate of less than one percent in the animal population, or common or greater than one percent.

And as a consequence of those decision rules, which were based upon their examination of a broad spectrum of animal bioassays that were available within the National Toxicology Program, or that had been submitted to the FDA as part of a drug registrations, the NTP via Dr. Haseman's conclusions came to the conclusion, that if you had a rare tumor in your control population, it was indeed appropriate to use the traditional and conventional p-value of 0.5.

However, if you had a common tumor, in order to avoid excessive false positives in your statistical evaluation for your pair-wise comparison, Dr. Haseman recommended that a p-value of 0.01 be selected for evaluation for statistical significance. Likewise, the FDA extended that type of thinking into trend-wise comparisons. Where, as the result of analysis of bioassay data that they had available to them they concluded that for rare tumors it would be more appropriate to use a p-value of 0.25 to established a statistical significance and for common tumors to drop that to 0.005.

The EPA issue paper that you have in front of you with respect to the treatment of

Glyphosate used the conventional 0.05 for both their trends and pair-wise comparisons. Addressing a little bit more about the statistical adjustment considerations for rodent bioassays. EPA of course did use Saitak method in their pair-wise comparison. And as a result, that did make a difference in terms of the ultimate establishment of statistical significance in pair-wise comparisons.

However, the Saitak method, as I just described, does not consider the impact of rare versus common tumors on the potential statistical evaluation of those rodent bioassays.

And as I just mentioned, Dr. Haseman in 1983 supported a pair-wise p-value adjustment to 0.01 for common tumors. And likewise, the FDA, as part of their now FDA guidance adjusts p-values for trend tests of rare and common tumors based upon the assumption that the rodent bioassay that they have submitted to them include at least two species studies with two sexes in both species. And of course, for Glyphosate as you well know we have 15 studies that evaluate Glyphosate for carcinogenicity. Certainly, that criteria is fulfilled.

And of course, as some of the conversation was placed on the table yesterday the availability of those extensive numbers of animal bioassays also creates additional statistical consideration which Dr. Haseman, who will be speaking immediately after me, will address in more detail. Obviously, the establishment of historical control data can be used to inform the significance of tumor findings. And in the EPA issue document they did indeed use historical control incidents and they applied it to four of the tumor types.

And that was of value in terms of further informing the relevance of those potential rumor types as being treatment related. But in addition however, as you could tell from what I have just been describing the historical control data that's available across rodent species and strain also provides important insights in terms of whether a tumor is likely to be a rare or common tumor. The question then arises what is the potential impact if those types of adjustments for both pair-wise and trend comparisons, based upon either the tumor type being common or rare, would make on the ultimately

statistical comparisons that the EPA issues document develop?

It's important to note that all of the tumor types that were examined and considered by any agency were indeed regarded as common tumor types if you use the definition of an incidence greater one percent in the animal background population. What is the impact then of those types of decision rule changes based upon either the FDA guidance for treatment of trend values or the Haseman guidance with respect to decision rules on pair-wise comparisons? In the EPA analyses, there was only one study with a significant pair-wise comparison established with a Saitek correction.

Of course, that was the Lankas study in 1981 and it was a response in testes. If you look at that same tumor type and you use the cutoff point of 0.01 for a common tumor which the testes response is you find that that is no longer significant using that particular decision rule. And of course, the testes tumor that was observed in the Lankas study was used and observed only at a high dose in that study which was significantly lower than the high doses used in the eight other rat bioassays.

And of course, the testes response that was observed in that bioassay was not replicated in the other rodent bioassays as well. There were nine additional tumor sites with significant trend test that were positive under the EPA criteria of P equal to 0.05. However, if you use the trend test criteria as recommended in the FDA guidance for common tumors you find that only two tumor trends, that of the male mouse hemangiosarcoma and the female mouse hemangioma, remain statistically significant under that FDA decision rule treatment.

And of course, both of those studies included a top dose of equal to or greater than 1,000 milligrams per kilogram per day. And one of those studies of course the top dose was above 4,000 milligrams per kilogram per day. Those studies also had particularly low tumor incidences in their concurrent controls despite clear evidence that those tumor types are common tumors in the general animal population that's available within the literature. In the last slide, then with respect to the sub question regarding the EPAs conclusion that tumors observed at high doses are not relevant to human health risk assessment.

There are several considerations that I believe support this conclusion. The high doses in bioassays are substantially separated from real world human exposures and the EPA RFS of 1.75 milligrams per kilogram per day. As I mentioned in an earlier slide the 1,000 milligrams per kilogram dose used in these bioassays was two million-fold higher than exposures readily identified in human biomonitoring studies. Additionally, no pair-wise tumor responses were statistically significant at those high dose levels.

The high dose tumor findings were limited to a single sex and/or species. And most importantly, which is key to any scientific evaluation, were not replicated across the wide body 15 available rat and mouse bioassays. Also, not shown on this slide, but I think is worthwhile mentioning, that there's also a lack of mechanistic plausibility associated with Glyphosate being an animal or human carcinogen. The compound is nongenotoxic and you'll be hearing more about that in just a few moments.

As was discussed yesterday, Glyphosate is not regarded as an immunotoxicant in specific tests designed to evaluate for immunotoxicity. As well as when you look at the generally toxicity studies for

Glyphosate you find no evidence in the overall histopathology or the clinical chemistry that would suggest that Glyphosate would be an immunotoxicant. There's also no evidence of the preneoplastic lesions or other type of events such as cell proliferations or cytotoxicity which would suggest that Glyphosate might have a mechanistic event accounting for carcinogenicity.

Of course, it has been suggested that oxygen stress may play a role. And I'll be speaking to you later this afternoon with respect to the plausibility of that particular mode of action. And lastly, let me close also with the observation that as you look across these studies you'll find little evidence of exposure plausibility for Glyphosate being a human carcinogen as well. With the reminder that the high doses used in this study, 1,000 milligrams per kilogram across these studies is two million-fold higher than doses that are routinely observed in high quality human biomonitoring studies. Thank you.

DR. JAMES MCMANAMAN: Maybe we ought to take a break now and then come back because we're close to the break time. Fifteen-minute break; be back here at 20 until.

[WHEREUPON A BREAK WAS TAKEN]

DR. JAMES MCMANAMAN: All right. We can move on to the next presenter then.

DR. HASEMAN: I'm Joe Haseman. And for more than 30 years I was the statistician at the NTP that was primarily responsible for the design analysis and interpretation of the rodent cancer bioassays that they carried out. And I'm listed as a contributor to approximately 300 of the technical reports that reported the results of their studies. My focus of my presentation today will be on two things, first my own statistical analysis of the Glyphosate tumor data and secondly a commentary on other statistical analyses of the data that has been presented in the comments to the OPP report by Dr. Chris Portier and Dr. Bob Terone.

The Glyphosate rodent studies considered by the EPA consisted of nine rat studies and six mouse studies. And because of the huge number of tumors within each of those studies there were literally hundreds of potential tumor trends examined. It's going to be inevitable that when you look at all those tumor trends across 15 studies you're going to find some significant trends, that's inevitable. Some

of them may just be just due to chance, others of them could be reflecting real carcinogenic effects.

And by the way, I am going to focus on the trend because the trend is the most sensitive test for detecting carcinogenic effects. My results will be predicated on the results of trend tests. In trying to evaluate these multiple studies there are several key questions you need to answer. First of all, does the overall frequency of significant trends reported in these studies exceed what you would expect to see just by chance alone?

A second key question is given that you're having some significant trends do you see a consistency of the trends with regard to tumor type or are they just sort of a random distribution of tumors that happened to be significant by the trend test? And then the third question is regardless of those two questions is there any tumor trend that's so significant that it's just virtually impossible for it to be a chance occurrence? And with that in mind I set out to answer these three questions for the Glyphosate data.

Now in order to do that, what you need to know is how many trend tests were actually carried

out for the Glyphosate data. And originally, I had data from two of the nine rat studies and two of the mouse studies. And since that time, I've gotten data from four of the other rat studies and a third mouse study. The numbers you'll see on the next overhead have been updated to reflect the more extensive data. And in order to be counted there had to have been the opportunity for there to have been a meaningful trend test.

And by meaningful trend test, I mean a trend test requires a minimum of three animals in order to have a chance of being significant by an exact test. If you only have one or two animals, no matter how they're distributed, you're not going to get significance. I didn't count those in my calculations. I just counted those that occurred in a sufficient number of animals for the trend test to have been significant.

Just to give you some idea, just some flavor of the number of tests involved; this is just a typical male rat study and the tumors that permitted a meaningful trend test: Adrenal gland, cortical adenoma and carcinoma and then the two combined adrenal gland pheochromocytoma, brain glioma, liver

adenoma carcinoma and then the two combined. Pancreas, islet cell adenoma carcinoma combined, pancreas acinar cell tumors, mammary gland adenoma, adenocarcinoma, parathyroid gland adenoma, pituitary gland adenoma carcinoma, skin keratoacanthoma, skin squamous cell tumors, subcutaneous tissue, fibroma fibrocarcoma, testes adenoma, thyroid follicular cell adenoma carcinoma combined, thyroid C-cell adenoma carcinoma combined, all sites lipoma liposarcoma combined, and reticulum cell sarcoma.

By my count that's 36 tumors and you can do the math across the 30 studies. Fortunately, it didn't come out to be quite that high. But that just gives you a flavor of you must have an appreciation of how many trend tests are possible before you can accurately interpret the results that were found in these studies.

What I found was that from those 15 studies there were 568 trend tests that were meaningful that could have produced significant results. And if five of them are significant by chance you'd expect to see about 28 significant trends and there were actually 11 that were noted by the EPA.

And I'm sure that many of you, when all these slides were presented yesterday one tumor after another, here's a trend significant, here's a trend significant, here's a trend significant, we discounted them all. But here they are, 11 significant trends. You might have wondered, good grief how can you discount so many significant trends? But what you don't realize is that by chance you would produce at least twice that number. Now I then refocused my calculations not to all trend tests but to all trend tests for unique tumor sites.

And by that, I mean at the liver you can look at liver adenoma, liver carcinoma, liver adenoma carcinoma combined. Three trend tests but one tumor site and they're all sort of measuring the same thing. If you reduce it to the tumor site only and take the combination analysis, the adenoma carcinoma, as the indicative analysis of a trend then the number reduces down to 368 trend tests per site with 18 expected by chance and seven, which I'll go into in a minute, which were found to be significant by the EPA.

And the strongest trend the EPA reported was 002 and that is also consistent with what you'd expect by chance. Now some people have

expressed a concern that the numbers are so different between expected and observed. But in all honesty, I'd have to say the differences aren't as big as those numbers would indicate. For example, you had just heard the previous speaker say that of the 15 studies there was one rat study that shouldn't have been counted. I took the tumor out of that study.

Another more subtle difference is that the trend test, because of the discreteness of the data, is not really operated at exactly the five percent level. And I've done a lot of work to confirm this for these data. It's operating overall at about the four percent level. You apply both of those adjustments to that 18.4 and it comes down to 13.5. And you heard Dr. Crump yesterday said that he had found some significant trends that the EPA has not reported as significant, but he had found them.

Now I can't independently confirm that, but I'm saying it's at least a possibility that those seven observed trends might increase slightly. But all that's doing is bringing the numbers together. You can jiggle those numbers a little bit to bring them closer together. But the important take home message from this is that all these significant trends

that you are seeing in the Glyphosate data are totally consistent but with what you'd expect to see by chance because of the multiple number of tests being assessed in each study.

I'm going to focus now on the answer to the second of my questions. Okay, there were seven significant effects which are less than chance but are they the same tumor over and over again? And if they were that might be cause for concern. But you see they're in seven separate studies, different sex, species groups, seven different targets sites. None of them replicated and the EPA did not consider any of them to be compound related.

In contrast, another analysis which I'll be discussing later, found three of these that he felt were significant: the thyroid tumors in the female rat which I'll discuss momentarily and the malignant lymphoma and hemangiosarcoma in the male mouse which I'll also be discussing. One tumor you don't see on this list is kidney in the male mouse. That's because when analyzed appropriately none of the trends were significant at five percent despite the contrary claims. I'll also be talking about that momentarily.

The answer to the three questions. First key question, does the overall frequency exceed what would be expected by chance? No. What about there being a consistency of target sights? No. And finally, is there one or more trends that are so strong to statistically they'd be unlikely to occur by chance? No. My conclusion is that Glyphosate is not carcinogenic in mice and rats. And the significant tumor trends you see are absolutely consistent with what you'd expect to see by chance.

Now going into the second part of my talk. There have been other evaluations of the same data, that some of which agree with my conclusions and some of which do not. Both Dr. Robert Terone and Chris Portier are internationally recognized experts in the field with much experience with rodent cancer studies. Dr. Tyrone examined the data focusing on the mouse because that seemed to be the species of interest. He concluded that there was no convincing evidence that Glyphosate renal tumors, lymphomas, or hemangiarcarcomas in the male mice. Now Dr. Chris Portier in his analysis reached a very different conclusion. There's very strong evidence in mice for these three tumors and oh by the way the thyroid

tumors in the female rats should be a positive finding also. Now, since Dr. Terone's conclusion agrees with my conclusion, the EPA's conclusion, the EFSA's conclusion and the BfR's conclusion Chris seems to be sort of the odd man out here.

And I want to go in a little more detail into his analysis partly because the panel was sent the results of his analysis and you've probably had a chance to look at it. And I anticipate there may be public comments later on his analysis since he found such a different result from the rest of us. And so, I'm going to spend the rest of my time looking more closely at what he did. The first thing you have to understand is that his trend test that he used was an approximate trend test. And it's well known that an approximate trend test exaggerates the significance considerable, particularly for rare tumors, as much as ten times.

A ten-fold difference in p-values relative to the exact test. In fact, when applied to the kidney tumor data in the early 1983 study, one tumor only in the high dose group by Dr. Portier's test is a significant trend. And two tumors as we'll see later is a highly significant trend. But as I

mentioned earlier you need a critical mass of three tumors really for an exact trend test to be significant. His test is greatly exaggerating the significance and that needs to be kept in mind.

And his p-values for the same tumors were different than the EPA. And it led Dr. Portier to the mistaken conclusion that the EPA was doing two-sided tests rather than one-sided tests. But that's just not true. The EPA clearly stated in their written comments, "We did a one-sided Cochran-Armitage test." And yesterday they stated verbally that it was an exact test. And I'm pretty sure that's what they did. What Chris was confusing was not a difference between one tailed and two tailed test, it's a difference between an exact test and approximate test.

The EPA was using an exact test and Dr. Portier was not. Now Dr. Terone independently pointed out in his written comments what Dr. Portier was doing with his approximate test. And Dr. Portier responded that, yeah, I agree with Dr. Terone that in cases where tumors are rare the approximate p-value can overstate the significance. Which is a real understatement. But he continues to assert, yeah, yeah, but even with the exact tests, my three tumors,

they are still significant when pooled -- and I'll talk about the pooling in a minute, but actually it does make a difference.

Consider the application of the approximate and the exact trend test to the kidney tumor data. Here is the kidney tumor data. And some of these results the approximate test results were reported in the presentations yesterday. That 002 trend in the Sugimoto study, I saw that flagged with an asterisk in this case as highly significant but it's not significant. None of those three trends that Dr. Portier reported as significant by his approximate tests are significant by an exact test.

And Dr. Portier admits that. He recalculates all of his kidney tumor rates by an exact test and now says yeah, yeah, yeah, none of them are really significant but overall it is significant. But what he fails to realize is that among other things the Atkinson study -- Dr. Terone independently pointed out, the most significant trend in his kidney tumor data is the decrease in the Atkinson study. If you did a one tailed test in the opposite direction that would have been a significant trend. And these other three trends are upward but they're not significant.

And the Kumar data wasn't even considered by the EPA because I think there was an infection or something in that study. That study was not part of the EPA evaluation. If you take that study out look to see what you have. You have two studies where there was a very slight, marginally, barely, not significant increase in kidney tumors. You've got one where there's a significant decrease in kidney tumors and one where there were no kidney tumors at all. I think most interpretations of that pattern of response would be no conclusive kidney tumor effect overall.

Dr. Portier's evaluation of the same data when he pooled by his test the upward trend is significant at the 001 level. And I just don't believe that when applied to this data. And I have the same feeling when he does a pooled analysis of the malignant lymphoma and hemangiosarcoma. And this just repeats what I said. Note that none of the three kidney tumor trends were apparently significant buy an approximate test or significant by an exact test. And the strongest and only significant trend is actually an inverse trend. Now another problem had to do with his use of the Poly-3 test.

The Poly-3 test is a very useful test. The NTP uses it to evaluate its cancer studies and when properly applied it can be a very nice tool to use. What it does is it adjusts individual animal's contribution to the tumor rate by taking into account their survival. And the animal is weighted differently depending on how much of the study he survived. The longer he survived the more he would be at risk for getting the tumor. That's a very useful test to analyze data within a study. And as I say the NTP uses it all the time.

But it does require individual animal's survival data because you're adjusting the survival for each individual animal. And it's really not designed, as Dr. Portier uses it, to extrapolate survival differences within one study of 18-months which might be bad animal's natural lifetime to a 24-month study which may be longer then the animals in the 18-month study would be expected to live. But that's another issue. But what does he do for his Poly-3 rates? He doesn't have individual animal data so he adjusts them in the following way.

He assumes in the 18-month studies that all of the animals, the tumor free animals, survived

to the very end of the study, 100 percent survival in all four groups, and adjusts the 18-month rate based on that assumption. Well I've never seen a bioassay with 100 percent survival across all the groups. I don't think that adjustment means very much. What's his Poly-3 adjustment for the 24-month studies? There is none. There's no adjustment at all. He calls it a Poly-3 rate but it's just an observed rate.

And you can confirm that by looking at his tables two, four, and six where he compares the trend for the adjusted to the unadjusted. For the 24-month studies, they're exactly the same p-value every time. And that's because he's not adjusting the rate. I think that's at the very least misleading to call it a Poly-3 rate when it's really not a Poly-3 rate. I guess that's enough on Poly-3 for now. Now let's consider his interpretation of the data itself. He considers the thyroid C-cell tumors in female rats in the Stout study to be a positive finding. There's the data, two, two, seven, and six. He calls that a clear dose-response.

Well it is significant, I'll concede, at the four percent level. It's not monotonic. The concurrent control rate is abnormally low. The normal

rate in controls is about the same rate seen at the high-dose. And this significant trend, if that's the best he could produce in hundreds of trend tests in the rats, I think most people would conclude that that is a false positive. That's exactly the sort of result that would be a false positive. And that's the only positive result that he claims exists in the rat data.

Now the mouse data is a little bit trickier because there are three tumors that show hints of effects in certain studies. And what he does to convince you that these are real effects is that he combines the data. He looks at two sets of rates which he combines, just literally pools them over the studies. The first one is analysis of what he calls observed or original rates. You've got two 24-month studies and three 18-month studies. And he just takes those and puts them together in one giant dose response.

And you just cannot combine 18 and 24-month studies. They may have very different tumor rates. They're not comparable. You can't combine them. And then he does a second analysis of the Poly-3 rates where he pools over the studies the Poly-3

rates which are those flawed Poly-3 rates from the 18-month studies based on the assumption of 100 percent survival. And the observed rates which aren't even Poly-3 rates from the 24-month studies. And that pool of unrelated tumor rates is also not very meaningful.

And then he's left with a trend test based on one control group and 15 doses because none of the doses were repeated. He's got now, by lumping them together, 15 doses in a control. He simplifies this in some of his analyses by taking five of the doses and pooling them together. For example, he treats a 15 mg per kg dose in strain one in in an 18-month study as equivalent to 20 times that dose, 300, in strain two, a different strain in a different duration study, 24 months. That's apples and oranges and tangerines. You can't combine the doses in the way he does either.

And it's just improper to pool data over different strains. I mean he's got different strains, he's got different labs and different timeframes. The data covers a 26-year time period. You've got data from 26 years apart and he's just lumping them all together. So in my humble opinion this analysis doesn't mean anything. But even if it

did, even if it did and the three pooled analyses are significant there are over 80 different tumor types that you could apply this pooled analysis to. I enumerated some of them.

You've got 80 candidates for this funny pool trend test and you've got three out of 80 that are significant. Well that's what you'd expect by chance. Once again after this elegant analysis, even if it's correct and I don't think it is, all you'd have is what you'd expect by chance. And he also does this relative to historical control data. And he misuses that too but I don't have enough time to talk about that. But I will bring up just the proper use of historical control data which applies not only to Chris' stuff but also to the EPA.

And I'm just going to tell you what I think the principles are and you can judge how they're being applied. First of all, the concurrent control group is always the most important control group. I think everyone agrees with that. However, historical data can be useful in some instances to help interpret effects but it's got to be used with caution. And the trick is finding data that are truly comparable to the study in question. And that can be a difficult thing

to do in some cases. And the sort of things you have to keep in mind and look for are, for example, surely the strains should be the same.

You shouldn't pull data over different strains, you can have very different tumor rates. The same lab ideally and the same timeframe. You don't want studies 22 years apart. For all these reasons the NTP, it cites historical control data in its appendices of its technical reports and it refers to it informally. It's part of a weight of evidence factor when making a conclusion but they don't do any formal test and there's a good reason for that. I think it's because the uncertainty as to the comparability.

I think you use historical data with caution. There are two other things that directly relate to how people have used historical data in these studies. The study duration should be the same. You cannot combine 24-month and 18-month historical control data and call that a proper historical control group. You can't do that. The more subtle thing has to do with pathology protocols. And by that I'm referring to the Knezevic study. And I apologize for misspelling his name. He, you'll recall back in '83,

the ’83 study evaluated kidney tumors and went to extraordinary lengths to find tumors.

They had the original exam, that's fine. Then they said well maybe we missed something. Let's go back and look a second time extra hard with a fine-tooth comb. And low and behold they found another tumor in the control group they’d missed from their routine examination. Then they said well, maybe we'll find more let's do a step section. They went back and did a step section looking for more tumors. And that level of rigor is not reflected in the historical control data unless you go back with the historical control data and do that same thing, look at it especially close and then do a step section.

It's not appropriate in my view. And that study is an example to compare those tumor rates to a historical control group that didn't go through all of the rigor that was done in this study. And I'm sure there are other examples that could be pointed out. But my long-winded talk is about over. My conclusion from all this was as I said before that I think a proper statistical analysis of the Rhoden data supports the conclusion that Glyphosate does not cause tumors in rodents.

DR. JAMES MCMANAMAN: All right. I think we'll open this area up for questions. This is related to the animal cancer bioassays. And so, we can have questions for doctors Bus and Dr. Haseman. Dr. Johnson?

DR. ERIC JOHNSON: Thank you, Dr. Haseman for so elegantly stating the caveat about use of historical controls. I think many times we overlook what you just said, that we should treat historical controls with caution. Now I have a couple of questions. When you look at the expected numbers of trend tests that's expected, that 28, and you observe only 11, I'm thinking if it was the other way around and we observed almost three times as many significant traces, so around 80, which were trend positive as the 28 expected we would have said this is not due to chance.

DR. JOE HASEMAN: If those numbers had been reversed that would have been strong evidence that there were some carcinogenic effects tucked away. And then you'd look at the 28 that were significant and try to figure out which ones were showing similar trends, which ones were very strong, and so forth.

And so, if had been reversed there would definitely be carcinogenic effects.

DR. ERIC JOHNSON: My question is, now that we get much less than what we expect by chance what's the interpretation for that? Is it a support of no trend at all or is it a red flag that there may be something wrong with the studies?

DR. JOE HASEMAN: What I honestly think is it, as I told you I could have decreased, in fact it did, when you take into account that one study that was excluded and you take into account that the trend test is not really operating at the five percent level that number drops from 28 down to a much lower number. It goes down to 20. I think Dr. Crump can tell you perhaps how many extra trend tests he thought he found that were significant that the EPA didn't report. But I'm thinking not only is the 28 too high it's probably more close to 20. But the 11 may be too low and it may be up to like, you know, 13 or 14.

What I'm saying is I'm not real concerned about the magnitude of the difference between expected and observed because I don't think the actual difference is as great as my calculations indicate for the very reasons that I said. I think

the observed is being slightly under reported and I think the expected is being over reported. And I tried to adjust that down to take that into account.

DR. JAMES MCMANAMAN: Dr. Crump?

DR. KENNETH CRUMP: Yeah. Dr. Haseman, I think your emphasis on trying to correct for these multiple comparisons is a very important problem. I appreciate your work on that. I think you could have gotten a little bit more accurate answer if you had looked at the number cases you had three tumors, the number of cases you had four tumors rather than just looking at the total number of tumors that were enough that you could get significance.

DR. JOE HASEMAN: I did do that and that was how I came up with the four percent. There were about 10 percent of the data had three tumors. And the exact p-value for those 10 studies was like 015. You probably calculated that. You get 015?

DR. KENNETH CRUMP: I think so.

DR. ERIC JOHNSON: And then another 10 or 20 percent had four exact tumors. That p-value was getting close, depending on the doses because most of these doses weren't equally spaced, that p-value was up around four percent. And then I looked at five

tumors and six tumors and the p-value started to stabilize at about 043. Anything above the 10 percent where it was low when you take a weighted average of 10 percent by 015 and then 90 percent times 043, that's how I got my 04. But I did consider how many threes there were and fours and fives and sixes.

DR. KENNETH CRUMP: Okay. Good. I did something similar to what you did. I only looked at three, I got tired of trying to read all that data, only looked at three studies. And just per study I got an average of between one and two positives per study. Which I think would be pretty close to what you came up with overall for that.

DR. JOE HASEMAN: We can go over our calculations in the break because I brought them with me if you want to. But I think the key point is we can fine tune these numbers but we can't escape the fact in the totality of the Glyphosate studies what we see as significant is consistent with chance. And we can tinker with the observes and expected and bring them closer together or a little bit separate but there's no way you're going to get a situation where there's more significance than you'd expect by chance.

DR. KENNETH CRUMP: Just a couple of other questions. You said you have to have three animals to have significance. Is that contingent on having four dose groups? If you have five dose groups is it still three?

DR. JOE HASEMAN: Yeah. The only case I really looked at I admit were three doses in a control because that's what most of the studies were.

DR. KENNETH CRUMP: They do have one that has five dose groups. I think it would be two.

DR. JOE HASEMAN: That's right.

DR. KENNETH CRUMP: For that one. What this is all trying to do is to correct for the multiple comparisons. But there are tests that you can actually apply to get a true p-value that corrects for the multiple comparisons by doing kind of a randomization test. I just wondered if you thought that might be an even better way to handle the --

DR. JOE HASEMAN: Well in light of what I found using my approach I would be happy to discuss this other test with you. But I would be astounded if it came to any other conclusion than what I came to.

DR. KENNETH CRUMP: It would just give you a more accurate overall p-value than just for the whole study.

DR. JAMES MCMANAMAN: Dr. Jett?

DR. DAVID JETT: Yeah. Thanks. That was really informative. This is Dave Jett. I guess my original question was a couple talks ago about the idea of having significant trends in the absence of any significant pair-wise comparisons. But I think your talk has brought me to another question. And that is this interesting idea of chance effects. In your denominator, when you're just looking at chance of probability, is it proper to pool all of the studies together? Or should you just be looking at renal tumors as the denominator, which would be far fewer studies?

DR. JOE HASEMAN: Well I think if I'm understanding your question it's appropriate to get a global picture of the false positive rate to look at everything. And then you can also focus in on certain tumors. But as I said there are 80 different tumors you could focus in on. If you focus in on renal tumors and do some analysis and find it significant that's again one out of 80. You could do all these

other things with adrenal tumors and pituitary tumors and all that. It would depend exactly what you're talking about.

You could bias yourself by weighting and looking at the data and saying, oh, these two or three tumors look impressive. There's no reason I would think a priori they would be there but by golly they're significant. I'm going to do something extra with them. And you just have to be careful. You just have to be aware of the fact that there's so many tumors out there that you could have found that effect for. That unless there's some reason that that particular tumor a priori was suspected for example as a target site I don't think there's any reason to do any special focus on it independently of the multiple comparison issue.

DR. JAMES MCMANAMAN: I think we're going to have to draw to a close there, because we're running a little short on time. We have about 50 minutes left for the Monsanto group to present. And if there's any time following the last final two presentations then we'll open it up for additional questions. I think the next presenter is Dr. Kirkland followed by Dr. Reiss.

DR. DAVID KIRKLAND: Thank you. Yes. Good morning. You heard quite a lot yesterday about the genotoxicity of Glyphosate. And I don't propose to go through the data in detail again. But what you also heard yesterday were about studies that were included, some were excluded, some were high weight, some were published, some were unpublished. And what I'd like to do is take a deeper discussion of how to apply a weight of evidence approach in the evaluation of genotoxicity. And this comes from the expert panel that Donna Farmer mentioned in the introduction which was published.

And I'll go into the details of that a little bit later on. I'll discuss the approaches to weight of evidence evaluation that we recommended in that publication and the conclusions that we reached on the genotoxicity of Glyphosate and compare those with the EPA approaches and the EPA conclusions. I hope I've got this correct from Dr. Ackerman's presentation. My apologies if there are any errors. The approach that EPA used took into account genotoxicity data from multiple test systems and end points.

But the assessment focused on those systems that the agency considered the most relevant for assessing genotoxic risks in humans. Although the totality of the genetic toxicology information was evaluated, a weight of evidence approach involves integration. Looking across both in vitro and in vivo results and an overall evaluation in particular of the quality, consistency, reproducibility, magnitude of response, dose response relationships, and relevance of the findings.

What this means is that studies evaluating gene mutations and chromosome elaborations, i.e., manifestations of permanent DNA damage are given more weight than DNA events that may be transient or may be reversible. For example, DNA strand breaks as measured in the comet assay. And in vivo studies in mammals were given the greatest weight. And in addition, more weight was given to doses and routes of administration considered the most relevant for evaluating genotoxic risk based on human exposure. And in a nutshell, we believe that that was a sound approach.

Just to summarize the EPA conclusions so that I can come back to them at the end. No

convincing evidence that Glyphosate induces mutations in vivo via the oral route. When I.P. injection was used, there were some positive but predominantly negative micronucleus studies. In the two cases where an increase in micronuclei were reported by the I.P. route the effects occurred above the reported I.P. LD50 and were not seen in other I.P. studies using similar or higher doses. There was limited evidence for questionable genotoxic effects in some of the in vitro experiments.

I'll come back to the questionable in a later slide. But when looking forward from in vitro to in vivo for the same end points the in vivo effects were predominantly negative. And therefore, since they were given more weight there was no verification of the positive in vitro results. And that is a consistent approach in terms of OECD guidance. The only positive findings reported in vivo were seen at relatively high doses that are not relevant for human health risk assessment. Those were the EPA approaches and conclusions.

Let me know just mention this genotoxicity panel was one of four and the other panelists are also genetic toxicologists each with

several decades of experience. What we did was, we reviewed all of the genotoxicity data including all of the regulatory GLP studies. And that report, David Brusick is the first author, has been published in this special issue of Critical *Reviews in Toxicology*. But again, in a nutshell, our approach and conclusions were actually very similar to those of EPA. So where do we start?

Well when you have a chemical like Glyphosate which has been through such extensive testing you end up with a massive database of studies, you heard yesterday, depending on where you look but certainly over 100. And those studies will be on different end points, varied test systems, different exposure methods. But then you find that the common tests have actually been repeated on multiple occasions. You've got multiple entries for the same end point in the database.

A really rigorous and systematic and critical approach to an evaluation of such a complex and extensive database is required. And in order to do that, you have to take into account that different cell types have different levels of accuracy in terms of predicting a genotoxic effect, or predicting a

human hazard. The p53 status, the karyotypic stability, the DNA repair capacity, whether the cells are from a rodent or a human origin all have an impact on how much confidence we can place in the results from those kinds of studies.

We know there's been a lot of work over the last 11, 12 years to try to reduce the number of misleading positive results that we get in particular from in vitro mammalian cell tests. And when you've got such a large database you're going to see some of those misleading positive results. They might be due to the fact that the test system say is a p53 deficient aneuploid rodent cell line. They may give positive responses with noncarcinogens. There is the non-predictive component to misleading positive results.

We may get a genotoxic effect due to indirect consequences of extreme conditions such as high cytotoxicity, high osmolality, low pH. Although generally we can control for some of those. Or we may get misleading results due to technical difficulties. In a weight of evidence approach the test methods, the test systems, and the end points should be assigned a weight that is consistent with their contribution to

the overall evidence. We came up with different categories of evidence weighting based on the following.

Different assay types should have different weights. You've already heard this from EPA yesterday from Dr. Akerman and from others. And it is strongly stressed in the recent OECD overview of the genetox test guideline revisions. The tests measuring permanent genetic changes such as mutations and chromosome damage should have greater weight than indicates tests that only measure, for example, DNA strand breakage. DNA strand breakage is a very early event in the mutagenic process.

And we don't know whether those strand breaks are going to be effectively repairs, whether they're going to be lethal, or whether they're going to turn into heritable mutations. They should be given less weight since they have a higher degree of uncertainty. The aggregate strength, the robustness of the protocols and the reproducibility are important. Studies conducted to GLP and according to OECD guidelines should have greater weight than studies lacking these attributes.

I just want to spend a minute or two on this because this talks to some of the questions yesterday about published versus unpublished. And I think it's worth just clarifying exactly what it means when a study is said to be GLP compliant. To do that a laboratory has to have a quality assurance unit which is part of a quality assurance program. That unit reports to management only and it monitors everything the laboratory does. The first thing is that a protocol has to be generated, which will address the objectives of the investigation.

The lab staff have to record absolutely everything in meticulous detail, dates, times, weights volumes, dilutions, speeds, temperatures. So that the study can be completely recreated if it's necessary. And the QA unit has to audit critical phases of the laboratory work. They also have to inspect that any results are being recorded properly. And then they have to audit the report to make sure that the results that are in the report reflect the data that are in the raw data files. This is a level of detail which you will never find in a publication.

Moreover, all of that review occurs before the reports ever reach the regulatory agency

where there is going to be another level of review on the quality of the study. We believe, and I think EPA took the same position, that studies conducted to GLP should have a considerable weight. Even though in many cases they may not be published, they may not have been through the peer review process of a journal publication, they've been through a very extensive set of reviews both at laboratory level and agency level. The number of pieces of evidence within a category also influences the weight.

If we have a majority of studies giving us concordant findings and we then find the odd study that gives a discordant finding that that should be sufficient to alter the direction and the strength and the weight of evidence. It's very tempting sometimes to say, well, I want to believe the positive result amid all these negatives. And we should be careful of doing that. And tests with greater relevance to humans should carry greater weight. You also heard this yesterday.

Data from in vivo tests are much more predictive of potential human hazard. They're much less susceptible to misleading results. They should carry more weight than data from in vitro tests or

from non-mammalian tests other than the Ames test which is considered to be predictive of potential human hazard. We put together a grid. We turned those approaches into four categories which I'll show you on a grid in a moment. Negligible weight was attributed to end points that are not linked to any adverse event that's relevant for carcinogenic hazard or risk.

And the only one that really fell into here was sister chromatid exchanges because we don't understand how they're caused, what is the biological relevance, and there is no longer an OECD guideline. Low weight was attributed to end points indicative of primary DNA damage which could be reversible and to other events not unequivocally linked to tumorigenic mechanisms. Moderate weight was given to those cases where the endpoint is potentially relevant to tumorigenicity.

But maybe the subject of secondary threshold dependent mechanisms such as in the case of cytotoxic plastogens or aneugens or in those cases where the test system exhibits a high rate of misleading positives with respect to carcinogen prediction. And the highest weight was given to those

end points demonstrated with a high level of confidence to play a critical role in the process of tumorigenicity. We put this grid together but I'm only going to focus on those studies in the high weight category for the rest of the talk.

Basically, those are in vivo, micronucleus, chromosomal aberration, gene mutation studies, and the Ames test. Now we included 44 mainly GLP studies that we had summarized in a paper in 2013, myself and Larry Kier. Those had not been reviewed by IARC but we believe they should have been considered. And from what I heard yesterday from Dr. Akerman I believe they were considered by EPA. And that's very encouraging. Why do we believe they should have been considered? Because detailed summary tables were provided each study was stated to have been conducted to GLP.

Almost all of the studies followed the relevant OED guidelines applicable at the time. Apart from the Ames test which is not routinely analyzed, statistically we tend to use a folding crease approach to the interpretation of the Ames test. But apart from that, statistical measures were given and the level of significance was given. And we provided

detailed methodology such as the bacterial strains tested or cell type used, data on individual replicates, how top concentrations were chosen, whether cytotoxic effects occurred, numbers of cells scored, doses and dosing routes for the in vivo studies.

In other words, a lot more information than you see in most published papers. When we include all of those studies and the left-hand bar there is for the high weight studies you can see that the overwhelming majority of high weight studies give negative results. There are two that give positive results and Dr. Akerman discussed them yesterday. Our conclusions were that yes, if you pay particular focus to the low weight studies then a lot of them are positive, five out of seven. But as we've already discussed in a rigorous weight of evidence approach they are low weight.

They are most likely to yield misleading positive results and they are the least clearly associated with the cancer process. The high weight studies were overwhelmingly negative, two out of 39 were positive and those were the two in vivo micronucleus studies or it's one micronucleus and one

chromosomal aberration. And there are questions regarding both of those in terms of their consistency, their biological relevance, the biological relevance of the result, and what exactly were the authors measuring.

Two out of 39 high-weight studies, and there are question marks even about those two positives. Just to summarize in a few words, Glyphosate is not electrophilic. It does not trigger any structural alerts in databases such as DEREK. No structural alerts for chromosomal damage, genotoxicity, mutagenicity, or carcinogenicity.

The 20 Ames tests on Glyphosate itself were negative. And by the way there's a lot of data on GBFs as well. And GBFs show pretty much the same pattern as Glyphosate does. We covered the formulations in the Brusick, et. al. paper and in the Kier and Kirkland 2013 paper.

Glyphosate does not induce gene mutations either in mammalian cells in vitro. It does not induce chromosomal aberrations in vitro or in vivo. There are a handful, four I think, positive in vitro micronucleus studies with Glyphosate. I put the word questionable there because three out of those

four studies were only positive in the presence of metabolic activation. And yet as you heard yesterday Glyphosate does not undergo extensive metabolic activation. Those results lack plausibility.

But even if those positive micronuclei results are real, why do we see micronuclei but not chromosomal aberrations in vitro? Is this a reflection of the fact that we score more cells in an in vitro micronucleus test because we can, because it's easy? And therefore, there is increased statistical power. Or is it telling us something about mode of action? Are we seeing aneuploidy leading to the induction of micronuclei, which would not lead to the induction of chromosomal aberrations?

Either way, whatever might be the explanation for those micronucleus responses in vitro as we've just discussed, there is strong evidence the vast majority of in vivo micronucleus tests even using the I.P route are negative and those that are positive are highly questionable. There is some evidence that Glyphosate can induce strand breaks in vivo. But the one study that's looked for DNA adducts didn't find any DNA adducts. Those strand breaks are not due to a direct interaction with the DNA.

And when we look in vitro we find again evidence of strand breaks but generally only under cytotoxic conditions. It may well be that the strand breaks in vivo are also a consequence of cytotoxicity. Either way those strand breaks do not lead to chromosome breaks because we don't get any chromosome elaborations in vitro or in vivo. There is no evidence that Glyphosate induces DNA repair, unscheduled DNA synthesis. Some reports of sister chromatid exchange; but, as I explained earlier, we gave those negligible weight.

It's not a recommended endpoint anymore and we don't understand the biology or the relevance of induction of SCE. Now just to spend a moment on non-mammalian studies because there's quite a lot of non-mammalian studies, I'm not talking about the Ames test here, in fish, reptiles, plants. Quite a lot of studies on Glyphosate that are in the public domain. These are not GLP studies. Many tests used unusual, nonstandard methods of treatment of exposure. Emersion in or surface contact with the test material. There are no international guidelines for such non-mammalian test systems.

And therefore, they are difficult to evaluate. The latest revisions to OECD guidelines make recommendations about test systems and they state specifically that if you want to use a nonstandard test you really need to justify it very carefully and have stringent validation data. Including the establishment of robust historical negative and positive control databases. You can clearly determine whether the test is performing well on any given day.

Now there are no databases of negative and positive control data on which to be able to judge the performance of these nonstandard tests in fish and amphibians and so on. And there are no results from validation studies that give us any indication as to whether the outcomes of those non-mammalian studies have any concordance with carcinogenicity. We decided that data from such nonstandard tests should not have significant weight in the overall genotoxicity evaluation and if I understood correctly the EPA actually excluded those studies for the similar reason.

I want to just take a minute on biomonitoring studies because this was raised a little bit yesterday. And I'm not talking about

biomonitoring in the sense that Dr. Acquavella did earlier this morning. This is about monitoring populations that have been exposed in terms of genotoxic endpoints. Because our expert panel believe that such studies can offer highly relevant information as long as they are rigorous. I'm going to briefly discuss three biomonitoring studies. The Koureas, et. al., 2014 study was mentioned yesterday.

That didn't measure a genotoxicity endpoint, it measured 8-hydroxydeoxyguanosine residues, i.e., evidence of oxidated stress. And Dr. Bus I think will touch on that when he talks about oxidative damage this afternoon. EPA assigned a low-quality ranking to these biomonitoring studies because there was a lack of exposure information on Glyphosate from the subjects that were sampled. And there were no quantitative measures of association between Glyphosate and a cancer outcome. We decided to actually discuss those studies and these are the three:

There's a 2007 paper from Paz-Y-Mino, et. al., which looked at the comet assay in humans exposed to GBP formulation spraying. There are some rather disturbing comments in the paper. One, that

the GBF application rate was reported to be around 20 times higher than recommended. But a large number of the exposed subjects showed signs of, and I'm almost quoting from the paper her, clinical toxicity consistent with acute intoxication. Now even at 20 times the recommended application rate you wouldn't expect to see acute intoxication. That doesn't make sense.

And we're not really sure what is behind that. The DNA damage that they found in that 2007 paper may be nothing to do with Glyphosate. Because you have to speculate that there must have been some other exposures leading to that acute intoxication. Either way, the damage could be due to the toxic effects rather than the inherent properties of whatever they were exposed to. More importantly, Paz-y-Mino followed up a couple of years later, the paper then appeared a couple of years after that and went back to the individuals from the same spraying areas and could not find any increases in chromosomal damage or chromosomal changes.

Whatever the DNA damage was due to back in 2007 it didn't become converted into identifiable chromosomal changes. Was it biologically relevant?

And the final study is a micronucleus study from Bolognesi, et. al., in 2009. They reported a small transient and inconsistent induction of micronuclei in individuals in three different GBF spray areas. Keith Solomon managed to isolate the data from self-reported spraying exposures. And the micronucleus frequencies compared with the different types of spray exposure or no spray exposure absolutely on the background noise. There's no differences whatsoever.

And that's probably what Bolognesi, et. al. meant by inconsistent. And they in any case concluded that the data suggested that any risk was low. We did review those biomonitoring studies but as you can probably tell our conclusion was that there was little or no reliable evidence that would suggest that DBFs across a wide range of end user exposures pose any human genotoxic risk. Finally, just to compare the properties, the pattern of results that you get with a known genotoxic carcinogen and the patentive results that you get with Glyphosate.

The left-hand column is the characteristic, the middle column is what you would expect to see with a genotoxic carcinogen, and the right column is what you see with Glyphosate.

Genotoxic carcinogens generally give positive results across multiple end points, not just a single endpoint. You generally find that they produce gene mutations, chromosomal damage, micro nuclei in vivo and in vitro. We do not see that with Glyphosate. Genotoxic carcinogens generally have structural alerts, Glyphosate doesn't.

Genotoxic carcinogens generally bind to DNA, they are electrophilic, Glyphosate doesn't. Genotoxic carcinogens tend to give reproducible results when the same study is repeated, Glyphosate doesn't. The results are non-reproducible, inconsistent, conflicting. Genotoxic carcinogens tend to give dose response or dose responses across a wide range of concentrations or exposure levels, Glyphosate doesn't. It tends to be the odd dose usually, perhaps a high dose, if it's giving a positive response at all.

And genotoxic carcinogens typically give positive responses at non-toxic concentration and Glyphosate doesn't. If it's positive, it's generally only under toxic conditions. So as in blue at the top of the slide there you look across these patterns there is virtually no concordance between a typical

genetic carcinogen and what we see with Glyphosate. From a critical weight of evidence review of all of the data on Glyphosate we agree with the EPA's conclusion that there is no evidence that Glyphosate poses a genotoxic hazard.

Just to pick on one or two of the sub questions within charge question four. As you can see, I think we followed very similar approaches in terms of how weight of evidence was approached, different types of studies included, excluded, given more weight et cetera. And we've reached similar conclusions.

We agree with EPA in terms of the relevant genotoxicity studies that were reviewed, the appropriate identification of the studies to be reviewed, a focus on the active ingredients not on formulations because of the complications of surfactants, the exclusion of a large number of non-mammalian assays, these are the plant, fish, amphibian type assays. And there was a complete exclusion of five studies because of faulty design which we didn't even look at because they're very old and certainly not robust.

We agree with EPA's reliance on in vivo studies as being more relevant to humans and that in vitro studies, apart from the Ames test should be given less weight. That whilst negative results in vitro provide assurance that you're not likely to see genotoxic effects in vivo, if you see positive results in vitro they really need to be checked to see whether they can be confirmed in vivo. And finally, I have to apologize, I'm afraid there's been a deletion and a frame shift mutation on this slide during the final edits.

I don't think it was spontaneous, I think it was induced by fingers that would not stay under control. Just to finish off we agree with the EPA regarding the relevance of the genotoxicity findings with respect to dose and route of exposure. Oral studies given more weight than I.P. Here's the deletion. It should say there was some positive I.P. micronucleus studies but they were outweighed. The results were inconsistent with five other studies that were negative at equal or higher doses.

And of particular note, is the NTP study, this is 13 weeks of dosing of over 3,000 mgs per kg per day looking at hundreds of thousands of

erythrocytes by flow cytometry and finding no induction of micronuclei. That was impressive data. The strengths and uncertainties associated with the weight of evidence and conclusion. Yes, some studies report positive genotoxicity but they are mainly seen in the negligible or low weight categories or with the I.P route of exposure. We believe that the weight of evidence approach, the conclusions of EPA are scientifically strong.

And that the data supports that Glyphosate is not an in vivo plastogen or genotoxicant. And that conclusion is not only in line with our expert panel report, Brusick, et. al. but also with the JMPR conclusions. And I won't waste time reading that at this moment. Thank you for your attention.

DR. JAMES MCMANAMAN: Thank you. I think we'll move on to Dr. Reiss.

DR. RICK REISS: I'm going to give a brief wrap-up and also comment briefly on the cancer classification. The Cancer Guidelines that EPA uses emphasize a weight of evidence review. And I won't read that quote but the bottom line is it emphasizes a weight of evidence review of all the available data.

What we have seen today is I think basically a weight of evidence review of all the individual lines of evidence including the epidemiology, the Rhoden data, and the genetox. And you could think of the classification as a weight of evidence of all those weights of evidence.

And I think if you see the conclusions from our weight of evidence reviews, the plain language without reading the guidelines in any great detail the plain language conclusion would be not likely to be carcinogenic. I'm going to briefly review some of the things we've talked about today just as a quick reminder. We had a Rhoden carcinogenicity across 14 available studies. And I should say we have 15 of these slides because we discovered the one study that wasn't applicable to Glyphosate about an hour before we had to deliver our slides so we couldn't fix that. We apologize.

But EPA did a very good analysis showing no compound related tumors in individual studies, lack of supporting evidence for carcinogenicity including dose response, progression, et cetera. Also, very importantly with this large database we saw no consistency across a large number

of studies. And I think we added to that with Dr. Haseman's analysis which did a rigorous multiple comparison analysis to show that there are no more expected statistically significant trends than you would expect by chance.

Dr. Kirkland just explained that the weight of evidence shows that Glyphosate is not a genotoxicant. It's positive in only two of 29 high weight studies and it shows none of the characteristics of a genotoxicant. We also showed a weight of evidence review of the epidemiologic data does not support an association for NHL. A few things that I think Dr. Acquavella added to the EPA analysis is that Glyphosate occupational exposures are extremely small due to its physical chemical properties.

Also, there are potential biases from many of the case control studies that limit their informativeness. And the only cohort study, the ag health study, showed no association. And I think importantly, Dr. Acquavella showed that there are more days of Glyphosate use in the ag health study than the case control studies. And that adds to the usefulness of the ag health study versus the case control studies

beyond the normal issues that you deal with with cohort versus case control studies. EPA has some criteria.

It's a long document in the Cancer Guidelines. But they list some criteria that you can use to decide what the appropriate classification is. EPA kind of boiled down their analysis to whether it's suggestive or not likely. And here are some of the criteria for a suggestive association, and I should say that a lot of these you'll see they point to a database where you'll probably have two Rhoden studies and maybe a limited genotoxicity database.

And you have some findings that you can't resolve any further with the available data that you have. The first you see you find a small and possibly statistically increase in tumors that's not contradicted by another study. Well we have 14 different studies so we're able to do that replication analysis. That wouldn't be applicable. The next one you see a small increase in tumors but insufficient evidence that they're not due to intrinsic factors, et cetera.

Again, we have a large database and EPA's individual analysis showed that none of the

individual studies showed any observed tumors. And then that large database that shows no replication. The next one, a positive response in a studies power, design, or contact limits the ability to draw a confident conclusion. Again, with this large database for Glyphosate, 14 Rhoden studies, that's not applicable. And you could also point to the large, robust database of genotoxicity data here as well.

The next one, a statistically significant increase of one dose but no significant response at the other doses and no overall trend. Well here's an interesting thing, in EPA's analysis there was one study with a significant increase at the high dose after the cited correction. And that was the Lankas study. But keep in mind that the high dose in that study was only about 32 milligrams per kilogram. And there was also an unusually low incidence in the controls and a lack of monotonicity. Interestingly though the Stout and Rueker study was a follow-up to that study to help resolve this issue, among others. That study didn't find these tumors. Again, Dr. Haseman's analysis showed that none of these statistically significant findings are unexpected given chance findings.

Moving to the descriptor not likely to be carcinogenic to humans. The first one really is the only relevant one here, lack of carcinogenic effect, both sexes in well designed, well conducted studies and at least two appropriate animal species.

We think quite clearly if you look at both EPA's analysis of the individual studies, the replication issue in Dr. Haseman's analysis, what you heard from Dr. Bus that you can say yes for that. These other criteria point to issues such as tumors being not relevant to humans but in animals or a threshold effect or an exposure route effect. And those we don't think are applicable in this case. Only the first criteria what you need to focus on. From that, we think the weight of evidence supports a classification of not likely to be carcinogenic to humans.

And we also note that that's consistent with all the other global regulatory authorities as Dr. Farmer pointed out. Thank you. I'd be happy to take questions, myself or any of the panelists, on any of the issues that have come up.

DR. JAMES MCMANAMAN: Thank you. I think we can open it up for questions to the last two

presenters or for any of the other presenters this morning, if you have questions. Yes, Dr. Johnson?

DR. ERIC JOHNSON: Eric Johnson. I'd like to ask Dr. Acquavella a couple of questions to assist us. One, the farming monitoring studies you did among farmers which showed that one outlier from --

DR. JAMES MCMANAMAN: Dr. Johnson, could you speak into the microphone?

DR. ERIC JOHNSON: Okay. The one study which you showed in your biomonitoring study of farmers in which there was an outlier, this guy had about 220 or something milligrams of Glyphosate in his urine. What is that equivalent to in terms of intake? Could you help us with that? What sort of intake would have given rise to such a level?

DR. JOHN ACQUAVELLA: I didn't get the last part of that. The 223 parts per billion in urine, what is that equivalent in terms of?

DR. ERIC JOHNSON: Intake.

DR. JOHN ACQUAVELLA: You mean how many carrots?

DR. ERIC JOHNSON: The dosage, in terms of dosage.

DR. JOHN ACQUAVELLA: Oh, okay. That's four times 10 to the minus three milligrams per kilogram. And, you know, there are outlier values that you question when you're doing analysis sometimes. That's a legitimate value. I didn't mean to call it an outlier in the context that maybe it's not a true value. It's a legitimate value, it's just very far removed from most of the other data.

DR. ERIC JOHNSON: Okay. The next question is, do you know of any other company which has conducted a study other than you?

DR. JOHN ACQUAVELLA: No.

DR. ERIC JOHNSON: None at all? What proportion of the Glyphosate market does Monsanto cover? I was just wondering if there are many other companies out there.

DR. JOHN ACQUAVELLA: Somebody else should probably take that question. It's kind of a marketing question I think.

DR. DONNA FARMER: Yeah. I don't know the exact answer. Mean we are one of the major Glyphosate registrants but there are numerous registrants all over the world. And so, we can probably get that information to you.

DR. ERIC JOHNSON: Okay. My last question to you is, was there exposure data available for Glyphosate for sufficient to OSHA, in terms of TLDs and things like that? Doesn't the company keep some exposure information which is required by law for OSHA purposes? Are those data available?

DR. JOHN ACQUAVELLA: You know, I don't know the answer to that question. There are rules that govern what kind of information has to be submitted to the government about workplace exposure monitoring and assessment. And I've just worked in the field with applicators. I haven't really worked on that kind of an issue with the manufacturing workers.

DR. ERIC JOHNSON: Okay. And finally, as far as you know, no biomonitoring study has been done on the manufacturing workers like you did on the farms?

DR. JOHN ACQUAVELLA: No.

DR. JAMES MCMANAMAN: Dr. Parsons?

DR. BARBARA PARSONS: My question is for Dr. Haseman. In your experience with NTP what is your opinion about how you interpret a study that produced three separate positive tumor responses and

how does that weigh into your evaluation? I'm thinking of Stout and Rueker. Three different responses at three different sites in one study.

DR. JOE HASEMAN: Well it would depend on the strength of the effect. You mean like thyroid tumors, liver tumors and --

DR. BARBARA PARSONS: Uh-huh.

DR. JOE HASEMAN: Well I think they'd all be looked at individually unless they were one in females and one in males of the same tumor. That would be given more weight. I think there's no general rule. I mean the weight of evidence would look at the factors such as how strong is the trend, is it seen in the other sex, is there supporting hyperplastic lesions, what's the historical control rate. Whether there's one effect, three effects or more, each one is judged more or less independently and it depends on the strength of the evidence.

Not every "significant trend" is flagged as a real biological effect. It's just a piece of the overall weight of evidence.

DR. BARBARA PARSONS: So you're saying observations of multiple tumor types in a study is not given any additional weight?

DR. JOE HASEMAN: My guess would be if you saw a marginal effect say in three unrelated tumors and you had a chance to say, well, individually none of them would be significant. But these tumors of the liver the spleen and the thyroid, because they're all together and all marginal the one thing the NTP might do in that situation would be say equivocal. They do have an equivocal level of evidence. And of course, it would depend on how strong it is.

But if these are three marginal effects that aren't really related but they're right on the borderline of significance I think there have been cases that taken collectively we feel these three tumors are equivocal. Rather than just dismissing if it was just one they might just dismiss it out of hand. But if there were several they might say well, a little bit, a little bit, a little bit. But it would depend how strong they are. If they're strong they'd call all three positive. If they're weak, you know, it just depends on the strength of the effect. It's hard to give general answers.

DR. BARBARA PARSONS: Thank you.

DR. JAMES MCMANAMAN: Other questions? Dr. Johnson?

DR. ERIC JOHNSON: This concerns the genotoxic studies. I mean, we're all aware that the EPA review, and also the Monsanto review, conclude that the overwhelming evidence does not show genotoxic effect for Glyphosate. But what worries me a little bit is the fact that the sister-chromatid exchange study, for it to just be downplayed by saying that we don't know what sister-chromatid means when this is an indication of a genetic abnormality and we've used it for decades. I mean it Benzene sister-chromatid exchanges were used as part of the evidence for Benzene genotoxicity.

I mean for us to say now that we don't know anything about sister-chromatid exchange therefore we should not consider that. I mean it just worries me a little bit.

DR. DAVID KIRKLAND: Yes. I take your point. I think what you have to do is to consider the sister-chromatid exchange data alongside all of the other data. For Benzene, there was clear induction of chromosome elaborations as well as sister chromatid exchanges. In fact, Benzene was one of the few

compounds that was actually found to be genotoxic in vivo before it was found to be genotoxic in vitro. Because when you put it into a culture dish it floats on the top and the cells weren't getting exposed.

The context is we know that Benzene produces chromosome elaborations, we know how Benzene is metabolized, we know the metabolites of Benzene bind to DNA. You put those sister chromatid exchange observations in the context of all the others. But when you look at Glyphosate, you've got sister chromatid exchanges and you've got DNA strand breaks. You've not got mutations, you've not got chromosome elaborations, you've not got mutations either in bacteria or in mammalian cells.

When we see these changes that are evidence of exposure, so a strand break or a sister chromatid exchange, for sure means the cells were exposed. But what we don't know is whether the manifestations of strand breaks and sister chromatid exchanges in those cells actually mean anything from a biological point of view. Do they have a consequence?

My response to your question is, if you see other evidence of genotoxicity in terms of the endpoints that we consider to be reliable, well

validated and with a clear association with tumorigenicity, if we were seeing mutations and chromosome elaborations, then those sister chromatid exchanges would add to the weight of evidence. When you see them in isolation, they don't.

DR. ERIC JOHNSON: I wouldn't agree that for that it's just a personal thing because I think sister chromatid exchange is not a normal phenomenon. You don't see it in normal people. When you see it when you administer a compound, it's an abnormal finding and it should be recognized for that.

DR. DAVID KIRKLAND: It's not abnormal in every case. There are some really strong inconsistencies and I'm not sure that I can remember the genetic conditions. There's Bloom Syndrome on the one hand and I think it's Down Syndrome on the other. There are two different genetic syndromes, one of which has a high increasing chromosome elaborations but no response in SCE. And the other has a high increase in SCE but no response with chromosome elaboration. And I can't remember which way around it is.

And therefore, it's not an all or nothing thing. Sister chromatid exchange is telling

you that the cell was exposed and it's telling you that the genetic material was doing its best to correct any errors that might have been there. We don't know that those sister chromatid exchanges go on to mean anything in terms of permanent damage. They may well be a reflection of the cell trying to repair damage that was there.

Let me turn this into why would you put strong weight on two or three positive sister chromatid exchange studies when you've got more than 90 gene mutation chromosome elaboration?

DR. JAMES MCMANAMAN: This is more of a discussion than a clarification.

DR. ERIC JOHNSON: I mentioned that one study was not and contributes to the overall weight of evidence. That's what I was saying. I was saying that this was a study which you did not find anything methodologically wrong about and which is a finding which is an indication of genotoxicity. And we've used it in the past for other compounds. And we should not just downplay it. Just leave it at that, that sister chromatid was found. That's it. We don't need to say that we don't know anything about the mechanism.

DR. JAMES MCMANAMAN: I think we're going to have to put an end to this discussion. I think that we've run out of time. And perhaps your concerns can be brought back up in the discussion of the charge questions. Daniele Court-Marques has asked to clarify something from yesterday. If we could have her do that, we'll then break for lunch. A brief clarification.

DR. DANIELE COURT-MARQUES: Thank you, Mr. Chairman. It's not really important, but just because we were mentioning the hemangiosarcomas and the number of tumors that were seen and there was a discrepancy between the results I report and the one from the U.S. EPA. And I just checked in the study report and actually it just mentioned that the authors of the study mentioned the same numbers for the 50 animals as the number of tumors that were seen were on the whole number of animals. I did not make this correction that the U.S. EPA did.

I just want to say that U.S. EPA did better work maybe than the authors of the study that did not report the lower number of animals where the incidence were found. I don't know if I made it clear.

DR. JAMES MCMANAMAN: Thank you.

DR. DANIELE COURT-MARQUES: Thank you very much.

DR. JAMES MCMANAMAN: So before we break for lunch a couple of points if I can make. One is that we have a very full schedule. In order to expedite the public presentations, I would like to make sure that Dr. Bus and Dr. Chukwudebe and Dr. Levine be present at the podium right after lunch. All three of you should be present so we can have good continuity in presentations. And then afterwards the remainder we will have Deborah Hommer, Scott Slaughter, Sabitha Papineni, and Jacob Vukich.

They should be ready to present following the first three. If you could just have your presentations ready and be sitting up closer to the podium that would be great. So now we'll take a one hour break for lunch.

(WHEREAS A LUNCH BREAK WAS TAKEN)

DR. JAMES MCMANAMAN: I think we'll get started. There's been a change in the schedule. Dr. Chuckwudebe -- am I anywhere close?

DR. AMECHI CHUKWUDEBE: Close enough.

DR. JAMES MCMANAMAN: I'm close enough. All right. Good. You will go first, from BASF. And then Dr. Bus will follow, assuming he can find his presentation.

DR. AMECHI CHUKWUDEBE: Okay.

DR. JAMES MCMANAMAN: All right.

DR. AMECHI CHUKWUDEBE: Am I close enough to the microphone?

DR. JAMES MCMANAMAN: You're good.

DR. AMECHI CHUKWUDEBE: All right. Good. Thanks, everyone, for being here. This afternoon I'm going to add more weight to what you heard yesterday and this morning. This will be a formal way to conduct a weight-of-evidence review on the carcinogenic potential of a test agent, in this case glyphosate as an example; and then to see whether the scientific weight-of-evidence analysis, how it conforms to conclusions from selected regulatory agencies, national and international.

The first thing is we're here because a test agent is under consideration whether it's carcinogenic. The primary definition is that cancer is a heterogeneous set of diseases that, at the core,

based on the dysregulation of cell division and homeostasis, it's not a disease that is very specific. It's heterogeneous, so by analogy with the way we understand infectious diseases, common bioassay systems came about just at the dawn when the industrial revolution and new chemicals came around.

For example, cancer or a carcinogen is not considered to be a discrete agent, it is a combination of the agent itself and endogenous factors. With this paradigm, it's inevitable that at the time when we know how to test for cancer, most products of modern chemistry like food additives, pesticides, were under consideration as suspect carcinogens.

The biological definition of cancer and carcinogenicity is more complex. It's a combination of exogenous and endogenous factors. It may not be a good regulatory or scientific practice, then, to classify every endpoint determining endogenous or exogenous factor to be carcinogenicity. For example, stress can be carcinogenic. Hormone imbalance can be carcinogenic. But we should not be in a position to say that a natural hormone, for example, can be put in the same category as arsenic or aflatoxin.

Cancer is a complex disease. It's an outcome of an interaction with a complex biological system that is multifaceted. Again, there is multiple morphological forms and mechanistic subtypes of cancer. And looking at these multifaceted forms, then a weight-of-evidence review is the best approach to study carcinogenicity.

In this sense, then, the U.S. EPA looks at the amount and quality of evidence with respect to carcinogenic potential because with a biological system, obviously, there's going to be many gray areas. It's going to be multifaceted. And so how carcinogens are defined is very important because it has implications for their recognition and regulation.

Having made hopefully an introduction that cancer is a multifaceted disease, let's look at a possible way to consider a carcinogen based on the weight-of-evidence review process. There are at least four cardinal points to consider in the weight-of-evidence review of a carcinogen. There's probably more, but I've just restricted to four highlights.

The first is molecular structure analysis, which includes in-silico evaluations. And this is usually the first stage in the coordinated

process to compare structure of physicochemical properties between carcinogens and non-carcinogens. This is more like first, it could be rational or it could be empirical.

Then there's genotoxicity test batteries on the premise that genotoxic events are crucial initiating steps in carcinogenicities.

And then there's chronic bioassays on experimental animals. And when properly conducted with sound biological underpinnings, they can be very useful and sensitive ways to determine the carcinogenic potential of test agents.

And then there is the human epidemiology studies. Properly conducted with the framework based analysis, again, they can be very useful for identifying causative agents and also the conditions that may predispose or not predispose to cancer. I will discuss these guiding considerations in a little bit more detail.

Starting with the molecular structure, there are some structural fragments associated with carcinogenicity and this can serve as sentinel indicators. These are usually collated together into knowledge-based systems that could either be empirical

or statistically based. This can be as simple as solubility, Log P, chemical reactivity, sensitivity to pH.

For example, I know that this morning there was a talk about glyphosate, whether it's in a salt form or as an acid. Whether it's in an acid form or in a salt form that can be readily disassociated, many structure activity softwares can differentiate between these. Glyphosate as an acid, many of the sources, especially when they are alkali metals or isopropanol main type, are very dissociable with constants of the other (inaudible) seconds.

There has been no chemical kinetics that has been able to measure the speed of disassociation. So for all intents and purposes, in a biological system, a glyphosate acid is treated the same way as a glyphosate salt provided that the dissociability is rapid as in ipa salt. Structure activity parameters give us very important information, but like in all biological systems, there can be gray areas.

There are some carcinogens that may have very similar structures. And then there are also compounds with very similar structures that either are

carcinogenic and the sisters are not carcinogenic; and one example, acetylaminofluorene.

These are sentinel indicators. And like all biological systems, the best way to get to a good outcome is to analyze all the evidence coordinately without exclusion, and in the end, weigh them based on evidentiary strengths. The first sentinel indicator is the structural component. And the puzzle pieces that get to the weight of evidence are analyzed further.

The next in this series is the genotoxicity. And genotoxicity and the biological basis for their importance centers on the evidence that the majority of chemical carcinogens are mutagens. And many of the mutagens are carcinogenic. And the relationship between these two outcomes is because of a factor common to all organisms, DNA, so that agents that cause mutation in the DNA can also be carcinogenic logically.

And like all biological applications, there are caveats. Promoters which are non-mutagenic may be missed by this system. However, if you take the totality of evidence together, it is logical to conclude that mutagenicity is a very strong indicator

for you to look forward and see whether there is carcinogenicity.

And so, among mutagenicity tests, like for compounds which have been in commerce for a long time, there could be mutagenicity genotoxic studies with different evidentiary restraints. We don't throw away any study, but you have to look at each study in isolation. How does it contribute to the eventual biological outcome based on what you know as the mechanism of action, the aggregate strength of this study, whether it's transparent, whether it follows biologically sound protocol?

As we have heard this morning, then, studies conducted in vivo tend to have more weight in terms of human relevance. Studies in mammalian studies are accorded greater evidentiary weight. And if you consider this, then, the totality of this of all the studies conducted on glyphosate, the majority of them with evidentiary strains lead to a conclusion that there is no plausible way this compound is genotoxic. And by inference, there is no expectation that a carcinogenic outcome is expected.

And then the next consideration is the chronic bioassays. And the biological relevance of

chronic animal studies derive a priori from the fact that they are mammalian systems in line with human systems, and that, however, there are differences in susceptibilities between different animals, even between different life stages.

And chronic bioassays are simple. But their simplicity can minimize the complexity of their evidentiary outputs. They can be sensitive or non-sensitive depending on the dose levels, the duration, whether it's a dietary application, whether it's as a solid or a liquid, the kinetics involved in that study, and other indices that reflect physiologic perturbation.

Chronic bioassays can be simple, but their outputs have to be analyzed with caution because, again, these are biological studies with many gray areas. And then in this sense, when you get other evidence from another biological study, such as epidemiology, that don't act in opposition to each other, they are supposed to be viewed as appositional evidence of not oppositional.

What is interesting is that most of the non-human carcinogens have been determined through epidemiology. However, the same cannot be said for a

majority of agents determined to be carcinogenic in chronic bioassays. In one peer et al. review, more than 500 currently marketed pharmaceuticals were reviewed. And these were carcinogenic in chronic animal bioassays, but not in humans.

And so, reliance on one biological path for data elucidation can obscure some important evidence for carcinogen identification. Reviews of chronic bioassays in rats and mice showed that glyphosate is not carcinogenic. Again, but as a caution, none of these pathways for reviews or studied systems is perfect in its own right; they have to be viewed in opposition to other test systems.

And then we go to the fourth guiding considerations, human epidemiology. This is the most powerful, when conducted properly, because, again, you see the direct human evidence, you get the direct human exposure. And one indispensable approach to weighing the strength of this evidence lies in the review and release of all data, whether they are associative or non-associative with hazards.

I know that funding systems and publication, there is more news when you report that an agent is hazardous. There is probably little news

to be made when you report that there is no evidence of hazard. There is implicit incentive to release information that is hazardous and that not be that aggressive in releasing information that shows safety. And this is not the case with studies that were considered unpublished data, which are based on regulatory studies.

You have to release the information, whether the hazard is there or it's not; conducted properly, provided that all information is released, that there's no exclusion, epidemiology is very powerful. And again, as we heard this morning, the expert panel that conducted this systematic review, on the published glyphosate epidemiology studies, came to the very conclusion that there is no evidence of carcinogenic potential.

We look at this idealized way to review the carcinogenic potential based on weight of evidence. If you look at four pieces of information, structural fragments, mutagenicity, chronic animal bioassays, epidemiology, the trend is that there is no association between glyphosate and cancer. The next topic then will be this scientific conclusion based on weight-of-evidence review process to see how multiple

national and international agencies have -- whether they agree with this form of evaluation or not.

I start with the U.S. EPA. I just go with the 2016 issue paper on glyphosate. Again, the Agency reviewed multiple databases and conducted the biological weight of evidence based on the decision logic approach; looked at all relevant biological indices for carcinogenicity including toxicokinetics, mechanistic approaches, mutagenicity. They looked at chronic animal bioassays on multiple epidemiology studies. And based on the totality of evidence, the strongest, the most conservative statement they could make is that this compound is not likely to be carcinogenic to humans, especially at dose levels relevant to human risk assessment.

And the New Zealand Environmental Protection Authority went even further. They conducted a recent review of evidence leading to glyphosate and carcinogenicity. And down their road to a conclusion, they made many preliminary observations that in studies expressing association between glyphosate and cancer, that there was a recall bias and that these studies, most of them, were not

controlled trials. And many of them had significant attrition weaknesses that should make them unreliable.

And one final thing they said is that these associations are not causation. And in these weak studies, there was no structured analysis such as a Bradford-Hill-type criteria. Based on the weight of evidence, New Zealand Environmental Protection Authority concluded that glyphosate is unlikely to be carcinogenic.

Continuing in this line, the FAO/WHO, that is the JMPR, the German Federal Authority on Risk Assessment, EFSA, arrived at their own conclusions, again, which you have heard yesterday. JMPR concluded, based on their weight-of-evidence, that glyphosate is unlikely to pose a carcinogenic risk to humans. And that Germany's Federal Institute for Risk Assessment came to the same conclusion. Again, using the same similar weight-of-evidence approach, different evidentiary strength of different studies and concluded that glyphosate is not carcinogenic.

Europe's EFSA, again, came to the same conclusion. The same datasets, they may differ in strengths they give to different studies, but the

conclusion is always the same, that glyphosate is unlikely to pose a carcinogenic hazard to humans.

And continuing, Australia's, APVMA, Japan FSC, Canada's PMRA in different languages came to the same conclusion. APVMA, from Australia, concludes that glyphosate does not pose a cancer risk to humans. Japan's FSC concludes that no treatment related hazard, including carcinogenicity, can be observed following exposure to glyphosate. And Canada's PMRA concludes that glyphosate is unlikely to pose a human cancer risk.

We've seen a remarkable case where a structured analysis based on a scientific process recognizing the biological system with all the gray areas. This scientific process leads to a conclusion that, in spite of apparent discrepancies in limited studies that glyphosate is not carcinogenic to humans. All international regulatory agencies, all, maybe with one exception, have also come to the same conclusion.

The question now is how do we define a problem that we have today. And I have a 1938 observation that may have some relevance here. That to date the problem is not a matter of skill or anything else. The problem is how do we define,

formulate, a problem that we have today. The problem, the basic problem, is how should glyphosate carcinogenic risk be communicated? Because we have seen the overall conclusion is that the risk is not there.

The best form of this communication should provide a biological context, recognizing the biological complexity of carcinogenicities. And this communication should not provide a mixed message to the public about what is or what is not a carcinogen. And this should also convey a risk-based paradigm that can inform a transparent public health policy.

Because cancer is a heterogeneous process, a hierarchical form of description is not as good as a narrative-based form such as the EPA is using. The EPA's current descriptive approach, based on their weight-of-evidence review process, has a very sound biological underpinnings, very sound scientific underpinning, and represents the most appropriate process. And thank you for your attention.

DR. JAMES MCMANAMAN: Any questions for this presenter?

(Whereupon there was no response)

Okay. Thank you very much.

DR. AMECHI CHUKWUDEBE: Thank you.

DR. JAMES MCMANAMAN: So if I could, Dr. Bus and Dr. Levine, if you could come up.

DR. STEVEN LEVINE: You could bring up presentation first. I'm going to go, and then Jim's going to follow me.

DR. JAMES MCMANAMAN: Okay.

DR. STEVEN LEVINE: We have sister talks.

DR. JAMES MCMANAMAN: All right. During this time, we can welcome Dr. Portier here.

DR. KENNETH PORTIER: I'm glad to be here. Thank you.

DR. JAMES MCMANAMAN: I bet you are.

Dr. Levine, you want to turn the mic off in the center? Not yours, but the one next to you. Thanks.

DR. STEVEN LEVINE: Which presentations did you want to do first, the New Farm or the CropLife? It looks like New Farm.

DR. JAMES MCMANAMAN: I think it looks like you are on the CropLife one, right?

DR. STEVEN LEVINE: Yes.

DR. JAMES MCMANAMAN: Okay. Did we do the wrong one?

MR. STEVEN KNOTT: Sorry. I thought we were doing the New Farm's next.

DR. JAMES MCMANAMAN: There you go.

DR. STEVEN LEVINE: Great. Thank you. I'd like to first start out by thanking the DFO, the Chair, and the panel for the opportunity to give these comments on behalf of CropLife America. My name is Steve Levine. I'm an environmental toxicologist with Monsanto. And Jim Bus will be giving a talk, also, on behalf of CropLife on oxidative stress following my talk.

What I'm going to give comments on today are the research plan presented in Section 7 of the Issues Paper. And there are currently no charge questions associated with Section 7. But I wanted to make a few comments on that this afternoon. Section 7 outlines a research plan. Section 7 outlines a research plan to develop publicly available MOA/AOP data for glyphosate, glyphosate-based formulations, as well as some of the components of those formulations, namely surfactants, which do have a well-established mode of action.

Section 7 was primarily included to address studies in the open literature suggesting glyphosate and glyphosate formulations may be genotoxic or cause oxidative stress or potentially impact other endpoints. As part of NTP's research program, they're going to initiate it with a systematic review of the literature. And we heard earlier this morning from Dr. Kirkland and yesterday from EPA about data quality criteria that can be used to evaluate the relevance and reliability of that open literature data.

As I said earlier, EPA does have a well-established data quality procedures, again, to assess the relevance and reliability of literature. And the recommendations that NTP would benefit from leveraging these criteria in their assessment to determine if data can be used quantitatively, qualitatively, or not at all in the assessment.

Another key point I'm going to make here, and I'll talk about more throughout the talk, is that mode of action studies need to be designed to minimize any confounding factors, whether that's cytotoxicity in in vitro systems or overt and systemic toxicity in in vivo studies.

When you are conducting mode of action studies, you're not simply testing for an adverse effect. Rather, you are testing for an adverse effect through a specific mechanism. You're testing a specific hypothesis here. And when you're doing that type of work, dose setting takes on greater importance, that the results are not confounded by an extraneous factor.

This is particularly important when you're testing molecules such as surfactants, which include detergents, because those molecules have non-specific activity and can easily confound the results of a mode of action analysis. And those surfactants are added to the formulation to spread the glyphosate on the leaf surface and increase its efficacy.

The mode of action of surfactants is well established, and there's a long history of safe use. And I'll talk more about that in a moment. But what is known is that surfactants can produce eye, skin, and GI irritation due to their surface activity. But GI irritation is a threshold effect only observed at high doses that would not be achieved under typical daily human exposures.

And we had a fair amount of information presented this morning and yesterday, as well, on realistic human exposures. Today, we got a nice presentation on refined exposures based on what is on commodity products as well as biomonitoring studies to give us a good idea there.

When you're testing surfactants, because of their surface activity, it's important that in any type of in vivo study that it's dietary exposures versus gavage exposures to really avoid that local GI irritation. And that's the approach that was taken by the Joints Inerts Task Force which developed toxicology databases for different classes of surfactants, including the ones in glyphosate formulations. And these studies demonstrated a large margin of safety for those surfactants and allowed those tolerances to be reinstated for those ingredients.

ToxSAC, which is at HED, which is their Toxicology Scientific Advisory Committee, did not identify any concerns for carcinogenicity include the absence of structural alerts for surfactants in ag formulations that were assessed for tolerance exemptions. And we also heard about the DEREK

predications from Dr. Kirkland for glyphosate. And the same was true for these surfactants that were evaluated.

As I had already said, surfactants demonstrate non-specific activity. And a nice example of this case study comes out of ToxCast where a number of surfactants were run through ToxCast. So ToxCast is a battery of about 700 in vitro assays looking at about 300 different cell-signaling pathways. And what this analysis for surfactant showed is that a disproportionately large number of hits in the mode of action assays with surfactants were confounded by cytotoxicity. They were very difficult to interpret.

These surfactants demonstrated low specificity because of disruption of cell membranes, protein-protein interactions, and effects on mitochondrial function. And these effects on cell membranes is what makes soaps such good sanitizers and really have been one of the most important molecules in human history.

Because of these non-specific effects, it makes it very difficult to address a specific mode of action. And many endpoints can be affected over the same concentration range. And to really

understand what's going on in a sequential way, you really need to do time-to-effect experiments when they're these types of in vitro experiments to understand the cascade of events, membrane disruption, effects on cytosolic proteins, mitochondrial function.

This picture up here, this diagram up here on the slide, is just a simple diagram to show -- on the right here, this is a typical surfactant, non-ionic surfactant which is commonly in glyphosate formulations. We have an alkyl chain which is hydrophobic, a hydrophilic head. And these are able to insert into the membrane, into the cell membranes. And at critical concentrations, high concentrations, enough can get into the cell membrane to cause disruption, affect ionic balance in the cell leading to cytotoxicity.

But again, this is a phenomena that happens at relatively high concentrations, much greater than you would expect under typical human exposures to these compounds through dietary exposures.

Back in 2010, the subcommittee on Energy and the Environment and the subcommittee on Health met and discussed primary validity requirements

for regulatory science. And these are all requirements that NIH had agreed to. The first was the identity and authenticity of scientific measurements must be verifiable within a defined range of precision. Okay.

This really talks to the studies need to be adequately powered and have probative nature. We've had discussions about what guideline studies are earlier in the SAP. And I just wanted to say that those studies are really designed to have the power and sensitivity to detect an adverse effect at the doses that are tested if such an adverse effect is possible at those levels.

Number two, measurements and observations must be replicable in independent hands. That's a classic hallmark of any good science.

And third, measurements and observations, i.e., endpoints, should not be confounded by extraneous factors. And this is particularly important for formulation studies and in vitro studies where surfactants are tested. And I just wanted to go through three quick examples of how these extraneous confounding factors could affect the

interpretation, in this case of in vitro results, just to give some examples.

Here's an example of an estrogen receptor competitive receptor binding assay. And on the left, we have Estradiol. And on the right, we have sodium dodecylbenzene sulfonate, also known as linear alkylbenzene sulfonate or LAS. This is found in laundry detergents. Billions of pounds of this are produced every year for cleaning purposes. What we see on the left is, again, the typical estrogen receptor binding curve. And we're seeing binding over about five orders of magnitude.

However, on the right, with the surfactant, we're seeing what some could interpret as a binding curve or perhaps a false positive, in this case. What's going on here is we're seeing a very quick decrease in binding over very few orders of magnitude, two orders of magnitude here, which is not characteristic of a competitive or a noncompetitive inhibitor. We're seeing something going on here.

And what it is denaturing of the receptor by high concentrations of surfactant added into the test system. And you could actually do secondary analyses on these types of data to

demonstrate it's either competitive or noncompetitive. And this is really an impact on a cell-free system. This is not competitive or noncompetitive binding.

And this is a figure out of Laws et al. 2006 who validated this assay for the endocrine disruptor screening program. And it was not an easy assay to validate because of the nonspecific effects of the universal chemicals that were tested through the system.

Here's a second example. I'm sorry if this is hard to see. This is an example looking at glyphosate in Roundup on inhibition of aromatase activity so steroid agenesis, the final step in steroid agenesis. In this assay, glyphosate was tested at levels that greatly exceed what humans, again, would be exposed to, and better approximate, actually, what's in the spray tank.

What I have with the red line here, the red dotted line, is what would be a limit dose for this type of assay in a regulatory study. That's 1,000 micromolar. That's a high concentration to put into an in vitro system. All the concentrations that were tested in this study are greater than 1,000 micromolar. But what we see with glyphosate is a

decrease in aromatase activities as concentrations test. This is, in fact, a pH effect. This is not inhibition of aromatase activity.

This is, again, actually denaturing of the enzyme at below physiological pH. We actually did this assay for the endocrine program. Glyphosate is not an aromatase inhibitor. And we tested up to a 1,000. The top concentrations confirmed that in this assay. But I just wanted to point out that there's a very strong confounder in this study. And if you actually look at the cytotoxicity data, the cytotoxicity data corresponds with the decrease in aromatase activity on the top graph.

The same is true when Roundup was tested. This was, again, put directly into cells in culture. And we can see cytotoxicity and effects on aromatase activity co-occurring at approximately the same concentration. This is not a direct inhibition, but rather, again, a non-specific effect of a surfactant on a protein.

The real big takeaway here is that in vitro data generated at the supraphysiological exposure concentrations that don't consider barriers, that don't consider metabolism, really must be

interpreted with extreme caution. And a fair amount of studies like this are in the literature for Roundup for glyphosate. That's why a data quality assessment in ranking these studies is so important before any information is used to inform an MOE assessment.

This is just one final example on this slide. This is, again, another example with steroid agenesis. We're looking at inhibition of progesterone synthesis. And this is with an alcohol ethoxylate, which is a very common surfactant used in the household for laundry products, dishwashing.

This is a product we use to wash our dishes with at home. It's good at cutting grease. But it's also good at disrupting cell membranes for the same reasons at these physiological concentrations. And you do find these in pesticide formulations. They've been a common replacement for nonylphenol ethoxylates, hard surface cleaners, rug cleaners, et cetera.

What I wanted to point out here was that not only are cytotoxicity assays important to run concurrently, but you have to run the right cytotoxicity assays. The first steps in steroid agenesis take place in the mitochondrial membrane.

That's where pregnenolone and progesterone are synthesized. In this assay, and this is from a paper I published several years ago, we actually looked at mitochondrial electrochemical potential. When that electrochemical potential is shot down, steroid agenesis is shut down.

And what we're able to show here is that disruption of the electrochemical gradient in concentrations below and at where we saw inhibition of progesterone synthesis were added in. That's really the explanation for effects on progesterone synthesis.

But again, we see many articles out there in the literature like this that really don't look at the right types of cytotoxicity assessments. And it depends how long your assays are, what type of cytotoxicity assessment you look at whether it's early, middle, or late event so careful consideration needs to be put there, as well.

What this was getting to is an example from Section 7 where there is a published graph where a number of different formulations that were bought off the shelf were tested against HepG2 cell lines. And the endpoint here was ATP production. That's what luminescence is measuring, ATP levels. And it's not

surprising to see concentration-dependent effects in this system at these relatively high concentrations.

One of the interesting things in this diagram here is that a formulation with a relatively low glyphosate concentration has the most significant effect. And the reason for that is that this formulation very likely contains pelargonicacid, which is added to some homeowner-use products to develop symptomology on the plant.

Glyphosate is a very slow-acting herbicide. And to keep homeowners from doing a second or third application because they may not have thought that they actually hit the weed, it's good to see a little bit of browning. At least they know they sprayed it. And what this does to create browning is basically strips off the cuticle, which has very similar properties to a cell membrane.

It's not surprising to see this formulation that is 1.9% glyphosate and likely pelargonicacid to have a curve way over here versus some of the higher concentration glyphosate formulations which are further over to the right.

And again, I just wanted to make the point that these types of studies have to be

interpreted with extreme caution, again, because of no barriers, not really having estimate of what reaches the site of action in the whole animal. And again, we're looking at relatively low exposures compared to what's being put into these in vitro systems.

I'm just going to end quickly with some closing remarks. Again, I wanted just to hit on this importance of having a data quality assessment of any literature that's used to inform a research plan or brought into weight-of-evidence evaluations to look at a potential mode of action and develop an adverse outcome pathway.

This is particularly important for in vitro assays because that's what sits at the front of an adverse outcome pathway. Generally, it's subcellular, cellular data, mechanistic endpoints. And if the wrong interpretation of the data is made at that point, it can really put you down the wrong road when you're going into animal testing.

Again, dose setting takes on much greater significance when investigating specific modes of action. Again, you're testing specific hypotheses, an adverse effect through an estrogen mechanism, an adverse effect through some other type of mechanism.

And that cannot be confounded by testing high levels of materials in in vitro systems which will you give you those wrong signals.

I'm going to stop there and pass it over to Jim. And he's going to pick up on some of these things when he talks about oxidative stress.

DR. JAMES BUS: Again, my name is Jim Bus. And good afternoon to all of you. I'm going to give you a very brief overview of the issue of oxidative stress as a potential mode of action for glyphosate carcinogenicity. This issue, of course, was brought to the table initially by the emphasis that was put forward in the IARC review of glyphosate in which they concluded that there was strong evidence of oxidative stress associated with glyphosate.

That is really the interest that should be before the SAP in terms of the carcinogenicity of glyphosate in terms of is oxidative stress, in fact, a plausible mode of action that might potentially account for tumorgenicity of glyphosate. I certainly should emphasize, and I'm sure you are more than aware, that this is not a specific charge question of the Science Advisory Panel. But it is certainly commented on in the issues document in Chapter 7.

As I just mentioned, IARC in 2015 in their review of glyphosate concluded that oxidative stress provided strong supporting evidence as a plausible mode of action that glyphosate could be probably to a human carcinogen. The actual EPA issues paper took notice of that conclusion.

It actually forwarded that conclusion to the National Toxicologist Program Workgroup for further evaluation. And as you can see there in the red, that particular workgroup looked at the available data that was included in the IARC review. And they did not agree with IARC that the data provided a strong or clear evidence for induction of oxidative stress, given protocol deficiencies that could produce questionable results. What I'm going to do with you, basically, for a few moments is take you through some of that data that led the NTP to that conclusion.

Push this button. It's important to note that, obviously, mode of action science has played an active role in decisions that IARC has made as well EPA for a number of years, appropriately so. And this is a slide that basically was presented by Dr. Chris Portier at a 2015 toxicology forum meeting

and modified from a slide developed from Vince Cogliano when he was at IARC.

And all this is intended to show you is that mode of action work, increasingly, has been taken very seriously in terms of how it can inform hazard and risk assessment decisions associated with chemicals that potentially might produce carcinogenic responses in animals.

And it illustrates that with mode of action information you have the potential options of using that information to inform when the human plausibility of the carcinogenicity of an agent could either be upgraded, in other words, it should be viewed as potentially greater hazard, or even potentially downgraded, as well, depending on what that mode of action information would tell you.

A few years ago, IARC appropriately did realize that, in fact, with the explosion of mode of action science that has entered into the world toxicologic science in recent years, and it's only going to continue to grow, probably exponentially, in the years ahead because of the advances in molecular sciences that are now playing actively in the field of toxicology.

They certainly recognize that there was a real need to begin to find a way that, perhaps, would better organize this vast and complex body of mode of action information so that it would better help individuals who are in the roles of making judgements about carcinogenicity of chemical agents so that they could have a way to organize that data into a way that might help them formulate better hypotheses and conclusions about potential carcinogenicity.

And that was illustrated and basically accomplished, at least in part, through a series of workshops that IARC sponsored and ultimately published in a paper in Environmental Health Perspectives authored by Martyn Smith and others, just in 2016. And IARC, basically, looked at a series of their class I carcinogens.

And they asked the question do we see some common characteristics across those compounds in terms of mode of action type of information that we might be able to use an opportunity to help us organize this complex database that's evolving with mode of action science. And here you have here the list of what they landed on, which was 10 key characteristics of human carcinogens.

And I've certainly highlighted there in red, which is the one which is the focus of the conversation today, is they identified oxidative stress as one of those characteristics of chemical agents that might potentially identify them as potential human carcinogens.

IARC, however, certainly realized that they were in the relatively infancy in terms of how this organization would proceed. And their analysis as such, at this stage in point, is not fully supported with robust analyses. By way of example, they entirely focused, in terms of developing these 10 key characteristics, only on their IARC Group I chemicals.

And then the individual characteristics that they identified, including oxidative stress, at least in the publication presented by Dr. Smith and others, really didn't go into any great depth in terms of explaining the fundamental biology of toxicology that would ultimately be understood to be contributed to those cancer outcomes. However, as you could see from the previous slides, there's clearly elements like cell proliferation which, I think, are well-

established elements within the toxicology community as key contributory elements to cancer outcomes.

And certainly, oxidative stress fits into that category, but although the literature they cite certainly only was based on two review articles, not any actual primary science. Also, IARC did not include in their evaluation in terms of their development of these 10 key characteristics whether those characteristics must also occur which compounds, which in their own evaluations are not generally regard as perhaps having a higher potential for cancer hazard.

And by way of example, if you just rapidly screen the literature, you quickly find that the same oxidative tests that they illustrate as evidence for glyphosate oxidant stress, if you apply those same tests to the class III compounds, you'll find many of those class III compounds have been tested the same way and also produce oxidant stress, as well.

But another interesting concept behind their development of these 10 key characteristics, particularly with respect to oxidative stress, is they didn't have any discussion at all about key

counterfactuals. And the ones I've listed here are two, I think, very important because they're both agricultural chemicals, paraquat and diaquat.

And for those of you who might be familiar with those compounds, these are, in fact, the prototypical oxidant stressors in the toxicologic literature. The primary and only metabolism of these compounds is to undergo redox cycling. And once they enter into the cell, the only thing they're going to do is sit there and spin off oxidative radicals.

But yet, both of those compounds, because they are agricultural chemicals, have been subjected to two species and two sex rodent bioassays. And neither of them are regarded as rodent carcinogens. So certainly, oxidative stress, per se, or chemicals that are really the most active as oxidative stressors are not producing carcinogenicity in our existing bioassay systems.

IARC then stepped forward and said, well, what we -- they did, in fact, realize the limitations that were associated with this initial analysis. And in fact, they identified that their primary purpose, at least initially, was to say how do we condense all this massive literature emerging from

the toxicologic literature into reasonable bins, so to speak, that we can begin to sort through and develop rational hypothesis for potential mode of action assessments.

But they certainly recognized that this particular process could fall prey to, for instance, scenarios where there's not a lot of particular mode of action information. And certainly, that applies to glyphosate. When you look at the actual mode of action information, and I'll comment on this in the next few slides, it is, indeed, very limited.

But most importantly, there was another key concept that IARC emphasized in their Smith 2016 publication. And that was mode of action science, obviously, is not as simplistic of just simply dropping papers into the bins of the different 10 key characteristics and then looking in those bins and counting the number of papers. And the number of papers, then, equate to the mode of action likelihood.

They emphasize that, obviously, there's a vast experience with dealing with mode of action information and that fundamentally what has to happen with those datasets is they have to be subsequently organized to form hypotheses that evaluate the

evidentiary support for mechanistic events as a function of other key relevant aspects of information that's absolutely critical to mode of action assessment.

For instance, consideration of dose-response, species specificity, or temporality of the response. All of those are recognized in the mode of action science community as being critical elements to any reasonable mode of action evaluation. The question then becomes in that IARC evaluation as classifying glyphosate as having strong evidence of oxidative stress, did they, in fact, follow those reasonable mode of action principles in terms of coming to that conclusion.

And I'll show you a few pieces of information relative to how they approached it. These are the datasets which they had available to them in terms of their evaluation of the oxidative stress. And on the left-hand side, they really focused on really two types of analyses that are important. Obviously, evidence of oxidative stress in human tissues in vitro because obviously, that gets as potentially relevant to humans as possible. And then, subsequently, the possibility of other data also

existing in other non-human but mammalian species conducted in vivo.

But clearly, what you can see from these studies that IARC was addressing that this endpoint, oxidative stress as it relates to glyphosate, actually falls into that category, as IARC even cautioned about, as falling into the category of having only limited evidence available. There is really only a total of 14 studies that were cited for both human in vitro and non-mammalian in vivo.

But more importantly, and it touches on what was just presented by Steve just a few moments ago, when you look at these particular datasets as they were presented, many of them -- in fact, the primary proportion of the studies that were examined were, in fact, conducted with formulations. And in fact, it was the formulations, as you can see in the third column over, that produced the primary responses in these oxidative stress studies.

But likewise, and equally important, you'll notice there in the fourth and fifth column the fact that most of these studies that were cited by IARC were either single-dose studies or single-time-point studies. And again, given the emphasis in mode

of action evaluations to have multiple doses or concentrations so that you could construct dose-response analyses and ultimately relate that back to apical toxicity events. A single-time-point study really doesn't provide much useful information in terms of informing mode of action.

And likewise, with time point, it's the same because if you don't understand whether the event that you're observing oxidative stress in this case is occurring early on relative to the subsequent apical events, it really is not informative in terms of where that fits into the overall process.

Another key consideration, of course, with mode of action studies is are they conducted in the relevant tissues. And in the case of glyphosate, for both the human in vitro and the non-mammalian in vivo, as you can see, most of them were not conducted in the tissues that IARC regarded as relevant for the apical mode of action issue of concern, which in this case was kidney tumors, which was the tumor endpoint which they put weight on, and possibly hemangiosarcomas. The tests that were done were not done in those tissues.

And then likewise, oxidative stress, there is a large body of literature by the oxidative stress research community that strongly emphasizes that when you're doing research in oxidative stress you need to be exquisitely aware of the possibility that, number one, if you're just using a single biomarker of oxidative stress, you can be very prone to coming to false conclusion. And that really, if you're doing oxidative stress research, you're much better served by having multiple biomarkers and indicators of oxidative stress rather than just a single one.

And again, as you can see from the numbers that I'm presenting here, all the studies that IARC had to evaluate essentially suffered from that particular difficult and/or they used methods which, again is well known in the oxidative stress they can be prone to artefactual responses. The bottom line there, there was a body of evidence associated with non-mammalian evaluations. And I'll come back to that in just a few moments.

As I mentioned before, a really key evaluation associated with mode of action evaluation is what is the context of dose and exposure. And here

I'll give you some dose relevance of what was observed for oxidative stress in those human cell tests compared to doses that were actually given to whole animals. As you might imagine, there is toxicokinetic data available for glyphosate in whole animals.

And really, the question that I'm posing here in that first major bullet is if you have a concentration that produces evidence of oxidative stress in an in vitro test system, how much of a dose would you have to give to a rat, by way of example, to get that tissue concentration or blood concentration that produced that oxidative stress response in vitro.

And in the case of a rat, we know that a single oral dose by gavage of 400 mg/kg will produce a maximum concentration in the plasma of 4.6 ug/ml. That's kind of the reference concentration which we need to frame the results of the in vitro studies that I'm describing in the next major bullet.

Four of the seven studies that were in this category of testing, in in vitro human cell types, were actually done at the LC50 concentrations of those materials on the various test systems. And as Steve indicated, when that happens, obviously, when you're at LC50 concentrations the cell is into very

significant biochemical disruption. It's almost impossible, in fact, it is impossible, to attribute dose-responses to a primary oxidative event versus a secondary event associated with massive cell disruption.

The other thing you'll notice with those four of seven studies, that they're, again, as Steve just emphasized there is a dramatic difference between when you test glyphosate acid or you test the glyphosate formulation. The first study was done as a formulation. And it produced its oxidative evidence at 40 ug/ml and the next one at 376. But when pure glyphosate was tested, you can see there's a dramatic difference in terms of the concentrations necessary to elicit the oxidative stress.

That same phenomenon was also seen in the next sub-bullet down, basically, where if you test at doses or concentrations less than the LC50 concentration, nonetheless, it still illustrates that glyphosate in liver cells, by way of example, still was negative at glyphosate concentrations of 900 ug/ml. Where the formulation, on the other hand, you could see in that same study, actually produced activity at a much lower concentration.

And the next two points merely illustrate, again, that glyphosate as a pure compound is relatively inactive in terms of inducing oxidative stress. The last line shows that in red blood cells a pure glyphosate did elicit oxidative stress at 42 ug/ml. But they used only a single biomarker of oxidative stress. Again, those results have to be taken with some question.

But more importantly, how do these concentrations really compare to how much of a dose you would have to give to a rat to get those concentrations. And as you can see from the red bullet down at the bottom, the test concentrations that produce the oxidative effects were anywhere from 9 to 820 times higher than the blood concentration resulting from dosing a rat with 400 mg/kg per day.

Even if you took that value of nine on the left side, in order to get to that concentration produced by the nine-fold higher, you would have to dose a rat with 4,000 mg/kg. And obviously, the others are very much dramatically higher, in fact, would stretch the dose in those animal studies to literally the tens of grams per kilogram of glyphosate per day.

And keep in mind that, of course, as we've mentioned in our conversations this morning, there's excellent human biomonitoring studies that said humans are not anywhere near exposed to 400 mg/kg. In fact, it's much more realistic, based upon biomonitoring studies, that those exposures are probably in the range of less than 0.005 mg/kg per day. There's a dramatic difference between the concentrations eliciting these oxidative stress in terms of what could be dosed to an animal and even far more different effects between what could be expected to be exposed to in humans.

Well, what about the animal toxicology studies producing oxidative stress? And again, you can fall back to the dose-relevance comparison. Again, as you heard this morning, there are a number of biomonitoring studies. And Dr. Acquavella described his study this morning where the maximum dose to a farmer is in the range of 4 um/kg/day. And the spouses and children are significantly lower.

There's also been a number of other biomonitoring studies that are available for glyphosate in humans. Those studies have been reviewed myself in a publication in Regulatory

Toxicology and Pharmacology in 2015. And those doses usually have been confirmed to be in the range of 0.1 to 5 um/kg/day as maximum concentrations that have been detected as a result of biomonitoring of humans environmentally exposed to glyphosate.

How do those dose levels compare to what was used in the animal studies? Well, two out of the seven studies used glyphosate at 10 mg/kg or 300 mg/kg. But importantly, note that those exposures were conducted by the intraperitoneal route of exposure. Of course, that circumvents the oral route of exposures to which humans are exposed to. And by giving them i.p. you basically dramatically increase the systemic bioavailability of glyphosate relative to what the environmental exposure would be, which would be oral.

Likewise, the next studies are equally high doses, again, conducted by i.p. Another one was done by dermal exposure. And that is even worse than i.p. because, obviously, the dermal absorption of glyphosate in terms of systemic absorption has been estimated at as less than 1 percent. A few other gavage studies, there was one drinking water study

done with a formulation at 0.38 percent of the formulation in drinking water.

But I should mention that that particular study was additionally confounded that after the animal dosing was completed, it was actually an evaluation of oxidative stress in brain tissue. They isolated a brain tissue slice. And then they co-incubated that slice with a 0.01 percent formulation, again. They really double-hammered those animals with respect to that study.

Again, when you step back and look at these dose levels that produced evidence of oxidative stress in these in vivo studies, again, you come to the conclusion that those doses are very substantially separated from maximally exposed individuals. This would be individuals directly handling concentrated formulations in the occupational scenario associated with pesticide applications. So again, there's a lack of dose relevance, again, of oxidative stress associated with these particular studies.

Just a few brief comments about non-mammalian evaluations, again, these are studies conducted with wildlife species. And all the studies, by the way, were conducted as formulations, which, of

course, renders their interpretation of very questionable value. Six of the 19 studies actually came from a single laboratory. And most of those studies actually resulted in negative or equivocal findings using oxidant-sensitive enzyme-based assays to measure changes in the comet assay.

And, again, they used native-caught European eel species. So, again, the biology of those species relative to how they might perform to mammalian systems is really unknown. There were only 2 of the 19 studies that actually tested pure glyphosate. One of those studies it was a comet assay, again, in the European eel. And that study was actually negative.

Another study, basically the only evidence that was demonstrated for oxidative stress was a very simplistic level of biomarker, a down regulation of the super oxide dismutase gene and an upper regulation of catalase. And that was done in zebrafish and in testes, which, of course, is not a target tissue for glyphosate carcinogenicity.

And one study in the environmental species was a mixture of eight pesticides in oysters. it's absolutely impossible to attribute any response

there to glyphosate treatment. The non-mammalian species, basically, do not inform the plausibility of oxidative stress as a human cancer mode of action indicator.

In conclusion, then, as you look across the oxidative stress literature that IARC actually reviewed, there was no evidence that IARC took the important steps of actually integrating the data analyses to form a reasonable mode of action hypotheses to assess the relevance of oxidative stress as a meaningful contributor to potential cancer outcomes.

In fact, it appears much more likely that what they simply did was to take these oxidative stress papers and drop them into the bin of oxidative stress as one of the 10 key characteristics and then say simply, well, because there are papers in the bin that must mean that there is strong evidence of oxidative stress.

In the actual monograph for IARC, no real attempt is made to really do the critical element of any mode of action assessment, which is to establish the relationship, as I've indicated, of dose temporality, coherence, consistent target organ

relevance. And none of those were addressed in the IARC Monograph relative to oxidant stress.

So glyphosate was certainly determined by IARC as having strong evidence of oxidant stress but, yet, when you go and evaluate what do they mean by "strong evidence," there is no place either in their preamble or in the Smith paper where they provide criteria that would allow their reviewers to differentiate what level of evidence would make the difference between classifying an agent as weak, moderate, or strong, which are the three categories which they have available to place a mode of action science into.

As a result, in spite of these substantial data deficiencies and actually, analysis of the science deficiencies, IARC, nonetheless, used oxidative stress as the basis to support, in part, IARC's classification as a two-way carcinogen. And as you can obviously tell from my evaluation of the data, I would believe that the oxidative stress evaluation of IARC falls far short of attributing oxidative stress as a plausible mode of action for carcinogenicity.

And I certainly would agree with the conclusion of the evaluators of the National Toxicology Program, which essentially came to the same point. Thank you.

DR. JAMES MCMANAMAN: Thank you. Any questions for Dr. Bus or Dr. Levine?

Yes?

DR. ARAMANDLA RAMESH: It's not a question, respectable to the Chair. Is there any time limit for presenters? Because I see there are 11 presenters. No offense. If everyone takes 30 minutes or 35 minutes, we will not be leaving the hall before 8:00.

DR. JAMES MCMANAMAN: Oh. Well, I think that we've got that under control. Yeah. We've got a timer up here. And if they exceed their time, a clown will come in a hook and they're off.

Questions? Dr. Portier.

DR. KENNETH PORTIER: So I was just wondering, has someone published on what's a good test for oxidative stress? I mean is there a solid science on establishing that?

DR. JAMES BUS: There are a series because oxidative stress has been around for a long

time. It's been a focus of the research in the mode of action science community for decades. And actually now, as I've mentioned, the conclusion -- and you'll find this in several very recent review articles, most of them coming out of the team of Barry Halliwell, who's one of the pioneers in oxidative stress research.

They all emphasize that when you do oxidative stress research, if you really want to get meaningful science, you have to look at multiple biomarkers for oxidative stress. Relying, for instance, just on a single formation of DNA adducts, for instance, is not enough. You really need to couple it with other types of elements. And those assays are available. The methods are there, but they have to be applied in an appropriate mode of action framework analysis.

DR. JAMES MCMANAMAN: Other questions?

Yes, Dr. Zhang.

DR. LUOPING ZHANG: Luoping Zhang. I have a question for Dr. Levine. I think you present a very interesting study from Richard 2005.

DR. JAMES MCMANAMAN: Dr. Zhang, put your microphone a little closer.

DR. LUOPING ZHANG: Just trying to just confirm. Are you sure that actually the Roundup does inhibit aromatase activity, right? That's what your data was showing. But you are saying that's because of the cytotoxicity. I just want to confirm. Is that what you really mean from that figure you showed?

DR. STEVEN LEVINE: Yeah. Aromatase activity is extremely --

DR. LUOPING ZHANG: Sensitive, yeah.

DR. STEVEN LEVINE: -- sensitive to detergents. In fact, in EPA's protocol they do state that. But the inhibition of aromatase activity was co-occurring with cytotoxicity. Aromatase, that's a P450 enzyme that's associated with a smooth endoplasmic reticulum. And it's associated with reductases.

From people who have done purification of proteins know that detergents are used. You could certainly affect the relationship between the reductases and the enzyme affecting its ability to pass reducing equivalents to catalyze the biotransformation. It is certainly a membrane effect, I believe, rather than a direct effect on the enzyme itself. Because it doesn't --

DR. LUOPING ZHANG: But at the least, you'll see it. At the least, the curve, you see it, right? You see the inhibition.

DR. STEVEN LEVINE: Yeah.

DR. LUOPING ZHANG: That's okay, right?

DR. STEVEN LEVINE: You do see inhibition, but it is a very steep curve. Surfactants produce their effects at threshold concentration. You see very rapid effects once you reach a critical threshold concentration. The slope becomes very steep. And if you actually look at the slope in that paper versus what would be classic aromatase inhibitor, it's a very different slope. And oftentimes, slopes in mode of actions are associated with one another.

DR. LUOPING ZHANG: Yeah. That raise my next question is because the slope looks quite different from the cytotoxicity. It's different, right?

DR. STEVEN LEVINE: Yes. They are measuring different endpoints. That cytotoxicity is actually looking at cell membrane disruption versus an enzyme effect.

DR. LUOPING ZHANG: Okay. I just want to confirm that that's what you're presenting.

DR. JAMES MCMANAMAN: Other questions?

(Whereupon there was no response)

DR. JAMES MCMANAMAN: All right. Thank you very much. Dr. Levine, you're excused then.

DR. JAMES BUS: I guess I get to stay here.

DR. JAMES MCMANAMAN: Thanks for your presentation.

DR. JAMES BUS: Thank you. I'm going to spend just a very few moments discussing the issue of does glyphosate bioaccumulation in human breastmilk and do an examination of the plausibility of that potential.

Obviously, that becomes important to the toxicology risk assessment community because, obviously, it addresses the potentially important health question of whether a potentially sensitive subpopulation, such as nursing infants which focus their entire diet, for instance, by way of example on breastmilk. Does that place them at a differential sensitivity to glyphosate toxicity based upon that type of dietary intake?

Turning to the key question, though, is why is there a concern at all about the potential for glyphosate in breastmilk? That concern largely arises through an internet non-peer-reviewed report that was published by an organization called Moms Across America. And they reported the detection of glyphosate in human breastmilk in 3 of 10 women that they had biomonitored across the country.

They reported concentrations of 166, 76, and 99 ug/L in those three women, which ranged across the country from Florida to Virginia to Oregon. And as a result of those concentrations in breastmilk, which would, indeed, be relatively high, it provided evidence of bioaccumulation in breastmilk. And of course, if that hypothesis is true, that would, indeed, present a unique exposure route to these sensitive sub-populations of nursing children.

They also did a corresponding glyphosate biomonitoring study, of a number of women, where they sampled their urine. And 13 of the 35 urine samples, in fact, were evaluated and they returned an average value of 18.8 ug/L. And I'll come back to that in just a few moments and what that potentially means.

The critical question, then, is does this biomonitoring data pose the potential for a human health threat to nursing children from glyphosate concentrations that might result from an environmental exposure? And we're going to take a look at, just for a very few moments here, what is the biologic plausibility of that potential exposure.

First of all, it's important to note that when that report was released there were a number of methodologic concerns that were immediately expressed relative to the issuance of that report. Dr. Ron Kleinman, who is the Physician-in-Chief at the Massachusetts General Hospital for Children working on behalf of the Genetic Literacy Project in 2014 noted that the milk assays used were an ELISA assay which had not yet been validated for breastmilk. They were only validated for water samples. And of course, breastmilk is a substantially more complex environment than water.

The report was also silent on the method in terms of how the validation might have been attributed to milk. There was no information whether such efforts had been made. And then also, there were

limited details on participant selection, sample collection, storage, and chain of custody protocols.

The EPA, in response to the MAA report, actually sent a letter to the MAA noting those very same concern and others. And that included that the ELISA method that was used was, at best, regarded as only a semi-quantitative screening assay that, in fact, validated LC MS/MS methods were available for actually measuring glyphosate in milk.

And more importantly, because the EPA had access to toxicokinetic studies submitted by registrants, they had already had information that studies in lactating animals indicate that glyphosate is excreted primarily in the urine and feces but not through breastmilk. Myself, as a result of being commissioned by the Glyphosate Task Force in 2015, in an open access publication in the peer-review journal Regulatory Toxicology and Pharmacology, I offered a critique focusing on some additional details relative to this MAA report.

And it really addressed the primary question of is the bioaccumulation of glyphosate in human breastmilk as reported in that report, in fact, is highly implausible when that information is

considered in context of four major issues. The animal toxicokinetics data, the MAA milk concentrations are also biologically implausible when compared to the actual human doses that are well demonstrated for human biomonitoring studies.

Likewise, those human biomonitoring studies indicate that the actual exposures to glyphosate could not give doses sufficient to produce those breastmilk concentrations. And lastly, the potential for bioaccumulation in breastmilk is opposing to the fundamental physicochemical properties of glyphosate, which would not make it appear to be a bioaccumulative compound.

I'm going to address each one of those briefly in the next few slides. Relative to the animal toxicology data, you've already heard in terms of the toxicokinetic information, glyphosate has only a limited absorption by the oral route and even less so by dermal. That those toxicokinetic data indicate that both in humans and in animals that glyphosate, when it is systematically absorbed, is rapidly excreted into the urine and feces as the parent compound.

And given the structure of glyphosate, it's not surprising that its distribution is almost entirely to water-rich compartments with rapid clearance once you terminate the exposure. There are also, again, in studies that had submitted by registrants to the agency evaluating the distribution of glyphosate measured as 14C-glyphosate in lactating goats given 5 mg/kg/day for multiple days, usually in the range of six to eight days.

In those dose experiments, toxicokinetic studies basically indicate that less than 0.01 percent of the administered dose was actually recovered in the milk because they were actually collecting the milk as well as the urine and feces in these studies. But likewise in that same study, the peak concentrations in milk were about 80 ug/L.

And you could see the same concentrations in blood were even higher at a 101 ug/L. This would not be the typical characteristic of a compound that has preferential distribution to milk. You would expect the milk to have substantially higher concentrations of glyphosate if, in fact, it had a preferential distribution to milk tissue.

But likewise, again, even after six to eight days of treatment of lactating goats, once that treatment was terminated there was rapid clearance from the milk once post-dosing was ended. The ADME data in lactating animals and in humans clearly are inconsistent with glyphosate being a bioaccumulative compound into milk.

Turning to how do these concentrations reported in the biomonitoring by the MAA report, how do they compare to actual real-world exposures? Well, as we've emphasized before, the maximum glyphosate external and systemic doses, as measured from human biomonitoring, in fact, are very low. They're generally, maximal in the range of about 4 ug/kg/day. But on average, very much lower even than that maximum value.

The maximum urine concentration that was identified in the MAA studies was 18.8 ug/L. And if you convert that to a daily intake dose, it would translate to a dose of about 3.3 ug/kg/day and about 0.66 ug/kg/day of an actual systemic dose. The value that they actually detected, in one of their women, as a maximum systemically absorbed dose, is really not out of line with existing biomonitoring studies that

have been conducted elsewhere around the United States.

But more importantly, you also will note in the MAA breastmilk concentrations actually were relatively close to the goat milk concentrations that were done in the toxicokinetic studies. But those goats, remember, were actually given 5 to 8 mg/kg/day. That's a dose that's estimated to be at least 2,000 times higher than what women might receive, and particularly, pregnant women.

There's been an analysis of women and what their dietary patterns are. And basically, you can estimate that their exposure would be no more than about 1 ug/kg/day. So again, it's a substantially lower dose. Biomonitoring studies clearly indicate that the MAA report in detection of milk concentrations are implausibly high.

The biomonitoring studies also confirm that even if those values were real, they're unlikely to present a health problem for nursing infants. As you can see at the very end bullet, and I think that's the key point to be made on this slide, that if you take the milk concentrations as reported in the MAA study, it would still translate to a very low dose

exposure to those nursing infants. Again, it's not likely to present a health problem.

Turning to the next slide then, what about the physicochemical characteristics? Are they at all indicative that glyphosate might have that potential to bioaccumulate in breastmilk? Well, glyphosate, of course, is an organic acid so it has a pKa of 2.3, inferring that it essentially has complete ionization at physiological pH. The octanol-water partition coefficient actually of glyphosate, not surprisingly then, is very low at pHs 5 to 9.

And you can compare that to the log or water partition coefficient for a typical agent which is known to bioaccumulate, a PCB, and you can see a dramatic difference in those values. When you pull that information together, coupled with the observation that, obviously, the toxicokinetic studies indicate very limited distribution to milk, that is entirely consistent with the physicochemical properties of glyphosate that would not suggest that it's going to have to have that potential to distribute to milk in any substantial quantities and certainly not bioaccumulate in milk.

By way of conclusion then, the MAA study certainly should be regarded as a preliminary study containing substantive methodologic deficiencies. The MAA report of high concentrations of glyphosate in human breastmilk is implausibly high when it's considered in the context of animal toxicokinetic studies and the physicochemical properties of glyphosate and what we know about the toxicokinetics of glyphosate in animals. There's no plausible means by which you could achieve the concentrations of glyphosate reported in the breastmilk in that particular study.

Therefore, the conclusion then is the breastmilk certainly is not regarded as a significant source of glyphosate exposure in nursing infants. Thank you.

DR. JAMES MCMANAMAN: Any questions for Dr. Bus?

(Whereupon there was no response)

DR. JAMES MCMANAMAN: Just have a quick question, this is Jim McManaman. If the concentration found in human breastmilk was equivalent, one sample, I guess it was, was equivalent to what was found in

goats dosed with 1,000 times higher. How do you explain that?

DR. JAMES BUS: Well, and that's, in fact, the artefact that I'm pointing to. The very fact that those --

DR. JAMES MCMANAMAN: You're saying it's not actually glyphosate?

DR. JAMES BUS: Well, yeah. It must be an artefact of the analytical measurement.

DR. JAMES MCMANAMAN: Okay.

DR. JAMES BUS: Because if it were true, you would have to expect that the humans would have had to have been exposed to massively larger glyphosate doses. Which obviously, we know from --

DR. JAMES MCMANAMAN: Or there's an alternative mechanism, I suppose.

DR. JAMES BUS: -- human biology is not the case.

DR. JAMES MCMANAMAN: Okay.

DR. JAMES BUS: So, yes. That's the point I was making.

DR. JAMES MCMANAMAN: Okay. I think we'll take a break now. This is the end of these set of presentations. And during the break, if we could

get Deborah Hommer, Scott Slaughter, Sabitha Papineni, sorry about that, and Jacob Vukich to the podium, we will begin the next session.

(Whereas a break was taken)

DR. JAMES MCMANAMAN: Okay. The building management heard this was a hot topic, so they decided to drop the temperature in the room. But we hope we're getting it fixed.

Okay. The next presenter is Deborah Hommer from Virginians for Medical Freedom.

Ms. Hommer. Push the button. There you go.

MS. DEBORAH HOMMER: All right. Good afternoon. My name is Deborah Hommer. I am living proof of the detrimental effects of herbicides being sprayed on our food. Three plus years ago, I was diagnosed with Hashimoto's thyroid disease. Within three weeks of going organic and gluten free, I had lost three inches around my waist, lost the foggy brain, was sleeping through the night, and I was sleeping hard, something I hadn't done in 10 years.

Presently, any time I eat gluten that not's organic I have the same issues. I am currently president of Virginians for Medical Freedom. I am

here in alliance with Moms Across America. And we are requesting your partnership in reversing the rising trend of autism. There is scientific evidence which shows that glyphosate is likely a major contributing factor to autism in many ways. We will review seven points regarding the connection between glyphosate and autism which we insist that you take into consideration in the assessment of glyphosate.

Glyphosate has been detected by multiple labs in multiple batches of tests to be present in the majority of childhood vaccines and in the flu shot. The MMR vaccine has levels of glyphosate 25 to 35 times higher than the other vaccines.

And let me just add here I did read Monsanto's response to using the ELISA method. But my rebuttal to them is that the FDA uses the ELISA method to evaluate vaccine effectiveness for both humans and for veterinarians. If the FDA uses it then our studies are good.

Okay. This is very significant because the MMR vaccine is the one reported by CDC Lead Scientist William Thompson that says: "To cause autism across the full study of children in the higher

levels in African-American boys. Glyphosate has never been tested or approved for injection directly into an infant's muscle tissue, which affects the bloodstream and has direct access to the blood-brain barrier."

No one can legally or scientifically say that injecting glyphosate into an infant is safe. Glyphosate is likely present because of the high residue levels allowed by the EPA. The EPA allows glyphosate residue levels up to 400 parts per million on GMO grains and grains sprayed with glyphosate as a desiccant fed to livestock. The livestock tendons in bone marrow are then used for gelatin and serums used in vaccines.

Monika Kruger's work has shown that glyphosate accumulates in these animal parts. Tests have shown high levels of glyphosate in gelatin, which vaccines are grown on. Other studies have also shown high glyphosate levels on soy and in eggs, which are also used in vaccines.

Glyphosate increases the impact of other toxins present. The presence of glyphosate in vaccines could very well explain why vaccine damage did not spike in 1921 when mercury was first put in vaccines. It was not until the late 1900s when there

was a huge spike in vaccine damage, autism. Exactly when GMOs allowed glyphosate-sprayed grains to enter our food, livestock feed, and apparently, our vaccine supply.

Scientists and we believe that glyphosate is working in conjunction with the other toxins in vaccines and food and has caused severe harm to an entire generation of our children. In the year 1975, when Roundup was brought to market, 1 in 5,000 children were on the autism spectrum, in 1985, 1 in 2,500; in 1995, 1 in 500; 2001, 1 in 250; 2004, 1 in 166; 2007 1 in 150; 2009, 1 in 110; 2012, 1 in 88. Today, 1 in 45 children are on the autism spectrum.

If the current rates of diagnosis continue as they are, by 2025 one in two children born will be on the autistic spectrum. 50 percent of our children will be compromised just 16 years from now. That's your grandchildren. With 50 percent of the entire generation on the autism spectrum, what will our society and education system look like, our healthcare budget, our military? The fact is we'll lose status as a world power if we do not protect our children.

Because glyphosate is never used alone, the presence of glyphosate means that the co-formulants are very likely present in vaccines, as well, which have been found to be 1,000 times more toxic than glyphosate alone. Any assumption that the presence of glyphosate in vaccines is acceptable is not taking into account the toxicity of the co-formulants which always accompany glyphosate.

Glyphosate has been described as scientists to impact the neurological system in three ways. It can break down the blood-brain barrier and allow toxins into the brain. It can destroy the beneficial gut bacteria and promote the proliferation of the pathogenic gut bacteria. The pathogenic gut bacteria have on the outer walls lipopolysaccharides which signal the vagus nerve to tell the brain to go on attack.

The stimuli microglia cells in the brain go on attack and make glutamate, an excitotoxin, which excites and eventually can exhaust the brain neurons causing them to die. The glyphosate presents calcium, which goes in and out of the brain cells, from exiting. When the calcium does not exit, the neuron dies. Anyone with reason can explain why a

child suddenly develops a tic, stammer, or does not make eye contact that part of their brain neurons have been damaged.

The chemical study released July 2016 finds IQ in children born to mothers who, during the pregnancy, were living in close proximity to chemical-intensive agricultural lands where organophosphate pesticides were used. We assert that all American children are being impacted by pesticides and herbicides insidiously solely through our food, water, and vaccines. And we are causing a dumbing of America and a more violent American through the chemical farming process. Glyphosate --

DR. JAMES MCMANAMAN: Ms. Hommer, you had five minutes, and you're way over time now. Are you about to wrap up?

MS. DEBORAH HOMMER: Yes. Yes. I'll go to my last one. Okay. Pederson from Denmark's pig studies showed a repeated and dramatic increase in miscarriage, birth defects, small litters, and infertility when his 30,000 pigs ate grains sprayed with glyphosate. Allowing pregnant women being injected with the flu shot or vaccine while growing a fetus is a recipe for disaster. Glyphosate has been

shown to remain viable in dark, salty water for 315 days. Our wombs contain dark, salty water.

These children that do survive have the highest rates of autism, allergies, asthma, autoimmune diseases, diabetes, and obesity in the world. One out of two American children are sick, and we are here discussing whether or not it is okay to spray a chemical on our food which destroys the immune system, stimulates cancer cell growth, is a neurotoxin, causes antibiotic resistance, and liver and kidney damage. The spraying of toxic chemicals must stop. You must have the courage to say enough, no more.

DR. JAMES MCMANAMAN: Thank you.

MS. DEBORAH HOMMER: We thank you for listening and having the courage to do the right thing, to rightfully and justifiably find glyphosate a carcinogen as the EPA documentation has shown since 1983.

DR. JAMES MCMANAMAN: Thank you very much.

Questions?

(Whereupon there was no response)

DR. JAMES MCMANAMAN: All right. Thank you very much.

Next up, Scott Slaughter.

MR. SCOTT SLAUGHTER: Hello. I am Scott Slaughter. And I am commenting today on behalf of the Center for Regulatory Effectiveness. CRE's comments focus on the federal government quality standards that apply at the EPA's cancer assessment. These quality standards also apply to this SAP review of that assessment.

In summary, EPA's glyphosate cancer assessment cannot use or rely on any SAP report or on any other report study, assessment, review, or any other information that does not meet these mandatory federal government quality standards. For example, the IARC glyphosate review is subject to these quality standards. And it does not meet them. Consequently, EPA cannot use or rely on the IARC review.

The overwhelming weight of evidence is that glyphosate does not cause cancer in humans. Any contrary EPA conclusion would be inaccurate and misleading and violate mandatory government quality standards.

I'll now try to discuss these points in more detail. This SAP is a peer review panel subject to federal government quality standards, including the

Information Quality Act, or IQA. The IQA is a federal statute that imposes quality standards on all information disseminated by EPA and by most federal agencies. Information and dissemination are broadly defined. EPA and other agencies cannot use or rely on information that does not meet these mandatory standards which are designed to help ensure that the government acts on sounds science.

Pursuant to its authority under the IQA, the U.S. Office of Management and Budget, or OMB, published an information quality bulletin for peer review. This SAP is a peer review panel subject to the OMB Peer Review Bulletin's requirements. CRE's written comments, which I hope you have by now, explain why the EPA cancer assessment and this SAP's peer review of it are subject to the most rigorous quality standards under the OMB Peer Review. In the interest of brevity, I will not repeat that examination in my oral comments.

I do, however, emphasize that the OMB Peer Review Bulletin requires that EPA inform the SAP reviewers, that's you, and I quote: "Of applicable access, objectivity, reproducibility, and other quality standards under Federal Information Quality

Laws." Based on what I've heard and read, EPA has not completely informed this SAP of these quality standards. Consequently, I've tried to fill in some of the gaps.

In general, OMB and the EPA IQA Guidelines require that EPA ensure, and I quote: "The objectivity, utility, and integrity," close quote of all information that EPA disseminates, uses, or relies on. The OMB and EPA IQA Guidelines explain, I quote again: "Objectivity focuses on whether disseminated information is being presented in an accurate, clear, complete, and unbiased manner. And as a matter of substance is accurate, reliable, and unbiased," closed quote.

Influential information like EPA's cancer assessment is subject to especially rigorous standards of transparency and reproducibility. EPA's IQA Guidelines explain that, and I quote again: "A will facilitate the reproducibility of such information by qualified third parties to an acceptable degree of imprecision. For disseminated influential, original, and supporting data, EPA intends to ensure" -- I want to emphasize that. EPA intends to ensure "reproducibility according to

commonly accepted scientific, financial, or statistical standards."

These IQA Quality Standards apply to all sources of information that EPA is considering for a possible use in a risk assessment like EPA's cancer assessment. This applicability includes information quote: "That EPA obtained for use in developing a policy, regulatory, or other decision," close quote. Like SAP reports or the IARC glyphosate review. This means that both the SAP report and the IARC glyphosate review must meet IQA standards before EPA can use or rely on them in the cancer assessment, which itself must meet these quality standards.

Therefore, if this SAP discusses the IARC review in the SAP's peer review report, then the SAP must determine whether the IARC meets IQA standards. I'll try to explain why the review does not meet IQA standards. First, however, to prove that I'm not making all of this up, I'd like to provide some examples of federal agencies rejecting similar studies or reports because they do not meet IQA standards.

As a first example, EPA was preparing an ecological risk assessment for the herbicide

atrazine. The available external non-EPA studies disagreed as to whether atrazine causes adverse endocrine effects in amphibians. CRE submitted a request for correction under the IQA which provides a statutory right to seek and obtain correction of any information maintained and disseminated by the Agency that does not comply with IQA standards.

CRE's atrazine RFC, request for correction, claimed that none of the available amphibian effect studies could be used for the atrazine risk assessment because none of the studies used test methods that have been demonstrated to be accurate and reliable. EPA agreed with CRE, did not use any of the studies, and supervised development of properly validated studies which were -- and other SAPs helped the EPA formulate the procedures for developing these accurate and reliable amphibian effects tests which were subsequently used by EPA.

As a second example, CRE argued to the National Oceanic and Atmospheric Administration that reports by the International Welding Commission Scientific Committee had to meet IQA standards. If the reports do not meet these standards, then NOAA

can't use them to regulate various industries under the Marine Mammal Protection Act.

NOAA wrote back agreeing with CRE. NOAA's letter stated and I quote: "Prior to releasing or relying on third-party information, such as IWC Scientific Committee reports, NOAA's National Marine Fishery Service must conduct a pre-dissemination review to determine that it is a known quality and consistent with NOAA's IQA guidelines."

As a third example, the U.S. Department of Health and Human Services informed the World Health Organization that HHS could not use a WHO report entitled, quote, "Diet and Nutrition in the Prevention of Chronic Disease," close quote, because the report does not meet IQA requirements. And your written materials contain links where you can find all these documents I've talked about online.

Now closer to home, the IARC glyphosate review is information that doesn't meet IQA standards. Therefore, it cannot be used or relied on by EPA. In reaching this conclusion, we relied on several documents that are identified with links in CRE written comments. I won't repeat this long list of documents in my oral comments. I do, however, suggest

that the panel pay particular attention to the public comments that have made during the last two days. And to the following documents which draw on EPA's record for this SAP.

The documents in the record are one, comments by CropLife America on EPA's glyphosate cancer evaluation; two, Monsanto's critique of the IARC review; three, comments submitted by Intertek Scientific & Regulatory Consultancy; four, comments submitted by Dow AgroSciences; and five, comments submitted by Joseph K. Hasemen, J.K. Haseman Consulting.

Based on these documents and based on other documents in this SAP record, and based on the extensive and quite excellent public comment that's been made over the last two days, the IARC glyphosate review is not accurate. It is not reliable. And it does not meet IQA standards.

And it cannot be used by EPA because, for example, one, IARC relied on study results that are not statistically significant; two, IARC relied on studies where there was no dose-response curve; three, IARC relied on studies where there was no consistent association between glyphosate and cancer; fourth,

there's no mode of action for glyphosate and cancer that's been demonstrated; five, IARC relied on studies that used non-standardized and invalidated test methods and procedures; six, IARC was bias in its exclusion of tests; seven, IARC used tests that are nor reproducible; and eight, IARC's conclusions are not biologically plausible.

Many other expert panels have reviewed glyphosate and cancer. None of them have concluded that glyphosate causes cancer. There is no reason to believe they're all wrong and that IARC is right. The overwhelming weight of evidence that's been presented to this SAP is that glyphosate does not cause cancer. Any different conclusion would be incorrect, inaccurate, and misleading. And it would be inconsistent with the government's quality standards.

In other words, EPA got it right this time. CRE appreciate this opportunity to comment. I also emphasize CRE's great respect for science advisory panels. We believe they are essential to ensuring that EPA's pesticides assessment and regulation are based on fact and science and not bias and political ideology. Thank you. And I'll try to answer any questions you might have.

DR. JAMES MCMANAMAN: Thank you, Mr. Slaughter.

Questions?

(Whereupon, there was no response)

DR. JAMES MCMANAMAN: All right. Thank you very much.

All right. Thank you very much.

I think we'll move on to the next presentation, Dr. Papineni. Am I anywhere close?

DR. SABITHA PAPINENI: I think, actually, for the first time you got it right.

DR. JAMES MCMANAMAN: Good. All right. I'm making progress.

DR. SABITHA PAPINENI: I was really happy to hear that.

Good afternoon, everyone. My name is Sabitha Papineni. And I am the regulatory toxicologist at Dow AgroSciences in the Human Health Assessment Group. And I really want to thank EPA and the panel for this opportunity to provide comments today.

And I'm here today to focus on our comment on the charge question five which talks about the EPA's evaluation process in the carcinogenicity

potential evaluation, particularly referring to the completeness, transparency, and scientific quality of the process.

And Dow AgroSciences supports and is in agreement with the EPA's evaluation and interpretation of the data. We believe EPA has conducted a robust, science-based assessment in a highly transparent manner in reaching the determination of the descriptor "not likely to be carcinogenic to humans" for glyphosate.

A brief background, again, we've heard it several times in the presentations. Glyphosate was first registered in 1974 in many countries, including U.S.A. And Dow AgroSciences is a technical registrant for glyphosate for more than 15 years in U.S. And the table I have here shows that over these years, there have been several evaluations and reevaluations by regulatory agencies across the globe. And consistently, they have come to the same conclusion that glyphosate is not carcinogenic to humans.

Except in 2015, the International Agency for the Research on Cancer categorized, for the first time, glyphosate as a Category 2A probable human carcinogen. However, if you look at the recent

evaluations of the subsequent reviews by other regulatory agencies, again, consistently these six regulatory agencies that I have listed in this table also concluded that it is not carcinogenic to humans. Again, consistency is one of the criteria for the Bradford Hill criteria.

EPA in its current evaluation for the carcinogen potential have relied on the 2005 EPA Guidelines for Carcinogenic Risk Assessment. And again, these are the improved guidelines which include the mode of action and also the human relevance framework, and sort of, again, using the defaults. Also, these are the improved methods over the 1996 interim guideline for carcinogen risk assessment. And again, based on these guidelines, there are five weight-of-evidence descriptors chosen.

More importantly, again, in order to establish the causal relationship between a cause and effect, EPA has relied on the modified Bradford Hill criteria which is a widely accepted guidance in order to establish the relationship. And this relies on the criteria, again, evaluating the multiple lines of evidence for strength, consistency, dose-response,

temporal concordance, and last, but not the least, the biological plausibility.

And we've heard the database of the glyphosate again. You know, there are multiple lines of evidence in, again, including the animal findings, metabolism studies, structural relationships with other carcinogens, mode of carcinogenic action information, and also the human data. And EPA has reviewed all these lines of evidence in their evaluation.

Coming to glyphosate, again, we've heard it several times. And it's an extensive database available to assess the carcinogenic potential. Again, EPA has used the 2010 framework for incorporating the human Epi data into the human risk assessment. And again, the framework that emphasizes on starting with the problem formulation.

Again, this is consistent with the WHO's updated chemical safety mode of action/human relevance framework. Again, asking to integrate the information at different levels of biological organization and again using the modified Bradford Hill criteria, which is the widely-accepted criteria.

Looking into the different lines of evidence, again, just a summary of genotoxicity potential here. To begin with, glyphosate does not have any structural alerts for any genotoxic potential. And there are nearly 90 genotoxicity studies. And I have it highlighted there because if you compare, again, going back to the slides presented by Dr. Niemann yesterday, typically for administration of a pesticide it would require -- this is way more than what is typically required for registration of a pesticide.

And these were extensively investigated, including the relevance and reliability of different endpoints. And if you look at the entire database, there is no convincing evidence that glyphosate induces mutations in the high weighted in vitro assays and also in vivo mammalian systems.

And the only positive findings, again, reported in the in vivo were seen at relatively high dose levels which are not relevant for human health risk assessment. And this is again, consistent with all the reviews from other regulatory agencies across the globe, including the WHO's JMPR.

Looking at the animal data, there are, again, 15 animal carcinogenicity studies which is, again, way more than what is typically required for registration of a pesticide across the globe with any regulatory agency. Again, the weight-of-evidence analysis from all the studies again concludes that it's not a carcinogen. And again, incidences that were observed either all the issues listed out there, the reason why it was determined that they're not treatment related.

Moving on to the epi data, again, there are 23 epi studies that were extensively investigated in the EPA's paper. Again, there was a confusion about 24 versus 23 yesterday that was brought. I think there were 24 epi studies that have undergone the detailed evaluation. But I think it was a Cocco 2013 paper that was considered for the evaluation because that was not considered informative because of the limitations that the study suffered from.

Again, there was no evidence of an association between glyphosate exposure and solid tumors. We did not find any association between the glyphosate exposure and leukemia or even Hodgkin's lymphoma. For the associations claimed for non-

Hodgkin lymphoma, again, chance and recall bias cannot be excluded. And the results contradicted with the higher quality Ag Health Study. Therefore, an association cannot be established based on the available data.

I think overall with a thorough integrative weight evaluation of all the data available, again, with no genotoxicity potential and no evidence from the animal data and no evidence from the epi data, I think the descriptor "not likely to be carcinogenic to humans" is strongly supported for glyphosate.

Concluding remarks, again, an extensive database, as I said -- again. It's a lot of studies when compared to what is required for a typical registration of a pesticide -- exists for evaluating the carcinogenic potential of glyphosate and the weight-of-evidence analysis conducted according to the 2004 EPA guidelines. Clearly, it has a strong support for the descriptor "not likely to be carcinogenic to humans" for glyphosate.

With that, I thank the panel for their attention. Thank you.

DR. JAMES MCMANAMAN: Thank you.

Questions?

(Whereupon there was no response)

DR. JAMES MCMANAMAN: Okay. Once you've finished your presentation, you don't have to sit up here. You can if you want to. But if you'd like to sit somewhere else, I believe that's fine. All right.

All right, Dr. Vukich.

DR. JACOB VUKICH: Yes.

DR. JAMES MCMANAMAN: You're up next.

DR. JACOB VUKICH: Thank you. Good afternoon, SAP panel members, EPA officials, and guests. My name is Jake Vukich. And I am the manager of U.S. Registration and Regulatory Affairs for DuPont Crop Protection. Thank you for providing time to me today so that I can present some brief comments on behalf of DuPont.

DuPont is a science company. The DuPont agriculture segment, which consists of DuPont Crop Protection and DuPont Pioneer, is an industry leader dedicated to using global science to deliver local solutions. Meeting the needs of the growing global population, including the need for new tools

that can help farmers grow more food per acre is at the very heart of DuPont's business.

From Delaware to Iowa and Minnesota to California, U.S. farmers face challenges. They solve these challenges by applying the tools of modern agriculture. These tools include crop protection products, biotechnology derived seeds, and the combined use of both.

One of the common tools is glyphosate. We are providing these comments today because glyphosate brings significant benefits to agriculture. It is almost important for DuPont and for all of agriculture to support science-based decision making and risk assessment methodologies that are consistent with the risk benefit mandates of FIFRA.

With that background, I want to direct my comments to three areas relevant to this SAP. Number one, our agreement with the EPA's evaluation process and its conclusions; number two, the benefits of glyphosate to agriculture; and number three, the benefits of glyphosate-tolerant cropping systems.

Our first area of comment is that DuPont is in general agreement with the process EPA used to evaluate the carcinogenic potential of

glyphosate and the conclusion reached by the Agency. On behalf of DuPont, I commend the Agency for their detailed and robust risk assessment. The Agency did a thorough job of evaluating and interpreting available data for each line of evidence, applying risk assessment approaches and not hazard-based approaches, and conducting proper weight-of-evidence analyses to reach its conclusions.

We support the overall conclusion by the EPA that glyphosate is not likely to be carcinogenic to humans at doses relevant to human health. Additionally, we note that this assessment, like any outcome of a regulatory action or decision by the Agency, should be consistent with the following regulatory principles. Regulation should protect human health and the environment while promoting innovation.

Decisions should be based on best-available scientific data and appropriate technical information. Regulation should be cost effective and commensurate with the risk. Regulation should be adopted through a public and transparent process. Regulation should accommodate new evidence and

learnings. And regulation should be consistently applied and enforced.

These regulatory principles have been outlined in several executive orders across multiple administrations and are reflected in the current risk assessment and to their current registration review process for glyphosate. Since the initial registration of glyphosate in 1874, numerous human and environmental health analyses have been completed for this herbicide. And all anticipated exposure pathways have been considered. I'd like to provide here some additional comments on this SAP process and in response to the charge questions from EPA.

Point number one, an extensive effort has been undertaken by the Agency to collect, evaluate, and integrate the multitude of studies that may inform the human carcinogen potential of glyphosate.

The EPA issue paper outlines the structured approach taken by the Agency to collect relevant studies and to outline study quality considerations for the epidemiology, cancer bioassay, and genotoxicity data that form the basis of this assessment. We support EPA's use of the World Health

Organization International Program on Chemical Safety mode of action human relevance framework as an underlying principle to integrate these multiple lines of evidence.

Point number two, EPA notes that a key component in its evaluation is the use of the modified Bradford Hill criteria, a widely-accepted method in the scientific community for investigating cause and effect relationships and to evaluate strength, consistency, dose-response, temporal concordance, and biological plausibility in a weight-of-evidence analysis.

In particular, we wish to highlight our agreement with the risk assessment approach used by EPA. Under FIFRA, EPA must weigh the risk of pesticides to human health and the environment against the benefits of those pesticides via a multistep process called risk-benefit balancing. Further, to approve or reregister a pesticide under FIFRA, the EPA must be able to define how the product may be used without unreasonable adverse effects on the environment or on human health. We are appreciative of the agency's effort with glyphosate, as well as with other products, to uphold this safety standard.

Point number three, another aspect of EPA's evaluation of glyphosate that we would like to highlight is related to animal studies and the exclusion of high-dose studies. We support the conclusion that there is an absence of corroborating pre-neoplastic lesions or related non-neoplastic lesions. We further support the agency's conclusion that there is a lack of progression to malignancy to support tumor findings.

We also support EPA's exclusion of high-dose studies in this human health risk assessment. As the Agency carefully noted, the high-end estimates of exposure based on the currently registered used for glyphosate in the United States have been calculated as 0.23, 0.47, and 7 mg/kg/day of body weight for potential dietary, residential, and occupational exposures, respectively. Thus, studies that observe tumors at doses approaching or exceeding 1,000 mg/kg/day of glyphosate administration are not relevant for human health risk assessment.

Point number four, the carcinogenic potential of glyphosate has been recently reviewed by a number of regulatory and non-governmental bodies around the world. The conclusion by EPA that

glyphosate is not likely to be carcinogenic to humans is consistency with the conclusions reached by other regulatory authorities, including the European Food Safety Authority, the Japanese Food Safety Commission, the Australian Pesticides and Veterinary Medicines Authority, the New Zealand EPA, and the Canadian Pest Management Regulatory Agency.

In May of this year, the World Health Organization's Joint Meeting on Pesticide Residues also concluded that glyphosate is unlikely to pose risk to humans. The scientific consensus of these reviews overwhelmingly supports the conclusion that this agriculturally important and widely used herbicide does not pose a carcinogenic risk to humans.

The second area of comment relative to this SAP that I would like to briefly address is the benefits of agriculture of glyphosate to agriculture. Simply put, glyphosate has become the most important herbicide in global agriculture. For farmers, glyphosate-containing herbicides provide simple, flexible, and cost-effective weed control.

Glyphosate herbicides can also control weeds that might otherwise persist for years. These weeds compete with crops for water, light, and

nutrients. For perennial grasses and their root systems, glyphosate has an average control rate of 90 percent. Unlike several other herbicides which act on either motocotyledons or dicotyledons, glyphosate is effective on both types of weeds thus providing broad-spectrum control.

By controlling a broad spectrum of weeds and their entire root systems, glyphosate has eliminated or reduced the need for mechanical plowing of the soil. This is important since cultivated land is prone to soil erosion and minimal soil disturbance practices are sustainable alternatives that help to protect the soil from degradation, encourage greater soil microbial biomass and enzymatic activity, and reduce greenhouse gas emission and energy consumption.

Glyphosate enables farmers to establish crops relatively quickly and easily because it can be used with a minimum tillage approach. This makes glyphosate a popular tool for many farmers that desire to incorporate these soil conversation practices into their operations. The use of glyphosate herbicides has become so widespread because of the benefits offered to farmers. Applying glyphosate before the new crop is planted has the potential to produce up to

30 percent higher yields at harvest, depending on the weed population and other environmental conditions.

Another important benefit for farmers is that glyphosate also breaks the green bridge in that it removes the weeds that might otherwise act as an intermediate host for parasites and other plant disease vectors when young crops are emerging. For instance, aphids are a common vector of plant viruses such as the barley yellow dwarf virus that can destroy up to half of many cereal crops. Applying glyphosate removes potential aphid host plants, reducing the risk of virus-carrying aphids transferring from weeds to the crop plants when they emerge.

My last area of comment relative to this SAP is in regards to the benefits of glyphosate to agriculture in glyphosate-tolerant cropping systems. Combining the broad-spectrum activity of glyphosate with crops tolerant to that herbicide has enabled simplified and efficient weed control which, in turn, reduce the need for alternative technologies such as tillage and hand labor. Glyphosate is currently used on the majority of corn, cotton, sugar beet, canola, and soybean acres in the United States.

Perhaps the most notable and economically significant impact of glyphosate is that it has supported a transformation in agricultural practices. Prior to the introduction of glyphosate-tolerant crops, soybean farmers had few post-emergent herbicide options that would control broadleaf weeds without injuring the crop. Following the introduction and adoption of glyphosate-tolerant crops, glyphosate displaced several other herbicides, lowered the cost of weed management, and reduced the amount of labor needed to manage weeds in these crops.

Today, glyphosate-tolerant crops are a foundation of U.S. production and exports of corn, soybeans, and canola thus providing significant economic returns to U.S. agriculture.

As I noted earlier, glyphosate alone and glyphosate used in combination with glyphosate-tolerant crops has reduced the need for mechanical tillage. This reduction provides many well-documented benefits to the farmers, the public, and the environment overall from savings in fuel and labor cost to reduced soil erosion, increased wildlife habitat, and improved water and air quality. Conventional tillage practices sometimes require as

many as five passes over the land with a plow. However, no till requires just a single pass to plant seeds.

A Purdue University study calculated that a farmer implementing conversation tillage can save 225 hours of labor per year on a 500-acre farm. That is the equivalent of four 60-hour workweeks saved per year. No till farming can actually be utilized, to drastically increase water infiltration and retention by the soil. Meaning there is less run-off and more soil moisture available for the crops.

A 2016 report from the National Academy of Sciences on the impacts of genetically engineered crops noted that it is difficult to establish a cause-and-effect relationship between the adoption of herbicide-tolerant crops and conservation tillage in general. However, the same report acknowledges that multiple studies have found that increases in conservation tillage and reduced tillage follow the adoption of herbicide-tolerant crops.

The association between conservation tillage and herbicide-tolerant crop adoption is strongest for soybean, cotton, and sugar beet. For example, an analysis of the relationship between

conservation tillage and glyphosate-tolerant soybean adoption found that adoption of that cropping system has a direct positive influence on the adoption of conservation tillage practices. With a one percent increase in glyphosate-tolerant soybean adoption leading to a 0.21 percent increase in conservation tillage.

A 2012 USDA Agricultural Resource Management Survey found that approximately 97 percent of soybeans grown in the U.S. were herbicide-tolerant. And 70 percent of U.S. soybean growers practiced conservation tillage. The economic benefits of glyphosate-tolerant cropping systems have grown from just providing farmers with simplified weed management to becoming the foundation of trade between exporting and importing countries. Specifically, glyphosate-tolerant soybeans drive most of the value created by U.S. export markets.

A 2010 report from the National Research Council within the National Academies of Science examined numerous reports and studies and noted that the availability of herbicide-tolerant soybean partially drove increases in soybean plantings

in both the U.S. and abroad, particularly in Argentina and Brazil.

The National Research Council went on to observe that increased soybean availability reduced prices making them a more affordable component of food and feed. Further, reduced feed prices were a significant benefit for livestock producers around the world because animal feed can represent half the cost of livestock production.

Maintaining access to this vital technology is essential not only for farm-level productivity but also for food security around the world. Reverting to pre-glyphosate-tolerance agronomic practices would have significant effects on labor requirements, significant environmental impacts, and would reduce the availability of commonly traded commodities. Notably, losing access to glyphosate would also complicate efforts to control weeds in other agronomic systems as well in non-agricultural settings.

In conclusion, DuPont is deeply invested in building resiliency in food systems around the world. Our investment in innovation and discovery supported farmers in the 20th century as they

increased agricultural productivity by more than 12-fold between 1950 and 2000. Today, we're providing the needed innovation as farmers rise to the 21st century challenge of increasing productivity by 60 percent between mid-2000s and 2050 in order to feed an expected nine billion people.

As a science company and a leader in the agricultural industry, DuPont strongly supports science-based decision-making by EPA. DuPont also strongly supports risk-assessment methodologies that are consistent with the FIFRA risk benefit mandates. Our ability to continue to innovate and bring new products to market depends on it.

EPA's conclusion, after a robust risk assessment that glyphosate is not likely to be carcinogenic to humans at doses relevant to humane exposure, combined with the fact that glyphosate provides significant benefits to agriculture, clearly supports continued registration of glyphosate consistent with EPA's risk benefit mandate.

Thank you again for your time and attention this afternoon.

DR. JAMES MCMANAMAN: Any questions?

Yes, Ramesh.

DR. ARAMANDLA RAMESH: This is Ramesh. Does DuPont manufacture glyphosate?

DR. JACOB VUKICH: We are a registrant of end-use products with glyphosate. We do not manufacture glyphosate.

DR. ARAMANDLA RAMESH: Okay.

DR. JAMES MCMANAMAN: Other questions? Dr. Johnson.

DR. ERIC JOHNSON: I'm a little bit concerned about the overemphasis on the 1,000 mg/kg threshold. Over and over we keep on hearing that anything above that is not relevant to this assessment. But most of the chemicals which we do risk assessment on to protect the general population, let's take dioxin, for example, the level of the dioxin concentration in the general population is like 2 or 3 or 5 part per trillion.

To determine whether dioxin causes cancer in humans, we rely on occupational studies which have orders of magnitude exposure much greater than 3 parts -- usually more than 1000 even. If you look at the Nial (phonetic) study, I think the highest concentration was, like, 33,000 parts per trillion. We have all these very high exposures which are in the

manufacture of the compound which we don't see in the general population.

Yet, that's what we use. We extrapolate if we find that it causes cancer among workers, we've used that regulate the compound. And here, again, with glyphosate, we have a situation in which we do not have any information whatsoever from the manufacture of this compound where we would normally expect high levels of exposure to this compound. That troubles me.

The 1,000 I think is overemphasized too much because in practice, we always use, as Dr. Crump here who has worked on Benzene, it's the same thing with Benzene. I think that nowadays the average exposure is maybe 0.4. On studies we did on biomarkers, 0.4 was the maximum, 0.4 parts per million. And yet in industry, which we used to determine that benzene was the (inaudible), the levels were more than 400 of the 1,000 parts per million. And we used that to extrapolate and to protect the population.

DR. JAMES MCMANAMAN: Dr. Johnson, maybe this is an important point to bring up during

the charge question discussion. But we should be asking the presenter about his presentation. And --

DR. ERIC JOHNSON: Okay.

DR. JAMES MCMANAMAN: All right. I think unless there are other questions -- oh, Dr. Portier.

DR. KENNETH PORTIER: Just a quick question. Do you roughly know how many people in DuPont are engaged in the manufacturing or the mixing of glyphosate, glyphosate products in the U.S., not worldwide?

DR. JACOB VUKICH: Yeah. As I mentioned, DuPont is a registrant of end-use products. As such, we source those products from other sources. We do not manufacture those products. DuPont folks do not. Right. Right.

Dr. KENNETH PORTIER: Okay.

DR. JAMES MCMANAMAN: Okay. Thank you very much.

DR. JACOB VUKICH: Thank you. Thank you.

DR. JAMES MCMANAMAN: Okay. We are running a little bit ahead of time. We keep switching around from running behind to running ahead. What we

would like to stay on track to give the panelists plenty of time to engage in discussion of the charge questions, which was rather limited at the outset. Running ahead is going to beneficial in the long term for the panelists.

What we'd like to do right now is to bring up Kevin Hoyer, Andy Hedgecock, and Martin Barbre, if they're here, for presentations.

And ask, since we are running ahead, I think we'll have some time for people who are scheduled to present tomorrow to present today. If the folks from Syngenta, Consumer's Union, and Department of Agricultural, and Moms Across America are here and could let us know that they're ready to present, that would be great if they could come up and let Mr. Knott know about your availability.

Okay. Mr. Hoyer, American Soybean Association.

MR. KEVIN HOYER: Thank you. Good afternoon. My name is Kevin Hoyer. My wife, Jody, and I run a 500-acre soybean and corn farm nestled in the bluffs along the Mississippi River located just outside West Salem in West Central Wisconsin. I also work for a local family-owned independent ag retailer

as their agronomy department manager where I am the agronomist and carry the certified crop advisory credentials, which is also known as a CCA. I'm also a member of the American Soybean Association.

I offer these comments today to represent American's soybean farmers who have embraced the use of glyphosate. This panel has the potential to create significant change for every single soybean farmer in the U.S. While I have no expertise to offer on the scientific issues related to the carcinogenic potential of glyphosate.

But as a farmer who handles this product on a regular basis, I rely on the EPA and its longstanding conclusion reiterating just this September that glyphosate is not likely to be carcinogenic to humans at dose relevant to human health risk assessments. Further, no regulatory agency in the world considers glyphosate to be a carcinogen. I do want to impress upon the panel how important glyphosate is in pursuing what I believe is our common goal, continually improving the environmental sustainability of our crop production while growing a safe and abundant food supply.

And there is perhaps no crop protection product that has a bigger impact than glyphosate. Glyphosate has been instrumental in allowing me to use conservation practices that are beneficial to the environment that I farm in such as utilizing no tillage and reduced tillage practices. One of my fellow soybean farmers reminded me that production of agriculture looked like just 40 years ago, before glyphosate enabled a weed control system that was effective, safe, and easy to use.

Before that, we depended heavily on cultivation and tillage to control weeds. As a result, erosion was rampant, stream quality was heavily loaded with sediment which carried loads of phosphorous, typically from animal manures which was surface spread and could easily enter the streams. The snow-filled road ditches in the winter were black from the wind erosion of the soil on that winter snow. Many farmers at that time still had open tractors without cabs and suffered the exposure to chemicals used in that time which were many times more harmful to humans than the ones we have in use today.

When glyphosate became available, even before the adoption of biotechnology in our seeds in

the mid-1990s, it became one of the fastest adopted technologies of my career. The simple weed control it offered convinced farmers across the country to take the risk of adopting no tiller reduced tillage methods because we could now control weeds with minimal risk. The organic matter in our soil began to improve. Soil loss declined, water infiltration rates improved, and yields continued to increase.

As available agricultural lands continued to decrease, we need viable tools to improve the sustainability of our ag community. The sustainability of the environment is highly important to me, as I see the remaining effects of erosion and over intensive tillage on the landscape in the rolling ridges and valleys that are prevalent in my region.

Then came the glyphosate-tolerant soybeans. ASA strongly supports biotechnology. We believe the development of biotechnology enhanced soybean varieties and their products can benefit farmers, consumers, and the environment. Today, approximately 95 percent of the soybeans grown in the U.S. are Roundup Ready. That has led directly to 70 percent of soybean farmers now practicing conservation tillage.

Now soybean farmers are moving to adopt cover crops. Again, glyphosate will be essential because it allows us to terminate those cover crops safely and easily. The alternative to this is Paraquat, also known as Gramoxone. That product cost twice as a much as a restricted-use product and has the skull and crossbones on the label along with the words "Danger poison," which is the most hazardous designation of the pesticides.

Glyphosate, in comparison, only carries the caution designation, which is the lowest hazard. Losing glyphosate would mean a tradeoff with significant cost to farmer, pesticide applicators, and consumers. These are practical implications of the decisions this panel will make.

To conclude, I can follow a lifetime of continuous change in agriculture and trace the adoption of glyphosate to broad advances in agricultural sustainability, improving soil, water, and air quality for every American. Scientific studies concluded over the decades have overwhelmingly shown that when used according to the label glyphosate does not present an unreasonable risk or adverse effects to human, wildlife, or the environment.

On behalf of America's soybean farmers, I encourage the Agency to conduct a timely science-based review of glyphosate that takes into account the decades of research demonstrating the safety of this herbicide and the important benefit it brings to farmers and our shared goal of agricultural sustainability. Thank you very much.

DR. JAMES MCMANAMAN: Thank you.

Any questions for Mr. Hoyer?

(Whereupon there was no response)

DR. JAMES MCMANAMAN: Okay. Thank you very much.

Next up is Mr. Hedgecock from FMC.

MR. ANDY HEDGECOCK: So my name is Andy Hedgecock. And I'm the Director of Global Regulatory Affairs for FMC Agricultural Solutions representing our subsidiary, Cheminova A/S, who is a technical registrant for glyphosate. Our end-use product registrations for glyphosate were acquired as part of our Cheminova portfolio earlier last year. We are not currently marketing these products for ag uses in the U.S. But we do sell glyphosate for ag and forestry uses elsewhere in the world.

In the U.S., FMC sells glyphosate products to partners who serve the consumer market through both outlets and hardware stores and garden supply stores. I am here to comment specifically on the agency's draft framework and use of epidemiological studies.

As you've heard from many others today, respected regulatory authorities in Canada, Japan, Australia, Germany, and the European Union, as well as FAO, WHO, JMPR, having access to a broad dataset and criteria for use have concluded that glyphosate is unlikely to cause cancer in humans. The U.S. EPA's Carcinogen Assessment Review Committee came to the same conclusion. We're pleased to see that the agency's overall conclusion about the carcinogenicity classification for glyphosate supports the conclusions reached by these global authorities.

Although the agency's review of the carcinogenicity of glyphosate was consistent was the conclusions drawn by other global regulators, we have concerns about the agency's use of epidemiology study outcomes in its risk assessment. We also are concerned about the precedent this sets for the

registration and registration review of other chemicals moving forward.

We understand that OPP has been adopting this new approach on epidemiology study reports are evaluated, weighted, and then integrated into the risk assessment process. Thus, impacting how regulatory decisions are made. The shift in approach to use epidemiological study outcomes in human health risk assessment is precedent setting. And likely will have dramatic implications for the evaluation of chemicals regulated by EPA under FIFRA.

In 2010, OPP developed a draft framework for incorporating human epidemiologic and incident data in health risk assessment. The draft framework was introduced during an SAP held that same year. This was the only time the public had an opportunity to review and comment on the draft framework, as EPA did not issue the draft framework for notice or comment. The draft framework was created to guide the agency's use of human epidemiological studies in assessing potential risk.

In the draft framework, EPA itself acknowledged the risk and limitations of relying on epidemiological studies for regulatory decision-

making. Six years after the 2010 SAP, EPA has not yet responded to the multitude of comments expressing scientific concern over the use of epidemiological studies in human health risk assessment. And the Agency has not finalized the framework.

Nevertheless, EPA has begun using specific epidemiological study outcomes incorporating the correlations or associations into human health risk assessments in recommending policy changes with the potential to greatly impact pesticide registrations and registration reviews. We have observed the Agency has applied this draft framework to its review of cancer endpoints for glyphosate and non-cancer endpoints for chlorpyrifos, all other OPs, and atrazine and has done so inconsistently to reach their conclusions.

We strongly believe there is a need for guidance that formalizes criteria for the use of human epidemiologic studies and reported outcomes in human health risk assessments. We suggest the guidelines establish a standard set of study quality or acceptability criteria both for inclusion and also for omission of studies that do not meet the standard set of criteria.

Toxicological exposure studies submitted to EPA for consideration during registration or registration review processes must meet strict design and good laboratory practice quality criteria with disclosure all analyses. An equally strict set of quality criteria must be developed and applied to epidemiological studies.

All lines of evidence going into the review and analysis of epidemiology studies should be transparent and have a formalized standard of evaluation. This should include strengths and weaknesses of the study design, ability to replicate the study, reliability and accuracy of methods used to obtain study data, appropriateness, reliability, and accuracy of the data analysis employed, how study data and reporting biases are controlled, and reporting quality and accuracy.

Because it is not possible to evaluate these parameters without having access to the study data, a mechanism must be included to make the underlying epidemiological data available to the EPA and to the registrant so the quality of the data can be established and the published analyses confirmed or refuted. EPA and those undertaking studies should be

held to the same quality standards and requirements to provide access to studies, methods, and data as registrants are required to submit for every registration and registration review.

We support a weight-of-evidence approach for considering and evaluating study quality. Weights afforded observational human epidemiological studies compared to harmonized test guidelines for animal toxicity testing that are specifically designed for the risk assessment must be developed. Vetted, well-documented, quality studies reflect the evaluation of all mechanisms of toxicity.

When data complex is seen and decisions must be made, more robust data should be used over data of lesser quality. Epidemiological studies may form a basis for additional investigation, but they should not be afforded greater weight than high-quality guideline studies specifically designed for regulatory use. To do so would result in serious damage to the scientific credibility of EPA risk assessments and call into question the entire regulatory process under FIFRA.

In summary, overall, we believe the agency's review of glyphosate carcinogenicity data was

comprehensive. The Agency appears to have appropriately reached the same conclusion as other respected global regulatory bodies that glyphosate is unlikely to be a human carcinogen. While we agree with the agency's conclusions here in the review of glyphosate, we believe there are significant problems with the EPA's use of epidemiologic studies in its glyphosate evaluations.

Our comments should, in no way, be seen as supportive of current EPA actions involving the use of epidemiological studies under the 2010 draft framework for other classes of chemistry. FMC has concerns about the use of the 2010 draft framework because of the inconsistencies in EPA's application and the use of the draft framework for prior chemical reviews that primarily focused on non-cancer endpoints. EPA is using that 2010 draft framework for regulatory decision making, without having responded to comments submitted six years ago identifying issues with the draft framework.

FMC supports CropLife America's request to have the revised draft framework subjected to public notice and comment. We encourage EPA to provide stakeholders the opportunity to help develop a

set of criteria for determining the reliability and acceptability of epidemiological studies for the use in human health risk assessment and for reestablishing a reliable, predictable process for pesticide registration and registration review.

Until the framework is finalized after consideration of all public comments, EPA should not employ the draft framework for decision-making. Thank you.

DR. JAMES MCMANAMAN: Thank you.

Questions. All right. Oh, Dr. Portier.

DR. KENNETH PORTIER: Can't resist. I was on that panel that reviewed the guidelines. And one of the discussions we had was about working with industry to develop epi studies in the manufacturing facilities to understand higher-dosed exposed humans. The nice thing about that is that you can incorporate a lot of what you're asking for, which is tight protocols, you know, good measurement, known population.

Of course, it's a healthy workforce so there's some issues there. But a lot of what you're asking for could come out of that. In a lot of other

chemicals, I'm seeing assessments. That's usually the best human data that we can have. Is that the kind of thing you're asking for here?

MR. ANDY HEDGECOCK: What we've heard throughout the process over yesterday and today is the ability to produce that data in worker exposure. I'm not an expert in that area or involved in that. My understanding is, from listening to Dr. Acquavella, that it would be difficult or challenging to produce. I would be open to being in part of that conversation on seeking that out from an FMC perspective.

DR. KENNETH PORTIER: And I apologize for not being here yesterday to listen to it.

MR. ANDY HEDGECOCK: That's all right.

DR. JAMES MCMANAMAN: Other questions?

Did you have a -- no, I'm sorry, Dr. Johnson.

DR. ERIC JOHNSON: Yeah. Let me just point out the fact that we have a problem also in academia, really, the lack of access to industry data. And I've been working for, what, 30 years, I think, in occupational studies. And not in one instance has industry granted access to their data. And that's very, very frustrating for us working in that field to

think that all the -- I mean to me it's troubling because all the data would be coming from industry.

And industry can decide what epi studies they want to do. And nobody has any control to it. Or industry can decide not to do any of the study at all just like we have now. In the glyphosate situation, there's not a single published study of glyphosate workers involved in the wholesale or manufacturing, not a single. And these are the groups that we rely on to get good data to extrapolate to the general population.

It's very troubling to us who are outside industry. And I think we really need, as a country, really, we really need to look at this issue of access to industry data for risk assessment. There are many facets.

I mean, even I'm doing work on bioassays and cancer. It's the same issue with the poultry industry. All the data is coming from the poultry industry. Not a single government institution has data on how are we exposed to viruses that concerns cancer in chicken. Not a single government institution has that data. And industry decides what they want to release to us. It's a big problem for us

outside industry. I think you are requesting good data, but that can only come with you, as industry, granting us access to industry data, as well.

DR. JAMES MCMANAMAN: Thank you, Dr. Johnson. All right. Dr. Ramesh.

DR. ARAMANDLA RAMESH: This is Ramesh. I have a different take on this. People in academia would love to do research on glyphosate provided somebody bankrolls their studies. Until that happens, we have to go by what we have in hand and see whether the rigorous QA/QC procedures have been employed, and that data is a robust enough to come to a conclusion.

It is not because no studies have been done by either government agencies or academia, does not necessarily mean that we what we have is not valued. But to my colleague, Dr. Johnson, we can debate further on this tomorrow.

DR. JAMES MCMANAMAN: All right. Thank you.

All right. I think we'll move on to Mr. Barbre.

MR. MARTIN BARBRE: Good afternoon. My name is Martin Barbre. I'm here today to offer my perspective as a farmer, someone who uses glyphosate,

and as past president of the National Corn Growers Association. I'm not here to engage in a debate about science or the safety of glyphosate, but rather, provide you with an understanding of how this product is used in agriculture and what it means to row crop farmers like me.

My son, Brandon, and I farm 6,000 acres raising yellow corn, white food-grade corn, seed, seed soybeans, soybeans, and wheat. Most of our crops are raised using either no till or conservation tillage practices. I'm a fourth-generation farmer. And Brandon and I are in the process of him taking over the farm in the near future. Brandon has taken over much of the day-to-day operation now.

Therefore, every farming decision we make is motivated by what is best for the long-term viability of the farm. From the crops we grow to choices and tillage practices, everything is done with an eye on the future. A key consideration for every farmer is what crop protection tools to use to ensure we raise a successful and healthy crop. One of the most important tools I use on my farm is glyphosate. And I am far from alone in this regard. Glyphosate is

the most widely used herbicide in the United States, used on over 90 percent of corn and soybean acres.

I and all growers take very seriously the types and amounts of crop protection products we use on our land. When applying glyphosate, my goal is to use the minimal amount, no more, to get the results I need. Typically for me, that means one or two applications on my corn per season using only three-quarters of a pound per acre. My children and grandchildren live on the ground where I grow corn. And I would never want to degrade the environment by overuse of any product.

Additionally, glyphosate allows me to use less benign modes of action thus reducing my and the environment to exposure while maintaining the efficacy of the herbicides. I seek to use all inputs as efficiently as possible both for environmental and health reasons and because it makes good financial sense.

In a typical season before I plant, I'll put down Basis Herbicide as a pre-emergent weed control so I can plant into a clean field. And the corn can start with no competition for water and fertilizer. A few weeks after the corn has come up

and before the leaves fill in the rows, if, and only if, there's weed pressure that has developed I can go over the field again to reduce that competition for resources and allow that crop to finish out the season.

After harvest, I'll allow that corn stover to sit on the land, preserving moisture and protecting the soil over the winter. Come spring prior to planting, I don't have to do major tillage on those fields to prepare them. The weed control and minimal tillage to get the crop in is all it takes to continue that cycle. It's been 18 years that I've been able to minimize soil disruption due, in large part, to glyphosate.

My use of glyphosate impacts several parts of my operation. Beyond controlling weeds, this product allows greater use of no till and conservation tillage on my ground saving fuel, labor, and emissions. We are able to farm more acres with the same equipment and labor force. These practices could not be done as widely prior to the introduction of glyphosate. The amount of control over my nutrient runoff, erosion, and water use has been enhanced as a result.

Before these modern tools were available, a major weed management tool was heavy tillage of the land. This involved more gallons of fuel, more wear and tear on equipment, greater exposure of the soil to wind and rain erosion, and less carbon that could be incorporated into the soil to improve soil health.

I run a business. And glyphosate helps that business run more efficiently. There is no economic incentive to overuse the product. That weakens my bottom line and works against my goal of running a profitable, sustainable operation. I care about my family, my land, and my business. And glyphosate is a tool that is safe to use to meet my environmental and economic goals. Thank you.

DR. JAMES MCMANAMAN: Thank you.

Questions.

Yes, Dr. Shepard.

DR. LIANNE SHEPPARD: I was curious as to whether you have considered or there's any need to use glyphosate shortly before harvest or for green burndown, for example?

DR. MARTIN BARBRE: We don't raise crops that use that procedure. For me, no.

DR. JAMES MCMANAMAN: Other questions?

(Whereupon there was no response)

DR. JAMES MCMANAMAN: Okay. Thank you very much.

Next up, we'll have Amanda Starbuck, Bill Freese, and Robert Hamilton.

Oh, yeah. Sorry. Before you come, we decided to do a short break, five minutes. We have some presentations to load. 10 minutes? All right. We'll do 10 minutes. So be back at 4:20.

(Whereas a break was taken)

DR. JAMES MCMANAMAN: Okay. I think we've had our break. We can begin again. Okay. I have next up is Amanda Starbuck from Food & Water Watch.

We're ready when you are.

MS. AMANDA STARBUCK: Well, good afternoon. And thank you for the opportunity to speak today. My name is Amanda Starbuck. And I'm a researcher at Food & Water Watch, a national nonprofit advocacy organization. We are concerned that the EPA's glyphosate assessment relies too heavily on industry studies, downplays positive findings, and

fails to consider toxicity of entire glyphosate formulations.

Today I delivered petitions from over 42,000 concerned citizens who are calling on EPA to suspend the use of glyphosate until it completes an unbiased assessment of whole formulations. Transparency is key to the scientific process. So is peer review. Alarmingly, the majority of studies incorporated into the glyphosate assessment lack both.

More than half were commissioned by industries that manufacture and market glyphosate. This conflict of interest can create biases and results in findings that are favorable to industry. Moreover, being unpublished, these studies have not undergone the rigorous peer review process, nor are they accessible to other scientists and to the general public.

Nevertheless, the EPA seems to favor these industry studies over those from the open literature. The assessment excludes several relevant studies uncovered during the open literature review, including any that focus on cellular processes.

This left out a study that found that glyphosate alone is toxic to human placenta,

embryonic, kidney, and neonate cells. Additional studies found that glyphosate alone is toxic to human cells, were labeled not relevant with no explanation given.

Alarmingly, one found that glyphosate causes the growth of human breast cancer cells. Leaving out such critical studies without justification is not transparent and calls into question EPA's intentions. Two studies are mentioned on the final page of the assessment with the tagline "Considered during review but excluded from analysis." Both conclude that glyphosate alone is genotoxic to mice and no explanation was given for either being excluded.

Another troubling trend is to drown out any positive evidence of the carcinogenicity of glyphosate. For instance, nearly half of the animal carcinogenicity studies found statistically significant of tumor growth. However, the assessment compares those results to unrelated control groups, effectively reducing their statistical significance. Many scientists have noted that comparing findings to unrelated controls requires caution and risk creating biases.

Additionally, roughly one-quarter of all genotoxic studies found positive evidence of genotoxicity. Yet, EPA concludes the assessment by saying overall, there is a remarkable consistency in the database for glyphosate across multiple lines of evidence. This is grossly misleading and creates the illusion of scientific consensus on the safety of glyphosate.

It should be noted that only one of the 56 industry genotoxicity studies found positive evidence compared to 21 of the 34 open literature studies, making them 35 times more likely to find positive results. Yet, by flooding the database with industry studies, EPA effectively drowns out these positive studies.

Finally, emerging evidence suggests that glyphosate formulations are more toxic than glyphosate in isolation. And moreover, that the toxicity of these formulations is not dependent on the concentration of glyphosate that they contain. Nevertheless, EPA's glyphosate assessment only reviews studies that look at glyphosate in isolation. A review that is protective of public health would take a more realistic view on the exposures that are

unlikely to happen, not an artificially narrow approach.

We urge the Environmental Protection Agency to immediately block the use of glyphosate herbicides until the Agency produces a fair and unbiased assessment of the carcinogenicity of entire formulations of products that are commercially available. Thank you for your time today.

DR. JAMES MCMANAMAN: Thank you.

Questions for this presenter?

DR. SONYA SOBRIAN: Okay. How would you rank GOP studies versus peer review? You talked about peer evaluation. And the open literature industry studies are done under GOP which means they're audited. Peer review studies don't have to be done under GOPs. You still rank them higher?

MS. AMANDA STARBUCK: Explain to me the GLP review process?

DR. SONYA SOBRIAN: They have to have written protocols. They have to follow standard operating procedures. And the data is audited by an independent audit.

MS. AMANDA STARBUCK: And the data can still be audited but there's no one there actually

watching them actually performing the evaluations in the laboratory.

DR. SONYA SOBRIAN: They can be.

MS. AMANDA STARBUCK: Okay.

DR. SONYA SOBRIAN: So I just wondered what was your understanding of good laboratory practices? And I guess you just answered the question.

MS. AMANDA STARBUCK: Yeah.

DR. JAMES MCMANAMAN: Other questions?

(Whereupon there was no response)

DR. JAMES MCMANAMAN: Okay. Thank you very much. Next up is Mr. Bill Freese from Center for Food Safety.

MR. FREESE: I appreciate the opportunity to be able to comment on Glyphosate today. My name is Bill Freeze. I'm the science policy analyst at the Center for Food Safety. We're a nonprofit group that supports sustainable agriculture. And we have submitted two sets of comments to this docket. And they are best accessed on our website where we also have about 50 supporting materials. I'm going to very briefly discuss a lot of material.

Almost all of it is covered in detail in our comments. I'm going to skate over a few points.

First of all, the problems the deviations of EPA's evaluation of Glyphosate from its guidelines for carcinogen risk assessment. And these points were largely covered yesterday. High dose issues, monotonic response not being a proper criterion in historical control data. I did actually want to take one example about how it seems to me that EPA misused historical control data. And this is the 18-month CD-1 mouse study. It showed very, very significant trend for malignant lymphomas, monotonic, although that wasn't mentioned by EPA for some reason. EPA partly discounted this study because it said the concurrent control incidence was low.

And yet it basically referred to literature historical control data, and included two-year studies, together with 18-month studies. Of course, you're going to have a higher rate of lymphomas in two year studies and those should have been excluded. When you do exclude them, you find that the concurrent control incidence was not too low. The issue came up yesterday that perhaps EPA wasn't giving quite enough credence to statistical

significance and I agree with that. I mean the EPA guidelines say that significance in either trend or pair-wise comparison is sufficient to eject chance.

That would seem to leave either the agent is actually carcinogenic, or there's secondary carcinogenic effects, secondary to excessive toxicity. EPA doesn't really choose either one. Usually we find it kind of just dismisses quite a few significant findings. Another issue that was raised, I believe by Dr. Sheppard, was is this a hazard or a risk assessment? And this really comes to a head with the whole high dose selection issue. The guidelines say that the high dose should be selected to provide a maximum ability to detect treatment related carcinogenic effects.

And it cannot serve this purpose and also approximate human exposure which seems to be what EPA is trying to do here, have it both ways. Again, the guidelines are very clear. There should be a clean hazard determination and only then should human exposure levels be taken into consideration in the context of a risk assessment. I looked at several other cancer assessments. And these two particular pesticides were judged by EPA to be likely

carcinogenic based entirely or primarily on tumors at 1,000 milligrams per kilogram per day or above.

And there was no suggestion in either assessment that these were excessive doses. Instead they looked at biological effects. Also, they were all negative for mutagenicity assays. This is covered in my comments but I urge the SAP to exclude four rodent studies that EPA evaluated, two of them from the 1970s. One of them is actually not on Glyphosate at all but rather on a Glyphosate contaminant known as N-Nitrosoglyphosate. The second has disqualifying deficiencies. And both of these were done by the notorious Industrial Bio-Test Laboratories which was convicted in federal court for falsifying animal studies including some for Monsanto in the 1970s.

Also, the two on Sulphosate should be excluded. It's the Trimesium Salt of Glyphosate with very different properties than other Glyphosate salts. I think if you look at the animal data properly you see things a lot differently than EPA does in the issue paper. And this, I should say, relies partly on the comments of Christopher Portier. There are 15 statistically significant trend findings. A lot of the nine highly significant. And you find multiple

positive studies for several different tumor sites. I just want to make a few brief points on the epidemiology.

EPA said that we have no clue what the latency period for NHL is, it could be one to 25 years, citing Dr. Weisenburger. I hope you folks have seen he submitted a comment to the docket saying for something like Glyphosate low-dose exposure he would anticipate roughly 20 years' latency for NHL. It would be five or six years for something like ionizing radiation. The other major point is EPA argued that if Glyphosate causes non-Hodgkin lymphoma, that one would expect later epi studies to have higher risk estimates than earlier epi studies, given the huge increase in Glyphosate use with Roundup ready crops.

And the problem with this idea is that total Glyphosate use is a very crude measure and it's basically composed of two factors. One is acres treated and the other is the rate that used. Now it is the rate of Glyphosate that is used which would approximate exposure, farmer exposure. And what I've done here is, and this is in my comments too, so basically what you can see is that the Glyphosate usage rates were actually quite high in the 1980s.

Which is also when the Epi study was done, De Roos, et. al., 2003 which found one of the higher risk estimates.

So actually, you would expect higher risk estimates in the earlier studies given the higher rate of Glyphosate that was used. Here the data point that I have is 1982. That's explained more fully in my written comments. To do an integrated hazard assessment I think if you take lymphoma for an example it seems like you have positive findings and all three major areas, the NHL in farmers and applicators, malignant lymphomas in three rodent studies. And by the way, the supposed viral infection, that seems to have sprung from speculation in Greim, et. al., the industry-sponsored review.

I haven't seen any proof that there is a viral infection. And in fact, EPA says it's only speculation in the DER for this study. The concordance here I think supports the whole idea that Glyphosate is a cause of lymphomas. Glyphosate clearly fits the hazard descriptor likely to be carcinogenic to humans. And there are two of five criteria I've listed here. One is an agent that has shown carcinogenicity in either two species or strains

or sites. And the other is one positive study with plausible but not definitively causal association in an Epi study.

If Glyphosate were to be properly labeled as likely to be carcinogenic then that would call for a risk assessment. And this would take us back to the eighties when EPA actually started this process and calculated a cancer potency factor for Glyphosate. This is explained more fully in my comments as well. I just wanted to mention, the question of bioaccumulation came up yesterday. And there is evidence that Glyphosate accumulates, if at a low level, in the kidney.

EPA has granted tolerances which are maximum permitted residues for Glyphosate in livestock kidneys. Animals that eat Glyphosate treated feed, they accumulate some level of Glyphosate in the kidney. And there are also some studies showing in particular renal tubular dilation at low doses. And this is in material that I've submitted to the docket. I just want to touch on a broader context herbicide-resistant crops in general. Basically, they've introduced us to a new era of unconstrained herbicide use.

By making the crop resistant to the herbicide farmers are able to apply it much more freely without concern for injuring the crop. This means applying it through much or all of the growing season rather than just early in the year. I just want to touch on three consequences. One is a sharp rise in herbicide use in American agriculture over the Roundup ready crop era. And this shows pounds per acre per year on three major crops that are now mostly herbicide-resistant. And especially in soybeans and cotton herbicide use has gone up dramatically.

There is also environmental harm. Glyphosate uses wiped out milkweed in Midwest crop fields which is a major factor in the decline of Monarch butterflies. Another issue is the drift, herbicide drift damages crops. In particular, Dicamba applied to Dicamba-resistant crops which are just coming out, is causing tons of crop damage in the Midwest. And of course, Glyphosate resistant weeds, which I'm sure you've all heard about, they now infest at least 60 million acres or more.

Basically, about half of all U.S. farmers say they have Glyphosate resistant weeds. Again, this is from intensive use of Glyphosate

selecting for resistance in various weeds. These Glyphosate resistant weeds have been termed what one reporter called an arms race. Which is a very significant opportunity for chemical companies. They are developing new herbicide resistant crops that are resistant to multiple herbicides: Glyphosate, plus 2,4-D, Dicamba, a score of others. This is all being sold as a response to Glyphosate resistant weeds.

Spray the 2,4-D and you'll control the Glyphosate resistant weeds. The trouble is it will lead to more resistance to these other herbicides. For instance, one impact will be a huge increase in 2,4-D with crops that are resistant to it. And this is a projection by USDA and Dow, the impact of introducing 2,4-D resistant corn and soybean. It's a really huge increase in 2,4-D that we're likely to see in the coming five years or so. Just briefly, one of the flaws in EPA's assessments paradigm is of course just looking at the active ingredient rather than the full formulation.

As I'm sure you know there are adjuvants in the formulations that farmers use. A lot of them in terms of herbicides are used to help increase the absorption of the active ingredient into

the crop. And there's always the question of whether these adjuvants could also increase human absorption as well. The other thing, and this I think is really important because folks were expressing frustration and I understand it yesterday, this idea of how do you assess Epi studies when you always have confounding with other pesticides?

Well one of the things that's happening now with these new multiple herbicide resistant crops is companies will be introducing multiple herbicide formulations such as Enlist Duo which is 2,4-D plus Glyphosate. More and more farmers are going to be spraying these two herbicides together. You won't be able to unconfound their exposure. They'll be exposed to both. How do you deal with that under EPA's current system? One issue of course is you can have interactions, synergistic effects, and I pointed out several endpoints where 2,4-D and Glyphosate seem to have a similar impact.

And yet there has been no assessment for the combination and what harms it might cause. So just briefly, benefits. There's really been no yield increase with herbicide resistant crops. This was recently confirmed by Natural Resources Council

reports. What they tend to do is reduce labor needs and simplify weed control at least in the short term before resistant weeds arise. And this had led to greater consolidation of farmland. And then finally, I'm not sure if you got this this morning from Monsanto, but there's this idea that Roundup-ready crops have helped reduce soil erosion on American cropland by reducing tillage.

If you look at USDA data though, what you see is that soil erosion hasn't really decreased at all. It's flattened out since about 1997 over the Roundup ready crop era. Whereas it actually did decrease before Roundup ready crops. There are real problems with this idea. And then I'll just finally address conflicts of interest. It's clearly baked into our regulatory system. The pesticide companies conduct or commission almost all of the animal studies for regulators.

I guess we have to live with that, but what bothers me is more and more we see the company scientists and their consultants interpreting the data that they generate. And in this issue paper we've had Greim, et al., again pesticide industry employees are consultants, Kier and Kirkland on the genotox data.

And then Tom Sorahan was mentioned yesterday. He reinterpreted the De Roos, et. al. as a consultant for Monsanto Europe. I really appreciate that you folks, independent scientists, are going to take, I'm sure, a very critical look at all of this data, and I thank you for your time.

DR. JAMES MCMANAMAN: Thank you, Mr. Freese. Questions? Yes, Dr. Johnson?

DR. ERIC JOHNSON: I'm Eric Johnson. Could you go back to that slide in which you mentioned something about exposures being highest during '74 to '87?

MR. BILL FREESE: Sure. Yeah. I kind of glossed over that. I'm sorry. The De Roos, et. al., 2003 study, if you remember was the combined --

DR. ERIC JOHNSON: You said cases were diagnosed '79 to '86 where Glyphosate usage rates were higher than what? I mean the thing came out in 1974. That's the period where they were lowest. I would say '79 to '86 was the period they were lowest compared to a lot of years.

MR. BILL FREESE: No. actually, the usage rates were actually higher in the 1980s based at

least on this one data point that I was able to find based on USDA data.

DR. ERIC JOHNSON: Please educate me. How are the usage rates different from the production?

MR. BILL FREESE: Okay. The usage rate is pounds per acre per year basically. That's how much Glyphosate a farmer applies per acre per year.

DR. ERIC JOHNSON: For the same area? You're saying in effect that the amount used for the same area of land has increased? Is that what you said?

MR. BILL FREESE: It was higher in the past.

DR. ERIC JOHNSON: In the past?

MR. BILL FREESE: Yeah. In the past. Yeah. Exactly. The huge increase in overall Glyphosate use that we've seen because of Roundup ready crops is mostly due to increased acres being treated which is represented in the in the bars on the graph.

DR. ERIC JOHNSON: Okay.

MR. BILL FREESE: So EPA really misinterpreted the data there.

DR. ERIC JOHNSON: So basically for us to interpret data the exposure was higher in the earlier period than in the later period. Is that right? I mean if you're talking about an individual using the pesticide it would have been higher in the earlier periods.

MR. BILL FREESE: Exactly.

DR. ERIC JOHNSON: Okay. Thank you.

DR. JAMES MCMANAMAN: Other questions? Yes, Dr. Sheppard?

DR. LIANNE SHEPPARD: Yeah. I'd like to follow-up on this because this is the first data I've seen. We heard yesterday that with the advent of Roundup-ready crops, that EPA believes that the exposure has dramatically increased because of that. But I didn't see any evidence that was presented to us by EPA. I appreciate that we've got something more than we had yesterday. My question to you is, is it really pounds per acre per year? It's more like pounds per person, right? Per person day or something like that.

MR. BILL FREESE: Yeah. That would be preferable. Believe me, I totally agree with you. I

think that this may be the best proxy that's available.

DR. LIANNE SHEPPARD: And based on what?

MR. BILL FREESE: This is USDA National Agricultural Statistics Service data. And basically, they collect very detailed statistics on pesticide use by crop. Including pounds per acre, number of applications per year on average, and percent area treated. And they've collected that since 1990. Before that, unfortunately they very seldom collected data. There was one data point that I was able to find from 1982. I mean it surprised me to be honest. I didn't think that this would be the case. But in the 1980s very few farmers used Glyphosate, at least in corn and soybeans.

That would be represented by the acres, the corn plus soy acres treated. But of those who did they seem to have used pretty high doses. Whether that's a good proxy for exposures, perhaps you can judge that better than I can.

DR. LIANNE SHEPPARD: And so you're not aware of any actual data on application like at the worker level? Application rates at the worker level

over time? I understand this is a proxy for what we care about and I'm just trying to -- by asking you, I'm trying to get at what we heard yesterday. Which is this speculative statement that per worker exposure has increased recently. And what I'm trying to get at from you is whether there's any data at all other than this out there in the peer reviewed literature anywhere to get at that.

MR. BILL FREESE: I'm not sure if this gets at it. But you notice I only ran the chart out to 2001, which corresponds to the cutoff date of De Roos, et. al., 2005. If you go out to the present, what you see is usage rates have actually increased to near 1982 levels. For soybeans, it's 1.4 pounds per acre per year, and corn it’s about one pound per acre per year. It really has gone up. Plus, the corn plus soy, the acres treated with Glyphosate has more than doubled over 2001. It's like 150 million acres of corn and soybeans now are treated with Glyphosate.

And just one other thing, I don't think any of the epi studies cover any period past 2001. Think about that too.

DR. LIANNE SHEPPARD: And the fact that the De Roos study doesn't cover exposure after

baseline, which was between 1993 and 1997. All of that exposure that happened between '93 and '97 to 2001 is misclassified in the dose response analysis. And is actually presumably misclassified to put too many people in the unexposed group.

DR. JAMES MCMANAMAN: Okay. Dr. Jett?

DR. DAVID JETT: This is Dave Jett. I just wanted to know, you made a statement about there's 15 significant trend studies. Are you talking about studies that are in the issue document that are currently there that's have significant trends? Or are you talking about studies that would be significant if they didn't use historical controls?

MR. BILL FREESE: Yeah. Let me explain. Let's see, EPA had 15 studies, correct, all together? Fifteen rodent studies? As I said, I think four should be excluded, which would take you down to 11. And then I added in Kumar 2001, which brings us up to 12. That's the 12 studies that I was dealing with. And I could have miscounted but I believe that there were 15 statistically significant trend findings in those 12 studies.

DR. JAMES MCMANAMAN: Okay. Any other questions? Dr. Portier?

DR. KENNETH PORTIER: I was just going to make a point. On that last graph, if you added in the number of ag workers who actually spray, and if that trend matched the acreage trend, then I would believe that the pounds per acre is the right metric. But I suspect we have increased agricultural workers so they're spending more time in the field spraying. Their exposure is probably going up because the amount is a shame, but they're doing more acreage.

MR. BILL FREESE: Okay. Yeah.

DR. JAMES MCMANAMAN: All right. Thank you very much. Okay. Thank you. Next up is Dr. Robert Hamilton from Valent Corporation.

DR. ROBERT HAMILTON: Good afternoon. My name is Bob Hamilton and I'm here on behalf of Sumitomo Chemical Company, a worldwide agrichemical manufacturer. Sumitomo is a research and development company that supports sound science and regulatory decision-making. I'm glad to be addressing the SAP today as you evaluate the carcinogenic potential for Glyphosate. And to briefly review the conclusions of international regulatory agencies on the potential for Glyphosate to cause cancer. My message is simple. My comments will be brief.

I have one slide to show. And I think you've heard a lot of what I'm going to talk about over the last few days. But I'd like to just briefly go through what's happened in the very recent past. We believe that an understanding of the global regulatory perspective from agency scientific worldwide will enable the SAP to make informed decisions. Today I'll review the results from 2015 and 2016 carcinogenicity evaluations in the countries of Australia, Canada, New Zealand, Japan, the U.S., in the EU conducted by EFSA and a report by the FAO/WHO/JMPR.

Since April of 2015, these seven authorities have independently conducted thorough weight of evidence assessments on the carcinogenic potential of Glyphosate and have all reached the same conclusion, it is unlikely that Glyphosate causes cancer in humans. I've summarized key points from each of the documents below. Forgive me for citing directly from the documents, but I think it's important to get the context. And I'll start with the 2015 evaluations and then I'll end with the most recent evaluation that was completed by Australia in September.

In April of 2015, Canada's Pest Management Regulatory Authority (PMRA), finalized the document titled *Proposed Reevaluation Decision for Glyphosate*. Since this was a reevaluation document, PMRA address many aspects of the compound not just carcinogenicity. However, the conclusion in the cancer assessment section states, “In consideration of the strengths and limitations of the large body of information on Glyphosate, which included multiple short and long-term lifetime animal toxicity studies, numerous in vivo and in vitro genotoxicity assays, as well as a large body of epidemiological information, the overall weight of evidence indicates that Glyphosate is unlikely to pose a human cancer risk.”

This is consistent with the other pesticide regulatory authorities worldwide. Including the most recent ongoing comprehensive reevaluation by Germany, which was published for public consultation in 2014. The United States EPA's cancer assessment review committee reported in their 2015 document. It was a thorough, detailed analysis. And they concluded that in accordance with the 2005 guidelines for carcinogen risk assessment, based on the weight of the

evidence, Glyphosate is classified as not likely to be carcinogenic to humans.

The European Food Safety authority in their November 2015 document titled Conclusions on the Peer Review of the Pesticide Risk Assessment of the Active Substance Glyphosate said, “Following a second mandate from the European Commission to consider the findings from the International Agency for the Research on Cancer, IARC, regarding the potential carcinogenicity of Glyphosate or Glyphosate containing plant protection products.

In the ongoing peer review of the act of substance 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 according to the regulation EC 1272/2008.” In March of 2016, the Food Safety Commission of Japan conducted a risk assessment on Glyphosate in which they concluded major adverse effects of Glyphosate were observed on reduced gain of body weight, GI tract, and liver. Glyphosate had no neurotoxicity, carcinogenicity, reproductive toxicity, teratogenicity, and genotoxicity.

In May of 2016, a report of the Food and Agricultural Organization of the United Nations and WHO, titled, *Pesticide Residues in Rood 2016 Special Session of the Joint FAO/WHO Meeting on Pesticide Residues*, the Glyphosate section of that report concludes that in view of the absence of carcinogenic potential in rodents at human relevant doses and the absence of genotoxicity by the oral route in mammals, and considering the epidemiological evidence from occupational exposures, the meeting concluded that Glyphosate is unlikely to pose a carcinogenic risk to humans via exposure from the diet.

New Zealand conducted an assessment in August of 2016. The overall conclusion is that based on a weight of the evidence approach, taking into account the quality and reliability of the available data, Glyphosate is unlikely to be genotoxic or carcinogenic to humans and does not require classification under HSNO as a carcinogen or a mutagen. And finally, Australia in September of 2016, the Australia Pesticides and Veterinary Medicines Authority, APVMA, finalized their report.

And their regulatory position was, based on the nomination assessment the APVMA concludes that the scientific weight of evidence indicates that exposure to Glyphosate does not pose a carcinogenic or genotoxic risk to humans. There's no scientific basis for revising the APVMA satisfaction that Glyphosate or products containing Glyphosate would be an undue hazard to the safety of people exposed to it during its handling or people using anything containing its residues.

I thank you for your attention. We believe that what you'll conclude from this illustration is that these seven independent regulatory bodies around the world have each conducted their own independent weight of evidence assessments of the carcinogenic potential of Glyphosate and have all unequivocally determine that Glyphosate is not carcinogenic. Please keep these global classifications in mind as you conduct your evaluation. Thank you.

DR. JAMES MCMANAMAN: Thank you. Questions for this presenter? Okay. I thank each of you for your presentations. At this point if we could

get representatives from Syngenta, Consumer's Union and USDA to come up. We'll start with Syngenta.

MR. MONTAGUE DIXON: Good afternoon panelists. Thank you for this opportunity to address you. My name is Montague Dixon and I'm a Regulatory Affairs Manager with Syngenta crop protection. I've worked in the industry for 27 years. First as a metabolism chemist then as an occupational and human risk assessor and then for the last 10 years as a regulatory affairs manager including responsibility for our Glyphosate products. I'd like to today commend the EPA for their efforts in preparations for this panel's review.

I'll be making a few prepared comments primarily focused on section seven, the proposed collaborative research plan for Glyphosate and Glyphosate formulations. The agency has performed a thorough review of the extensive data of human disease association studies and animal cancer and mechanistic studies and has arrived at the appropriate conclusion that Glyphosate is not likely to be carcinogenic at doses relevant to human health risk assessment. This conclusion is fully justified with similar conclusions

reached by other regulatory authorities around the world.

In 2005 the EPA published the revised cancer risk assessment guidelines which provide an established framework for the evaluation of all available and relevant science to inform the cancer risk assessment. The agency's revised guidelines are based upon internationally developed and accepted processes under the auspices of the World Health Organization's International Program for Chemical Safety. Which established a framework for analyzing mode of action for cancer and human relevance of animal tumors that may arise from exposure to a chemical.

This framework was carefully developed and established and has been updated and enhanced and has been shown to be very effective at informing human health-based decisions. There are numerous chemical specific examples using the IPCS framework that have been published in peer reviewed literature. The agency's integrated risk information system and pesticide programs also use this framework as described in the Cancer Guidelines in order to make human health protective decisions on the suitability

of data from laboratory animal and other studies for cancer risk assessment.

The proposed approach for evaluating the carcinogenic potential presented in the paper referenced in section seven has not undergone an equivalent level of validation, acceptance, and use. And while the work of Smith, et. al., may be interesting it has not risen to the level of scientific value of the information analysis that the U.S. EPA's 2005 Cancer Guidelines and the IPCS framework provide.

For cancer evaluation and interpretation with respect to human relevance the EPA in collaboration with the National Toxicology Program should use the World Health Organization's mode of human relevance framework that has stood the test of time. It's scientifically defensible and has been well validated to determine the potential for human cancer risk. More specifically it's not clear what benefits are offered if the U.S. EPA partners with the National Toxicology Program to perform experiments using various EPA approved and registered formulated products that contain Glyphosate.

The active ingredients in the final products containing those active ingredients are well tested according to regulatory guidelines and are thoroughly evaluated by regulatory authorities all around the world including the U.S. EPA. There is no discernible value to further test a product that has already been fully tested and evaluated. Herbicide products are highly regulated or are subject to evaluation under a number of legislative mandates around the world.

And in the United States under the Federal Food Drug and Cosmetic Act, the Federal Insecticide Fungicide and Rodenticide Act, the Food Quality Protection Act, the Clean Water Act, and the Safe Drinking Water Act. The U.S. EPA along with other sister regulatory authorities around the world require registrants to perform large numbers of studies that are designed specifically to inform efficacy and safety decisions including the potential to cause disease in humans such as cancer.

These studies are performed by the registrants under rigorous oversight using internationally agreed to and validated test guidelines through the Organization for Economic

Cooperation and development and EPA's own test guidelines provided by the Office of Chemical Safety and Pollution Prevention. And they're also conducted under the guidance of the Good Laboratory Practice Act. All of this testing and scientific evaluation is required before an active ingredient such as Glyphosate and formulated products that contain an active ingredient can be registered or sold.

In addition to the extensive data the registrants provide, the regulatory agencies also routinely review publicly available databases, including peer reviewed literature for relevant information that will provide additional knowledge during the review processes such as the regularly scheduled registration review. The evidence for this is indeed in the in-depth literature search the agency performed for this present activity. The U.S. EPA commits massive resources and staff time and contractor dollars to fully evaluate pesticides, both the active ingredient as well as the formulated products including the components of the formulated products.

These products have been on the market with years or even decades of safe use and have been

thoroughly tested and repeatedly evaluated by the agency, by EPA. The research arm of the U.S. EPA and other federal agencies in collaboration with the National Toxicology Program, most certainly perform vital services searching for solutions to important public health issues.

However, this is not one of those. It would be an inefficient use of the valuable resources, both time and money, of the EPA and the NTP to perform additional experiments on complex mixtures that are the formulated products. Which would likely be uninterpretable and have already been well tested and thoroughly evaluated. Furthermore, there's a large number of formulated products that contain Glyphosate. Many of these products also contain other active ingredients and the co-formulates often referred to as the inerts.

There are more than 1,500 potential inerts that are approved for use in these products. Additionally, any new inert product, before it could be used in a pesticide product, has to go through a rigorous safety evaluation. I encourage the EPA to reconsider their proposed collaboration with the National Toxicology Program on the basis that such a

program would generate data that would be redundant to the massive amount of data already available for evaluating Glyphosate and other products that contain Glyphosate.

These products have been fully evaluated and approved for use as part of the rigorous registration process. One only has to look at the docket for this current SAP to see the massive amount of data that's already available on Glyphosate and its associated formulation. Thank you.

DR. JAMES MCMANAMAN: Thank you. Questions? All right. Thank you very much. Next up is Dr. Sheryl Kunickis from USDA.

DR. SHERYL KUNICKIS: Thank you very much. My name is Sheryl Kunickis. I'm the Director in the Office of Pest Management Policy the director in the office of pest management policy and I represent the U.S. Department of Agriculture. I appreciate the opportunity to be here today. And I thank each one of you for coming and for your careful consideration of this SAP. I also want to thank Dr. Jack Housenger. In his opening comments yesterday, when he referenced and he acknowledge the value of

Glyphosate to U.S. agriculture, he hit it right on the nose.

And I also wanted to thank two of the public speakers. Mr. Hoyer who grows soybeans and Mr. Barbre who grows corn. Frankly, there's not much I can say because they bring it back. They take the science and everything that we know about Glyphosate and they translate it into real world application. And as they use crop protection tools, they take into account how it can be used on their farming system, how it impacts the crops that they use, how it controls the weeds in this case. And they also look at how it will affect their families.

And I think that’s a really important point. So now I’ll go back on script. And I want to just remind everybody, because I think you’ve heard much of this many times today, Glyphosate is the most important pesticide for U.S. agriculture. And USDA is very supportive of EPA’s conclusion that Glyphosate is not likely to be carcinogenic to humans. Over the past decades, Glyphosate has been extensively studied and tested. And we applaud EPA’s thorough and dispassionate weight of evidence analysis of this large volume of data and information.

The conclusion reached by EPA that Glyphosate is not a human carcinogen is shared by other major risk-based assessments recently conducted by regulatory bodies that you just heard about. And I won't list all of them, but we certainly acknowledge each one of those authorities. Glyphosate has been well-known since the mid-1990s because it has been the primary herbicide used in genetically engineered or GE corn, soybeans, and cotton. It has been termed, and you heard this earlier, a once in a lifetime herbicide due to its low toxicity and its flexibility for use.

The benefits of Glyphosate include excellent crop safety in GE crops, a broad range of weed control, applicability in minimal and no till as well as conventional tillage production, and flexibility and economy of use. The typical cost for Glyphosate averages four to five dollars per acre. Planting GE crops has also led to the increased adoption of conservation and no till production practices. These conservation tillage practices have many positive environmental impacts including enhanced soil quality and reduced soil erosion.

Glyphosate provides consistent weed control and simplified weed management in these

cropping systems. Glyphosate is important not only as a weed management tool in GE systems. The herbicide has been used safely in the U.S. since the seventies for general weed control and as part of an integrated control program in orchard crops, specialty crops, and aquatic or riparian lands and range lands. Glyphosate has no soil activity, which allows flexibility of use in high cash value cropping systems and in vegetation management.

It can be applied in many ways including spot treatments and as directed application. Many of these systems have limited options for weed control. And weed management practices have not been selected for weeds that are resistant to Glyphosate. Three examples of situations where Glyphosate is important include -- and some of these you may not have thought of -- Glyphosate is used to control emerged weeds prior to planting vegetable or fruit crops. Weed control prior to crop emergence is needed because few herbicides are registered for use after the crop emerges.

And growers often rely on tillage or hand labor for weed control. And I'll go off script. I just recently saw a report where manual hand pulling

is becoming a little more common. And to many of us who are perhaps a little bit older we may remember doing that and it's not very much fun. The second point, Glyphosate is used to control emersion and floating weeds such as cattails and water hyacinth in aquatic systems. These weeds if not managed can impede water flow, decreasing water supplies needed for irrigation.

A problem that can threaten or exacerbate drought conditions or increase the cost of irrigation. In other situations, the weeds can cause water to stagnate or pond which provides habitat for mosquitoes to breed. Thus, effective weed control is an important component of integrated pest management for mosquitoes and mosquito-borne diseases. Glyphosate is used as a selective treatment to control invasive annual and woody plants in riparian habitats of on range lands. If not managed these plants can create a monoculture reducing species diversity and threatening resources and endangered species.

While growers do face new challenges with Glyphosate-resistant weeds in cotton, soybean and, to a lesser extent, corn and other GE crops, Glyphosate continues to control many weeds that occur

in production agriculture. And thus, is an important tool to manage weeds with a diversity weed management system in these crops. In addition, Glyphosate's low toxicity is an important benefit compared to some other alternatives which is reinforced by EPA's conclusion in the issue paper that Glyphosate is not likely to be carcinogenic to humans.

USDA supports this determination and looks forward to the SAP's review of the EPA's findings. Thank you.

DR. JAMES MCMANAMAN: Thank you. Questions? Yes, Dr. Sheppard?

DR. LIANNE SHEPPARD: Yeah. I'm going to probably reveal more than I want to with this question. But certainly, there are pesticides and herbicides that are used widely in agriculture and have been declared carcinogenic, is that correct?

DR. SHERYL KUNICKIS: Yes, ma'am.

DR. LIANNE SHEPPARD: Yeah. Okay. I mean, I appreciate what you were telling us about the importance of it, but I'm not clear how that has a bearing on the decisions that we're tasked here to make. Since these products can still be used even if they're declared carcinogenic.

DR. SHERYL KUNICKIS: I'm not sure they --

DR. LIANNE SHEPPARD: But didn't you just tell me there are many pesticides and herbicides that are approved for use even though they are --

DR. SHERYL KUNICKIS: I thought you meant historically. In the past.

DR. LIANNE SHEPPARD: No. I mean even currently. I mean Clorphyrifos is still used in agriculture. Right?

DR. SHERYL KUNICKIS: It's not.

DR. LIANNE SHEPPARD: It's not? Okay. See I'm showing my naiveté. Which is probably why I'm on the panel because I don't know too much about pesticides.

DR. SHERYL KUNICKIS: Yeah. I'm not aware where we're using carcinogenic pesticides right now frankly. I'm not aware of that. I thought you were talking about throughout history; I'm fairly sure EPA has taken those off the market.

DR. LIANNE SHEPPARD: So the implication by what we're hearing is if there's a decision that this is carcinogenic it could go off the market? Is that the idea?

DR. SHERYL KUNICKIS: That's a call the EPA would have to make. Yeah. I'll let Dana speak to that.

MS. DANA VOGEL: Hi. This is Dana Vogel, Health Effects Division. There are a lot of different pesticides that have different cancer classifications. Some have quantitative analysis, like quantitative assessments of cancer risk. Other don't. And those assessments are done as part of the risk assessment. So just for an example, Chemical X, any pesticide, if it was declared a likely carcinogen -- I'll just make that up, this is totally hypothetical -- and we gave it a Q-1 star we would do an assessment to determine what we would estimate the cancer risk to be.

And it would be determined, based upon policy, whether that is above or below a level of concern. Does that answer your question?

DR. LIANNE SHEPPARD: Yes. The decision about whether this is carcinogenic or not then generates the next steps with the risk assessment, which then generates what can be done with respect to how it's used?

MS. DANA VOGEL: Yes. That's right.

DR. JAMES MCMANAMAN: Other questions? Okay. Thank you very much. Okay. As I mentioned, we're trying to provide the panel with sufficient amounts of time to discuss the charge questions. With that in mind, I'm looking for anyone else who might be here who is scheduled to present tomorrow morning. If they're here tonight we can try to fit you in. Someone from the Consumer's Union, Michael Hanson if he's here, Moms Across America, there are three people if any one of them are here?

The Immediate Life and Beyond Pesticides, Nichelle Harriott. I understand Nichelle is here. We're counting on you to show. Anyone from AVAAZ -- A-V-A-A-Z or Peter Infante? Okay.

DR. ERIC JOHNSON: I hope you'll give me an opportunity to ask questions of some of the industry people like DuPont, FMC, and BSF. Because I have an important question.

MS. NICHELLE HARRIOTT: Okay. All right. Nichelle?

MS. NICHELLE HARRIOTT: Thank you. These comments will be brief as I'm sure many of us have had a long day and would like to get home. I

just want to thank the panel for this opportunity to present oral remarks.

My name is Nichelle Harriott. I am the Science and Regulatory Director at Beyond Pesticides. These oral comments or a summary of written comments submitted to the docket in October.

The panel's review of the carcinogenic potential of Glyphosate comes at a time when Glyphosate use is at an all-time high. Over 280 million pounds of Glyphosate are estimated to be used in the U.S. as of 2014 on over 100 crops and other non-agricultural use sites. The agricultural uses of Glyphosate are tied mostly to genetically engineered crops that are engineered specifically to be tolerant of the herbicide.

Since the most cultivated crops in the US for Glyphosate tolerant corn and soybeans which also make up the cornerstone of ingredients common to the American diet it is critical that a comprehensive human health assessment with a special review of carcinogenic potential is completed with review of all available evidence as we have heard today there is conflicting conclusions regarding Glyphosate’s

carcinogen which has elevated the controversy surrounding continued use of this chemical.

IARC found that there is sufficient evidence of carcinogenicity in experimental organisms to classify Glyphosate as probably carcinogenic to humans. Based on the published publicly available independent scientific literature IARC also found sufficient mechanistic evidence in animals for genotoxicity and oxidative stress.

Mechanistic evidence and other relevant data are useful in providing evidence of carcinogenicity and also help in assessing the relevance and importance of findings of cancer in animals and in humans. Possible mechanisms by which substances increase the risk of cancer may include changes in physiology, changes at the cellular level, and changes at the molecular level, including genotoxicity.

To this end, studies have shown that Glyphosate exposure does indeed induce DNA and chromosomal damage in mammals and in human and animal cells in vitro, but studies find an increase in blood markers of chromosomal damage. Glyphosate has also induced a positive trend in the incidence of the renal

tube carcinoma in male mice. Studies show that Glyphosate increased pancreatic islet adenoma in male rats. Glyphosate, Glyphosate formulations, and the degredate AMPA induce oxidative stress in rodents and in vitro.

Most importantly however, is the need to review Glyphosate formulations which are the most relevant to assessing carcinogenicity. The public, through exposures on their farms, gardens, food and playgrounds, are exposed to Glyphosate formulations commonly known as Roundup. And not just the single active ingredient.

It is important to note here that IARC reviewed Glyphosate and the formulated products, which are the most and only relevant substances for evaluating Glyphosate risks to human health. A number of published studies performed with Glyphosate-based formulations of unknown composition, find positive results for genotoxicity when tested in vitro and in vivo. The co-formulate, Polyethoxylated tallow amine or POEA, has been shown to be more toxic than active substance Glyphosate for several toxicological endpoints, namely acute reproductive and developmental toxicity.

And there is evidence of DNA damage in vitro at high doses. An assessment of this substance, as it relates to Glyphosate's carcinogenic potential, must be conducted in order to clarify the genotoxicity, carcinogenicity, reproductive developmental toxicity, and even endocrine disrupting potential of this co-formulate.

EPA notes in its issue paper that it's collaborating with the National Toxicology Program to evaluate Glyphosate in product formulations and the differences in formulation toxicity. However, it is safe to assume that the findings of this collaboration will not be available until after the registration review of Glyphosate is complete. Meaning this important information regarding formulation toxicity, in our opinion, will continue to be a data gap for Glyphosate putting people at risk.

Since Glyphosate formulations contain numerous other ingredients EPA must investigate the totality of these formulations and their carcinogenic potential as these chemical mixtures have the most relevance to human health. EPA has been urged numerous times by my organization and others to evaluate chemical mixtures. Especially those commonly

formulated together as part of the agency's risk assessment process.

The scientific database shows that Glyphosate formulated products kill human cells, particularly embryonic and placental cells, even at low concentrations. Studies have found that the formulated Glyphosate products reduce human placental cell viability at least two times more efficiently than Glyphosate itself, disrupts aromatase activity and MRNA levels, and induces a dose-dependent formation of GNA adducts in the kidney and liver of mice. A process that can potentially lead to carcinogenesis.

As part of this review process, we urge the EPA to make publicly available all data reviewed. If the information and studies submitted by the registrants is the basis for conflicting carcinogenic conclusions, then EPA must publicly release these studies so that they can be independently peer reviewed.

The science of Glyphosate is expanding and public concern is increasing. EPA must therefore be very transparent in how it has come to its conclusion that Glyphosate is not likely to be

carcinogenic to humans, given the evidence found in independent peer reviewed studies.

We urge EPA and this panel to be diligent in examining all independent peer reviewed data regarding the carcinogenic potential of Glyphosate and its formulations, and to take a precautionary approach to potential risks. We believe Glyphosate formulations, to which farmers and consumers are most exposed, are the most relevant for evaluating risks to human health. Finally, we encourage full transparency on this evaluation so that the public confidence can be assured during this process. I thank you for your time and consideration.

DR. JAMES MCMANAMAN: Thank you. Questions for Dr. Harriott? Okay. Thank you very much. I'm going to go down the list a little farther. Anyone from Bayer Crop Science here? Organic Consumers Association? American Sugar Beet Growers? Natural Resources Defense Council? Okay. We have a few more minutes. Dr. Johnson had some additional questions for some of the presenters earlier today. If they're still here we have some questions for you.

DR. ERIC JOHNSON: My question is for representatives from the major companies like DuPont,

VSF, and FMC. I mean companies like that. Because the question we asked before was whether these companies manufacture Glyphosate and the answer we got was no. And I think we asked the wrong question. What we would like to know is how do these companies handle Glyphosate. I mean how as a business? Do they formulate it, are they distributors? Can each of them tell us how they handle Glyphosate, please?

DR. JAMES MCMANAMAN: Do we have representatives from any of those companies here?

DR. JACOB VUKICH: Yes. This is Jake Vukich from DuPont. As I mentioned before DuPont holds end use product registrations. We do not manufacture Glyphosate technical. And in sourcing our end use product registrations, we do not manufacture those end use products either. We don't have any DuPont folks who are exposed to the manufacture of the formulations or the technical.

DR. ERIC JOHNSON: Obviously, you have interest in Glyphosate as a company. What do you do with Glyphosate?

DR. JACOB VUKICH: What we'll do is we will see the formulated products. And then we'll get them registered under DuPont registration, get the

appropriate labels for those products and then market them into the corn, soybean, whatever marketplace would need our products.

DR. ERIC JOHNSON: So you do have workers who handle this stuff as a wholesale?

DR. JACOB VUKICH: The DuPont workers that would handle Glyphosate really would be our field development folks who may put out trials. And they fall into the same category as agricultural workers, not manufacturing workers.

DR. ERIC JOHNSON: So you would receive this product already packaged from companies like Monsanto?

DR. JACOB VUKICH: In some instances we do. And I can't go any further beyond that because that becomes confidential business information.

DR. ERIC JOHNSON: So you don't receive the powder itself that you can --

DR. JACOB VUKICH: No. We do not. No. I will say, though, what we consider Glyphosate to be from our perspective is a third-party product in that we're not a basic registrant of Glyphosate. In evaluating what we would do with third party products, we conduct internal stewardship reviews. we do kind

of what we call internal peer reviews of the evaluations and risk assessments that are conducted by regulatory agencies.

We do have our toxicology folks, our product chemistry folks, our residue chemistry folks take a look at what's available for Glyphosate and to confirm that it falls within our internal stewardship guidelines. And that where we're registering the product is a legal use and is already labeled by EPA.

DR. ERIC JOHNSON: Right. But you mentioned that it's not all of the product that you receive already packaged. That's what you just answered me. So how do you receive the rest?

DR. JACOB VUKICH: Again, some of that is confidential business information and is contained in what we call our confidential statement of formulas. I really don't want to release that in a public forum.

DR. ERIC JOHNSON: Okay. Next. Same question. And your company is what?

MR. ANDY HEDGECOCK: I'm with FMC. I'm relatively new in my role within FMC and don't have all the details of what we do in terms of third party purchases or manufacturing that came from our

Cheminova acquisition in 2015. My understanding, if I can speak across FMC and probably the industry is we source it from other companies, we can produce it ourselves or we could also toll manufacturing it and having someone else produce it for us.

I can't speak to the specific questions that you're asking about FMC in particular, but would be open to having that conversation with you at another time when I would have that detail.

DR. ERIC JOHNSON: I was just curious. These are well-known companies you're working for, and you seem to have difficulty telling us what your company does with this product. I mean, it seems to me rather unusual. Just a simple question. What does your company do or how does it receive it? I don't see what the secret is. I mean it's a question of we're just trying to identify workers that's going to be studied. That's the underlying reason why I'm asking these questions.

MR. ANDY HEDGECOCK: Understood, and my point earlier during my presentation. I think talking to previous company epidemiologists who have looked at worker exposure. John Acquavelle I think spoke to this in his history on looking at it from A

perspective of the manufacturing of Glyphosate and the difficulties in it. And I don't want to speak for him. I listened to him that day as you did as well.

DR. ERIC JOHNSON: Right.

MR. ANDY HEDGECOCK: So I think that would be the best conversation for you to have.

DR. ERIC JOHNSON: I heard about it. I mean he spoke to us. He answered our question. I'm trying to find out about the other companies that use Glyphosate.

MR. ANDY HEDGECOCK: I understand.

DR. JAMES MCMANAMAN: All right. Well I think that they've answered it to the best of their ability. Since there are no other presenters here I thank you gentlemen for coming back up for additional questions. And we'll begin tomorrow morning at 8:30.

[WHEREAS THE MEETING WAS ADJOURNED FOR THE DAY]

* * * * *

DAY 3

MR. STEVEN KNOTT: Today's Session of the FIFRA Scientific Advisory Panel reviewing EPA's evaluation of the carcinogenic potential of glyphosate. This morning we're going to be continuing our public comments session. And at this point I want to go ahead and turn it over to Dr. McManaman, our chair for the session.

DR. JAMES MCMANAMAN: Good morning on this brisk Thursday morning. What we'll do, as we always do, is go around and have the panel reintroduce themselves. I'm Jim McManaman. I'm a professor at University of Colorado.

DR. MARION EHRICH: Marion Ehrich from Virginia Tech. Pharmacology, toxicology, permanent panel member.

DR. JOSEPH SHAW: I'm Joe Shaw, permanent panel member. I'm a toxicologist from Indiana University.

DR. KENNY CRUMP: Kenny Crump. I'm invited temporary panel member. I'm a statistician.

DR. LAURA GREEN: Good morning. Laura Green, chemist and toxicologist and temporary special government employee, I guess.

DR. ERIC JOHNSON: Eric Johnson, Department of Epidemiology, University of Arkansas for Medical Sciences.

DR. BARBARA PARSONS: I'm Barbara Parsons from the Division of Genetic and Molecular Toxicology at FDA's National Center for Toxicological Research.

DR. ARAMANDLA RAMESH: Good morning. My name is Aramandla Ramesh. I'm from Meharry Medical College.

DR. KENNETH PORTIER: Good morning. I'm Ken Portier. I'm a biostatistician and Vice President of The Statistics and Evaluation Center at the American Cancer Society. And in full disclosure, I am Dr. Christopher Portier's older and, I like to say, smarter, brother.

DR. JAMES MCMANAMAN: Better looking too? Better looking too?

DR. KENNETH PORTIER: Oh, I can't claim that. I'm sorry.

DR. JAMES MCMANAMAN: Ok.

DR. KENNETH PORTIER: But I would say, Chris and I have very similar degrees in biostatistics from UNC Chapel Hill, whereas he went into NIEHS, and I spent 27 years at the University of Florida in agriculture and environmental research. I'm very familiar with agricultural practice. And then the last 11 years working in public health at the American Cancer Society. And I've done a few of these SAPs so I bring some experience to the panel. Thank you.

DR. LUOPING ZHANG: Hi, I'm Luoping Zhang and my job professor in toxicology, in the Division of Environmental Health Sciences at the University of California, Berkeley.

DR. DANIEL ZELTERMAN: Good morning. I'm Dan Zelterman, professor of Biostatistics at Yale. I do work in cancer studies and cancer clinical trials.

DR. EMANUELA TAIOLI: Good morning. I'm Emanuela Taioli, professor at Mt. Sinai School of Medicine, and I'm a cancer epidemiologist.

DR. LIANNE SHEPPARD: Good morning. My name is Lianne Sheppard and I'm a biostatistician from the University of Washington. And I'm also a member of the Statutory Clean Air Scientific Advisory

Committee. So, like my colleague Ken, I also have a fair amount of experience. But never with a FIFRA panel so it's a little different.

DR. DAVID JETT: Dave Jett, director of the NIH Chemical Defense program at NIH, National Institutes of Health. Adjunct professor, School of Medicine, University of Maryland, Toxicology.

DR. JAMES MCMANAMAN: Okay. As Steve mentioned we have a few more public commenters to go through this morning. If I can have the representatives from the Consumer Union, Mom's Across America, The Immediate Life, and AVAAZ, A-V-A-A-Z. If you could come up to the podium, we'll assemble you together for your presentations

Okay. So first up there is Dr. Michael Hansen from the Consumers Union.

DR. MICHAEL HANSEN: Yes, thank you for the opportunity to address the SAP on the topic of the carcinogenic potential of glyphosate. My name is Michael Hansen, I'm a senior scientist at Consumers Union, the policy and advocacy arm of Consumer Reports.

This assessment of the carcinogenicity of glyphosate is needed, given that total use of

glyphosate in the U.S. is estimated at 280 to 290 million pounds in 2014, a 250-fold increase in usage compared to 1974, when it was first introduced, and a 10-fold usage since 1993, when it was last reviewed by EPA.

We urge the SAP to tell EPA that their present assessment of the carcinogenic potential of glyphosate is inadequate and needs to be redone. We feel that if this reassessment is done properly, the EPA would make a conclusion similar to that of the IARC, e.g. that glyphosate is a probable human carcinogen.

For Charge Question 1, we agree with EPA's call for more data on formulated products containing glyphosate, particularly given the evidence that surfactants such as POE-tallowamine may make the formulated product much more toxic, as noted by a study submitted to USD in 1997, and by the conclusion of a 2015 European Food Safety Authority report that noted: "Compared to glyphosate, a higher toxicity of the POE-tallowamine was observed on all endpoints investigated." And noted that "genotoxicity, long-term toxicity and carcinogenicity, reproductive/developmental toxicity and endocrine

disrupting potential of POE-tallowamine should be further clarified."

This information led the European Union member states, in July 2016, to ban POE-tallowamine from glyphosate-based products. In contrast, POE-tallowamine is still allowed for food and nonfood uses in the U.S. and its use could be putting people at risk. We urge the SAP to explicitly support the call for more data on formulated glyphosate products and to incorporate these data into the carcinogenicity risk assessment.

Charge question 2 on the epi studies. We disagree with the EPA's conclusions that "the association between glyphosate and the risk of NHL cannot be determined based on the available" for many of the same reasons as laid out by Dr. Portier, Dr. Sass and Bill Freese in their comments to the SAP.

EPA should not have given more weight to the Agricultural Health Study by classifying it as high quality, given the problems that 1) the median follow-up time is 6.7 years may not be enough to detect NHL; the latency could be up to 20 years. 2) Only 61 of the 71 NHL cases, with some exposure to glyphosate, were considered in the EPA analysis of

cumulative exposure by terciles, making it more difficult to find a significant effect. And 3) the use of a 95 percent confidence interval, rather than a 90 percent confidence interval.

Use of a 90 percent CI would be more appropriate as it is more like conducting a one-tailed statistical test at a significance level of .05. A one-tailed statistical test is a more appropriate for a toxic chemical such as glyphosate, which can be assumed to have only a harmful effect and not a healthful effect, as a two-tailed statistical test implies.

As for the argument of the highest risk measures are coming from studies where there was a lower exposure to glyphosate, Bill Freese, yesterday presented compelling evidence of just the opposite. E.g., higher glyphosate usage rates in pounds per acre per year, and thus exposure to pesticide applicators in the 1980s, compared to the 1990s, which correlates with a higher estimates of the NHL risk in the De Roos et al. 2003 study, based on data from '79 to '86, compared to De Roos et al. 2005, based on data from '93 to 2001.

The drastic increase in glyphosate use in the late 90s through 2000s, come as a result in drastic expansion in the acreage of corn, soybeans and cotton that are treated with glyphosate as a result of genetically engineered glyphosate tolerant crops, which allowed more farmers to apply glyphosate than in the 80s.

The three meta-analyses that link glyphosate with NHL, Schinasi and Leon, IARC 2015, and Chang and Delzel (2016), all have odds ratios of over 1.0 with lower-bound CIs at 1.0 or above. And all found at least on statistically significant association between glyphosate usage and NHL. Even the industry-sponsored meta-analysis characterized their finding as "marginally significant positive meta-RRs for the association between glyphosate use and the risk of NHL and multiple myeloma.

The EPA's 2005 Guidelines for Carcinogenic Risk Assessment define "suggestive evidence of carcinogenic potential" as, in part "evidence of a positive response in studies whose power, design, or conduct limits the ability to draw a confident conclusion." The data from the epidemiology studies are consistent; relative risks are positive,

meta-analyses are positive, significant in the meta-analyses, and consistent with the animal evidence -- see charge question 3.

However, chance, bias and/or confounding cannot be ruled out. IARC looked at the data and concluded there was "limited evidence of carcinogenicity in humans," which is defined as "a positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence." This would be consistent with EPA's "suggestive evidence of carcinogenic potential."

In conclusion. The SAP should recommend that EPA change their view of the epidemiological studies to "suggestive evidence of carcinogenic potential," since their present conclusion gives no weight to the human evidence at all in their final evaluation.

And then finally, for Charge Question 3, on the Animal Carcinogenicity Studies. There were nine rat carcinogenicity studies and six mouse studies, with four of the rat studies showing

treatment-related effect in various organs, including thyroid tumors. And four of the mice studies showing treatment effects in renal tumors, hemangiosarcomas and malignant lymphomas. In all the cases, EPA considered the data were not treatment related, in violation of their own 2005 Guidelines for Carcinogenicity Risk Assessment.

For both the rat and mouse studies, EPA rejected positive findings "due to lack of pairwise statistical significance, lack of monotonic dose response, absence of preneoplastic or non-neoplastic lesions, no evidence of tumor progression, and/or historical control." Or evidence found only at high doses in absence of excess toxicity. Each of the arguments EPA uses to dismiss positive findings are not valid.

First, the Guidelines say that a significant trend test is sufficient --

DR. JAMES MCMANAMAN: Dr. Hansen, you requested five minutes and you're well over that now.

DR. MICHAEL HANSEN: Yes, I just have a minute or two and I'll be done.

So first the trend test is sufficient for a positive finding; a significant pairwise test is

not needed. Second, there is no mention in the guidelines of the need for a monotonic dose response.

The 2014 National Academy report on nonmonotonic dose-response, for endocrine disruptors, recommended that EPA consider nonmonotonic dose-response relationships. Some in vitro and in vivo animal studies have suggested that glyphosate may interfere with hormonal activity. And scientists, including endocrine experts, have stated that proper testing of glyphosate for endocrine activity is needed.

Third, dismissing significant findings which lack preneoplastic or non-neoplastic lesions makes the assumption that tall mechanisms, by which a chemical induces tumors in animals, will involve enough stages such that there would be a historically identifiable preneoplastic lesion from which the final tumors are formed. As Dr. Portier has noted, this assumption has not been shown to be true.

Fourth, EPA uses an outside historical control dataset to dismiss a positive finding in one study and fails to use an equally valid historical control data set to assess the importance of renal tumors in another study.

EPA should use concurrent controls, where possible, as the Guidelines notes.

In addition, as Dr. Portier notes, EPA used a historical control dataset from animals that lived 24 months to compare a response in a study that only lasted 18 months. If EPA had used the methodology, used by the National Toxicology Program, the Poly-3 adjustment to adjust the length of time an animal is in a study --

DR. JAMES MCMANAMAN: Dr. Hansen, I think we're going to have it to draw it to a close here.

DR. MICHAEL HANSEN: Okay.

DR. JAMES MCMANAMAN: You've provided the committee with the --

DR. MICHAEL HANSEN: Yes. We just ask that the animal studies should be redone with the proper assumptions being followed from the Cancer Guidelines.

DR. JAMES MCMANAMAN: Okay. Thank you. Any questions for Dr. Hansen? Yes, Dr. Sheppard?

DR. LIANNE SHEPPARD: Yeah. You didn't speak to this, but since you represent the Consumers

Union, maybe you can help me understand this. How important is the residential use of glyphosate?

DR. MICHAEL HANSEN: Well, the use is -- about one-third of the total use is actually non-agricultural. And that would include all home and garden uses, but that also includes uses on rice and whey, et cetera. There isn't a breakdown there, but it's about one-third of the total when you look at EPA data.

DR. LIANNE SHEPPARD: And is there -- no, I guess that's it. Thank you.

DR. JAMES MCMANAMAN: Other questions? Okay. Thank you very much.

Next, we have Moms Across America, Laura Mayer, Marghi Barnes, and Kathy Blum. Are you here? Okay.

You have 15 minutes and I'll give you a little leeway, but as Dr. Hansen found out, we can't go too far. Okay.

MS. KATHY BLUM: My name is Kathy Blum. I'm a concerned mother, a holistic nutrition educator and a member of Moms Across America. Thank you to the distinguished panel of the FIFRA SAP, for hearing the following comments on behalf of Moms Across America; a

national coalition of unstoppable moms who reaches over 300,000 like-minded moms per week. We are here today to request your serious consideration of the information that we present; also, of your obligation to protect the American people and life on Earth.

As a holistic nutrition educator, I work with clients whose health improves when they and their families switch from food grown with toxic herbicides to organic diets.

I present to you three points to consider in your assessment of glyphosate, and whether or not it is a safe chemical to allow on our food. My first point. Glyphosate is everywhere. It's in our air, our water, our soil, our food, our beverages. It's in mother's breastmilk. Children are exposed to glyphosate in many areas; playgrounds, parks, ball fields and their own backyards.

The EPA allows glyphosate to be sprayed on our food and feed crops. And residues are allowed at .2 to 400 parts per million. These levels have been shown to be harmful in many animal studies. While many would like to ignore it, the fact is the tests initiated by Moms Across America, and many other

groups now, have proven the widespread contamination of glyphosate in our food and our bodies.

Glyphosate has been found in tap water, our children's urine, mother's breastmilk, PediaSure feeding tube liquid, cow's milk and recently in many foods at shocking levels. For example, Lucy's gluten-free cookies; 452 parts per billion. Lay's kettle potato chips; 452 parts per billion. Doritos; 670 parts per billion. Honey Nut Cheerios; 670 parts per billion. Cheerios; 1125 parts per billion. What did you have for breakfast this morning? These levels are unacceptable. Any amount of glyphosate is unacceptable.

Studies have shown that even at very small amounts, .1 parts per billion, glyphosate destroys the gut bacteria, stimulates the growth of breast cancer cells, kills placental cells and causes harm to living things indiscriminately. By allowing glyphosate-based herbicides to be sprayed on our food and feed crops, you are allowing America to be poisoned through our food and water.

My second point, glyphosate does have carcinogenic qualities. And the EPA has known about this since 1983. In the 1980s, data supplied by

Monsanto to support its position that the tumors were not related to glyphosate exposure was considered by the EPA to be "not convincing". This same data is now somehow not being questioned in the same way nor being used in a precautionary manner. It's being used to protect the chemical companies, not the people.

And independent study on Roundup in mice revealed cancer promoting effects. Roundup was found to promote cancerous tumor growth in the skin of the mice. Scientists at the IARC, the cancer arm of the World Health Organization, have found what appears to be a strong link between pesticide exposure and the blood cancer Non-Hodgkin lymphoma. This is information which cannot be ignored.

You cannot ethically declare that glyphosate is not likely a carcinogen when people exposed to the weed killer glyphosate, through Roundup by Monsanto, had double the risk of developing Non-Hodgkin Lymphoma. By finding glyphosate is not likely a carcinogen, you're not protecting the farmers and consumers, you're doubling their risk of getting cancer.

And my third and final point, glyphosate-based herbicides cause many forms of harm.

And all forms of harm need to be considered in your decision making. Glyphosate is never used alone. It's always used with other formulants, which have been proven to be a 1000 times more toxic. Glyphosate has been scientifically proven to be a neurotoxin, cause placental cell death, cell damage, organ dysfunction, brain impairment, uterine changes; it causes cardiovascular toxicity, liver and kidney damage, and in the EPA's own words it was known to be a reproductive effector.

Glyphosate is an antibiotic. It was patented by Monsanto as an antimicrobial agent and it kills many microbes, especially the beneficial ones. Glyphosate promotes the growth of the pathogenic bacteria such as E coli and salmonella, increasing digestive issues and illness in American people and increasing the growth of bacteria on our meat.

Leading scientists agree that it is possible that glyphosate is a key driver of the problem we face today with multiple antibiotic resistance among certain pathogens. Glyphosate does not dry, wash or cook off. We ingest it. We simply cannot afford as a nation in debt to continue to allow antibacterial chemicals to be sprayed on our food.

In assessing glyphosate, it is unscientific, unreasonable and irresponsible to only look at the impact of glyphosate being a carcinogen, especially in any assessment on whether or not to revoke the license. We are being poisoned and our children are being poisoned. All of us are guinea pigs in this horrendous, toxic experiment. You have an opportunity now to stop this. Our lives depend on it. Thank you.

DR. JAMES MCMANAMAN: Thank you. Are there -- will there be other presentations or is this it? Okay. There's one more. Sorry.

MS. MARGHI BARNES: That's a hard act to follow. My name is Marghi Barnes. I'm with Moms Across America. And I live on the Eastern shore. A lot of the issues that I deal with have to do with animal agriculture and the environmental and health hazards of that, which include a lot of exposure to ammonia in our air, and also contamination of our waterways. We also have a lot of monoculture farms which are meant to grow food for animals so they're actually subject to lower standards, I believe, when they grow their food.

So not only am I concerned as a mother for the food that my child ingests, I'm also very concerned about the spraying. Children in rural areas are becoming more and more sick, especially with respiratory diseases, asthma, lung disease. Eastern shore of Maryland is absolutely through the roof with lung disease and asthma.

In fact, to say I find this so funny, this is a mask that is being marketed. This is becoming fashion, this is fashion. They actually have fashion shows now for masks to protect people from bad air quality. And that bad air quality includes pesticides and herbicides. There's even a beautiful picture of a family all wearing these very fashionable air masks.

We're not just being effected by glyphosate through the food we eat, it's also in our water, it's also in our air. It's everywhere. It is like glitter. You cannot get rid of it. I mean you can't even avoid it even if you wanted to. Which is really not a, you know, the American way.

But I wanted to ask you what is the first thing everyone here sees when you walk into a Home Depot? You see a giant effigy of Roundup in

front of you. You know, they always stack them up in this beautiful, creative, artistic way. It's this mountain to impress you when you walk into the store. You know, you need this. You have to get your Roundup.

Everyone is using Roundup. They think it's safe. They trust the EPA to protect them. They don't understand that when everyone is using pounds and pounds and pounds of this stuff it reaches a critical mass. There's a saturation point.

What is the saturation point for glyphosate to the point where we can't put any more of this in the environment? I mean, I don't think there's a study for that. I don't think we have nearly enough epidemiological studies on how this effects children who have grown up in a world that is much more toxic than the world we grew up in. They're being exposed to a lot more dangers. And we're seeing that. Children are having a really hard time with their health compared to us.

I was reading about adjuvants with glyphosate, especially aluminum sulfate. I was reading about how it effects the penile gland and there's studies now that are suggesting when

glyphosate is combined with adjuvants it's twice as harmful. And then I go to a farm site and it's all these farmers asking, well how much aluminum sulfate do I combine with the glyphosate.

You know, so people are combining this, they have no idea that they're creating something that is so potent, if you will, you know, this is getting dangerous. When it's gotten to the point where we can't get away from it even if we wanted to. And especially as mothers, we're very concerned about how these things are just being let out into the environment and there's nothing we can do about it. We're relying on you to protect us and to protect our children more importantly. Thank you.

DR. JAMES MCMANAMAN: Thank you.

MS. VIRGINIA KOLAKASKI: My name's Virginia Kolakaski, I'm here speaking for Laura who couldn't be here today. I'm here also representing millions of mothers who couldn't be here and who don't even know that this is occurring.

This all became very aware to me when I lost my brother to cancer at the age of 33. I want to say from a personal level, I've pretty much always been a conscientious mother and had my kids eat and

drink, consume organic foods. But personally, while we're putting it all out there, I have had an experience with horrendous menstrual cramps for 30 plus years. And once I started learning about glyphosate, what's sprayed on cotton fields, et cetera, I switched to organic. And upon doing that, immediately was cramp free. I think that's pretty amazing, and I've been that way for two years. That's my own personal experience. I'm going to share with you some points Laura was going to talk about today.

Thousands of mothers see their children's health improve when they're children avoid glyphosate-based herbicides and eat organic. As a representative of mothers across the nation, you must know that there are thousands, if not millions of us who have reason to believe that glyphosate-based herbicides are largely responsible for our children's skyrocketing health issues.

One mom, Zen Honeycutt, has reported that her son had a sudden onset of autism symptoms at eight years old. His doctor tested his urine and he had high levels of fungus, c-diff, bacteria, gut dysbiosis and 21 different food intolerances. He also tested positive for glyphosate in his urine at eight

times higher than what was found in European studies. He was the only one of her three sons who was eating wheat. And she had just learned that was sprayed with glyphosate as a drying agent to make it easily harvestable.

They eliminated wheat and went all organic and within six weeks retested him and his glyphosate levels were no longer detectable and his autism symptoms were gone. They have not come back in over three years of eating organic.

Another mother, Susan T., said the most impacting issue is my children's health. They've shown great improvement after eight months of a GMO free and glyphosate free diet. My eight-year-old has had chronic acid reflux since he was born. My 11-year-old has ADHD and chronic diarrhea. They both are cured of their digestive problems after eight months of not eating GMOs and toxins. And for the first time, her ADHD son brought a report card full of A's and B's without any medication. I don't know what proof other people need, but this did it for me.

One of her children had numerous supposed environmental allergies which have disappeared since the elimination of GMOs and

glyphosate. Since then, allergies, eczema and behavioral issues have disappeared. And that was another quote by Terry H.

Pediatricians have seen remarkable improvements in patients who avoid glyphosate-based herbicides and eat organic. As a teacher who sees increasing health issues in my students I present to you a statement of pediatrician Dr. Michelle Perro regarding EPA HQOPP 2016 through 0385. I'm a pediatrician of 35 years. Of the past 15 years, I've seen a precipitous drop in the health of children.

I have studied their gut immune responses as well as their intestinal microbiome and what I have learned was shocking. I have found extremely high levels of antibodies to foods, intestinal permeability, and abnormal T and B cell function. Their microbial diversity of their guts is low and overabundance of potential pathogens. In addition, there is early evidence of autoimmune markers, which a decade ago was rarely found.

When I removed glyphosate from the diets, many of their symptoms and findings resolved. Therefore, I was able to surmise that the abnormal findings or link to glyphosate and its associated

adjuvants. I have found glyphosate to act as an antibiotic and a chelator. In particular, I have found extremely low levels of magnesium and zinc as well as other minerals. This significantly impairs neurocognitive development function.

Both of these minerals are involved in over 200 chemical reactions in the brain alone. Simple correction of these nutrient issues had significant improvement on school performance, focus, mood, lability and sleep. Glyphosate approval needs to be put on hold. I have studied and clinically treated children for the past decade. Without a doubt, ill health is directly correlated to the ever-increasing application of its usage.

I just ask you all to please consider seriously renewing the license of glyphosate. I truly, truly believe in my heart of hearts that this is a decision that you can make for the American people going out as our administration changes and things are really -- the environment sounds like to me is not going to be a consideration. Thank you.

DR. JAMES MCMANAMAN: Thank you. Now we can open up to questions for these presenters. Marion.

DR. MARION EHRICH: Okay. Marion Ehrich, Virginia Tech. For Kathy Blum, these cookies and things, what was the assay method used for the calculations of concentrations?

MS. KATHY BLUM: I'm sorry. What did you say?

DR. MARION EHRICH: What is the assay method? How were they analyzed?

MS. KATHY BLUM: You know what, I don't know that. But I have all the studies and sources attached to my notes. And you have them all.

DR. MARION EHRICH: I have to go look?

MS. KATHY BLUM: Yeah, that -- unfortunately I don't know how -- I don't know the technical details of the studies.

DR. MICHAEL HANSEN: They're all ELISA.

DR. MARION EHRICH: Okay. There we go.

MS. KATHY BLUM: Thank you.

DR. JAMES MCMANAMAN: Other question? Okay. Hearing none then thank you very much.

I have next someone from Immediate Life. And you're from AVAAZ?

REVEREND BILLY TALEN: I'm Reverend Talen from Immediate Life Church.

DR. JAMES MCMANAMAN: Can we use a microphone? I don't know if you were here, but we're on a pretty tight schedule and you have five minutes. That's what you requested.

REVEREND BILLY TALEN: Something about us gives you the impression we'll go over time?

DR. JAMES MCMANAMAN: No, no. It's just something about human nature that gives me the impression that that may be a possibility.

REVEREND BILLY TALEN: Well, I'm very happy to cede time to the Moms Across America. We are also coming from the vantage point of being parents. We discovered up in Brooklyn, New York, that a playground in Prospect Park was experiencing the spraying of Monsanto's Roundup in a proximity that we didn't think was appropriate. We started a Freedom of Information Act request with the lawyers from our group and we discovered that there's a lot of spraying in the parks of New York City. And that it is also going out across the country.

We started filing FOIAs in scores and then hundreds of cities and towns across the country. And we have created an interactive map of the spraying sites in school systems and parks, city, state and

national parks. And you have all that information. This is called the United States National Map of Poisoned Parks and Playgrounds. And it makes it possible for parents to click down and get closer and closer to the ground with their point of view until they can determine if a spraying site is near where their child might frequent in his or her playing.

Now we know, as just mentioned, there's a political cloud hanging over this room, this proceeding. We have people who are avowedly against the controls that we're asking for with glyphosates, coming into power and we have the EPA, decades ago, saying in its records that it was aware of the dangers of glyphosates. Probably everybody in this room and many of the people probably at this square table, this impressive meeting table, we've lost loved ones to one of the many diseases that the Moms Across America were listing for us.

We're -- especially with children and young families, pregnant, young women who are around playgrounds, around the areas in National Parks, around school yards, ball fields, around picnic areas and hiking areas -- we're very aware of the cancers that come from, we believe, from glyphosates.

And we ask that you let some kind of Toto pull the curtain back and see that Monsanto executive at those levers distracting us with some kind of marketing creation of -- the war on cancer would be a good example. But just their advertising and the way that they demonize the science that seems to be arranged against their possible bottom line. We ask you to free yourself of this tremendous prejudice that has kept this toxin in so many of our homes and in our bodies, in our food, in our air. The Moms told us all about that.

Now we have the prospect now of looking for new ways as this new administration comes in, finding new ways, a new social movement, a new kind of environmentalism that isn't so ready to accept fossil fuel money, for instance. A new kind of environmental movement that uses litigation, that uses culture, that uses a whole new pallet of activism. In our work, we're using songs, we're performing. We're going into public space in a new way. We're going to many of these parks and playgrounds. We're going in -- we've been inside of the Parks Department of New York performing in their offices. Now as my voice rises, I

feel as if I'm starting to preach right here. Amen, Dragonfly. Yes, go ahead.

MS. ROBIN LAVERNE WILSON: Hello everyone. My name is Robin Laverne Wilson. I'm also known as Dragonfly, but they would not put that on the previous ballot. I was also the Green Party's senatorial candidate for New York State. And I am both an aspiring State's woman and a culture worker along here with Reverend William Talen here.

And I just want to interject and make sure that we do not overlook the racial disparity of the effect of glyphosates on society. And when I say racial disparity, I also mean class disparity. Because classism and racism are the two tracks that capitalism railroad runs through communities. I am the daughter of a career combat medic, career in Vietnam. And the 20 years of life that I got to experience with my father, I saw him experience prostate cancer, radiation burn from the prostate cancer, gout, lupus, diabetes, congestive heart failure, angioplasty, PTSD, et cetera.

And from the testimonies that you've already heard, I think you can agree that glyphosates have a physical and mental and emotional and at this

point, even spiritual effect on families and communities. And from the research that the Immediate Life Church has been doing, we can prove to you the classist and racist disparity. And who gets sprayed, who gets drenched with poisons and who doesn't. Who gets goats to come and clean up their park? And who has to eat poisoned food and drink poisoned water?

REVEREND BILLY TALEN: Thank you Robin. We have a new era that we're coming into right now.

DR. JAMES MCMANAMAN: Mr. Talen, I'm not sure where you're at but we're at --

REVEREND BILLY TALEN: Are we at our five minutes? That's the new era. We're at the end of the five minutes.

We just returned from Standing Rock. Standing Rock has taught us the new environmentalism, that this administration coming in that is declaring its hatred of the Earth, we know what you need to do now to stop the pipeline. Glyphosates are a pipeline and the glyphosate pipeline will be stopped by people who are evolving into life. Amen. Thank you so much for your attention.

Praise be: (All singing) Monsanto is the devil. No to glyphosates. Monsanto is the devil.

No glyphosates. Monsanto is the devil. No glyphosates. Monsanto is the devil. No glyphosates. Monsanto is the devil. No glyphosates. Monsanto is the devil. No glyphosates.

DR. JAMES MCMANAMAN: I think they should do a recording. Yeah, I mean this has been nice.

So, okay, next up. Dr. Hashad?

DR. DALIA HASHAD: Good morning. In the words of the previous presenter, that's a hard act to follow. I'm Dalia, I didn't bring with me a chorus, no theater, but I come as a representative of AVAAZ, and as a representative of over two million people who have called for an independent and transparent evaluation of glyphosate.

Today, what I do bring with me is over 5,000 individual comments, unique comments written for you from AVAAZ members across the United States. Here's a printout. You don't all have a copy, but there is a link and people are continuing to comment. These are -- think of these people as your neighbor. These are the average people who are here and want their voice heard in the room and their concerns.

Most of the public concern falls into four categories. The first is the real concern that glyphosate is classified as a human carcinogen. The second, is that the public can't meaningfully control or avoid exposure. The third, is that much of the science is corrupted by pesticide and chemical industry after influence. And the last, the fourth, is that government bodies are not appropriately responsive to public concern for the need for protection.

One of our members -- I want to share the voices of our members who wanted to be here, but wrote in. Dear EPA panel, your job is to protect the people of our nation and environment. The evidence is overwhelming that glyphosate has permeated our lands, water and food. It has been overused and now is present everywhere. The World Health Organization has determined glyphosate probably causes cancer and studies show it damages DNA. Protect our health, not corporate profits. Please ban glyphosate. That was Arthur Mallow (phonetic).

We've seen thousands of these really heartfelt thoughtful comments that people across the U.S., they're impacted by the science. They

understand enough of the science that clearly shows that there's a plausible association between glyphosate and cancer. And that's enough to satisfy the EPA's own Guidelines for Carcinogen Risk Assessment.

Dr. Arti Chandra writes to you. I'm a primary care physician who practices functional medicine, an approach to chronic issues that looks at underlying group causes to patient's symptoms and disease processes. It is clear from accumulating scientific research that glyphosate poses clear risks to the biochemistry of the body and to the DNA. This is particularly worrying, in light of the fact that for almost all citizens, as been previously mentioned, glyphosate is unavoidable. Our consumption is invisible and we have no way to mitigate the risk. We have no choice in the matter. We can't pick foods that aren't contaminated and we can't keep it out of our bodies.

AVAAZ member, Jacqueline Weller (phonetic) writes to you, the average U.S. resident, man, woman and child already has glyphosate in our cells because it is everywhere. On our food, on our lawns, school grounds and parks. Now that scientists

say it is probably a carcinogen, we must ban its use. We need the EPA to provide informed, unbiased representation for us in this critical matter over which we the people have no control.

AVAAZ member Vince Rabino (phonetic) wrote in, please ban the use of glyphosate. Much of the science that says glyphosate is safe is financed by the chemical companies who want to keep their product on the market. Please, put our health before corporate profits.

That can be tough when we're talking about a multibillion dollar business fighting hard to protect their profits. But making people sick to keep industry healthy is criminal. A recent YouGov poll found that 86 percent of Americans are supportive of the EPA using studies from independent scientists in their safety assessments. 62 percent support the EPA suspending the use of glyphosate as a precautionary measure until more independent studies can be conducted. Sadly, we've already put the cart before the horse. 18.9 billion pounds has been used globally. And in 2014 alone, enough glyphosate was sprayed in the U.S. to leave more than 3/4 of a pound of the active ingredient on every harvested acre of

cropland. We ask that you exclude compromised studies supported by the glyphosate industry invested actors. We ask you to classify glyphosate as likely to be carcinogenic to humans and to immediately commission the independent studies that we need.

I'll close with the words of an AVAAZ member, Rachel Messer (phonetic). She says what so many around the country are asking of you now. Please protect the health and future of the American people. Our families, our children by blocking the use of glyphosate. Thank you for your integrity, thank you for your courage in standing up to toxic chemicals and powerful corporate interests. Thank you very much for your consideration.

DR. JAMES MCMANAMAN: Thank you. Any questions for Dr. Hashad? Thank you very much.

DR. DALIA HASHAD: Thank you.

DR. JAMES MCMANAMAN: Okay. Next up, if we could get Dr. Peter Infante, David Spak from Bayer Crop Science and Alexis Baden-Mayer from Organic Consumers Association?

I don't -- are you trying to find Dr. Infante a pointer? I'm just wondering are we trying to find a pointer for you. We're looking. We

had -- yeah. Fingers don't work from where you're at, do they?

Okay. Well, I guess we're stuck with what you have. Do your best.

DR. PETER INFANTE: Okay. Thank you. Given the short time that I have for my presentation, I'm going to focus on the epidemiological studies of the -- is there something here I'm missing?

DR. JAMES MCMANAMAN: That just goes to show that pointing is one of mankind's early human advancements.

DR. PETER INFANTE: Okay. I'd like to let everyone know I'm now qualified on the pointer. I think. Let's see. No, I'm not. Did it go in? Okay. Thank you.

I'm going to focus on the epidemiological studies related to Non-Hodgkin Lymphoma. Is this the advancer here? Okay. What this slide shows are the publications that are used in the various meta-analyses to estimate the risks for exposure to glyphosate in Non-Hodgkin Lymphoma. The ones that are picked out in yellow, those are the point estimates that I used from the six studies that were the studies that EPA has focused on in its

review. And I have also added the Cocco for a separate analysis.

For the De Roos 2003, my preferred analysis is the logistic regression analysis which is the top row there because the hierarchical regression analysis that some people have used in their meta-analyses adjust the actual data in the study for opinions about cancer based on how EPA and IARC have evaluated the pesticides that were adjusted for. The 2.1 there, that logistic regression analysis is based on adjustment for 47 other pesticides.

The hierarchical regression analysis adds on top of that this adjustment that's based on opinions about cancer. And these opinions change over time. The same data and the same type of adjustment will change as more information is available on the evidence of carcinogenicity. And the other point is that the hierarchical analysis is based on Non-Hodgkin Lymphoma, but if these other pesticides show evidence of any cancer. To me, it should not, in my opinion, be the preferred analysis to rely upon.

In the right-hand column, it shows the relative weights that the studies played in the meta-analyses. And the second De Roos, 2001, everyone

has used that. The Eriksson, 2008, 1.5, everyone's used that. Hardell, 1.5, that's the same everyone else has used. For the McDuffie study, I've chosen the risk estimate of 1.4 because that's based on the Hohenadel et al. update of McDuffie which adjusted for doing further pathological review of the Non-Hodgkin Lymphoma cases and they reclassified, I think, four cases. Then the Orsi, everyone has used that.

And the Cocco, 2013 I thought I was a reasonable study and it's for B cell lymphoma. And you say well, why are you including B cell lymphoma in a meta-analysis of Non-Hodgkin Lymphoma? And I thought well, it certainly didn't seem unreasonable to include it on a separate analysis because 85 percent of Non-Hodgkin Lymphoma is B Cell Lymphoma. And the Cocco study only evaluated B cell lymphoma.

These are the results of the meta-analysis. The top ones say EPA 2016. That analysis I did based on the data on page 64 in the issue paper taken from the Forest plot. And that Forest plot shows the point estimates in the confidence intervals but it does not provide a meta-analysis. The meta-analysis that I did shows that essentially identical to the IARC 2015 analysis

which isn't surprising because it's the same studies and the same data points.

Schinasi does a meta-analysis shows 1.5 that's statistically significant and as you can see in the next column the two studies were adjusted for other pesticide use but he did not use the -- he used the Hardell unadjusted and the Eriksson unadjusted. And they did that in their analysis. Chang and Delzel, they show risk estimates ranging from 1.3 to 1.4 that are statistically significant. I presented the results for Model 4 but there are four models in Table 3 of Chang and Delzel that need to be reviewed if you haven't looked at them yet. Because what they are, they're combinations of different data points from the same six studies. They all show relative risks between -- or meta risks between 1.3 and 1.4 that are statistically significant.

Then in what's called, this presentation, that includes the six studies that IARC has -- that EPA has considered in its review of Non-Hodgkin Lymphoma. The exception that I used the Holland et al update of the Duffy study and I used the De Roos logistic regression analysis without the hierarchical adjustment because I don't really think

that's an appropriate adjustment. It's certainly not the most informative in this study. And with that I come up with 1.37 which is essentially the same as what Chang 2016 because they're 1.4 is really based on the same studies that I have where it says this presentation.

Then I added Cocco which is a Non-Hodgkin Lymphoma so that would make a total of seven studies and the risk estimate -- meta risk doesn't change. It's 1.4 because it only contributed four cases. It's a small study. Then I did one more meta-analysis excluding De Ross 2005, and what you see is you have a meta risk for Non-Hodgkin Lymphoma of 1.67 that's statistically significant. Now you're going to say well why did I exclude the Agricultural Health Study? Well, it's going to become, I think, obvious, as we continue on.

To further review this there are like, one, two, three, four, possibly five meta analyses that all demonstrates statistically significant increases in Non-Hodgkin Lymphoma with a range of between 1.3 and 1.5 to 1.6.

In summary of epidemiological studies individually five of the six studies demonstrate a

relative risk greater than one. All of the meta-analyses conducted to date demonstrates statistically significant results. Three of six studies have significantly elevated risks for either ever/never or those that were part of a dose response analysis that were at the high end of the dose response.

Now you say, well, the 2.1 there, that's from the De Roos 2003 and you know, EPA states that there's no -- in the document, states there are no studies that demonstrate statistically significant increase. That's simply not the case. You have it in De Roos 2003 and that analysis, as I mentioned, is adjusted for 47 pesticides. Eriksson 2008 for more than ten days of exposure you have an odds ratio of 2.6. It's highly significant. For McDuffie, more than two days per year, you have an odds ratio of over two that's statically significant. You have three out of six studies have been conducted that demonstrate significantly elevated risks for Non-Hodgkin Lymphoma.

Now if I can get this to move on. Okay. Now two of three studies have evaluated dose response were statistically significant. You have Eriksson shows that less than 10 days versus more than

10 days in the upper estimate there, you've got 2.36. That's highly significant. McDuffie shows an exposure response relationship more than two days per year. The odds ratio is over two-fold. The only study that doesn't show it is the De Ross 2005 Agricultural Health Study.

Also, there is one out of one study that evaluated latency indicates an increased risk by latency. You see in the Eriksson study, less than 10 years versus more than 10 years. Latency you have then a significant increase in the more than 10 years of latency group. In my opinion, this is pretty impressive evidence in terms of glyphosate in Non-Hodgkin Lymphoma.

Now let's talk about the De Roos study which is been characterized by many as a null study. Note I have null in quotes. First of all, the study is a short -- represents a short follow-up period. This isn't latency. There's a difference between latency and follow-up period. This study has a very short follow-up period since they were enrolled in the study between 1993 and 1997 and followed to 2001. That's a maximum eight years' latency. The study indicates a median of 6.7 years of follow-up. Seventy

percent of the cohort that's followed in the 2005 De Roos study is younger than 60 years of age. Forty-six percent of the cohort is less than 50 years of age. This is a very young cohort.

If they, well, gee, it looks as if it's a very young cohort. Is there any indication in the data from the study that in fact, you know, this might be considered a young cohort aside from looking at the distribution of the ages? When you look at the number of deaths so far diagnosed in that study, remember when they were enrolled in the study, they had to be cancer-free. You only have a maximum of eight year's follow-up in this study. Now when you look at -- only 3.3 percent of the cohort has been diagnosed with any cancer.

And you say, well, what does that tell us? Well, if you look at data for the U.S., 42 percent of U.S. males are diagnosed with an invasive cancer over their lifetime. You might say, well, that's over their lifetime. But this cohort was only followed for up to eight years. That's exactly my point. It has not been followed for a long enough period of time to be able to evaluate any cancer response in the cohort.

When I was at NIOSH in the industry-wide studies branch, all of the studies we did were cohort studies. I like, I prefer cohort studies. And I was at OSHA for 24 years, almost 95 percent of the studies related to occupational cancer were cohort studies. I've looked at a lot of cohort studies. And I think they're good. It's a good method to use, but you have to follow the cohort for a long enough period of time and you have to allow the cohort to age into the years when cancer develops in order to evaluate the cancer risk from any chemical exposure.

The problem is that you don't get enough yield. Like I've heard the comments about this is a large cohort, but there are 71 glyphosate exposed workers who developed Non-Hodgkin Lymphoma. If you look at the case control studies and add them up there are 140 cases. You have twice as many cases of Non-Hodgkin Lymphoma in the controls. And so, that's one advantage of case control studies that you don't have to wait 30, 40 years to identify the cancers. That you can go and identify the cancers and then look at the difference in exposures. Also, you cannot evaluate latency in the De Roos 2005 study. You

simply cannot do it because you do not know when the first exposure occurred.

So in my opinion of this study, it's too young of a cohort for them to develop cancer. The follow-up period is too short and for those reasons, I think that you cannot rely on this study. And let me further explain my point.

DR. JAMES MCMANAMAN: Your ten minutes is over by quite a bit.

DR. PETER INFANTE: Well, I only -- I can go through the rest of them very quickly --

DR. JAMES MCMANAMAN: Okay.

DR. PETER INFANTE: -- and I was told like approximately ten minutes. I promise to --

DR. JAMES MCMANAMAN: I'll give you a little leeway.

DR. PETER INFANTE: I promise to keep within like a 95 percent confidence interval.

DR. JAMES MCMANAMAN: All right.

DR. JAMES INFANTE: Okay. Thank you. Now here are data from the UK because -- data in the UK with epidemiology cancer trends is essentially the same as it is in the United States. But I used the UK data because I'm just using this for an illustration

and I could find this chart here that I thought was very nice. Now when you look at the data by age of diagnosis at the bottom, over on the right is rate of cancer per 100,000 population. And these are invasive cancers.

Here's where the De Roos cohort is. Approximately 50 percent of them are followed beginning at 50 years of age. When you look up here at this blue line, this is males, cancer incidents for males, total cancer

between

-- see this part of the curve here, the blue line? That's where the cohort has been followed. You don't start to see cancer develop in people until like 55 and older when you start to see an exponential increase. My point is with this graph to show you that the cohort is -- it's a young cohort and it's being followed for this particular -- for this time in its life when cancer development is very low.

And when this cohort is followed for another 20 years it will be a very helpful to evaluate the carcinogenicity of glyphosate. So in my opinion the De Roos 2005 study is uninformative in terms of risk of cancer and I'm surprised that no one else has

pointed this out. It's very clear from many of us that spent their life evaluating cohort studies.

You know, it's like doing a cancer bioassay and terminating the animals by one year at the latest. You're not following it long enough for cancer to develop. It's the same thing in this cohort. And this is why I'm justified, I feel, in excluding De Roos cohort from the meta-analysis because at this point in its follow-up it's an uninformative study.

Okay, the study also --

DR. JAMES MCMANAMAN: Can we just wrap it up in a couple more comments? Because we're way over now.

DR. PETER INFANTE: All right, yes. There's exposure misclassification I'll be glad to answer questions about it. Now here's the other thing in the study, the comparison group. The comparison group to the glyphosate exposed farmers are other farmers not exposed to glyphosate. Ninety-one percent of them are farmers. Farmers are known to have an elevated risk Non-Hodgkin Lymphoma. You're evaluating Non-Hodgkin Lymphoma in a group and comparing them to another group that's known to have an elevated risk of

Non-Hodgkin Lymphoma. Furthermore, in addition to that, 53 percent of them have been exposed, in the table you can see, in the study 53 percent were exposed to 24D. If you look at the Schinasi meta-analysis for 24D, it shows a 1.4 risk that's statistically significant. So then when you do your analysis of ever versus never in that cohort, the never exposed to glyphosate in fact have an elevated risk of Non-Hodgkin Lymphoma because they're farmers and half of them were exposed to 24D which indicates a further problem.

Could I -- I'm almost finished?

DR. JAMES MCMANAMAN: Almost?

DR. PETER INFANTE: Yep.

DR. JAMES MCMANAMAN: Okay.

DR. PETER INFANTE: So here are the EPA descriptors, according to their Cancer Guidelines and top is the highest evidence carcinogenic to humans all the way to not likely to be carcinogenic to humans which is what the EPA issue paper indicates right now.

Okay, so what does not likely to carcinogens mean, according to their EPA cancer policy? This descriptor is appropriate when the available data are considered robust for deciding that

there is no basis for human hazard concern. I mean it's clearly not there. Suggestive evidence cover; this descriptor covers a single positive cancer result in an extensive database that includes negative studies in other species. Then on the bottom part of it is an example. The increase in tumor in a single -- single -- animal or human study. That's likely to be.

Likely to be. Here we are. Now adequate evidence is considered what the descriptors describes the broad spectrum but they use the term lightly does not correspond to a quantifiable probability. And I think that's important in terms of these Cancer Guidelines. An agent demonstrating a plausible but not definitively causal association between human exposure and cancer. That's what likely is.

Summary and conclusions; based upon my review of the six epidemiology studies EPA relies upon for its evaluation of Non-Hodgkin Lymphoma risk, in relation to the criteria presented in EPA's Guidelines for Cancer Risk Assessment, data for glyphosate exposure and risk of Non-Hodgkin Lymphoma clearly exceed the proposed descriptor not likely to be

carcinogenic to humans. And I conclude on the basis of the epidemiological evidence for Non-Hodgkin Lymphoma that glyphosate should be categorized as likely to be carcinogenic. Thank you.

DR. JAMES MCMANAMAN: Thank you. Any questions for Dr. Infante? Okay. Dr. Johnson had his hand up first.

DR. ERIC JOHNSON: I'd be grateful if you can share with us any data that you have on the latency of Non-Hodgkin Lymphoma.

DR. PETER INFANTE: For Non-Hodgkin Lymphoma?

DR. ERIC JOHNSON: Yes. What's the latency based on other --

DR. PETER INFANTE: The latency?

DR. ERIC JOHNSON: Well, you know, it varies. And it depends on the exposure. Like for example, an individual exposed to chemotherapeutic drugs, they have a short latency. Individuals exposed to radiation like from the atomic bomb, they have a short latency period. Those who were exposed -- by short, okay, I'll say within, you see cases in those situations within 10 years from treatment with anti-neoplastic agents or from radiation exposure.

When -- if you look at the studies related to toxic chemical exposures you see latencies ranging anywhere from 10 to maybe 30 to 40 years.

And in fact, the EPA, in its comments on the data say that well, it's not known what the latency period is for Non-Hodgkin Lymphoma and they site Wiesenberger (phonetic) 1992. Well, Wiesenberger study does not support it could be any time. It states exactly what I just stated that for these very high doses, to very toxic agents, you have a shorter latency period. And for exposure to toxic chemicals at lower level exposure, you would have a relatively longer latency period.

In fact, he sent a comment that I saw on the docket saying that EPA is incorrect on its assessment that the range of latency for Non-Hodgkin Lymphoma can be anywhere from 1 to 25 years. In fact, the other two studies that they cite, one of them shows that there's no elevated risk in latency until 26 or more years. That's the Kato study related to organic solvent exposures. And then the third one is the study of rice workers in Italy who were first exposed before 1950 and in that particular situation

you don't see an elevated risk until after 1975 so it's got to be a minimum of 25 years.

And those are simply the three studies that EPA is citing to say well, we don't know what the latency period is. There are some indications of latency in those studies. And it's not all over the place. And in fact, if you look at benzene exposed workers, Dr. Crump probably knows this data, that you see with refinery workers, you see elevated risks of Non-Hodgkin Lymphoma and multiple myeloma from 30 or more years. You can see it shorter, but you see the same thing with organic solvents, you'll see it with benzene, there are a lot of -- rubber workers exposed to solvents, some containing benzene in the rubber industry; they have a relatively long latency period.

It depends on the type of exposures. And I think to sum it up I would say that if you have low level exposure to a toxic agent, in general, you're going to have a longer latency period. Certainly, more than 10 years, maybe more than 20 years. It depends on the exposure. And it depends on -- for an individual, it depends on what else they're exposed to. You know, we don't live in a world where we're exposed to one toxic agent at a

time. Plus, we have our own genetic component of what we're susceptible to. I would say certainly I would think for the most part more than 10 years, but I suppose there could be exceptions.

DR. ERIC JOHNSON: This issue is a challenging one, the latency and Non-Hodgkin Lymphoma. I mean, it makes it difficult for some of us to clearly interpret those results. Because latency we tend to give one number. When we give one number it is just the average. It is always a range. And so, one has to factor in that range when one determines whether is it possible to see case due to that exposure or not.

DR. PETER INFANTE: You're correct. There is not one number. That's the average. Obviously, you've got latencies on both sides of whatever are the average or median latency period is.

But I would say from my experience looking at data from a lot of different datasets on Non-Hodgkin Lymphoma you see elevated risks. If you look at the NCI study of benzene, for those at more than 10 years of exposure they have a four-fold risk of Non-Hodgkin Lymphoma.

DR. ERIC JOHNSON: If you can help us out.

DR. JAMES MCMANAMAN: Dr. Johnson, we're going to have to -- it's got to be questions, not a back and forth here. It's not a discussion.

DR. ERIC JOHNSON: No. What I'm asking Dr. Infante, if he can share with us some of that data because that would be helpful for us to look at. The latency on Non-Hodgkin Lymphoma because it's becoming so critical in this evaluation.

DR. JAMES MCMANAMAN: I think he just shared it with us verbally and if you can provide us with references to that, that would be wonderful.

DR. PETER INFANTE: Let me make a note. I can do that. I will do that, yes.

DR. JAMES MCMANAMAN: Okay. Dr. Green had her hand up first.

DR. LAURA GREEN: Just quick. Thank you, Dr. Infante for that very interesting assessment. I have two questions. First, have you tried to find any data on manufacturers?

DR. PETER INFANTE: No. I mean, I don't have access to that.

DR. LAURA GREEN: We've been asking about it. It doesn't seem to exist. Just wondering if you had tried to find any.

Second, the Ag health workers De Roos and colleagues were of course aware of their short follow-up period and mentioned that in their papers, a limitation. I mean, to be fair, it's not, they knew that and it is what it is. But they also promise us, and it's 11 years ago now, that there's going to be a follow-up study. I'm wondering if you've tried to contact De Roos et al. and see if they're ready with their follow-up. Or if not, why not?

DR. PETER INFANTE: Well, I, in fact, I did contact the National Cancer Institute because they presented abstracts at two meetings in the last year. The most recent was at the IARC 50th Anniversary meeting. And at that meeting, the data from the abstract -- it was in May of this year -- the data from the abstract indicate, it looks like there are several subtypes of Non-Hodgkin Lymphoma that, you know, may be elevated. But you need to actually look at the study to evaluate all the methodology. I think Hawa (phonetic) is the first -- in the -- I submitted

written comments today, and I have the reference for the abstract.

But anyhow, NCIs response to me was that it was still undergoing peer review and as soon as it was ready for publication they would release the results. I don't know, maybe the SAP could ask EPA to request the results from that study. Because the point is that when you've got subtypes -- when you have an overall significant increase in Non-Hodgkin Lymphoma, obviously, some of the subtypes are going to show a higher risk than the overall risk.

And that's another thing, is in this document, I think you should ask the EPA to include a review of the subtypes. They didn't do that. They said they were only going to look at total. And Eriksson shows a significant increase in some subtypes and there are probably other studies as well.

DR. JAMES MCMANAMAN: Dr. Parsons.

DR. BARBARA PARSONS: So I just have a simple question. In your presentation, you referred to the age of the cohort regarding Non-Hodgkin Lymphoma. I think you said 70 percent --

DR. JAMES MCMANAMAN: Dr. Parsons, can you put the microphone a little bit closer?

DR. BARBARA PARSONS: -- 70 percent younger than 60 years, 46 percent younger than 50. I just thought it would be informative to know what's the average age of diagnosis for Non-Hodgkin Lymphoma?

DR. PETER INFANTE: The average age of which?

DR. BARBARA PARSONS: Diagnosis for Non-Hodgkin Lymphoma. Are you aware?

DR. PETER INFANTE: You know, I don't know, but I will be glad to provide it. I should look that up. But my point is in terms of the length, it's the young cohort -- approximately 50 percent are younger than 50 years of age. And when you began the follow-up they were all free of cancer. They had to be to be in the study.

You're saying that in a four to eight-year period of follow-up you're going to -- at people, men that are that young -- you're going to identify a significant increase in specific cancers? You know, I kind of doubt it.

This cohort, I think is going to be a good cohort when it's followed for 20, 25 years. But not right now. It has its limitations. As was pointed out to me, Blair et al. (phonetic) said, I

think it was a young cohort, is that what you said? You had indicated that the NCI said that it was short follow-up period.

DR. LAURA GREEN: Yeah, they specifically said that the short follow-up period precluded precise effect estimates.

DR. PETER INFANTE: Yeah. Well, the latter part's an understatement. The first part is --

DR. LAURA GREEN: Well, it's what they wrote.

DR. PETER INFANTE: Well, it absolutely does. Because I just don't think at this point in the follow-up in can inform us about the cancer risk from glyphosate. And that's, you know, just look at the data yourselves. You can see how -- it just cannot. It's too -- I think it's a good cohort, it just hasn't been followed long enough.

DR. LAURA GREEN: Yeah, I think we all would love to see the most recent data. I think that's pretty clear.

DR. PETER INFANTE: But then I don't think you can say it's a null study. I think it's an uninformative study.

DR. JAMES MCMANAMAN: That was Dr. Green. Dr. Zhang?

DR. LUOPING ZHANG: Hi. Dr. Infante, from your second slide, I noticed that you put down, you know, the Hohenadel (2011) since you happily say provide us some paper and --

DR. PETER INFANTE: Sorry, I want to make sure we're on the same slide. What's it called?

DR. LUOPING ZHANG: Just second slide. The Table 1.

DR. PETER INFANTE: Table 1. Okay.

DR. LUOPING ZHANG: The Hohenadel (2011) paper. Also in your comments, you put Hohenadel corrects McDuffie's results. Could you --

DR. PETER INFNATE: Expand on that? Yes. Yes.

DR. LUOPING ZHANG: Yeah. What did they correct and why they correct and it looks like this is -- the 2011 results, the paper was included in Chang 2016 meta-analysis. Why they replace it?

DR. PETER INFANTE: Okay. They updated McDuffie because when they did the pathology review in the McDuffie paper, they further had expert pathology review and that review indicated that there were, I

think, four cases, at least in the exposed, that were reclassified that were not Non-Hodgkin Lymphoma.

DR. LUOPING ZHANG: I thought already there was four cases in the exposed and two controls. Oh, that's the Cocco, that's the Cocco, sorry. I take it back.

DR. PETER INFANTE: So that's the most updated data on McDuffie. That, I think it was very good for Chang and Delzel to include the update of that based on their analysis of glyphosate in the Hohenadel (2011) paper. And for that study they came up with a risk of 1.4 include looking at glyphosate by itself and glyphosate plus malathion and then taking like an average of those two risks they come up with 1.4 in the what was the McDuffie study for the relative risk of Non-Hodgkin Lymphoma. And that's what they used in their Model 4. Model 1, 2 and 3 are different combinations. But whichever model they use, the results are always statistically significant.

DR. LUOPING ZHANG: So do you have the updated paper, 2011? If you do would you share it with us?

DR. PETER INFANTE: Yeah, I don't have it here with me today but I could email it to Mr. Knott.

DR. LUOPING ZHANG: That would be good.

DR. PETER INFANTE: You know, you mention that, but that's not in the EPA review.

DR. LUOPING ZHANG: It's not.

DR. PETER INFANTE: But it is --

DR. LAURA GREEN: Actually it is and I'm confused and I actually -- I know we're not supposed to be having a conversation but I actually would love Dr. Infante's opinion on this.

DR. JAMES MCMANAMAN: Well, it sounds like a question to me.

DR. LAURA GREEN: It is a question. Yeah, and maybe EPA can talk to us about this also. Because I was confused by this. No, EPA does site Hohenadel et al. (2011) and they say two things about it. First, they say we're not evaluating it for quality because McDuffie et al has a larger number of cases and is more complete. I thought to myself that's a little weird. How can a paper that was 10 years earlier be more complete?

Then I looked and I looked that EPA looked also and in their Figure B.3, here's what EPA reports and I can't go any further than this, but I just wanted to ask you if you had. EPA shows us not really a Venn diagram, but shows us two circles.

EPA reports that Hohenadel et al., while you're quite correct that they corrected for pathology reassessment, apparently for reasons unclear to me, but maybe to you, Hohenadel et al. report only on 19 exposed cases and 78 exposed controls, whereas McDuffie, which is the same cohort, is much larger. Instead of 19 exposed cases, there's 51 exposed cases and instead of 78 exposed controls, there's 133 exposed controls. I'd like to know, since I am not familiar with Holland et al, if you know why there's that big difference and maybe we can ask EPA later when we're talking?

DR. PETER INFANTE: You know, I can't, I can't remember that. I'm sorry.

DR. JAMES MCMANAMAN: Okay. Dr. Sheppard.

DR. LIANNE SHEPPARD: Thank you for those updated pieces of insight. I wanted to ask you a little bit more about latency and specifically

because you commented that only the Eriksson paper had analysis of latency and while it's not as specific as one would like to glyphosate, there is what I would consider a very interesting latency analysis in Hardell et al. And I was wondering if you looked at that at all carefully? Because there were actually two that I thought were pretty interesting.

One is about -- it's all herbicides. Some of their analyses break out glyphosate but most of them don't. All herbicides, it talks about induction period which I think is what they are referring to as latency. And it has relative risk for -- or odds ratios for 10 year periods, 1 to 10, 10 to 20, 20 to 30 and greater than 30. And all of the odds ratios are relative to the 1 to 10 and they're all elevated. The first one 10 to 20 years is 2.32 with confidence interval of 1.04 to 5.16.

That suggests for Non-Hodgkin Lymphoma with respect to herbicide exposure that the latency is around -- the most important latency period is around 10 to 20 years. Although it's elevated in all the periods and they're not really that different odds ratios. 1.63 and 1.7 for the later periods. And then so I guess, if you thought at all about this. And

then there was another piece I wanted to also ask you about because I think it's also relevant for interpreting the Agricultural Health Study. And that is about instead of latency, they look at time span between last exposure and diagnosis. And there they also look at 10-year periods, and the highest odds ratio there is for the 1 to 10-year period; suggesting that that recent exposure is also important, I guess is what I'm trying to say. Which is a little bit different than latency but also gets at timing.

Anyway, I mainly wanted to ask you what you thought about the Hardell paper, and specifically about some of these analyses if you've thought about them at any depth.

DR. PETER INFANTE: Well, I had forgotten to mention the Hardell paper, but I think that's kind of consistent -- that's analysis based on herbicides, kind of consistent with what we were talking about, like 10 to 20 years because that's the first latency interval for herbicides that shows like a significantly elevated odds ratio.

I think that's another indication that you're talking about at least 10 years to 20 and I would say more -- in fact more years. Because even

the upper bound of the latency period showed a significant increase even though the odds ratio is a little lower. I mean, you don't have real large numbers here. That's with Hardell.

Regarding the Agricultural Health Study and the analysis by diagnosis from last exposure --

DR. LIANNE SHEPPARD: Well, this is also in the Hardell paper. It wasn't in the Agricultural Health Study. This analysis about time between last exposure and diagnosis. I just think it's relevant to interpreting the Agricultural Health Study since all of those cases were -- or all of the exposures were calculated from baseline and didn't update as time went on.

DR. PETER INFANTE: Well, I think it's a little more of a complex issue than is apparent when you first look at analyses by time intervals since last exposure to diagnosis. Because for that -- the reason for that last exposure to diagnosis may be related to, well, what was your exposure at the time you were exposed?

I think it gets confounded with that. And I think it's not -- I think it's not so simple to evaluate what's really going on. And not just in this

study. I've seen it with benzene also. The intervals since last diagnosis. I think it's a more quagmire to get into. I don't -- I just think it's difficult to make a lot of scientific sense out of it. Because there can always be extenuating circumstances.

DR. JAMES MCMANAMAN: Okay. Thank you, Dr. Infante. I think we're going to have to move on now. We've covered this pretty well. I appreciate your comments.

Next up is David Spak from Bayer Crop Science.

DR. DAVID SPAK: So good morning. My name is Dr. David Spak. I'm currently the stewardship manager for Bayer of Education Management in Research Triangle Park in North Carolina.

Let me first thank the EPA for allowing Bayer to provide comments this morning. And although the subject matter of this meeting is about the carcinogenicity potential of glyphosate I would like to talk about the benefits of integrated vegetation management which I'll refer to as IVM, which also includes the use of non-selective herbicides such as glyphosate in these non-agricultural type settings.

Under FIFRA, the agency must not only evaluate the hazards of an active ingredient but also consider the benefits the product brings to society. Bayer, in conjunction with IVM Partners, Incorporate, has conducted research designed to improve habitats for pollinators, birds and other wildlife along public rights of ways including railroads, roadsides, utility rights of way through the use of IVM practices.

IVM employs various management techniques including chemical, mechanical and other cultural practices to maintain a healthy native plant community that's complimentary to ensure safe transportation and reliable energy transmission as well as improving habitats for wildlife and pollinators.

And even though glyphosate is considered a non-selective herbicide, glyphosate can be used selectively by targeting specific plant stages of growth, using specific application methods or rates to achieve control of the target vegetation while having no to minimal impact desired vegetation.

Some of the benefits resulting from IVM practices that include these directed foliar sprays of glyphosate to control invasives and release low

growing vegetation, include reducing or eliminating mowing, improving wildlife habitat, reducing carbon footprint, reducing erosion, lowering the risk of wildfires and also reducing overall maintenance costs for public utility and transportation companies.

For example, under the 2005 Energy Policy Act, utilities can be fined a million dollars per day for power outage occurrences. Using IVM methods, utility companies can increase the reliability of electric power and reduce power outages usually associated with poorly managed vegetation. IVM also encourages pollinator diversity because native prairie and meadow habitats are typically suppressed by undesirable brush and invasive plants. Herbicide use is necessary to remove these plants and allow milkweed, asters and wildflowers to grow and provide nectar and pollen for pollinators in addition to providing primaries for bobwhite quail, turkey and other wildlife.

Ravines and rights of way borders provide additional nesting and forage sites when mountain laurel, blackberry, blueberry, viburnum and other shrubs are retained. In some areas where trees and invasive plants were treated with herbicides, rare

orchids that have been dormant for many years are springing into life.

As open meadow and prairie systems are restored so are the native plants and wildlife habitat with no additional planting required. Also within three years, about a third of the maintenance budget can be saved by eliminating the need for routine mowing.

So just in conclusion, at Bayer, we're committed to the safety and environmental stewardship associated with our products throughout their entire life cycles. We work hard to reduce the environmental impacts of our products and activities, improve our resource and energy efficiency and develop new technologies, optimized process and innovative products that serve to protect and benefit the environment.

We promote using the right tool at the right time. As modern agriculture changes in an increasingly complex business and regulatory environment we're also collaborating with many different organizations around the country from industry non-profits to government agencies, to universities and other educational partners in order

to ask the right questions and find the best solutions.

So once again, thank you very much for allowing us to provide comment this morning.

DR. JAMES MCMANAMAN: Thank you, Dr. Spak. Any questions?

Yes, Dr. Ramesh?

DR. ARAMANDLA RAMESH: Dr. Spak, is Bayer involved in manufacturing and marketing of glyphosate?

DR. DAVID SPAK: I'm not really qualified to answer that question. We have a business that was divested recently that included a product that contained glyphosate. But that would be best answered by someone else within Bayer Crop Science.

DR. JAMES MCMANAMAN: Other questions? All right. Thank you, Dr. Spak.

Next, we have Alexis Baden-Mayer from Organic Consumers Association.

MS. ALEXIS BADEN-MAYER: Good morning, Mr. Chairman and members of the Scientific Advisory Panel. I am Alexis Baden-Mayer, political director of the Organic Consumers Association. Today I speak on behalf of 120,000 members of our organization who

signed our petition asking the Environmental Protection Agency to follow the World Health Organization's classification of glyphosate as a probable human carcinogen.

The reason why so many people care about this issue is because people are actually dying from Non-Hodgkin Lymphoma because they were exposed to glyphosate. It's well established that farmers have lower overall death rates and cancer rates than the general population, but farmers are more likely to get certain cancers including Non-Hodgkin Lymphoma.

It's time for the EPA to acknowledge that while too many farmers and pesticide applicators know only too well that exposure to glyphosate can cause cancer. And I have longer written comments but I want to jump to the second piece of my comments which are testimonials that I've collected from people who had been exposed to glyphosate and who are now either dead or suffering from Non-Hodgkin Lymphoma.

This is a testimonial from the wife of Dean Brooks (phonetic). She says my husband of 27 years, Dean Brooks, passed away from Non-Hodgkin Lymphoma, stage 4 on July 11th, 2016 this year. He suffered greatly with this disease due to using

Roundup on weeds on a ranch we live on in Northern California. His pain and suffering due to glyphosate is unforgivable. There is no reason that this product should not be labeled as a poison unsafe to use. Having been a healthy athlete all his life he was reduced to an underweight man fighting just to live, albeit with great pain and side effects such as scabies, shingles and more.

The chemotherapy alone is enough to take one's life or what is left of one's life through numerous infusions. Dean's life, as well as the other victims of this vicious poison must be honored and the inaccurate labeling of this product must be altered to toxic, can cause Non-Hodgkin Lymphoma. That's from Deborah Brooks (phonetic) in Irvine, California.

From Jimmy McFarland (phonetic) in Texas, he says my name is Jimmy and I live in Texas. In the mid-1970s I got involved with Roundup at my place of employment and used it until the early 1990s. I was the herbicide operator for a county in Texas. I used Roundup every growing season until I was told that I had Non-Hodgkin Lymphoma. I was treated with chemo for nearly a year. I still have to go to my oncologist yearly to be checked. My health really

went down after that. I had to retire early. I still remember the salesman from Monsanto saying that Roundup was not as toxic as table salt and he would mix a cup of Roundup with water and drink it. That's from Jimmy McFarland in Texas.

And from Vickie Layborne (phonetic) in Missouri, she says, in July 2012, my husband, a completely productive, healthy individual was diagnosed with CNF Lymphoma brain cancer at the age of 62. The illness came on suddenly and he died September of 2012. My husband was exposed to Roundup sprayed on our ten-acre farm for years as well as neighboring farms.

From Dave Hendrix (phonetic), Vancouver, Washington. I was diagnosed with Stage 4 Large B-Cell Lymphoma after applying Roundup and Rodeo for a period of 10 years. When I first learned the active ingredient, glyphosate, had been linked to lymphoma, I was shocked. Because I was a licensed applicator, requiring continuing educational classes sponsored by the state. After several of these classes, a Monsanto representative would stand in front of the class holding a glass of Roundup and

saying Roundup is so safe, you could drink a glass without any harm to your body.

Plus, as a licensed applicator, I relied on the material safety data sheet produced by Monsanto, to ensure the property owners that the herbicide I was applying was safe. My cancer treatment consisted of a year of chemotherapy and radiation treatments to my right shoulder, where the largest of the four tumors is located. The residual effects of the chemotherapy caused neuropathy of my feet and fingers. I have a difficult time walking with constant pain and very poor circulation.

The tumor in my right shoulder caused damage to the bone and nerves requiring pain medication, on a daily basis. I worked through the chemo and radiation treatments until I completely ran out of energy. And I couldn't seem to regain the energy required to maintain a full work day. I had no choice but to take medical retirement.

This retirement came six years early so my retirement pension has been greatly reduced. And I don't have the health to enjoy retirement, even if I could afford it. That was from Dave Hendrix, Vancouver, Washington.

And then Sylvia Peters (phonetic), California. She says my father died of Non-Hodgkin Lymphoma. He worked for Robert Hall an agriculture company owned by Robert Hall and in a fluent coastal community of Encinitas, California for decades. My father was the person who sprayed the pesticides and fertilizers for Robert Hall's 40 acres plus and two other greenhouse sites in Encinitas, California.

The only protection my father was given by the owner of the agriculture company was a paper-thin mask and he wore a long sleeve shirt. My father had a work related torn muscle on his shoulder from carrying the spray hoses on his shoulders for years. While he was getting X-rays for his torn muscle injuries, the doctors found Non-Hodgkin Lymphoma in his chest. As a result of the glyphosate he was exposed to, my father suffered greatly.

And then from Dorothy Baker (phonetic) in Washington. I noticed about a year and a half ago, I started getting tired. I had no energy. I got tired very easily. The doctor diagnosed me with lymphoplasmacytic lymphoma. I started treatment in the spring of this year and I didn't realize how fully time consuming cancer is. It just amazes me. Now I'm

on maintenance but there is no cure for this cancer. I will likely be on maintenance for the rest of my life. I go back in for treatment once every two months for chemotherapy. I will have to have chemo treatment for the rest of my life.

I used Roundup for many, many years around my yard, along the road, in the garden, around the edges of the landscaping around my home. I never worried about it because I felt safe using it. Everyone is using it. I wish I had known at the time. If it can save anyone from the same fate by writing to the EPA, I would hope so. From Dorothy Barker in Washington.

And then from Oweda Hubert (phonetic) in Georgia. For approximately eight years I used Roundup on my three acres around flower beds, along fence lines, road ditch to control weeds. Living in rural Georgia, cotton fields adjoined my property. These fields were sprayed by tractors plus planes.

In 2004, I was diagnosed with Non-Hodgkin Lymphoma, Stage 4. I have been through six months of chemotherapy. It has taken my lifestyle away. I have always been a very active person, but now I am limited to simple housework. My energy level

has decreased by at least 80 percent. Realizing this is non-curable, it has taken a toll on myself plus my whole family.

And then from Bruce Alster (phonetic), in Wellington, Florida.

DR. JAMES MCMANAMAN: Ms. --

MS. ALEXIS BADEN-MAYER: I have just one more.

DR. JAMES MCMANAMAN: Okay. Good.

MS. ALEXIS BADEN-MAYER: I used Roundup year-round for about 13 years for weeds alongside my driveway and between my pavers. I stopped using it since I found out I have cancer. I was reading about lymphoma and saw information about Roundup being linked to cancer. There is no negative label on the Roundup container like there is on cigarettes. I don't smoke, by the way.

But I had no warning. I had no idea. This year I was diagnosed with Stage 4 Lymphoma. I had two surgeries in June. During one surgery, they took out seven lymph nodes. Three were really bad, and four were surrounding. I feel discomfort every day underneath the arm where they removed the lymph nodes.

A couple of weeks later, another surgery found out the lymphoma is in my bones. Because it's in the bone, the doctor says they can't really do anything. They say chemo won't help.

I deal with symptoms but at times I feel really sick. Sometimes up to three times a day I have a fever of 102 to 104. When that happens my fingers also hurt. Different parts of my body hurt. It's like having a deep case of the flu. Sometimes it can last up to an hour or two hours. This can happen several times a day or not at all.

I also have night sweats or itching. I don't have a rash but my skin just itches. I fast one day a week, hoping that the cancer is not being fed. The doctors told me to change my diet because they feel cancer cells feed on sugar. On the days I fast, I drink only plain water. I am fatigued out. And that's from Bruce in Florida.

And I just want to say two more things if you will indulge me. I want to answer a question that was asked of Amanda Starbuck yesterday from Food and Water Watch. I was listening on the phone so I don't know who asked the question, but it was about good laboratory practices. Okay. The issue is bias.

And the good laboratory practices cannot exclude bias when the studies are being done by the industry.

And one of Amanda's findings in the research, she looked at the studies that EPA covered, 131 studies. 71, more than half, were unpublished industry studies. And then she looked at the results of those studies. And the industry studies were 30 times more likely to find glyphosate's toxicity -- oh sorry. The independent studies were 30 times more likely to find glyphosate's toxicity than the industry studies. That's something the good laboratory practices program, while it does do a great job of recordkeeping, making sure that everything can be check, it does not eliminate bias.

And many studies have shown that good laboratory practices can't eliminate bias and that industry studies are more likely to find that a product is safe than an independent peer reviewed study. That's the important point that Amanda was making and I just wanted to clarify that. I included a link to this.

And then just the very last thing, I've never met Dr. Infante before and I hope that he's not upset by me mentioning this, but I can't believe that

he was removed from this panel. And I've also never communicated with him. I just want you to know that he has nothing to do with me making this statement and he probably doesn't want it made because he didn't say anything about it, he used all of his time to talk about the science.

But this could happen to any one of you. He was just as qualified to sit on this panel as each of you, and I really feel that if you all don't speak out as scientists, not just this process, but all of the processes of federal agencies are in jeopardy. And things are not going to get better any time soon.

I think now is the time to speak up about this type of injustice and we can't let Crop Life, the pesticide lobbyist, tell the EPA who can and who cannot sit on a scientific advisory panel.

DR. JAMES MCMANAMAN: All right. Thank you. Any questions for this presenter? Dr. Johnson?

DR. ERIC JOHNSON: Not so much a question as a comment and that is that the issue of Non-Hodgkin Lymphoma, it's a challenging one for this panel, I think really. The reason I am saying that is because Non-Hodgkin Lymphoma and Leukemia for that

matter, both have been known to occur in farmers at a higher rate way before glyphosate was introduced.

And I even go further to say that those excesses have been observed way before chemicals were being used on a wide scale in the U.S. We have to take that into account in trying to tease out is glyphosate contributing to that. It's not a simple problem.

MS. ALEXIS BADEN-MAYER: I certainly understand that. I'm not blind to that, yeah.

DR. ERIC JOHNSON: And the next thing is that I'm really very disappointed that we're talking about transparency, we expect the EPA to be transparent, but we're not seeing that from industry. I mean, this panel, I, myself, my colleagues, have asked simple questions of industry people to see what do your companies manufacture? What's their business? And they've just been reluctant to just tell us something we can just find on the internet. Really.

And last night somebody sent me an email -- somebody was listening to this, they sent me an email, in which they listed all 15 companies which either manufacture or handle -- these are the type of things that make people so suspicious of industry.

Really. I think it hurts industry more than anything else. That's no transparency.

DR. JAMES MCMANAMAN: Thank you, Dr. Johnson. I think that this is something, again, is more appropriate for the charge question discussion.

Dr. Portier, did you have a question?

DR. KENNETH PORTIER: I just wanted to make a comment about what you said about GOP. One of the big issues that these panels always deal with is publication bias. Independent researchers, when they do research, if they find something positive, they publish. If they find something negative, usually it stays in their filing cabinet. The industry studies kind of help balance that publication bias. We have to worry that the things we're seeing that are in the published literature is kind of one side of the issue.

And it's very hard for us to go to individual researchers and dig into their filing cabinets and say can you tell me have you ever done a glyphosate study that you got nothing back from? And why didn't you publish it? And 10 years ago, it's very common that they don't publish when they don't have a positive finding.

Because editors say you've got nothing here to say, why do I care. Now it's more recently, you're seeing much more push for negative results to be published. But that's not uniform across the published literature.

MS. ALEXIS BADEN-MAYER: So you're trying to say that the companies would publish their data in peer review journals but nobody will take their studies because they show negative results?

DR. KENNETH PORTIER: Well, I'm not going to infer what the companies do or don't want to do. There's no incentive for them to publish it like academics have.

MS. ALEXIS BADEN-MAYER: Maybe the incentive should be that they have to publish to get their data into a government regulatory process. Because that's the only fair way to be able to compare these studies is for the companies to have to publish peer reviewed literature and then they get to have it considered in the regulatory process. That would be fair. What we have right now where we have unpublished studies and that is the basis of the EPA's decision, that is completely unfair.

DR. JAMES MCMANAMAN: Dr. Jett?

DR. DAVID JETT: Yeah, I just wanted to -- Dave Jett, NIH, and I just wanted to question something that you raised, Dr. Johnson that you actually might be able to help with the answer. Do we know if there's any increases -- maybe in any diseases in organic farmers?

MS. ALEXIS BADEN-MAYER: Not that I'm aware of. I'm sure that Monsanto would have put out that data if they could show that organic farmers get a certain type of disease more often than conventional farmers. I'm sure if that data were available, it would be plastered all over everything.

I'm guessing that -- you know, I was just looking on cancer.gov, that's where I got the information about farmers generally having lower rates of cancer. They're out and about. They're healthy. They're doing things. They're active. They probably have better diets than most of us because they grow their own food.

And my guess is that organic famers don't -- but I will look that up because that's a great research question and perhaps someone looking to prove organic farmers are healthier has collated that evidence. You know, I work at Organic Consumers

Association so I should have that at my fingertips if it exists but I'll look to see if anybody's done that.

I did also want to respond to something you said about how we actually have to look at the evidence, we can't just say well farmers get Non-Hodgkin Lymphoma more often and you mentioned that farmers got Non-Hodgkin Lymphoma before glyphosate entered the market.

The World Health Organization's study is really strong. It shows evidence of cancer across all three categories. We have the animal studies show evidence of cancer, the epidemiological studies show evidence of cancer, and the mechanistic studies in the lab show evidence of cancer. There is certainly enough evidence to link Non-Hodgkin Lymphoma to cancer. And I'm not arguing that other chemicals don't cause farmers to get cancers.

DR. ERIC JOHNSON: Well, the issue --

DR. JAMES MCMANAMAN: I think we have to move on there now. To include some of the other presenters. Thank you. So, yes, Dr. Spak?

DR. DAVID SPAK: I just wanted to -- can I make one more statement about -- and I apologize, I'm a little bit nervous. We do have a few

glyphosate-based products that are sold through Bayer Crop Science. We had a divestiture of one of our consumer products that had glyphosate -- that contained glyphosate. Again, I just wanted to just confirm that yeah, we do -- when it comes to whether the manufacturing and the sourcing of the active ingredient is through Bayer or through another source, that's where I was out of my area of expertise and that's handled by somebody else. I just wanted to say that.

DR. JAMES MCMANAMAN: Yeah, thank you for that disclosure. All right. Next up we have Luther Markwart from Sugar Beet Growers Association. And James Braille (phonetic) from the Natural Resources Defense Council.

Mr. Markwart, you're first.

MR. LUTHER MARKWART: Thank you. My name is Luther Markwart, I'm the executive vice president of the American Sugar Beet Growers Association and co-chairman of the Sugar Industry Biotech Council. I'd like to thank the panel for the opportunity to present to you today.

For the past 34 years, I've represented all the sugar beet growers in the United States who

are family farmers in 11 states and for three years prior to that I represented the growers in Michigan and Ohio. And during nine years of my youth, I raised sugar beets as a 4-H project on our small farm, hoeing weeds alongside migrant labor. Those are my credentials for working hard and hating weeds.

Our farmers produce sugar beets on almost 1.2 million acres and they are also owners of seven regional farmer-owned cooperatives that consist of 22 processing factories and produce about 58 percent of all the sugar grown in the U.S. The American sugar beet industry is essential to provide a strategic commodity for our nation's food supply.

Weeds have always been our grower's biggest agronomic problem in crop production. In the mid-1990s, our grower leaders pressed Monsanto and the independent seed companies to create Roundup ready sugar beet seed. That meant adding one gene to the 27,421 genes in a sugar beet. Once it was deregulated in 2005 and seed became available in 2008, we had the fastest adoption rate of the technology of any commodity anywhere in the world. Today we use 100 percent Roundup ready seed and the future of our

industry depends on the continued use of this technology.

The main environmental benefits we have achieved are 1) we've replaced 13 herbicides that were used in different combinations and applied four times a year. We would typically use three to four herbicides per application which means there were 12 to 16 herbicides applied to the crop each year. Now we typically use only glyphosate and it is applied twice or at most three times per year. Glyphosate is the safest alternative both for the environment and the applicator compared to any of the crop protection products we used in conventional sugar beet production.

We've removed hand labor from our fields, eliminating the exposure of field workers to all pesticides and herbicides. By substantially reducing tillage, emissions have been reduced from fuel usage and kept carbon sequestered in the soil, reducing greenhouse gasses. Along with reducing soil erosion and conserving precious water resources.

It is also important to note that the sugar derived from the sugar beet is free of any DNA or protein. The sugar is the same as sugar derived

from conventional or organic sugar beets or sugar cane. We've identified 25 specific environmental benefits from using this technology and we submitted the list on September 9th, 2015 to the National Research Council Committee on Genetically Engineered Crops under the National Academy of Sciences. A copy of that document was simultaneously provided to EPA's administrator, assistant administrator of chemical safety and pollution prevention and the director of pesticide programs for their review. I'm submitting a copy of that today with my statement for your review.

I would also remind the panel that the EPA has conducted two environmental assessments and a full environmental impact study released in May of 2012 and ask that you refer to them for any further assistance that you may need. We understand that your primary focus is on the human safety of glyphosate. Our farmers want the safest crop protection products they can use because they and their families and neighbors live in the environment where it is applied. We know full well that for 40 years, no regulatory authority agency around the world that has studied this product views glyphosate to be a carcinogen. This is precisely one of the important reasons we've

embraced the technology. Regulatory authorities in the United States, Europe, Canada, Japan, New Zealand and Australia have recently reaffirmed that glyphosate does not cause cancer. We trust and embrace those results.

Thank you for the opportunity to present our views today.

DR. JAMES MCMANAMAN: Thank you. Any questions for Mr. Markwart? All right. Next up is James Braille from the Natural Resources Defense Council.

MR. JAMES BRAILLE: Thank you this esteemed panel for the opportunity to provide comment today.

DR. JAMES MCMANAMAN: Oh, sorry. We've got -- I guess we got James Braille, did you say?

MR. JAMES BRAILLE: Yes.

DR. JAMES MCMANAMAN: Oh, okay. I'm sorry. I thought you said a different name. I thought, oh, I got the wrong information.

MR. JAMES BRAILLE: No, I'm sorry. Thank you for the opportunity and I know it's a marathon so I'll be brief. I'm James Braille from the Natural Resources Defense Council, Citizens

Environmental group based here in Washington. My colleague Dr. Jennifer Sass is unable to speak today so I am going to present a summary of her comments today.

Her full report which is on the docket is also being circulated to you currently as well as a letter from Dr. Christopher Portier in response to an industry report by Joseph Haysman (phonetic). So please refer to our written comments for details and I'll be brief in summary.

First, NRDC is concerned that EPA violated its own Cancer Guidelines by dismissing evidence of Non-Hodgkin Lymphoma in humans. Even the meta-analysis of many epidemiological studies that was sponsored by the agri-chemical industry Chang and Delzel, 2016, reported a statistically significant risk of NHL cancers when glyphosate exposed individuals were compared with individuals never exposed to glyphosate. IARC's analysis reported similar results.

Second, NRDC is concerned that EPA violated its own Cancer Guidelines when dismissing evidence of elevated cancer in rodent studies. The Cancer Guidelines say either a statistical trend test

or a pairwise test is sufficient to establish statistical significance. However, EPA wrongly rejected cancer events in experimental rodents that was significant in a trend test if it wasn't also significant in a pairwise test.

Third, and most importantly, NRDC is concerned that EPA in some cases relied exclusively on study summaries provided by the agri-chemical industry without consulting the original studies or disclosing the sponsorship of those summaries relied on. The article by Kier and Kirkland, 2013 was sponsored by a consortium of glyphosate manufacturers including Monsanto.

Fourth, NRDC is pleased that EPA requested more data and more scrutiny to fully evaluate formulated products containing glyphosate given the toxicity of surfactants. In fact, a report submitted under contract to the USDA in 1997, 20 years ago, warned that surfactants added to glyphosate products made them much more toxic and warned that surfactants -- that very little toxicity information is available of the formulated products.

Earlier this year, in July 2016, European member states voted to ban certain

surfactants such as POE-tallowamine from glyphosate based products including Roundup. Unfortunately, here in the U.S. it continues to be allowed as an inert ingredient, essentially unregulated in pesticide products despite possible toxicity.

The point that was made earlier on the board that I heard a few minutes ago, about publication bias. I think that it's important to examine and that we have a duty to examine all possible injury to citizens and to investigate that fully because financial bias is also a possibility.

In conclusion, preventable harm to farm workers, pesticide applicators and the public will continue if EPA fails to address the scientific evidence of cancer hazard. Thank you.

DR. JAMES MCMANAMAN: Thank you. Any questions for this presenter? Okay. If not, then thank you both very much. All right. Well that concludes our public commenter's statements, presentations. We'll take a break now for 15 minutes so what, be back at five till.

[WHEREUPON A BREAK WAS TAKEN]

DR. JIM MCMANAMAN: We're going to get started. We have a lot of ground to cover and some challenging questions.

DR. LUOPING ZHANG: What do we do with this? It's the registration document?

Oh, okay.

MR. STEVEN KNOTT: This is Steve Knott, the DFO. For the panel members, I just wanted to provide a clarification for one of the documents that was just distributed. It's the glyphosate summary document for registration review. That was a written comment that was sent to one of the panelists in an email, related to the registrants of glyphosate. That is being provided as a written comment and it will be placed in public docket with the email and the registration review document. So just to clarify what that was.

DR. JIM MCMANAMAN: Okay. If the Agency is ready, we'll move into the charge questions. And just as a reminder, the charge questions are meant to be a discussion amongst panel members, related to those specific charge questions, and not to involve either the Agency or any of the outside public presenters.

It's just us talking amongst ourselves. They get to ask the questions --

DR. LAURA GREEN: I'm sorry. You can or cannot ask them questions?

DR. JIM MCMANAMAN: Well, they'll have their chance for them to ask clarifying questions, but in the discussion of the charge questions, it's the panel.

DR. LAURA GREEN: We don't ask them questions.

DR. JIM MCMANAMAN: That's right.

MR. STEVEN KNOTT: Just to clarify that a little more. They're going to ask the charge questions. You will begin your discussion. If there is a need for clarification, you can ask the Chair if that's a possibility.

DR. JIM MCMANAMAN: But they'll read the charge questions into the docket so that we have that into the public record.

And with that --

MS. DANA VOGEL: I'm reading the first question.

DR. JIM MCMANAMAN: Okay.

MS. DANA VOGEL: This is Dana Vogel of

the Health Effects Division. Charge Question 1: The Agency has collected a multitude of studies that may inform the human carcinogenic potential of glyphosate through a systematic review of the open literature and toxicological databases for glyphosate and glyphosate salts as described in Section 2.0.

Please comment on the agency's methods to collect references for this evaluation, including the completeness, transparency, and appropriateness of these methods. Please also comment on whether there are additional relevant studies, that can inform the human carcinogenic potential of glyphosate, that were not included in the current evaluation.

DR. JIM MCMANAMAN: Okay. The lead discussant on this is Dr. Green. And the associate discussants are doctors Sheppard and Zelterman.

Dr. Green.

DR. LAURA GREEN: Thank you. Dr. Chairman. Guess that's the right way to say it, and EPA. And I also just wanted to say on behalf of us panelists, we really appreciate all the comments that you all have provided in writing, orally. We even like the musical interlude, if there are any singers still left.

We are a little overwhelmed by the amount of information here. And I think we've all worked pretty hard, but there's a lot of stuff here. And so, if some of our comments may be seen in opposition to each other, or that we haven't formed a consensus about certain things, I would like to say, at least from my point of view, that there's still work to be done. And we're going to try very, very hard to say everything over the next day and-a-half, I guess, that we are thinking. But I'd like to say, at least on my behalf, that things that we've gotten today, for example, that I haven't had a chance to digest, we may have additional thoughts.

I'm going to try very hard to put all my thoughts out there, and I'm sure my fellow panelists are going to do the same. But I guess I'm asking a little indulgence, or at least a little foreshadowing or something. Is that okay?

Okay. Having said that, I'd like to start answering Charge Question 1 and ask my fellow panelists to weigh in as they would like. You've asked about completeness of literature, review and collection, transparency, and appropriateness of your methods. I'll start with the easy stuff.

Transparency, yes: A+. You were very transparent and helpful to us, in writing specifically, what your literature search strategy was; why you included what you included. Why you excluded certain things or minimized certain things. I think transparency, unless any of my fellow panelists feel otherwise, I think there are no issues.

Let me just ask around the table. Is there disagreement in that?

DR. JIM MCMANAMAN: I think they'll get a chance to say if there is a disagreement if there is.

DR. LAURA GREEN: Oh. I should just keep going?

DR. JIM MCMANAMAN: You just keep going.

DR. LAURA GREEN: Okay. Next, you've asked whether there are additional relevant studies that could inform your assessment. Well, yes, of course there are. You know about many of them because they will be picked up in your search strategy in your searching. And I assume that you have been updating that searching, either in a formal way or an informal way.

As is well known, there have been publications throughout 2016 that are potentially relevant to your analysis, but again, they'll clearly be picked up in both your formal and informal searching. I'm speaking not only of the publication by Chris Portier and many colleagues, which I think was cited in your draft, but only in a very limited way.

And if I can just say, as a little digression, I wondered why that publication was mentioned in only a very limited fashion. And I'm suggesting maybe it requires a little more discussion on your part. But it's possible that maybe you just got the paper, you know, as you were finishing the draft. I'm not sure because, you know, a lot happens in a short period of time.

I at least am willing to give you the benefit of the doubt, assuming that you mostly wrote this draft in 2015 and then you got a whole bunch of new stuff in 2016 and you didn’t have a lot of time to assimilate it. If so, we feel for you, but we assume that now that it's almost 2017, you'll have time to assimilate the 2016 publications.

So not only Chris Portier and

colleagues, but obviously, the expert analyses by John Acquavella and colleagues, Gary Williams and colleagues. And I forget the other two main authors, but, you know, the stuff from critical reviews in toxicology. Again, that's clearly going to be picked up by your searching strategy, formal or informal.

But I would like to mention at least one paper, which happens to be by Dr. Zhang -- no relation, apparently, to Luoping Zhang, at least that we know of -- that would not come up in your search strategy. I brought a copy with me, and obviously, I'm happy to email it, but I'm happy to give you a hard copy; it came out just two months ago. It's from the Beijing Institute of Technology. The first author is Chao Zhang, and it's entitled, "Health Effect." I think it's supposed to be Health Effects. But it's "Health Effect of Agricultural Pesticide Use in China: Implications for the Development of GM," where "GM" of course, stands for genetically modified -- not General Motors -- of GM Crops.

This is one of, I think, a series of papers. And I don't know if they're all -- this one happens to be in English, which is how I know about it. I think you would not find it in your search

strategy because glyphosate is not mentioned anywhere in the title. And it doesn't have any of the other search terms that I think you use. I'm wondering whether in you search strategy, this next go around, you can search through the abstracts also because glyphosate is clearly in the abstract. This is, by the way, published in Online in Nature.

As I think a lot of you know, nature.com now has an online publication series called Scientific Reports. They are peer reviewed. This was submitted in June. It was accepted in September and published two months ago now, October 10th of 2016. And I bring it up because it looks to me to be, possibly, the tip of what I hope is an iceberg of reliable data from outside of the U.S. and possibly outside of the English-speaking world. I'm not sure about the latter.

But I just want to briefly talk to you about this and then, you know, obviously, ask you to look at this paper. These investigators from the Beijing Institute of Technology went to three provinces in China, identified farmers who had high, medium, and low uses of pesticides and herbicides of all kinds. Divided the groups not only into high,

medium and low, but into six different categories. And in particular, with regard to herbicides, there's a glyphosate use category and a non-glyphosate use category and then other herbicides, including biological materials, with which I'm less familiar so I'm not going to speak about them with any expertise.

These investigators looked at 35 health indicators -- oh, I should say they note that they do not have biological exposure data. They don't have urine or blood from any of these farmers and they note that that's a limitation, but they do have pretty good questionnaire data. I would say as good as any of the questionnaire data, frankly, in any of the studies we're looking at. Otherwise, from Scandinavia and the Ag Health Study in the U.S.

They have good questionnaire data. They asked all the farmers to keep, you know, very detailed records of what they used. They looked at 35 health parameters; none of them bear directly on carcinogenic risk. But I'm hoping that if you all can communicate with these investigators and maybe some of the epidemiologists in your units, may actually know some of these investigators.

They're all in China, but as I said,

the article is written in English and my guess is that, you know, somebody in EPA probably knows some of these folks. I would think this might be a very important cohort for getting information about things like, you know, chromosomal abnormalities and circulating lymphocytes or something like that, which was not the subject of this paper. This paper looked at renal function, nerve conduction studies.

Anyway, there's a lot there. And as Dr. Johnson and others have been struggling with -- well, speaking for myself, I don't think that any of the existing epidemiology studies are nearly as helpful as they would be if they were high level exposures like in manufacturing workers. And absent that, it's possible that some of these Chinese studies, especially given high, medium, and low exposure rates, and given good records, might be informative.

I'd very much like that to be added to your list of papers to be thought about, I guess. Okay. Let's see.

DR. LUOPING ZHANG: Could I just add one comment on your -

DR. JIM MCMANAMAN: Sorry, not at this

time. The way it's organized is that the people involved in the charge questions get a chance to comment and then we'll open it up to the panel to comment. That's how the game is run.

DR. LAURA GREEN: You're the wrong Zhang. Okay. I'll try to be more brief because I do want to leave lots of time, obviously.

Okay. Next, I want to talk a little bit about the scope of your analysis. We are of mixed minds, I think, about your scope. We understand that you need to limit yourselves to the active ingredient, which is technical glyphosate [sic] or glyphosate acid. But as I've said before and I continue to feel, a salt is not a salt is not a salt. And if it were just a simple sodium salt, for example, of glyphosate acid that were used commercially, you know, it's all dissociated; who cares?

But I'm not completely convinced that an isopropylamine conjugate, even if it is completely dissociable as a salt, I'm not completely convinced that that is identical in all toxicologic and epidemiologic criteria characteristics with regard to a simple salt or the acid itself.

I'm wondering if there's a middle

ground and I'm wondering if maybe your analysis could be extended just a little bit to include not only glyphosate acid, but isopropylamine as a chemical because obviously, it is. I mean, to amino propane, right, is a chemical. And if in fact -- and I do not know this to be the case -- but if in fact, most formulations are of the isopropylamine salt, then it seems to me that slight widening of your scope is not too much to ask.

I've been thinking about it a lot and I actually looked into whether isopropylamine has ever been tested by the National Toxicology Program, right. Turns out it hasn't been. That's kind of weird. And it turns out, further, that the NTP considered testing isopropylamine a long time ago. I can't remember, the '80s or the '90s. But it decided, nah, it doesn't rise to the level of importance so we're not going to look at it. And they went out and looked at some other secondary amine. Okay, because you remember it was very fashionable to be concerned about secondary amines because they can nitrosate under certain conditions and some nitrosamines are in fact, potent carcinogens.

I understand the NTP's logic at the

time to kind of say eh, we don't really have the time or the money or the interest. But it's not entirely clear to me now, today, in the 21st century, if again there is this much isopropylamine salt in use. It's not entirely clear to me that isopropylamine is no longer all that interesting.

As I said, I've looked, I cannot find any cancer bioassays on isopropylamine. You should look to, because maybe I didn't look hard enough, I don't know a lot about the metabolism of isopropylamine, either in the gut or by mammalian enzymes in the liver and elsewhere, but you can imagine it ultimately goes to probably acetone and a few other things. It's probably benign.

I mean, I don't mean to make a mountain out of molehill, if that's the right expression, but I don't want two amino propane or isopropylamine to get a total pass. Because again, I think it's -- well actually, let me make it more clear. To my mind, as a toxicologist, glyphosate anime is so darn nontoxic that it's hard for me to believe that isopropylamine isn't more toxic, right. I mean, just because it's not sexy, it doesn't mean it isn't more toxic.

I don't think it's a lot of extra

burden on the agency, so I at least would like you to expand your scope to specifically look both at studies that look at the absorption distribution metabolism and elimination of not only glyphosate acid, but glyphosate isopropylamine. Because as I've said, to my mind, it's certainly more water soluble. Obviously, isoelectric point is much higher so you'd expect better absorption. I assume it's used in the formulations because it is more soluble and more bioavailable, at least to the plant.

It's a little disturbing to me that in the ADME section of your report, there is no, unless I missed it, there's no mention of absorption, distribution, metabolism and elimination of isopropylamine salt of glyphosate. I imagine you have that data and maybe you just didn't think it was important. And maybe it isn't, right. I could be all wet about this. But again, because that's the thing that's actually used in commerce, not the acid, which at some level is just going to precipitate out, right.

And let me say I think it goes the other way as well. My understanding, incomplete as it is, about the noncarcinogenic toxicity of glyphosate is that early on, pathologists were seeing salivary

gland changes at very high doses in dosed -- I think it was rats, not mice, but I could be wrong. And at first that was attributed to glyphosate, but then someone realized, wait a minute, it's just the pH. It's just the pH effect. All right. I mean, these are really high doses, after all. And with that much glyphosate acid, you're going to have a nonspecific effect of the fact that, you know, as you towards saturation, it's like pH 2, which is not good for your tissues, except if they're in your stomach, right.

I think you can get both artefactual results focusing only on the acid, which are actually irrelevant. And I think it's possible that we're also missing something, because, again, we're not looking at the more neutral compound. I mean, it's just (inaudible) and it's not neutral, but you know, it's much closer to neutral than glyphosate acid. So anyway, you get my point.

Let me go a little further because some of us on the panel would like you to really expand the universe and look at surfactants and all the different formulations. My own opinion is that that is not practical, and I don't think it's EPA policy. I don't know a lot about FIFRA policy, but my incomplete

understanding is that, you know, you care about the active ingredient. Maybe, hopefully you care about if conjugants are different, but, you know, easy to study, you'll look at that. But you do not ask your registrants to give you test data on potentially hundreds of different formulations.

I at least, don't think you need to expand your scope to surfactants and other things. But I would say something else, which is your document is a little schizophrenic. Because it says on the one hand we're only focusing on the active ingredient. But obviously, you're not, because all the epidemiology studies, by definition, involve formulations.

You do have a little bit of a mismatch and it's okay, but I think the way to resolve the mismatch, if I can suggest, is that if and only if there are cancer bioassays on a formulation, you certainly should include those. I mean there are, I don't know how many scores, possibly hundreds of studies, on glyphosate formulations involving other endpoints that don't involve you, right. I mean, not only ecotoxicology studies, but, you know, effects on the nervous system or whatever. I mean, I'm not

suggestion you do that.

But to the extent that you're concerned about carcinogenicity, and to the extent that there may be bioassays of glyphosate-based formulations, I would believe that it would be appropriate for you to include the bioassay data; just as you've, by implication, included the epidemiology data because you have no choice. As has been determined ad nauseam now, apparently, neither you nor anyone else has access to glyphosate workers or people exposed uniquely to glyphosate outside of a glyphosate-based formulation.

Again, to make a more, I would say holistic and coherent database, if there are toxicology studies on glyphosate-based formulations that bear on cancer -- not other stuff, but the bear on cancer -- I feel they should be included. The natural segue now is to Séralini, the infamous study that was published and then retracted and now republished.

I believe Dr. Sheppard mentioned earlier in this meeting that you all should consider it. I agree. I happen to think it's a crappy study, but that's my own opinion. I should not say crappy,

should I?

I happen to believe that it's a compromised -- well, I happen to believe that the probative value of that study is limited. I should say it in a more distinguished way. I apologize, Dr. Chairman, for saying something -- I grew up in New Jersey, so it's obviously, isn't it?

DR. JIM MCMANAMAN: Thank God it wasn't New York.

DR. LAURA GREEN: Touché. Westfield, New Jersey, Exit 135. Okay. I personally think that Séralini group is biased. I think their data are of very limited probative value, but that's only my opinion. And it seems to me, clearly relevant.

I feel you should put the study in, you should discuss its strength and weaknesses, you should do whatever you want with it, but I don't think you should ignore it because it's back in the literature.

Okay. Let me see if I have other things. Sorry, I talked so long that my computer timed out on me. Okay. Yes. One of us panelists noted there's another Séralini group study by Benedetti and colleagues (2013). You consider it to be of low quality ranking and you didn't evaluate it

in detail. I agree with you. I don't think it's a reliable study that requires much evaluation, but at least one of my fellow panelists disagrees. He or she asks that you at least say something about it. There's another Séralini study, Mesnage, I think or Mesnage -- I don't know how to say it -- et al. (2014), same thing.

And then there's another study that I think is also of limited probative value, but you should perhaps, see for yourself: Cox and Surgan (2006). And obviously, in our written comments, we'll provide the full citation if those are not easy for you to find.

Okay. Next, one of my fellow panelists noticed that one of the public comments seems to allude to studies done, "From areas in Latin America where glyphosate is sprayed heavily." It's not clear what the refers to, but there is at least one researcher mentioned in the news article which provides that limited information. He's Dr. Fernando Minas at the National University of Rio Cuarto in Argentina. And also, someone mentioned -- and again, these will be in our written comments -- from the Pontifical Catholic University in Quito, Ecuador, we

don’t know if either researcher or either group has reliable data of probative value, but we ask you to check it out.

Next, in terms of your search criteria and exclusion criteria, I've already mentioned, but let me reiterate, that while I do appreciate that using exclusion criteria such as the word "aquatic" gets rid of a lot of irrelevant stuff, I object to you using the word "water" as an exclusion criterion, so please put that back in. Because obviously, studies that have titles such as, “A Study of Glyphosate in Drinking Water,” should not be excluded. And by your search criteria, it would be. That's just weird.

By the way, you’re going to get a lot of other stuff when you include water. I apologize ahead of time for the poor peon who has to go through 500 irrelevant papers. But, you know, that's why you get paid the big bucks.

MS. DANA VOGEL: When do the big bucks arrive?

DR. LAURA GREEN: I'm sorry? When do the big bucks arrive? Yes, I don’t think our panel is allowed to give you a raise. Trust, if it were up to us, you'd have it.

Okay. One of my panelist's notes that you noted that there are 18 studies that you've relied on, but you don't have access to the primary reports. My fellow panelist, he or she, recommends that you sequester those in some way and see whether taking them out of your analysis, either quantitative or semi-quantitative or qualitative, whether removing those changes your opinion and if so, how?

Okay. I've mentioned this also, but let me stress it because obviously, lymphoma is kind of the big elephant in the corner or maybe front and center. Whenever we speak about lymphoma genesis, obviously, we speak about the immune system. I think Monique may have mentioned that there's at least one paper that you're aware of or maybe you've done a data evaluation report on that speaks to immunotoxicity; I at least would love to see an entire section, however large or small, in your report on all test regarding glyphosate and the immune system. Because frankly, when you get to you Section 5, like what does it all mean and you're sort of saying, well, we don't really think the lymphoma data are real, it would be nice to know what the immunotoxicity say.

And not to put too fine a point on it,

but as you know, the only well-known, bona fide, huge risk factors for non-Hodgkin lymphoma are things like HIV/AIDS, profound immunosuppression in organ transplant patients. I mean, as you may know, there, we're looking at relative risks or odds ratios. I'm not sure what the right term is, frankly, because I'm just a toxicologist. But we're looking at relative risks for people with AIDS getting an HL of 60.

Okay. Not 1.5 or 1.8, 60, right. And for people who are immunosuppressed because they have organ transplantation, we're looking at relative risks on the order of three to 300. Okay.

We know how to cause lymphoma in people. You really mess with their immune systems. And I will go further and say that to the extent that is believed that 237 ATCDD is a lymphomagene about which there's some controversy. But to the extent it's believed that 237 ATCDD or dioxygen is a lymphomagene, as I think everyone knows, it's a heck of a immunotoxicant at very low levels.

To my mind, as a toxicologist, if something is a bona fide lymphomagene, it's really going to mess with your immune system at realistic levels. Okay. If you have data on glyphosate, either

at realistic levels or mega levels or anywhere in between and the immune system, this toxicologist, at least, would be really edified to read it.

Okay. I want to suggest one other thing that you do when you go back to your literature searching. And this, I think, will be more informative and you won't have to wade through 500 irrelevant papers. As Dr. Johnson has mentioned, and I believe Dr. Infante mentioned as well, going back many decades, more often than not, lymphoma seems to pop up in farmers. It's not universally true, or farming would be an IARC-established cause of lymphoma, which it isn’t.

Okay, but when you look across the farming literature, and there are dozens of papers, going back to the '50s, certainly the pre-glyphosate era. Two things are true; first, farmers don’t get a lot of ordinary cancers like lung cancer because they don’t smoke much. And you know, they're out getting exercise, et cetera.

But they do, more often than not, get excess lymphoma. It's not a lot. It's odds ratios of like 1.5, 1.8, but it's exactly, it's exactly the relative risk range we're looking at here. Okay? I

feel that you should have a section in your report that speaks to NHL and farming as a general topic, okay. because there are a lot of issues here and, as we'll talk about later, it's really complicated.

I think right now the reader of your document doesn't understand that there's a much larger literature on farming and NHL. And whether it's other pesticides or whether it's the very different antigenic environment of a farm -- which I happen to think it's what's relevant here -- or whether it's animal viruses which may have some crossover potency with regard to some forms of non-Hodgkin lymphoma. There's a lot going on a farm, both viral, bacterial, microbiological, fecal matter, manure, right? You name it.

I feel you need that in context. Again, and it's because all of the data we're talking about are of farmers. We don't have glyphosate-exposed people. We have farmers who use glyphosate. That's a different thing. Farmers who use glyphosate are not glyphosate exposed people the way, for example, that benzene exposed people were benzene exposed people back when Dr. Infante and others were discovering them dropping deal of leukemia because they were, you know,

exposed to 1,000 parts per million of benzene in air. You have a very different epidemiologic dataset here.

I wanted to mention one cool thing. When you do that literature search, which I trust you'll do, on farming and lymphoma, you learn something really cool; which is the country that has the largest rate of lymphoma is the world is New Zealand, followed by Australia. I started thinking, well, maybe it's all due to sheep. But anyway, the point is, who knows? I think we could all write a grand proposal right now. The effects of proximity to sheep on non-Hodgkin lymphoma risks.

Oh, yes. One of my panelists had the very helpful suggestion that EPA ought to get itself the software that allows you to write a paper where you can imbed the reference and click on that and then it comes up with the abstract or maybe the whole article online. I don’t know whether you all have that.

And what's it called, without identifying who you are?

DR. LIANNE SHEPPARD: It's called HeroNet. And EPA uses it for other panels.

DR. LAURA GREEN: Okay. The no longer

anonymous fellow panelist says that you all have it. Maybe you guys in pesticides don't have it, but someone's got it over in air and radiation, or where it is. Or maybe ORD. Anyway, if you know what she's speaking of, then note it. And if not, please ask Dr. Sheppard afterwards.

Okay. I think those represent my comments. And I guess now I'd like to know what other people say.

DR. JIM MCMANAMAN: Okay. Dr. Sheppard, do you have anything to add?

DR. LIANNE SHEPPARD: Well, my colleague was very thorough and actually covered, I think, the majority of my written comments already. To elaborate a little bit more, the HeroNet database is an incredibly useful tool, where every reference in the document is hotlinked to the database. And if somebody has access, they can download the pdf document right there. And if they don’t have permission, they can at least read the abstract and get the reference.

It's been -- I speak for myself, but I'd imagine some of my colleagues on the panel feel the same way. It's been incredibly time consuming to

navigate the docket and to find the materials and to actually check things out. And our time, as panelists, is much better spent reading the literature and thinking about the issues, then it is trying to find materials which are available but are not referenced in a way that's easy to find and involves a fairly time consuming search. I benefit from being at a large university, so I have a really excellent library behind me and I've actually made more use of that in getting materials, at least, in the peer-review literature than I have from the materials provided by EPA.

Using the HeroNet database, which is already available within EPA, would be an incredible advancement for you all and I strongly encourage that.

The only other point I wanted to make is there's a paper, Buonsante (2014), an environmental research which is titled, "Risk Assessment Insensitive Toxicity Testing May Cause it to Fail." And in there, it cites a paper by Benedetti (2004). I'll get you the exact reference. The effects of subchronic exposure of Wistar rats to the herbicide glyphosate-biocarb. And the reason I bring that up is because it suggests that the levels for risk assessment, the

LOAEL/NOAEL should be much lower based on that paper. I think that that's also a Benedetti paper that should be looked at. And I don't have any further comments on this charge question.

DR. JIM MCMANAMAN: Thank you, Dr. Sheppard. Dr. Zelterman.

DR. DANIEL ZELTERMAN: Well, I don't have much more to add. Dr. Green was quite thorough, and definitely appreciate that.

By far, EPA seems to have a very thorough access to complete published data, and certainly, the historic 10G FIFRA data documents. But simply having access to the document that you put in your filing cabinet is very different from saying there was access to an independent review, an independent analysis of those data. I was missing so much of that.

Going forward, there seems to be little incentive for independent research, because there's already a lot of data indicating that there's lack of an effect. What was it Dr. Portier was talking about, the publication bias. If you're going to look for something you want to publish significant findings. There's very little incentive for someone independent

of the agency, or independent of the industry, to go out and spend a lot of time analyzing data, only to find that there's nothing to be found.

All right. To drive home this point, let me point out that if you're going to try and show safety, there's an incentive for performing small, sloppy studies with lots of variability that are going to mask the exposure effect. But if you want to show an exposure effect, you have to have large sample sizes, high quality precision to minimize the amount of statistical variability. And these are very conflicting objectives.

I don't know how we're going to get around that, except, perhaps, saying that you really do need an independent analysis of the existing data. I don't know how you get by that, but that's something that's definitely lacking and missing. We have access to the 10G data, and it would be very much worthwhile to see greater analyses of that by independent bodies.

Thank you.

DR. JIM MCMANAMAN: Okay. At this point, I'll open it up to the entire panel for comments. Anyone has anything to add to the charge question. Comments? Dr. Zhang?

DR. LUOPING ZHANG: It's maybe not for charge question, just following Dr. Green's found in the Zhang, et al. paper. But I really thank you for constantly mentioning that China or the study from China, as everybody knows, China is a big agricultural country, so the pesticide use definitely, you know, globally, we shouldn't be ignored.

But I wanted to add a comment. Now, my experience to searching for a research paper published in Chinese or from China, most of the paper actually does have English abstract in the title. Generally, from the (inaudible), you actually shouldn't miss it, at least for the abstract. But if a paper is published in Chinese, you may have a little bit of trouble to find the original, but I think there is a way to request. I mean, that's how I do it. If I want to find a Chinese article, I just send it to my Chinese collaborators and their students can usually find it for me.

But at least, for you to identify if the paper is relevant or not, you can easily do that. But also, Dr. Green was mentioning the papers from Nature, published in Nature. I just wanted to make sure if it is really Nature Journal we're talking

about. Because there is another nature, it's a Chinese Nature that is a totally different journal. Since we happen to see your paper, so I don't know. I just want to mention it here.

DR. JIM MCMANAMAN: Okay. Other comments? Dr. Parsons.

DR. BARBARA PARSONS: I have to get this out of the way. As an FDA employee, I have to say the views and opinions --

DR. KENNETH PORTIER: Please get closer to your mic. I'm sorry.

DR. BARBARA PARSONS: I'm sorry.

DR. KENNETH PORTIER: I'm getting old. I can't hear.

DR. BARBARA PARSONS: The views and opinions I'll be expressing today and tomorrow are my own. My comments are not a formal dissemination of information by FDA and does not represent agency position or policy.

DR. JIM MCMANAMAN: You may need to bring the mic a little bit closer still.

DR. BARBARA PARSONS: Still closer.

DR. KENNETH PORTIER: You need a smaller computer.

DR. JIM MCMANAMAN: Yeah, there you go.

DR. BARBARA PARSONS: So I want to echo something Dr. Green said in that I was also struck by this question of the scope of the evaluation as it relates to glyphosate technical and the formulations. I think that's a critical thing. And I agree that epidemiology is all based on the formulations, and the rodent carcinogenicity data and the genotoxicity data are on glyphosate technical. There's a disconnect there.

I would like to say we should analyze any available data on the formulations, in terms of rodent carcinogenicity and genotoxicity. But at the same time, I have to say that I don't think I could've handled any more data.

I still think that you should consider that and at the minimum, in your document, explain why you chose to do it the way you did and maybe what is your plan to come to terms with this disconnect.

Thank you.

DR. JIM MCMANAMAN: Yes, Dr. Sheppard.

DR. LIANNE SHEPPARD: In my previous comments I also neglected, since you covered the formulations, I neglected to iterate that I also am

strongly encouraging that the formulations be considered; at least what's published in the open literature should absolutely be evaluated in addition to what has been evaluated, because that's evidence that will help us to understand. If for no other reason, it's evidence that will help us to understand the epidemiology and therefore, it's really important that that be considered and not excluded.

DR. JIM MCMANAMAN: Other comments? Okay. I'll go back to the Agency.

MS. DANA VOGEL: We're good at this time. Thank you.

DR. JIM MCMANAMAN: Okay. All right. Next charge question, Charge Question 2.

DR. ANWAR DUNBAR: Okay. Charge Question 2. As a part of its analysis, the Agency has considered 58 individual epidemiological studies investigating the potential for an association between glyphosate exposure and numerous cancer outcomes.

Detailed study evaluations were performed to determine overall quality rankings for relevant studies. These evaluations took into consideration study characteristics, including study design, exposure assessment, outcome assessment,

control for confounders, statistical analyses, and risk bias.

At this point, I just want to make a note that it's 22 not 23 studies for the next sentence. Twenty-two studies were considered informative with regard to the carcinogenic potential of glyphosate. A) please comment on the agency's review and evaluation process of relevant epidemiology studies to inform the human carcinogenic potential of glyphosate.

DR. JIM MCMANAMAN: Okay. The lead discussant on this charge question is Dr. Johnson. Associate discussants are doctors Jett, Portier, Sheppard, Taioli, and Zhang.

We'll start with Dr. Johnson. Let me encourage and just remind the panel to address your comments to the other panelists rather than to the Agency; for a couple of reasons. One is, that's what we're supposed to do; but two is, the reason why we're supposed to do that is because it helps generate discussion and promote discussion amongst ourselves about the specific comments and the relevancy of the data.

I think it's just a good habit to get

into. Although, it's just so easy to say oh, they're sitting over there, we'll talk to them. But just pretend that they're not there for now.

DR. ERIC JOHNSON: I'd just like to clarify that what I'm going to say does not take into account what my colleagues in our group have said, because I just did not have time to receive their comments. I mean, I was assigned this task because I think somebody was supposed to do it, wasn't here.

DR. LAURA GREEN: Right.

DR. ERIC JOHNSON: The OCSPP conducted a systematic review following the recommendation by the National Research Council. They adopted what they call a "fit for purpose" approach in identifying high-quality studies and also adopted the approach of transparency that were followed, really, throughout the review process. I think those two things were followed throughout the review process.

The studies for review were initially identified from open literature search or standard databases such as PubMEd, ScienceDirect and Web of Science. And then these searches were supplemented by various other methods which include peer review scientific journal publications, registrant-generated

studies submitted to the Agency as required under FIFRA, internal reviews and databases, OPP routine evaluations of the epidemiologic literature, evaluations by OPP and other organizations, other governments and academia.

On the face of it, this is really an extensive review. However, there is room for some concern -- from my point of view -- there is room for concern over the completeness of the review process for the following reasons. And I'm not sure whether they're justified or not. The Agency will have the opportunity to put me straight.

It was noted that only nine of 58 epidemiologic studies, selected for review through the open literature searches, were identified. Only nine of the 58 epidemiologic, which were finally identified for review purposes, only nine of them were identified through the open literature search.

That came to me as a surprise because, I mean, most of our review would rely on the search of standard databases like PubMed, ScienceDirect and so forth. That came to me as a surprise.

It sorts of suggests to me that maybe the Agency -- and I don’t know how justified I am, and

the Agency has the opportunity to clarify that again -- but it suggests to me that maybe the Agency needs to do a more reliable, comprehensive and effective -- and use effective techniques in conducting open literature searches than they've done in this particular review.

The second area of concern was that the scientist from the Agency revealed that they had made no attempt to identify studies of workers involved in the manufacture of glyphosate for the review. The evaluation in EPA reviews of this nature, this group of workers is usually excluded for study is quite unexpected for me. I mean, I've never heard of that happening before.

Historically, for other chemical and physical agents like asbestos and benzene and whatever, it has been this group of workers, workers in manufacturing, that has contributed predominately in scientific evaluations of the potential carcinogenicity of chemicals and physical agents that pose threats to the general environment and general population.

Some of the advantages of using this group of workers, that have been leveraged before in risk assessment, include 1) that they have much higher

exposure levels and wider exposure gradients that permit easier detection of effects, if any, than using groups like users, such as applicators and the general population. The manufacturing group have much higher exposures and much wider exposures gradient to them than applicators in the general population.

Secondly, they comprise a well-defined group that is easily followed up. Third, the exposures are usually better documented than what we find in the general population or even amongst peers, for that matter.

Fourth, they can be studied in high-quality cohort and nested case-controlled studies that are much better designs than the usual population or hospital-based case-control studies. I am a firm believer of nested case-controlled studies within cohorts. Workers and companies that manufacture, formulate, handle or sell glyphosate on a wholesale business -- and I emphasize the word wholesale business -- to me, comprise a promising resource that should be tapped by the Agency.

I can go back to my experience when I was at IARC. I was given the job of setting up the International Agency study of workers exposed to

dioxin, phenoxy herbicides, and chlorophenols, and furans. And at the time, the expert committee said, worldwide, there are only 1,000 workers exposed to these compounds. And that was my job now to put this cohort together. And in the end -- long story short -- we got over 20,000.

I mean, you can use the internet and you would be able to -- I used to see IARC in France and be able to identify France and various countries; and that's how we got the numbers up to 20,000.

I think there is that possibility that the Agency can also identify companies that handle this thing on a wholesale basis. And that's where the science should be really. And it may not even be those who manufacture. I think the companies that formulate and handle and sell probably have much more workers than those who manufacture. It's possible, I think.

I would guess because there are 15 or 16 companies which are registrants who manufacture or handling this compound. And I think many of them belong to the latter group of formulators and people who sell. There is a really good potential to try to identify populations, at least for future study, if

not for asking about studies that have been done in their workers.

In relation to that, I think it's a little bit surprising that the Agency has not requested these types of studies from the registrants at that time; either renewal of registration, which would be more appropriate when it's 15 years later. They should request those data; have you've done studies on your workers who were exposed to glyphosate?

I think that should be really part of the agency's requirement, just like they require all the toxicological data and so forth, they should require those. It's really an important resource. Without it, I can't imagine us being able to detect environmental carcinogens in the future. We do need the access to industries. It's as simple as that. I'm involved in that area and I'm very much concerned about the lack of access to industry data. And that's the only way we can protect the general population by having access to industry data.

I have to point out that NIOSH faced a similar situation with dioxins, and NIOSH had the legal power to get access to the company's data. Even

though, they did not relinquish it initially, but under law, they were forced to give NIOSH access to all the company's data. And that's how NIOSH had such good data on dioxin. I think the Agency should not shy away from such attempts to try and improve this risk assessment by being aggressive accessing data.

As we learned yesterday, at least one company had done a study -- had a small cohort of manufacturing workers. That at least shows that that data can be there.

The third point that had a little bit of a problem, was the fact that we were charged to evaluate the active glyphosate acid; however, all the epi studies, as we know, concern people who are exposed to formulations.

Whatever conclusions we make would be in relation to formulation and not to what the Agency has charged us to do. In the evaluation of the epi studies, study quality considerations that were tailored specifically to studies investigating the association between glyphosate exposures and cancer occurrence, with primary literature and associated meta-analysis evaluating association between glyphosate exposure and cancer outcome being the focus

of the analysis. Glyphosate and cancer is the focus of the analysis of the studies which we were asked to give you.

Each study was judged to be of high, moderate, or low quality in each of six domains; and those six domains were study design, exposure assessment, outcome assessment, confounder control, statistical analysis, and susceptibility to bias.

I think this is a sound, appropriate, and acceptable approach. Although, how they arrived at the final ranking was not clear to me. I mean, they ranked each of those six, but the final ranking of all the studies were just low, moderate, and high quality. I don't know how they arrived at the final global ranking.

While the classification of studies in the low-quality category appears quite appropriate to me, the separation of the three studies in the high-quality group from others in the moderate group, I think is questionable. For one thing, the Koutros, et al. (2013) study is not a case-controlled study, as the Agency mentioned. It is a cohort study.

In effect, in the high-quality group we have three studies, two of which are cohort studies

and those two cohort studies are from the same cohort. Secondly, the usual higher ranking of cohort studies, vis-à-vis case-controlled studies, which we all normally accept, I don't think it's applicable in this particular review. Because as I mentioned, two of the three studies were from the same cohort and this cohort has certain limitations, in my view, that do not justify its separation into high-quality ranking above the studies classified as moderate quality.

I don't think it's clear that the studies in the current high-quality group can be meaningfully separated from those in the moderate group. Really, I just don't think that can be done. I don't think that the differences between those studies and those in the moderate group are so distinct that one can make that separation.

Also, while the Agency correctly determined whether studies had adjusted for exposure to other individual pesticides as one of the important criteria for quality assessment, which I 100 percent support, it has not considered the equally important exposure to farm animals, sort of cattle, pig, sheep, poultry, et cetera, that also needs to be adjusted for in determining the quality of epidemiological studies.

As I mentioned earlier today, farmers have been known to be at high risk of leukemia and lymphoma way before any pesticide was widely used in the United States. And the candidate for those excesses have been oncogenic viruses that are present in these animals and also the issue of immune stimulation from exposure to antitoxin, which is particularly relevant when it comes to leukemia and lymphomas.

I think, especially in the few studies, in fact, which experimented with animals as a risk factor, some of them found pretty substantial risk associated with animals. I think it's important to consider both, exposure to all the individual pesticides as well as exposure to farm animals, in trying to tease out what is due to glyphosate.

The Agency pointed out that the direction of confounding from these exposures might be -- it's one direction. That it might be to inflate any effect of glyphosate in the absence of statistical control. I don't quite agree with that because the effect of confounding really can be either way. And I can quote two studies. The study by De Roos et al. (2005), is one example where it shows that adjusting

for all the individual exposures can increase the use for glyphosates rather than decrease it. Also, there was a study by Sheila Bazarin in 1990, which also showed a similar opposing effect. The confounding can work both ways.

Overall, bearing in mind the concerns that I've expressed above, this has not detracted from the fact that the overall agency's review and evaluation process of the relevant epidemiologic studies to inform the human carcinogenic potential of glyphosate, to me, is otherwise adequate, apart from those reservations which I mentioned.

DR. JIM MCMANAMAN: Thank you, Dr. Johnson. Dr. Jett.

DR. DAVID JETT: I have a few comments and some of them are sort of bigger issue comments that probably will and have been covered elsewhere. I'm going to add just a few comments on the process.

Before I do that, I wanted to talk about a couple of big issues and sort of following on from a lot of Dr. Johnson's concerns about manufacturing. I believe I recall when this came up that the Agency stated that this is probably more under the lane of OSHA rather than EPA. It's unclear

if that OSHA activity impacts on the regulatory decisions made by EPA; that maybe should be included in any kind of follow-up. That was one issue.

Manufacturing registrants; I think it might help us and others to determine the quality of the data submitted from registrants if more detailed information on the process of the internal peer review of the studies, and the process of selecting the studies and extracting data, that might, I think, help some of the questions that have come up.

As far as the process, I just had a couple of minor things. In being involved over the past two or three years now in these systematic reviews, I know that they are only as good as the process. For instance, the reviews that we do at NIH, we have protocols that are 50, 60, 70 pages long that we then post on the website and solicit external comment on the protocol, even before we do the review. I think when I read this, the first thing that struck me was it's a little bit lacking detail, although there may have been some citations to some other documents that EPA has on file, that describes it in more detail. But that was my first impression.

One issue that I thought about was, the

selection process is usually done by more than one person so that you can then come to some consensus of the articles that were selected. And I think I mentioned that earlier when I was asking questions of the EPA.

Let's see. And really, the only other thing is something I just saw on, I think it was on page 2, NT 2, paragraph 2. It says studies submitted to the Agency are evaluated based on OECD, OCSPP or OPP test guideline requirements. And I just wondered if, you know, are these harmonious? Are there conflicts? And if so, how are they resolved in these guidelines?

I probably am finished. Oh, one other thing. One second. This always happens when you're reading aloud. I may have raised this earlier. It appears that, again, the new articles that came in -- the newest articles that came in were identified from review articles and then you saw articles that were mentioned in the review and went out and got them. I just think that that -- maybe that's a misunderstanding, but if it's true, you know, I think you should've also done a separate literature search as well. And then finally, I have a comment on cohort

studies, but I'm pretty sure that that's going to be covered later, so I'll leave that alone.

That's it.

DR. JIM MCMANAMAN: Thank you, Dr. Jett. Dr. Portier.

DR. KENNETH PORTIER: Thank you. I want to start by taking Dr. Parson's disclaimer; replace her name with my name. Replace Food and Drug with the American Cancer Society. My comments are my comments and not those of the agency, of the Society.

I want to commend EPA on this effort to incorporate human data into risk assessment. I was on the panel that reviewed the use of epi data in risk assessment back in 2010, and I think they've made a lot of progress since then on actually tightening up on what was pretty loose back then. I mean, that was not that long ago, but I think they've made big efforts here.

As you read this section that lays this out, we know that the goal of the epi study review and evaluation process is really to talk about each study's contribution to the strength of evidence regarding the human carcinogenic potential of glyphosate. But sometimes it seems like the goal is

to bend them into high, medium, and low. There's a little bit of tone there that needs to be addressed because you don't really want that coming out.

The goal of the process is not binning; the goal of the process is quality evaluation. I think in your document, each study is evaluated on its own merits, taking into account not only the general characteristics of the type of study, but also how the specific study designers attempted to strengthen, or not, the information ultimately obtained.

Dr. Johnson and Dr. Jett had discussed some of the aspects of study quality that are described in Table 3.1. And they've kind of made some suggestions for more detail. I'd like to talk a little bit about the statistical analysis issues. It appears that higher quality studies, used more appropriate and more powerful statistical analysis than the weaker studies. But that's about as far as I can go in my assessment, because I needed a little bit more detail.

My first suggestion is that the discussion of study power, which is in the study design domain in Table 3.2, really needs to be separated from that of the methodology model

discussions. And right now, the power discussion is linked to the analysis discussion. And really, the power discussion belongs in the design section. How good of a design was this? How many individuals did they capture?

In fact, I would've taken the study design domain and kind of organized it a little bit more differently. I would've had a study design section where the study type, the sample size, participant selection and randomization controls were discussed. You know, questions asked about how exposures and outcomes are captured; efforts to reduce confounding and potential biases. It would've been nice to see did they ask those questions in the study design.

Then there's some study implementation issues that involves, you know, what attempt did they make to get everyone selected actually involved in the study. I mean, that's a big problem with epi studies. You say I need 120 people and 90 of them answer the call. What about those other 30? How much attempt did they make to get those other 30? The completeness of the questionnaire design.

Often, they report, you know, what

fraction of the respondents completed their questionnaire. And that can be very important because if they, you know, only got halfway through and quit, you may be missing key demographic information or whatever. It would've been nice -- and often this is in the writeup of the study.

And then finally, there's the data analysis section which includes the handling of missing data, the analysis models, the adjustments for confounding and everything else. That's kind of the study design section.

And then I started thinking a lot about the confounder control issue, and some of the things that I would've liked to have seen summarized; probably belongs in an appendix somewhere, but really, you know, there are about 21 pesticide chemical groups and 80 active ingredients that farmers are somewhat exposed to. It would've been nice, somewhere, to have kind of a summary of all of those and where EPA assessment on these things hold. Just so we can get an idea of well, potentially, what are farmers exposed to? Lindane. Some of these, I know, are confirmed carcinogens. Some are suspected carcinogens. In fact, I think a table like that is not a bad addition

to any of the OPP risk assessments that inform agri chemicals.

We keep reminding ourselves that humans are not just exposed to one of these things at a time, but they're exposed to a mixture. And then the other thing, under confounder control, that I think is very important and actually hasn't been mentioned today; is that only a small fraction of these studies really did adjustments for smoking and smoking duration. And we know farmers are terrible in their smoking characteristics.

The farmers and the farmers' wives. I don't know the recent statistics on that, but a few years back, they're in a high category. And I was scanning through your Table 3.2, maybe half of them mentioned some aspect of smoking control. I think it's important to be able to see that. When I'm trying to assess the strength and the uncertainty of each of these studies, I want to see that control.

And finally, it would've been nice, some of the studies talk about well, yeah, we tested for an association with smoking and it wasn't significant. That's fine to know. I would like to know whether that smoking was still in the model when

they assess the relative risk of pesticides exposure because some researchers will test and remove and others will leave it in.

You know, my personal preference is -- even though it's maybe statistically not significant -- there's a lot of biological reason for leaving it in the model. And as I read the discussions, I think that was kind of important in some of these epi studies. Some of them left it in, some of them left it out. And taking them out leaves more variability to be explained by pesticide exposure; that relative risk can actually go up because you tested a confounder and then you dropped it from the model.

At the end of the process, each study is assigned an overall ranking and that's what's the right-hand column in Table 3.2. You know, as you look through that and you read the discussion, there's a high concordance between what you described as a high study and what you ranked as a high study. I think that table does, at least, provide me confidence that you've defined a process and you followed the process, which is important to me. And I think I'll leave it at that.

DR. JIM MCMANAMAN: Thank you, Dr.

Portier. Dr. Sheppard.

DR. LIANNE SHEPPARD: Thank you. Picking up on Dr. Portier's most recent comment of defining the process and following it, I think that's important, but I would revise the process. And one of the things that -- while superficially it looked like the quality rankings were useful, I felt like ultimately, they were really inadequately nuanced. And that in the end, I didn't see that there were important distinctions between the medium and the highly-ranked studies. And that by making that distinction it was not helpful and it allowed for some post-hoc things to be done later that I also didn't think were appropriate, statistically.

I really would recommend removing the distinction between medium and high studies, and they either pass or fail. And then I also very much liked Dr. Portier's binning of the criteria. I thought that was very helpful thinking. And then with respect to the specific criteria, I didn't think the study design is as black and white as the document presents. There's a lot more behind that. And I think the concept of a realized study design is important, not just the fact that it's a cohort study, but what was

the realized design of the study because this is an extremely early report from the Agricultural Health Study.

And while in principle it may be better, in many, many ways, you know, realized design with respect to this publication has some important issues that need to be weighed into the evaluation and therefore doesn't make it so much higher quality than the other studies that were reviewed.

We heard today about the young ages and the low cancer instance to date, and we will hear more, I'm sure, by my colleague, Dr. Taioli, about the selection issues. And they're all really important. In general, study power, I think, was given way too much weight.

As I said earlier this week, you know, once a study is completed, you don't need to talk about power. The results are the results. The confidence interval tells you what you need.

The only way that I would consider power is to make some a priori cutoff that you say it's just plain too small based on something. And that's a hard and fast line and that's it. And that's defined in advance. I mean, we could discuss whether

that should be done based on exposed cases or just total cases. I mean, I think that's something maybe we should hash out a little bit and provide you some advice on. I think my current bias would be on total cases, total events, but I'd like to hear the opinions of my colleagues on that.

The 2010 EPA epi study evaluation that Dr. Portier talked about, also talks about potential for statistical bias; and that's something you didn't consider in your evaluation. I give one example, De Roos, et al., reported the pesticide adjustment estimate for multiple myeloma. There were 32 cases and 23 parameters in that model.

Now, as a statistician, that's too many parameters for 32 cases. Yeah, 15 of those were for the pesticides included in the model. That's a concern in general. And of course, it's difficult, right. You want to draw the conclusions you can, from the data you have, and you want to include all the possible confounders. But it's a really good way to make stuff go away, is to put too many parameters in a model.

You really have to think hard about what belongs in a model, and what doesn't belong in a

model, and why. And it's fine to do sensitivity analyses and report all that. I love to see supplements. A lot of papers did not have them, which I thought was extremely disappointing, because I wanted to see a lot more of what was behind those things.

Exposure measurement error is really, really important. You know, and it's a huge challenge in this literature that all of these studies are relying on questionnaires. You know, there is literature, I think it's the Zahm and Blair paper -- I'll make sure I get that right, as I revise these comments -- to suggest that proxies don't differentially report pesticide use by case and control status. And that biggest challenge with proxy reporting is a higher prevalence of "don't know" responses in both the cases and controls. And it's important to recognize, I thought was really important in those case control studies that had to rely on proxies for the cases, they went out and found deceased controls as well. They were at least comparable on the use of proxy information.

But I think that recognizing the limitation about over-reporting pesticide use for

cases is balanced by some other considerations, and this paper suggests that that's not a real problem in the pesticide literature.

I think the discussion of confounding shouldn't assume a direction. And it would be more useful to consider the bounds of the role of confounders unaffected estimates. You know, there's literature from -- the lung cancer literature that suggests that omitting an important confounder, even like smoking, doesn't necessarily confound effects estimates that much.

While omitting confounders is clearly a concern, I think that I'm actually almost more concerned in these studies about the over adjustment by pesticide use and the problems that may come into the analysis from that. And many of these studies put a lot of pesticide indicator variables in the model.

And the consideration of other pesticides, I think Dr. Portier's comments were really excellent on this. I thought the consideration of that was really pretty superficial. You know, by not considering specific groups or active ingredients, I think we're really missing something really important.

I also wanted to comment that the

reference group and analysis has important implications for the interpretation of the results. You know, in the Agricultural Health Study, they are all farmers that are registered pesticide applicators. What does that say about the underlying, you know, who they are -- who the unexposed individuals in that study are. It's also in the dose response analysis. It's important to recognize that the reference group there is the low -- is not the unexposed, which is what you would think, but it's the lowest exposure group.

The reason De Roos, et al. did that, was because they were concerned that there was some differential bias in the -- that there were some differences in the unexposed group in that study; and therefore, they did not want to do the dose-response analysis using the unexposed as the reference group. But it's easy, you know, when it's all lumped together. We say oh, there's no dose response, but we don't even really think, oh, well, the dose response, the reference group is exposed. It's still a low-dose group. It's not an unexposed group.

And that's one example. There were several of the case control studies that had the

reference group as having no exposure to any pesticides whatsoever, as opposed to other ways of adjusting, of dealing with pesticide use. And I wondered the implications that had on the analysis. So again, the choice of the reference group has an important implication.

Let's see. I think I've said a lot of this. I probably have a lot more to say about the Agricultural Health Study, but maybe I can come back to that later.

Thank you, Dr. Sheppard. Dr. Taioli.

DR. EMANUELA TAIOLI: Okay. I have a few comments. One is in agreement with the selection criteria that Dr. Jett was mentioning before. I think it's very important that there are at least two people doing the selection and two people scoring the quality independently. It’s very important in a process. Maybe you did it, but it didn’t appear clear in the document.

Then I have some addition about the study design. I think the introduction, it's very black and white about epidemiological studies, and unfortunately, our life is not that black and white. Although we think that cohort studies are the gold

standard and we all like it, it depends on how the cohort study is designed.

I will come back in a second about the Agricultural Study. On the other side, the case-control studies which are prone to bias and everything gets written in a document. That's actually the study of choice for the rare disease. Non-Hodgkin lymphoma is a rare disease. From what I am concerned, I don't find it very unusual that there are so many case-control studies; because the type of diseases they were looking at were rare diseases. I don't find it as such a reason for scoring a study alone, in terms of quality.

By looking at the score of the agricultural study, which was scored high, I really don't agree with that completely, for several reasons. Some of them have been mentioned today, which is the short follow-up. Everybody said that. Also, there is a very small number of incident cases; for example, of non-Hodgkin lymphoma, just because when you use a cohort study for a rare disease, you get a few cases. That's how life goes.

Another thing that I have concerns with is the inclusion -- so this is kind of a prevalent

cohort because everybody who registered, at that time, entered the cohort. But then the historical exposure has been built up, retrospectively. We don't have a denominator who are the farmers because everybody I looked at the average -- backward exposure is an average of 15 years before the interview.

In those 15 years, a lot of farmers who were very susceptible to exposure may have died and never had a chance to register. We don't really know what is the background denominator of this population. And if that happened, which we don't know, then we expect no risk for the disease of interest during the follow-up, which is what we are seeing.

I have a lot of concerns with this. And I'm just thinking today, but I want to think a little bit more, that even excluding the prevalent cases, given this historical retrospective construction, may not be the best option, but I'm not completely sure about that. Maybe it's something we would want to think about. And then I had the same issue about the comparison group because everybody is basically exposed because of the fact that they are registering. They are exposed to other pesticides. They are not really a baseline if we're looking for a

baseline.

I think that there are a lot of issues that we may discuss more, but I don't find this study as informative as it's written in the document. And I think that perhaps having a follow-up of this study, of just of the newly registered, new user, followed over the following 20 years, may be the most informative information that we can have on the issue. And I'll stop there.

DR. JIM MCMANAMAN: Thank you. Dr. Zhang.

DR. LUOPING ZHANG: It's always good to be the last because then, you know, my panel members already expressed most of my opinion. But I just want to maybe echo some of my fellow members' comments. For example, Dr. Jett also mentioned about newly population papers or maybe newly accepted papers, if that should be included finally in this report or not. I guess maybe Dr. Green also mentioned that on the first day -- I'm trying to encourage discussion.

Should we have a cutoff date? Like a date after 2016, that would be a good timeline or something? I think that's something, as a committee, we should even think about. Because we can't let it

go on forever. We have to have a cutoff. That's number one.

Number two, if you look at the charge question, I think we mentioned that too, but I just want to make sure, 23 studies, it's not 23, it's 24, right? Three high quality, as you know, and 21 medium. But what we know from what Dr. Portier and Dr. Sheppard mentioned, is that really good to eliminate all the low-quality score studies?

I think maybe we have to, I mean, I know later, maybe today, this is going to come back. For example, you know, let me just put an example, Cocco (2013), which was included in IRAC and it was also included in 2015, you know, your own previous report that rated low, then you discard it, and should we revisit, just something like that? I just want to make sure that all the paper selections, you know, we as a group really fully agree.

Anything else? Oh, another thing is about the bias. The risk of the bias from, you know -- Dr. Jett also mentioned that I think we, also, as a group, we really should think about it carefully. And luckily, we have a lot of biostatisticians on board. How do we really manage, for example, recall bias from

the case control study?

I mean, when we get into maybe discussion in 2(d), this is going to all come back, but I just want to mention it now. And how should we really deal with this? But as a bias, is it possible, potential bias or risk for the bias? But can we manage it somehow? Let's say, can we using, I don't know, I'm not a trained biostatistician, but if there is a risk, can we, let's say using bootstrapping idea.

Even for this human study, we can't repeat a thousand times. But mathematically, if we can make it happen a thousand times to repeat these human studies, what would be the potential risk.

I don't think it's good for EPA just to say we exclude this because it is a bias. It could be a bias. Of course, everything could be, but can we manage that? Can we access that?

I think that's why also my panel member, Dr. Jett, you know, mentioned and also provide as a table. I think we should go into that table and see if we can quantify the way to manage this bias risk. I get so excited. Let me see if I forgot anything. So basically, (inaudible) analysis; I think maybe there is no, what's the best. You know, what we

should use.

I think that maybe I would like to stimulate that discussion. And I really want all my biostatistician colleagues to help me really understand how we can make a conclusion from the specific question charged. You know, help me to make that conclusion. Thank you.

DR. JIM MCMANAMAN: Okay. Thank you. We'll open this up to comments by any other panel members. Dr. Portier. He had his hand up first.

DR. KENNETH PORTIER: My understanding with epi studies is they rarely don't publish. It's more of the animal studies that they'll kill a couple hundred rats or mice, you know, and nothing shows up. It goes into -- but you spend the money to do an epi study, you're going to publish something. I'm less worried about report bias with epidemiology studies. Wouldn't you agree, Dr. Sheppard?

DR. LIANNE SHEPPARD: I think with respect to reporting, there's another subtle issue in epi studies, which is, you know, what analysis you finally report, versus what analysis did you do. That's typically not very transparent and could affect what's reported.

DR. KENNETH PORTIER: And that's why I like your idea of being able to look at the supplements. And then I thought to myself, except that editorial boards want less methodological discussion these days and they said, well, we're going to put that in the supplement and then we never see the supplement. We're not only missing the follow-up analysis that you did, that didn't come up positive, but we don't get a good picture of the methodology they followed. And it's a real problem. It's being discussed quite a bit in the scientific literature.

DR. LIANNE SHEPPARD: I mean, I do think with electronic publications now and certainly in the world that I work, it's much more common that there are online supplements that are pretty detailed. And when we need to drill down into the study, you look at them and if you're just reading the study to try to get a handle on the results, you don't bother. But, you know, for this kind of evaluation you absolutely need that.

DR. KENNETH PORTIER: And, you know, coming from an agency that does long-term cohort studies, I mean, the American Cancer Society Cancer Prevention Study I, is just ending now. It's 45

years in duration. And the members have been followed that long. All right. And we have another one we're just starting up and we're making a long-term commitment to be able to do those studies. We don't even give out that data.

Our epi group does not believe in open publication and open science for many reasons. A lot of it having to do with confidentiality, and trying to follow people for 40 years and convince them that you're going to protect their anonymity, and those kinds of issues. There are a lot of reasons why we don't see everything. But that's another problem, too.

The triple A quality epi study that you'd really want to be able to dig into, is proprietary for 40 years, until everyone dies or they close the study and get permission. Especially with cancer studies, that's kind of what they do. Can you get access to the details of the nurse's study? You know, all these big, long-term epi studies, you don't have any details from that.

I wanted to follow up on a statement you made, Dr. Sheppard, about power. I tend to agree with you. You know, power is what you intend to do.

What you actually achieved is important. But sample sizes are part of it, I'm more interested in achieved responses, like you said. It's actually the fraction of how many people responded, to how many people you shot for, that's the quality of the implementation. And we don't always get that.

Sometimes they say I talked to 100 people. I tried to talk to 500. Four hundred of them refused to talk to me, 100 did. Here's my results. And it's, again, less of a problem in epidemiology that's done really well, much more of a problem in like, marketing where it's anybody's answer. But some of the studies that are low quality that were done by post-docs or graduate students, I have real problems, especially the ecological studies. There's usually a real response bias going on in those studies if you look carefully at them.

DR. LIANNE SHEPPARD: But that's not statistical power, right. That's more selection.

DR. KENNETH PORTIER: Yeah.

DR. LIANNE SHEPPARD: And I agree with you, selection is super important.

DR. JIM MCMANAMAN: Other questions. Yes, Dr. Green.

DR. LAURA GREEN: Hi. Couple of things. I want to echo Dr. Sheppard and Dr. Zhang and other people's feelings that your quality ratings seem a little arbitrary and ultimately unnecessary. I mean, I'm just a kill them and count them toxicologist, I'm not an epidemiologist. But it strikes me that eliminating a bunch of things a priori, without actually spending the time to look through the data on individual studies, makes you look a teeny bit biased or a teeny bit lazy; and I don't think you want to look either biased or lazy. And my antennae, if that's the right plural, were raised when you all just said that Cocco, et al. epi lymph study is low quality.

I mean, I can tell you as someone who reads the lymphoma epidemiology literature a lot, that the Cocco, et al. researchers are arguably the most important lymphoma researchers in the world. There are a series of studies called epi lymph, and there are scores of them that cover at least six European nations. There were, in that study that you all considered to be low quality, 2,000 cases of non-Hodgkin lymphoma and 2,000 controls, roughly, a little bit more. I don't see how that's a low-quality study.

Now, having said that, there are clear reasons that the Cocco, et al. study do not inform the question of whether glyphosate is a carcinogen. Okay? But that's a different issue from whether the study is no good. And I, for one, am insulted, on their behalf. I mean, if Cocco et al. read that you all considered their study to be low quality, they'd be really mad and they'd be right. I mean, they really know more about lymphoma than any group of researchers in the world. Literally, in the world.

Now, I would say further that if 2,000 cases and 2,000 controls, there are only six people exposed to glyphosate, then either the Europeans are not using glyphosate, which strikes me as weird; maybe some of the marketing people in Monsanto need to get going or something.

I mean, how can there only be six people out of 4,000 in Europe who has used glyphosate. Like, that's weird. There are problems with the study. But to call it low-quality and not to look at the data as the data present themselves, again, looks like you're being biased or lazy, and I don't want to be either one.

DR. JIM MCMANAMAN: I don’t think they

they're saying low quality, they're saying low value for this --

DR. LAURA GREEN: Well, but look at the data. And the other thing to be said -- okay let's take it at face value. Let's say it's true that there's only six glyphosate-exposed people among 4,500 Europeans, which again, I don't think so. But anyway, it looks to this simple kill them and count them toxicologist, like the reason the study was rejected is they didn't like the odds ratio because of a lot more than one.

Okay, let me finish. It's a lot more than one, but as my friend Charlie Pool used to say, it like the tarp at Fenway Park, it covers all the bases, right. Like, confidence intervals from, I don't know, like .7 to 70 or something. I mean, I'm forgetting, maybe .7 to 20.

I mean, obviously, it's a very limited, probative value when you have four expose cases into exposed controls. I mean, duh. But the data are the data. And I think Dr. Infante was right to include it in his meta-analysis. I have other issues with his meta-analysis, but I think he's right to include it. I believe that Delzel and Chang included it. I could

be wrong.

You know, don't throw it out. I mean, it has very limited value, but that's why we have confidence intervals, right?

DR. ERIC JOHNSON: I think the other reason why --

DR. JIM MCMANAMAN: Dr. Crump had his hand up first. We'll go with him and then with Dr. Johnson and Dr. Ramesh.

DR. KENNY CRUMP: I think the Agency did a very incredible job for the most part, identifying strengths and weaknesses in the relatable studies. But I do think there is an important omission which needs to be rectified. I'm talking about the problem of recall bias in case-control studies. I would like to talk a little bit about that and also present a couple of slides as I talk about this.

But by recall bias, that is the tendency for cases --

DR. LAURA GREEN: It looks like you're being loaded as we speak.

DR. LIANNE ZHANG: did you say you wanted to present some slides?

DR. LAURA GREEN: Yes. I think it's being loaded.

DR. KENNY CRUMP: I don't need right now.

DR. LAURA GREEN: Do you have them?

DR. KENNY CRUMP: Yes, she's got them. I got it worked out.

DR. LAURA GREEN: Oh, okay. I'll calm down. I'm hungry.

DR. KENNY CRUMP: I would like to spend a little time on this. Is it a good time to break for lunch?

DR. JIM MCMANAMAN: No. I think we ought to finish this. We're in the middle of it.

DR. KENNY CRUMP: Recall bias is a tendency for cases, people that are sick, when they are asked to recall previous exposures, they may be very concerned about what exposures may have caused this sickness. And so, they will be much more serious than controls about thinking about their exposures.

The cases they may take more time and think about more about recalling their previous exposures. And this would cause, what we call, exposure bias. That's the tendency of cases to recall

more exposure than the controls.

The effect of this kind of bias is to inflate odd ratios, make them bigger than one. The IARC monograph by Breslow and Day (1980), which I sort of consider the bible on case-control studies, this is what they had to say about the potential for recall bias.

Bias, especially that resulting from non-comparable information from cases and controls, are also potentially serious. The most common of these is recall bias, which may result because cases tend to consider, more carefully than do controls, the question they're asked, or because the cases have been considering what might have caused their cancer.

The weakness then, of case-control studies is that in the end, the investigator must appeal to subjective or only semi-quantitative arguments to the effect that the information that he has from cases and controls is equivalent in source and quality.

I expect that is as true today as it was 35 years ago, when it was stated. Here is what a more recent paper that appeared in the year 2000, in Nature, Griem and Shultz had to say. This was a paper

that reviewed potential problems in epidemiological research.

"In case control studies that rely on memory of remote exposures, recall bias is pervasive. Cases tend to search their memories to identify what might have caused their disease, healthy controls have no such motivation. Therefore, better recall among cases is common."

Now, recall bias will not affect cohort studies or case-control studies nested in cohort studies because these studies will question the participants about their exposure before they were sick; so, we're only talking about non-nested case-control studies.

When I was reviewing these case-control studies, I was interested in what they had to say about the potential for recall bias and a lot of them didn't say anything I found out. Some of them gave a few references, and I tracked them down, but they were relatively uninformative. The only study I found that had potential useful quantitative information, on this problem that is related in the slide up here, was an old study by Blair and Zahm (1993), that Dr. Sheppard referred to a few moments ago.

This study reported case-control data from studies in which the cases and controls have been interviewed about their pesticide exposures in two different ways. First, they said just generally, just tell us pesticide you were exposed to, with no kind of prompting. They got all the information. Then they went back and had a list of pesticides. Were you exposed to this? Were you exposed to this? Were you exposed to this? They got two list of exposures.

And you might guess, the second list was much more extensive than the first list. This was their conclusion; the number of insecticides and herbicides volunteered by cases and controls however, was quite similar, providing no support for recall bias. But no analysis was reported to justify that conclusion. I have re-analyzed those data from that old study, and that's what reported up here on the chart.

I calculated as many odds ratios as I could. The left-hand column, the first box there, is the odds ratio or exposures to one or more insecticides versus exposures to none. The box below that is exposure to two or more versus exposure to none. The box below that is exposures of five or more

versus exposure to none.

The column to the right of that is the same analysis having used the second method of probing, where they listed the specific pesticides and asked them if they were exposed to them. And you can see and compare the number unexposed cases in the upper left box, 64 to the number of cases in the box to the right of that, 34. You can see how you poll these cases makes a big difference in what you come up with. I did the same thing for herbicides, so you get the same thing on the right over there.

The blue boxes are the odds ratios that I got from these data. And the interesting thing is, every single one of them is bigger than one. They go up to even greater than two. But I think even more interesting is that five of them are statistically significant. The ones in yellow are the lower bounds and they're all bigger than one, so those five are statistically significant. And all of them come from the very detailed polling and questioning. That suggests to me that if you try to do a better job of questioning, asking more detailed questions, you may be exacerbating the problem of control bias that affects the cases, perhaps more than it does the

controls. And that's what I would --

DR. LAURA GREEN: Kenny, these are Blair and Zahm's own data?

DR. KENNY CRUMP: Yeah.

DR. LAURA GREEN: So how can they conclude what they concluded?

DR. KENNY CRUMP: That's kind of my point. I don’t know.

DR. LAURA GREEN: Wow.

DR. KENNY CRUMP: But they did not do an analysis to support their conclusion.

DR. LIANNE SHEPPARD: We'll have to look at this more carefully. It’s Table 9 in Blair and Zahm.

DR. LAURA GREEN: No, you'll have to look at it.

DR. KENNY CRUMP: Sure. Sure.

DR. LIANNE SHEPPARD: Some of us will have to look at this more carefully.

DR. KENNY CRUMP: I hope you do. Yeah, this table certainly does not support the author's contention.

Okay, now I want to look at the glyphosate studies. Show me the next chart.

The EPA did an analysis of 12 case-control studies that would be potentially subject to control bias. I have them at the top of this table. These are all non-nested case-control studies. And down at the bottom of the table, I have the six studies that would not be subject to control bias. There is one prospective cohort study and there are five nested case-control studies.

The top part of the table are studies that would be subject to recall bias. The bottom part of the table would be studies that should not be subject to control bias.

DR. LAURA GREEN: Recall bias. You said control bias. You mean recall bias.

DR. KENNY CRUMP: Yeah, I keep saying control bias. Keep correcting me. Thank you. When I say control bias, I mean recall bias. I'm sorry. That's the way my mind works in a way.

I did something very simple. I went through all the studies and I just counted the number of ORs that are bigger than one and the number that are less than one. It's a very simple thing to do. You can probably do something a little bit more sophisticated, but I think this proves our point.

I listed all of those, number bigger than one and number less than one for each of the studies. And remember, all of these studies are not just of glyphosate, they're for dozens of pesticides. This is the result from analysis from dozens of pesticides in these studies. I took the number bigger than one, the number of less than one in each of the studies and then I took the ratio. And that's the rightmost column.

And I think the thing that's important to notice here is that by and large, almost all of these numbers are bigger than the numbers on the bottom, which is, I think, what you would expect if there was control bias --

DR. LAURA GREEN: Recall bias. Recall bias.

DR. KENNY CRUMP: -- recall bias being responsible for what is going on here. There is one odd one out, the Lee case control. That's a quite different response. But by and large, the numbers in the top part of the chart are larger than those on the bottom part of the chart.

If you look at the non-Hodgkin lymphoma -- well three of them anyway -- the Eriksson, the

Hardell, and the McDuffie, those three studies, practically all of the odds ratios were bigger than one. Interestingly, those three studies also, in some of their analyses, in their unexposed group, they removed people who had been exposed to any herbicide, not just glyphosate. That would cause selection bias, and it will also exacerbate the effect of recall bias; because you're taking out from the unexposed group, cases more than you are controls. That would make the ORs increase.

At any rate, I see in this -- you see just what I would expect to see if recall bias is important and what's going on in studies.

DR. LAURA GREEN: Wait. Can I ask a couple questions about this? Because first of all, this is startling. But second, I'm not sure I completely understand.

If we can just focus on one that's got big numbers but a small bias. So Koutros, et al., right, which is second from the bottom, which is the nested case-control study, within the Agricultural Health Study that focused on prostate cancer.

I don't understand. It's only looking at prostate cancer. And are you telling me that

because there are so many pesticides and herbicides evaluated within the Ag Health Study that there are that many separate odds ratios?

DR. KENNY CRUMP: That's what I got. Not all of them are in the published paper, but if you look at the note down there at the bottom, some of them you have to go online. But I went through both online and in the published paper, and that's what I counted.

DR. LAURA GREEN: There are basically 400 variables, essentially?

DR. KENNY CRUMP: No. There are 400 -- well, they did a whole bunch of analyses with a whole bunch of --

DR. LAURA GREEN: Four hundred analyses I mean, yeah.

DR. KENNY CRUMP: -- pesticides.

DR. LAURA GREEN: Wow. Okay.

DR. ERIC JOHNSON: Koutros et al. is not a case-control study.

DR. LAURA GREEN: Yeah, it’s nested within the Ag Health Study.

DR. ERIC JOHNSON: No. It’s a full cohort study.

DR. LAURA GREEN: No.

DR. ERIC JOHNSON: It is. It is a full cohort study.

DR. KENNETH PORTIER: Can you turn your mics on so we can hear you?

DR. ERIC JOHNSON: Koutros, et al. study is a full cohort study. You just looked at prostate cancer only, but it's a full cohort study. It was not a nested case-control study.

DR. LAURA GREEN: Well, maybe it's just semantics. I mean, it is all the -- my understanding, again, as a simple kill them and count them toxicologist, so maybe I read this wrong. But my understanding is that Koutros, et al. took all of the prostate cancer cases and evaluated them.

DR. ERIC JOHNSON: Yeah, what they did was --

DR. LAURA GREEN: Within the Ag health study.

DR. ERIC JOHNSON: They looked at exposed group and unexposed group and compared the frequency of prostate cancer in exposed versus unexposed, and got a rate ratio by Poisson regression analysis.

The analysis is Poisson and stated right in the abstract. You can see it from the abstract. It says that this Poisson regression is the rate ratio. It's not a case-control study.

DR. LAURA GREEN: Okay. I stand corrected.

DR. JIM MCMANAMAN: This is all really informative, but are we off target a little bit here? We're supposed to be addressing the evaluation process.

DR. KENNY CRUMP: I'm almost through.

DR. JIM MCMANAMAN: Okay.

DR. KENNY CRUMP: I'd like to say a couple more things. Based on what I've said, I'm concerned that the results from these non-nested case-control studies may be reflecting what we see from recall bias, more than it reflects what it would reflect on exposure to glyphosate.

I think this will also have implications for the meta-analyses of all of these. There are four -- usually, I think, there are four or five of these case-control studies that are subject to recall bias that go into the meta-analyses. These biases don't cancel each other out; they are all in

the direction of raising the OR. That will bias the meta-analysis just like it would bias each one of the individual studies.

Okay. I think that's it. Thank you.

DR. JIM MCMANAMAN: Okay. Dr. Taioli.

DR. EMANUELA TAIOLI: Yeah. This is actually -- between cohort and case-control study, it's the beginning of the first class of epidemiology, but nobody says this is the best or this is the worst. They give you a table and says, these are the plus and these are the minus. You have plus here, you have minus there. Unfortunately, you don't have all the plus on one side; because otherwise, it would be very simple. If you look at this lower, they are all derived from the agricultural cohort study, which is a negative study.

You look at it the other way and you only have -- I counted the cases -- you have 61 cases of non-Hodgkin lymphoma, and 13 multiple myelomas. You have a small number of cases because the cohort has short follow-up and it is looking at rare disease. You have numbers that are high for cancers that are more common. That's the problem of a cohort study. And you never get out of that. You have either recall

bias or the issues of cohort studies. You don't have a solution to these weaknesses that the two designs have.

DR. LAURA GREEN: Okay.

DR. KENNY CRUMP: Yeah. I think probably despite the best efforts of epidemiologists, this seemed to be a problem that's very difficult to solve. But we still have to -- if there are biases in the study, we have to recognize them.

DR. JIM MCMANAMAN: I have a question. Is there a consensus, amongst the panel members, that the evaluation that the agency used in this process wasn't adequate for risk assessment? Are these studies all fraught with so much error, and so many problems, that they are not informative at all?

DR. LAURA GREEN: I'll take a stab at that. That's not what I was going to say, but I'll take a stab at it.

DR. JIM MCMANAMAN: All right.

DR. LAURA GREEN: Well, I think we're getting ahead of ourselves a little, actually. But let me say it depends. I think we may be saying that -- well, my answer to your question is the following: it depends on the endpoint.

Certainly, when the agency looked at high and medium quality studies, with regard to solid tumors, and came to a conclusion that there is no reliable evidence of carcinogenicity, I expect -- although we haven't talked about it yet -- I expect that this panel will be in agreement.

It depends on which cancer I think you're talking about and which set of studies.

DR. JIM MCMANAMAN: I'm asking about the carcinogenic potential. That's the question.

DR. LAURA GREEN: Oh, well, then I think, if I can, I would answer it in three bins, just the way the agency presented it.

They talked about all the stuff for which there is like, really no reliable evidence, and neither IARC, nor anyone else, thinks it's reliable; so, solid tumors, you know, and leukemia. I don't think anyone thinks the agency did that wrong. In other words, I think there's universal agreement, among the panel and frankly the scientific community, that there is zero reliable evidence that glyphosate has been associated epidemiologically with solid tumors and/or leukemia.

DR. LUOPING ZHANG: We're not there

yet.

DR. LAURA GREEN: We're not there yet.

DR. LUOPING ZHANG: Also, that's because there is a limited number of studies.

DR. ERIC JOHNSON: I think the studies are good studies. We've all reviewed many, many, many studies, as far as good studies are concerned. And there is nothing terrible about those studies, those 24 studies, that would make me be concerned. But like every study, sometimes we say it's epi study, but also in experimental study, it's not a perfect study. Each study has to be taken individually in some cases to interpret it. In some cases, it's straightforward.

For example, the Agricultural Health Study, there is a problem with that cohort study. And even though normally cohort studies are strong design, in this particular issue, there is a problem with it for various reasons, which people who are bona fide, I don't want to go over them with that. However, we cannot accept it as a gold standard, in this particular issue, because the Agriculture Health Study, we cannot accept it as gold.

In total, those 24 studies are good studies. There's nothing terrible about them that

would make me want to throw out any of the data.

DR. JIM MCMANAMAN: Okay. Thank you. I've been asked, reminded, that we are supposed identify ourselves. I think we became a free-for-all here for a little while.

I'm sorry, Dr. Ramesh had his hand up a long time ago.

DR. ARAMANDLA RAMESH: I don't have a question. I have a comment. The Agency, in one of their presentations, mentioned about confounding controls. And I think they did it on the first day. Dr. Perron presented, I believe, occupational exposures to diesel exhaust fumes, solvents, UV radiation and some other variables. But I do agree that it could have been better presented separately, either as a table or as a footnote. But the Agency did bring it into all models.

DR. JIM MCMANAMAN: Thank you. And Dr. Ehrich.

DR. MARION EHRICH: Okay. I think we're taking our eye off the prize, which is the weight of evidence. And that's more than just these epidemiological studies. I think, I'd like to throw that out again.

DR. JIM MCMANAMAN: Well, that's not part of the charge question, so --

DR. MARION EHRICH: Well, it is; because it's, do you inform the human carcinogenic potential. This is part of it.

DR. JIM MCMANAMAN: Yeah, but the epidemiological studies, though.

DR. LUOPING ZHANG: We're on 2(a).

DR. JIM MCMANAMAN: We're on 2(a).

DR. DAVID JETT: Right.

DR. JIM MCMANAMAN: Dr. Jett.

DR. DAVID JETT: This is Dave Jett. And what I was going to say is, to your question, we should be, at this point, just focusing on the process.

DR. MARION EHRICH: Yes.

DR. JIM MCMANAMAN: My question.

DR. DAVID JETT: Selection and evaluation process, not whether the studies are good or not. But really, is this a good way of trying to find those good studies? I thought that's what this question was about.

DR. LAURA GREEN: Well then, I think the answer to the question, if I can summarize it is,

Dr. Sheppard and others -- and I would agree with her -- fault the agency for discounting some studies or putting them in arbitrary bins, medium versus high. I don't know if it's a consensus, but I certainly agree that to eliminate certain studies, like Cocco et al., a priori is a bad idea, and is unnecessary. Because unless I am missing something, that's the whole point of having confidence intervals and detailed evaluation. I think that's sort of a consensus, isn't it?

DR. JIM MCMANAMAN: Wait a minute. Dr. Portier.

DR. KENNETH PORTIER: I got my flag up. Put your flag up.

DR. JIM MCMANAMAN: Everyone will get a chance to be heard.

DR. KENNETH PORTIER: To quote, you know, a statistician's quote, "All models are wrong, some models are useful." I think the same thing with this process, you know, the process has been very useful. I was able to follow it. It was clear and it helped me work through all the issues there.

Is it a perfect process? No. We've got some suggestions on how they can improve that

process. But my assessment was, this was a really good-faith, good professional effort to review these studies and provide us some strength of evidence back. When we get into these discussions about the values of the findings toward glyphosate carcinogenicity, we have to keep in the back of our minds, yeah, but is this a good study or a horror story? And they've helped us with a framework to do that. I think that was their goal, is to provide that framework.

My vote would say, no, Jim, they have a decent process here. It can be improved, but it helped me, and question, to be.

DR. JIM MCMANAMAN: Dr. Zhang.

DR. LUOPING ZHANG: It's really good to have a last name start with Z. It’s always the last, including you.

I just want to comment on Dr. Crump's presentation. I want to thank you. You, at least, addressed my question as how to access, you know, how to discuss, or limit thinking about the recall bias, right. You got us started.

I sort of agree with Dr. Green, I'm not so sure I really got it, all the numbers of what you did. Maybe this afternoon we'll come back to that.

Your comment or suggestion, it sounds to me, if a case-control study always has this recall bias, maybe we should suggest to epidemiologists, don't do that. because if you did, we can't include your data anyway because of the recall bias. This is one thing.

And the second -- I forgot the second. That's a recall bias. Anyway, I'll come back. I don't have a second one. But it makes me think, if it was consistently a recall bias from a case-control study, why all these epidemiologists want to do it?

DR. JIM MCMANAMAN: Well, you know --

DR. LUOPING ZHANG: But if you did it -- so that's why I'm thinking, we want to have maybe a statistical way or some way to qualify this risk. That's basically my point. I don't know how, but I just don't think now to consider. That's maybe not a good approach. So anyway.

DR. JIM MCMANAMAN: If it's about statistical modeling, we can hold it. If it's about the charge question, do you have a comment.

DR. ERIC JOHNSON: Just consider that these issues will come up for certain types of studies, and then we can efficiently address those.

DR. JIM MCMANAMAN: I think that we probably have gathered lots of evidence that statisticians' brains are mainly on cocaine because they'd rather argue about statistics and approaches than eat. I think we'll go back to the agency and ask if this is informative in relationship to the charge question. Or if you need clarification.

DR. MONIQUE PERRON: Towards the charge question and plus, this has been informative. But we did want to clarify just a couple of things before we break.

One thing, in terms of the process for the scoring for the epi studies, I think it was a little bit of confusion. I think the information yesterday, or two days ago -- it's all a blur at this point -- regarding how we had gone through all of the lit studies, was one person categorized them and then two other people Q/A'ed that information.

In terms of the epi studies, we actually had two people look at a study, and then two others after that look at the study as well. And then there was actual discussion as well beyond that, after the fact, if we weren't in agreement or if there was additional information to add to that point.

I believe somebody also made a statement that we just eliminated studies. Again, the studies, again, were gone through a ranking to determine whether they would be informative to the carcinogenic potential. It's not about the quality.

And there is a statement, that is hidden in all of that, that says that these rankings are specific to this evaluation. We're not trying to say that a specific study is of low quality, altogether, in total. It was that there were deficiencies or limitations, that we then thought that that study would no longer be informative.

And in terms of Cocco, I would say that it wasn't just that there were a low number of cases of controls, we also noted that there were some control selection issues. There were other things that weighed into that. And just because it was included by another agency such as IRAC, or even ourselves during 2015, formal quality evaluations were not conducted by either of those instances.

Just be aware that, just because something has been included in the past, it doesn't mean that it should be included now.

DR. LAURA GREEN: Yeah, all fair

points.

DR. ANNA LOWIT: One more quick one. I know everyone is hungry, including myself. This question is about a review process. And as Dr. Portier has alluded to, we've been working through these issues for a number of years now. The process that you have before you is what we have sort of evolved into.

The SAP, back in 2010, recommended we actually come up with a scoring system for epidemiology. In fact, the NAS has pushed the agency to create these scoring systems so that you can put things in bins, and put your emphasis on things of more quality as opposed to -- maybe value is a better word -- science value for your question versus the lower value.

To the extent that a few of you had some really constructive comments about reorganizing the table or adding, you now, sort of rejiggering those things, that would be really helpful to make sure it appears in the report. We would also request that you recognize that, if we get advice on eliminating the binning process, it's counter to what the NAS has recommended to the agency, and previous

panels have recommended to us.

DR. JIM MCMANAMAN: All right. I think with that, we'll break for lunch now for an hour. We'll be back at 2:10.

[WHEREAS A LUNCH BREAK WAS TAKEN]

DR. JIM MCMANAMAN: I think we've convened our entire panel and we're ready to read in the next charge question.

DR. ANWAR DUNBAR: Okay. I will read questions 2(b) and 2(c).

Just 2(b).

DR. JIM MCMANAMAN: Don't confuse us.

DR. ANWAR DUNBAR: I'm sorry. Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and solid tumors, leukemia, Hodgkin lymphoma and the agency's conclusion regarding these cancer types described in section 3.6.

DR. JIM MCMANAMAN: Okay. That was Dr. Dunbar from the EPA. And the discussants on this are Dr. Zhang as the lead discussant. Doctors Crump, Green, Johnson, Sheppard and Taioli. We'll start with

Dr. Zhang.

DR. LUOPING ZHANG: For the 2(b) question, I'd like to congratulate the EPA panel. It seems like from the information that I've received from my fellow members, Charge Question 2(b), seems that we mostly agree with your conclusion based on the selected studies; which means it's only focused on the 24 human studies from the high and the medium quality scores.

Our group generally agrees with the EPA's conclusions, there is no association between glyphosate exposure and solid tumors, leukemia, and Hodgkin's lymphoma. However, the data upon which this evidence is based is very sparse. And based on the tables you provided, Tables 3.3, which include all the solid cancers and 3.4, including non-solid cancers, you can see they are really limited numbers of available human studies, mostly for the specific tumor types. Its' only like one study or two, maximum, for most of the solid cancers, except the multiple myeloma and non-Hodgkin lymphoma. That's the next question, so I don't want to go there.

Therefore, I think, the availability of the epidemiological data is still extremely limited,

which prevents more in-depth discussion of the association. That's my comment. That's the general information, I gathered, from 2(b) group, but please comment if I missed anything.

DR. JIM MCMANAMAN: Dr. Zhang, have you concluded?

DR. LUOPING ZHANG: Yeah, I finished.

DR. JIM MCMANAMAN: Okay. All right. Sorry. Dr. Crump.

DR. KENNY CRUMP: I see, essentially, no evidence of an association between glyphosate exposure and leukemia or between glyphosate exposure and any solid tumor, based on the evidence presented in the epidemiological studies. Even if you forget about the possibility of recall bias, there's still no evidence of an effect.

I also agree with EPA's conclusions of no evidence of association between glyphosate and leukemia. I also agree with EPA's conclusion of no evidence of association between glyphosate and any solid tumor or Hodgkin lymphoma, based on the evidence that we have currently.

However, I would add to say that the data of which this evidence is based is quite sparse

and not definitive. That's all.

DR. JIM MCMANAMAN: Thank you Dr. Crump. Dr. Green.

DR. LAURA GREEN: Remarkably, I have nothing to add.

DR. JIM MCMANAMAN: Thank you, Dr. Green. Dr. Johnson.

DR. ERIC JOHNSON: The same.

DR. JIM MCMANAMAN: Same. Use your microphone.

DR. ERIC JOHNSON: Nothing to add.

DR. JIM MCMANAMAN: Thank you, Dr. Green. Or, Dr. Johnson. Sorry.

Dr. Sheppard. You guys are confusing me.

DR. LIANNE SHEPPARD: Yeah. I do have a couple more things to say than my colleagues. I agree that there are generally few studies looking at the various tumors; and that the studies that are available do not suggest that glyphosate elevates cancer risk. However, I thought the summaries of the relevant studies, Table 3.3, should be expanded to consider topics such as the timing of the cases and the timing of the exposure assessment, both with

respect to the registration of glyphosate and uses patterns that have changed dramatically over time. We also need more details on the exposure assessment.

The dose-response summary should call out that the reference groups were exposed in some cases, particularly in the Agricultural Health Study. Also, whether or not there were any lags considered in the analysis. There are probably a few other things that could also be incorporated in that. I wanted to discuss, and this is a good time to do it, the conclusions that can be drawn from negative epidemiologic study. One of the things that's important is quantifying the risk estimates that are consistent with the effects.

I also, as my colleague Dr. Crump did, relied on my former colleague, Norm Breslow and his Breslow and Day text; this time Volume II on the cohort studies, and extracted some stuff verbatim that I think is important for consideration here.

For studies in which no excess risk is demonstrated, a complimentary approach should be taken. The data should be examined for their adequacy in ruling out a positive effect, and for the level of excess risk which they are compatible; and also, for

whether alternative explanations are possible; i.e., whether biased or confounding may have produced an apparently negative result when a real effect existed.

Now I'm not saying that that's true in this case, I'm just saying that this is an important aspect of interpreting negative results from epidemiologic studies. The evaluation of apparently negative evidence has been the topic of a recent publication. That's a Wald and Dahl paper from 1985. Obviously not recent from our point of view, but recent from when they wrote this textbook.

And some of the points that should receive attention; what are the confidence limits of excess risk? And this is, I think, an important point throughout the epi section, is interpreting the confidence limit, both the upper and the lower end. And particularly the upper end and for null effects tells you something about what elevated risk the data are consistent with, and what can we rule out. And that can be important, to think about what's important. What can we rule out? Is it a risk of 1.5 that we can rule out, and above? Or is it three or is it nine? I mean, those are very different numbers.

How do the dose levels observed in the

present study compare with the levels of which other segments of the population are exposed? Has sufficient time elapsed, between the start of exposure and the end of follow up, for a potential risk to have expressed itself fully? And this is a question, I think, has come up several times in the context of the Agricultural Health study.

In this respect, it is useful to examine the excess risk seen ten years or more after first exposure; for which, the confidence intervals will surely be considerably wider than for the cohort overall. In fact, in the Agricultural Health Study, it's not clear we even have that ability to do that yet.

Is there any reason to suspect that this cohort is substantially lower risk than the general population? Another question that needs to be asked. And what is the consistency with the other studies? I just wanted to get that all in the record.

DR. JIM MCMANAMAN: Thank you, Dr. Sheppard. Dr. Taioli?

DR. EMANUELA TAIOLI: Yes. I basically agree with the other discussants of the group. I wanted to stress that for some cancer types, there is

only one study available. And usually those cancer types are derived from the same main cohort, so there's very little available to be evaluated. I think that needs to be put on the record.

DR. JIM MCMANAMAN: Thank you, Dr. Taioli. Okay. I will open this charge question up to other panel members. Any comments?

All right. I'll go back to the Agency. Do you need further clarification?

DR. MONIQUE PERRON: No, we're good. Thank you.

DR. JIM MCMANAMAN: Okay. Then we'll read the next charge question, 2(c).

DR. ANWAR DUNBAR: Okay. This is 2(c). Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and multiple myeloma. Please comment on the agency's conclusion as described in Section 3.6.

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The discussants on this are Dr. Taioli, who is the lead discussant, doctors Crump, Green, Johnson, Sheppard, and Zhang.

DR. EMANUELA TAIOLI: The first thing is that the Agency reported five studies. I believe

there are four on multiple myeloma, because it seems to me that the Pahwa (2012) -- I don't know how to say it, and Kachuri (2013) are reanalysis of the same dataset, but that's up for discussion.

Three case control studies and one cohort. A total of 67 exposed cases. The reason meta-analysis in 2016, which is Chang and Delzel, which I don't think was available when the report was prepared. The meta-estimate of these four studies is 1.4. The intervals are 1 and 1.9. There is definitely insufficient data produced for assessing an association between multiple myeloma and glyphosate. The only available data is the suggestion of a positive association through the meta-analysis.

DR. JIM MCMANAMAN: Thank you, Dr. Taioli. Dr. Crump.

DR. KENNY CRUMP: Of the five studies, used to evaluate the relationship of exposure of glyphosate and multiple myeloma, four were case-control studies and one was a perspective cohort study. Only the perspective cohort study, control for exposure to other pesticides. It seems to me the subjects in that study were professional pesticide applicators. And so, the exposure should be a little

bit higher, in that study, than other studies of just people. That's a positive for that study.

Also, that study was the only one of the five that use the measure of glyphosate exposure that, at least conceptually, captured the full cumulative exposure, intensity-weighted cumulative exposure; as opposed to some of the other studies used, ever/never or days per year, and other case-control studies.

I think the prospective, the De Roos study, clearly stands out as being superior when the five studies are considered in a group. In particular, it was the only one that was not subject to potential bias recall. This study provides no convincing evidence of an association between glyphosate and multiple myeloma, although there was a nonsignificant suggestion of a dose response.

But, you know, the study involved, at most, 32 multiple myeloma cases -- I shouldn’t say power, because it's already been done. Anyway, the power was probably pretty low for taking any association that may exist. I think that's all.

DR. JIM MCMANAMAN: Thank you, Dr. Crump. Dr. Green.

DR. LAURA GREEN: Yes. For the umpteenth time, I am no epidemiologist, but I do want to comment on this, recognizing that I could be wrong about almost everything I'm about to say; I'm willing to be corrected. Unlike my feelings that are going to be expressed a little bit later, regarding NHL, I am a little troubled by multiple myeloma, and here's why.

I am fond of the De Roos, et al. study. I realize it has limitations, but I think it's powerful, if I can use that word in the nontechnical sense. And if I can direct my fellow panelists' attention to Table 3 in De Roos, et al. (2005). I don’t know which of you all have it. I'll give you a moment in case anyone wants to do it with me. Play along. Raise your hand when you're ready. Okay. Good. All the epidemiologists are with me.

I'm going to embarrass myself here, okay, because almost everything I'm going to say is wrong. But I'm going to give it a shot because they are paying us $50 an hour, so what the hell.

You'll see that multiple myeloma is on the bottom row, right? And you'll see that exposure, which I take with a grain of salt because I don't believe these exposure estimates; but for sake of

discussion, we'll see that exposure is divided into tertiles. And we'll see risk estimates for multiple myeloma, according to tertiles, going from 1.0, to 1.1 to 1.9.

Now, as Kenny has pointed out, the odds ratio, that trend is not a significant trend. The P for the trend is .27. But go along to the next column, the intensity weighted exposure days, and if you're following along with me this time, according to tertiles, it goes from 1.0 to 1.2 to 2.1. And the P for trend is now .17.

Well, I don't know, that's still not all that impressive, but it's getting there. You know, I'm a little impressed by this, and if I can redirect your attention now to the previous table, Table 2, which I don't understand but I'm very intrigued by. If you look at the bottom row there, there's multiple myeloma. And as was mentioned, there are only 32 cases, which by the way, is not so few. Oh, and by the way, I think, gives lie to the notion that all of these are young people, or more precisely, that there's no power in this study. I mean, there are more than 2,000 cases of cancer in this study.

I don't understand why we don't think

this is powerful. But again, I'm using "power" perhaps, in the wrong sense.

Anyway, we have 32 cases of multiple myeloma in this cohort, after X years of follow-up. Or X is, I forget, seven or something. Three-quarters of whom are explosive glyphosate. Now here's what I don't understand, the relative risk, that is not adjusted for anything other than age, is 1.1. Pretty unimpressive.

But when it's adjusted for all kinds of other things, it jumps from 1.1 to 2.6. Now that's like weird to me, okay? Because if you look at all the other adjustments, all the other cancers don't move much when you adjust them. Like, look at lung cancer, okay. The effect estimate adjusted only for ages 1.0 and then when you adjust for everything else, it goes from 1.0 to 0.9. I mean, that feels about right to me. And all the other things don’t move around all that much.

I don't understand, and I would like to understand, why for multiple myeloma and multiple myeloma alone, the effect of adjusting for not only age, but also so-called demographic and lifestyle factors and other pesticides, more than double the

odds ratio. More precisely, doubles the relative risk.

Can someone help me out here?

DR. KENNY CRUMP: Welcome to the wonderful world of statistical modeling. I think it's probably just something you probably cannot -- there is not a particular reason for it, it just happens that way.

DR. LAURA GREEN: Oh, come on. Really?

DR. KENNY CRUMP: My guess.

DR. LAURA GREEN: Really? It just happens?

DR. KENNY CRUMP: Sorry. That's what I think.

DR. LAURA GREEN: Okay. Anyone else?

DR. JIM MCMANAMAN: That was Dr. Crump. Dr. Sheppard.

DR. LIANNE SHEPPARD: Well, there's a couple of reasons. One is the reason I cited earlier, there are 32 cases and 23 parameters in that model. There is also --

DR. LAURA GREEN: Wait, wait. I'm sorry. Does that mean that I should disbelieve it or I should believe it more?

DR. LIANNE SHEPPARD: I'm less likely to believe it.

DR. LAURA GREEN: You think it's just bogus?

DR. LIANNE SHEPPARD: Well, I wouldn't go that far. All epi results should be taken with a grain of salt. I would put more grains of salt in this evaluation than others.

DR. LAURA GREEN: I should not be worried by this, or not impressed by this?

DR. LIANNE SHEPPARD: Well, I think, you know, picking out one cancer with these issues to focus on, and excluding another cancer, which is where we're probably going to go next with non-Hodgkin lymphoma, with sort of the opposite issues, when the issues are the same sort of in both of them, I would just down-weight all of it, is my opinion.

DR. LAURA GREEN: Okay. Well, that's helpful.

DR. LIANNE SHEPPARD: There's a couple of other things. There is a Sorahan paper, as it says in the EPA document -- it's funded by Monsanto -- that did some reanalysis. Because there is a lot of selection that goes on in the two different columns in

this Table 2. There is quite a huge dropout, somewhere it says, but I don't have it in the front of my mind.

DR. LAURA GREEN: Yeah, it's Footnote F.

DR. LIANNE SHEPPARD: Yeah. There's a huge number of people that have been dropped because they couldn't remember which of the 15 pesticides they asked about. They couldn't remember about all of them. And if they couldn't remember one of them, they were booted from the analysis.

DR. LAURA GREEN: I see. It's just a lot of messing around, basically. Or something.

DR. LIANNE SHEPPARD: Well, there's a lot of something.

DR. LAURA GREEN: Okay.

DR. LIANNE SHEPPARD: Yeah. And then the other thing to be aware of on Table 3, you've only got 19 cases. Well, that's partly because of this selection that goes on because of the pesticide adjustment, where you've got 19 cases and still got 15 parameters for pesticide adjustment plus the other adjustments that are made.

DR. LAURA GREEN: But we do have a dose

response --

DR. LIANNE SHEPPARD: Yeah, I understand that. And actually, the highest estimate, the 2.1 estimate for the intensity-weighted, is fairly well reproduced by the sensitivity analysis of Sorahan. That's an interesting point, you know where they look that the selection issues. I haven't drilled down well enough to say, you know, how well all of them are. And, you know, picking one number out of a bunch is fraught with peril. But that one. At least, I think their estimate was like 1.8 or something, so it's not 2.1, but it's not that far off.

But also, yeah, we've only got 19 cases in that analysis. Also, the referent group is exposed, so what does that number mean?

DR. LAURA GREEN: But doesn't that bias the estimate toward the null?

DR. LIANNE SHEPPARD: It should make it lower. You're right. It should make it lower. Because you're comparing towards somebody who is presumably elevated in risk, so the comparison --

DR. LAURA GREEN: Well, potentially elevated. But it seems to me it doesn't bias it --

DR. LIANNE SHEPPARD: Presumably, yeah.

DR. LAURA GREEN: -- away from the null, certainly.

DR. LIANNE SHEPPARD: Well, it's not -- I wouldn't call it biased; I would call it a different comparison than the one people tend to think about when they think about this analysis.

DR. LAURA GREEN: Okay. Let me press you a little bit more. There's another reason I'm interested in this, and a special reason that I'm really eagerly awaiting De Roos, et al. (2017), or whatever.

Multiple myeloma is, of course, a form of lymphoma, but it is a separate thing. And although you can sort of classify it as a lymphoid neoplasm, which it is, it's not NHL, and it's never really been NHL, except in some weird sense.

Okay. That's the first thing. Multiple myeloma is easy to diagnose and distinguish from the other types of B-cell lymphoma, number one.

Number two, multiple myeloma is not a cancer -- correct me if I'm wrong, Dr. Infante, or anyone else. But I believe that multiple myeloma is not a cancer, which we typically see, in elevation, in farmers. That's interesting to me.

We have a cancer here. It's a lymphoma, to be fair, but it's not a sort of farmer's lymphoma. Okay. And it's a weird kind of cancer. All right? Because as you may know, basically nothing causes it. You can smoke until the cows come home, you don't get multiple myeloma at any higher rate than a lifelong non-smoker.

Multiple myeloma is like a really weird disease. And on the one hand, sure, we only have X number of cases, but, you know, it's more than five or ten. I mean, correct me if I'm wrong, but epidemiologists are often making conclusions based on like, ten cases. Right?

I think at a minimum, I mean, obviously, I'm not an epidemiologist, I don't understand the statistics, I don't know why these trends are not statistically significant. They're sort of getting close. I don't know if I should care about that. But I think at a minimum, unlike NHL, about which I am very agnostic, I at least think that multiple myeloma is something that we should, at least, keep a very open mind about. And I'm not completely sure that that's reflected in the document.

I'm not saying this is evidence that

glyphosate is associated with multiple myeloma, I think that is too strong. But it looks a lot more dose-related, to this toxicologist, than anything else. And I just think we need to worry about it, at least a little.

DR. LUOPING ZHANG: Could I just follow -- thank you, Dr. Green. Actually, you raised the question --

DR. JIM MCMANAMAN: Is it related?

DR. LUOPING ZHANG: This is related. Okay. When the data on multiple myeloma looks like -- you know, seems that if we could fairly conclude if there is a non-statistically significant trend there. That's basically your question, right, look at the data.

But I'd like to hear from the biostatistician, what do you think? If you look at the relative risk, it is kind of increased from 1.0 to 1.1 to 1.9 or just from 1.0, 1.2 to 2.1. So even though it is not significant, but my basic question is that, we can say this is a statistically nonsignificant trend? I'm just trying to see if that's basically your question.

DR. LAURA GREEN: That is my question.

DR. LUOPING ZHANG: Yeah. It's basically mine too. It's good. Back to your multiple myeloma question, I think, number one, multiple myeloma is a cancer.

DR. LAURA GREEN: Of course.

DR. LUOPING ZHANG: And I think it's also associated with many different chemical exposures.

DR. LAURA GREEN: No, not in my opinion. No. I was only saying that it is a lymphoid neoplasm to be sure, of course. I mean, it's a cancer of antibody-forming cells.

But my point is, it is so readily distinguishable clinically, and pathologically from other lymphomas, that it is not like NHL. And when we say, in colloquial terms, NHL has increased in farmers a lot, we don't mean multiple myeloma; we mean all those other B-cells and T-cells lymphomas.

DR. LUOPING ZHANG: Separate them. Definitely. Okay.

DR. LAURA GREEN: Okay.

DR. LUOPING ZHANG: Yeah, Okay.

DR. JIM MCMANAMAN: Okay. Actually, before we open it back up to the entire panel, Dr.

Johnson gets a chance at this first. Dr. Green, are you complete with your comments?

DR. LAURA GREEN: Well, for now.

DR. ERIC JOHNSON: I want to correct the fact that multiple myeloma is one of those cancers associated with farming.

DR. LAURA GREEN: Oh, is it?

DR. ERIC JOHNSON: It is. And also, we're seeing it in poultry workers, also in meat workers. It is.

DR. LAURA GREEN: Really? I stand corrected.

DR. ERIC JOHNSON: And another thing we have to take into account is that all these analyses involve multiple comparisons. I mean, we have like, 27 or 30, 50 chemicals which have been analyzed for. And for us to be giving weight to nonsignificant findings is a little bit troubling. Let's look at it and ask this question. If the odds ratio relative risk is 0.5, should I say that then this thing is protective?

DR. LAURA GREEN: Yes.

DR. ERIC JOHNSON: At 0.5?

DR. LAURA GREEN: It depends on the

confidence level.

DR. ERIC JOHNSON: When it's not significant? I mean, we would have a job, really, going through all those odds ratios, which are not seen. It's really problematic. We fuss a lot about a priori when we have statistically significant results, and now we want to include nonsignificant results? It would be a nightmare.

DR. LAURA GREEN: I take your point. And first of all, thank you for correcting me. I did not know that multiple myeloma was increased in farmers. I stand corrected.

I was careful, I think, to say I don't take this as evidence of an association. I take it, instead, as something a little bit less than that, but more than dismissing it. And let me be very precise; if, when we get the paper, next year, whenever De Roos, et al. get around to writing up the data, and let's say instead of 32 cases of multiple myeloma, we have, I don't know, pick a number, 70.

Let's say now we have 70 cases of multiple myeloma. All I'm saying is, would we be surprised, if with 70 cases, all of a sudden, the dose response relationship, which we see preliminarily in

here, is reproduced; and because we have twice as many cases, now it's a statistically significant trend?

I'm only trying to think ahead and say, that I don't think we should be surprised if the follow up -- I mean, if these first seven years are reproduced in the next ten years, or whenever the follow-up is, we're going to have at least twice as many cases. And I don't think any of us should be surprised if this "suggestive" dose-response relationship becomes a significant one. I'm not saying it will. I'm not saying it won't.

I'm just saying that, unlike the solid tumors, which I, for one, am dismissing as being like just never going to happen. I mean, the results from De Roos, et al. are impressive to me. There are a lot of person years here. I know there's only seven years, but there's a lot of person years. And I was taught that that's what matters.

I mean, there are 2,000 cases of cancer in this paper, okay. This is not a nothing paper. This paper has small confidence intervals around colon cancer, around lung cancer. This paper is definitively negative for everything except multiple myeloma. And I just don't know how worried to be

about it. And I don't think we should just say it's a non-positive finding that convinces us. And maybe that's not where were saying. And I'm not saying it's a positive finding, but if I can use a word I like, I think it's equivocal.

DR. JIM MCMANAMAN: All right. Thank you, Dr. Green. Dr. Johnson, do you have anything more to add to the charge question?

DR. ERIC JOHNSON: No.

DR. JIM MCMANAMAN: Okay. We'll move on then. I'm still working through this. Dr. Sheppard is next.

DR. LIANNE SHEPPARD: Thank you. You know, I think this has been a very interesting discussion. And I can understand from your scientific basis, why you are intrigued by this result. I think if we're going to upweight the multiple myeloma result in the Agricultural Health Study, we also have to upweight the non-Hodgkin lymphoma, dose-response result.

We have to be fair. But my feeling is that I would take both of them with a pretty big grain of salt. When the study is done later, it wouldn't be a surprise if we see a dose response in both. That's

my opinion. But, you know, we're not there. We don't know that. I think there are reasons to be somewhat more concerned about the multiple myeloma results, not because of the science; I'm speaking as a statistician, and I appreciate the scientific perspective; I think we get a full point of view when we have both, but because of the small numbers.

That's why I'm more concerned about the multiple myeloma results, even though they popped out as more interesting, than I am about the non-Hodgkin lymphoma, relatively speaking. But frankly, I don't trust either of them. I think it's just too early to say, overall.

I think they're intriguing. If anything, they're something to pay attention to. Do they give us evidence that this isn't? You know, no. Maybe they are suggestive, but the maybe is still in there, I think. The epi evidence is what it is.

I wanted to speak a little bit more with -- well, for me, the fact that this outcome is somewhat connected with non-Hodgkin lymphoma, scientifically, leads me -- that's one reason why I might trust it a little bit more. You actually provided a compelling case why you think of it

differently. But I've heard it stated that it should be in the same basket. And so, from that point of view, I consider it a little bit stronger than I might have otherwise.

There are some things I wanted to say about the Agricultural Health Study. Forgive me, if I'm repeating myself a little bit. I want to make sure it all gets in the record. We've acknowledged that it's licensed pesticide applicators, so it's not only agricultural workers, but specifically, those seeking licenses for, and intending to use pesticides. I wonder how that affects, for instance, organic farmers if they're systematically excluded from the target population. It also misses pesticide users who aren't registered.

For instance, in my own state of Washington, pesticides are allowed to be applied by individuals who aren't registered, as long as it's done under the supervision of registered users. The missing maybe less of a scientific issue, as long as it's representative of the target population. But I would think we're thinking of the target population here as all farmers. And I'm not convinced that it is all farmers. And if anybody has insights into that,

I'd be really open to hearing those. That's one thing that concerns me. And I really wonder who the unexposed members of the Agricultural Health Study are, given they're all licensed applicators of pesticides.

It almost seems like it's an unrepresentative, unexposed population because you have to be licensed in order to get in the study. I just wonder if there's a systematic difference. In fact, the reason that De Roos, et al. didn't use unexposed workers in their dose response analyses, was because they were concerned that the unexposed group, based on the evidence in Table 1, was systematically different from the more highly exposed workers.

They made that choice, intentionally, for scientific reasons that were well grounded in their thinking. But that also, I think, you know, gets back to my generic concern about this study.

The fact that, as my colleague, Dr. Taioli, already talked about the selection issues; the population is potentially over-represented by workers that are less susceptible to carcinogenic effect of pesticide exposures. And workers with short latency wouldn't have been sampled if they had already gotten

their cancer. And we've heard about the age distribution being on average, young. That doesn't mean there aren't older people in the cohort, but the median age is pretty low.

One thing that I alluded to, at some point, and I wanted to make sure is clear, is the data analysis with the exposed/unexposed, which I think also affects the -- not the exposed/unexposed, the dose response analysis.

I think there's a potential for really severe bias because of the fact that the cumulative exposure days and the intensity-weighted exposure is all based on baseline, which happened between 1993 and 1997. And I guess, based on some of the statistics, it seems like most of the recruitment happened closer to '93/'94, is the impression I got from some of what I read.

But there was a huge increase because of the licensing for GMO foods in 1996. And so, all of the people that were in the exposed group, that were in the low group, they're more likely to be misclassified higher, systematically higher. Because as you follow them over time, right? Because okay, in '93, '94, or '97 when their baseline question, when

you're close to it, that's a decent measure.

But as you follow them up to 2001, say, then because of the increased usage of the pesticides, they would've -- presumably, if they were users, they would've increased their use. They might've moved into another category. Whereas, it's unlikely that the higher exposed people would've moved down a category because of the change in the registration and the use of glyphosate.

There's this interplay between the study and the overall trends in society that were going on, that have to be thought about and haven't really been brought out at all. I'm actually pretty worried about all of the dose response analyses in the Agricultural Health Study for that reason. And another reason why I don't put as much credibility on that multiple myeloma, nor the non-Hodgkin lymphoma one either for the same reason. Because the misclassification is almost certainly biased towards too many people in the low exposure group, and as you move forward in time in the study.

And I see my colleague, Ken Portier, thinking about that. I'd love to talk about that more because that's not something that's come out at all.

But I work a lot in air pollution epidemiology and I'll probably say something about that later because there is some big fundamental differences and insights from that. But we think a lot about pollution trends because that's a big deal in air pollution. The Clean Air Act has actually worked really, really well.

DR. LAURA GREEN: Thank you, EPA.

DR. LIANNE SHEPPARD: Yes. Thank you, EPA. And because of that, you know, there's a big trend in society that's relevant to responses; and so, you need to think about that in the context of these studies. And EPA did bring that up in their document, although I think how they brought it up was incorrect. And I'll try to make some more comments about that, but not about this outcome, when I speak again later.

I've already talked a couple of times about the large number of parameters. And I think with multiple myeloma, that's even more of a concern. And in an exposure response analysis, you know, there are 19 cases, and the pesticides alone is 15 parameters. And then just another thing, with respect to the adjusted analyses in Table 2, we don't even know how many cases were lost, which is another thing that's not transparent and not helpful. That's it.

DR. JIM MCMANAMAN: Thank you, Dr. Sheppard. Dr. Zhang.

DR. LUOPING ZHANG: No more additions.

DR. JIM MCMANAMAN: Thank you, Dr. Zhang.

Okay. So now we'll open this up to the entire panel. Dr. Green?

DR. LAURA GREEN: Actually, I want to hear from Dr. Zelterman first.

DR. JIM MCMANAMAN: Okay. Good.

DR. LAURA GREEN: What do you mean good?

DR. DANIEL ZELTERMAN: Very good. I can help you out here. How is that you find three odds ratios increasing? It's not significant. You get a P value of .1 -- I'll tell you where that comes from.

Okay. There are three odds ratios and they come with enormous confidence intervals. For the most part, they're really the same. So now take a sample of size 3 from the same thing --

DR. LAURA GREEN: Wait, wait, wait. Let me follow this.

DR. DANIEL ZELTERMAN: There's three

odds ratio --

DR. LAURA GREEN: Well, they all overlap.

DR. DANIEL ZELTERMAN: Enormous overlap.

DR. LAURA GREEN: Correct. Okay.

DR. DANIEL ZELTERMAN: They're all huge.

DR. LAURA GREEN: But the point estimates double.

DR. DANIEL ZELTERMAN: Even so. Even so. Here goes.

DR. LAURA GREEN: Okay.

DR. DANIEL ZELTERMAN: Here goes. I've got to put on my mathematics hat. I have three numbers that are sampled from the same population; what is the probability they're increasing?

The answer is one of six, which gives you a P --

DR. LAURA GREEN: I'll take your word for it.

DR. DANIEL ZELTERMAN: Well, you have three choices with the first one, the smallest; and you have two choices for the second.

DR. LAURA GREEN: A factorial.

DR. DANIEL ZELTERMAN: Yeah, it's a factorial. And you have two choices, the second and the third one is the biggest. The P value is one over six or .17.

DR. LAURA GREEN: So you're telling me this is exactly what could be consistent with chance?

DR. DANIEL ZELTERMAN: With chance. That's exactly what you saw.

DR. LAURA GREEN: Okay. Here's why I don’t get that.

DR. DANIEL ZELTERMAN: Oh. I thought it was so --

DR. JIM MCMANAMAN: Come on, just embrace the math.

DR. LAURA GREEN: No. Well, okay, I get it. But why does the P value for trend -- can we look together at that table again?

The P value for the trend in the first time when it goes from 1.0 to 1.1 to 1.9 is .2.7; and then it's 1.0 to 1.2 to 2.1 to .17.

DR. DANIEL ZELTERMAN: The second one.

DR. LAURA GREEN: Yeah, but why is it getting so much closer to like, .05, if what you just

said is true?

DR. DANIEL ZELTERMAN: No, no. It's getting closer to one over six. Because the confidence intervals are so big, the intervals are essentially sampling the same thing.

DR. LAURA GREEN: Okay. I hear you. I should not be impressed by this?

DR. DANIEL ZELTERMAN: No, don't be impressed.

DR. LAURA GREEN: Okay. I'm unimpressed. But I still want to say a couple of things. I want to ask a few more questions about De Roos. Am I right or wrong that it's person years at risk that matter as opposed to just years? Which is it?

DR. LIANNE SHEPPARD: Person years.

DR. LAURA GREEN: It's person years.

DR. JIM MCMANAMAN: That was Dr. Sheppard.

DR. LAURA GREEN: Thank you, Professor Sheppard. I should take your course in Epi 101.

Okay. It's person years and we have 57,000 people and 2,000 cancer deaths. Why is this not a useful study? I don't get it.

DR. LIANNE SHEPPARD: Well, we're not talking mostly about the all-cancer analyses. We're talking about the subgroup that's only got 32 cases in it.

DR. LAURA GREEN: Well, for multiple myeloma, yeah; but for NHL, we got 92 cases, 77 percent of whom are exposed to glyphosate.

DR. JIM MCMANAMAN: Wait. The charge question is multiple myelomas.

DR. LAURA GREEN: Oh. I'm sorry. We can stick with multiple myeloma. Okay.

DR. JIM MCMANAMAN: We just had Dr. Zelterman explain this.

DR. LAURA GREEN: Sorry. Go ahead.

DR. EMANUELA TAIOLI: What happens is that if you have a follow-up, that is not enough to have people develop cancer. You have a small number of cancer even if you start with 2 billion people. And then the other issue is, as always in the cohort study, you have a chance to set one-time exposure. Like, it happens with smokers, right.

DR. LAURA GREEN: Right.

DR. EMANUELA TAIOLI: These are the smokers and then they quit smoking, you will never

know. You have classified them as smokers, unless you interview them again, right. That's why, I think, the general comment is that we are missing a lot of pieces in this study. If we had another follow-up, more cases --

DR. LAURA GREEN: Yeah, but you can --

DR. EMANUELA TAIOLI: -- you can say something. But right now it's very difficult because the uncertainty is very large.

DR. LAURA GREEN: But it's not. I mean, look at the confidence levels, they're pretty tight. I mean, I'm sorry, but even for multiple myeloma, for which we only have a lousy 32 cases, okay; the confidence interval about the age-adjusted odds ratio spans not .5 to 2.4. That's tighter than in a lot of the other data that we're like, taking seriously. And I mean, correct me if I'm wrong, but we have a reasonably tight confidence interval.

We have 75 percent of these cases are exposed to glyphosate. We have more glyphosate exposure than probably any other study because these are licensed pesticide applicators. And they were exposed for years before they were interviewed. So like, I don’t get it.

DR. JIM MCMANAMAN: Okay. We have to a) use your microphone, and b) identify yourself. I'm going to get hit in the back of the head by the people doing the transcription.

Okay. That was Dr. Taioli and Dr. Green during that interchange. Dr. Portier.

DR. KENNETH PORTIER: I wanted to get back, just briefly, you raised the issue of it moving from 1.1 to 2.6 after the adjustment.

DR. LAURA GREEN: Yes.

DR. KENNETH PORTIER: When I see something like that happen, I worry that we started out with an unbalanced case control population. That something in the adjustment shifted things. You may have had younger in the case group and older in the -- or the other way around in the case of multiple myeloma. You may have had older in the case group and younger. And the age adjustment is trying to bring them together and the odds ratio shows up.

Anytime it jumps like that, I go back and look at the demographics to find out where was the unbalance. The second thing is, when I think of multiple myeloma, I don't think of a leukemia. I think of a myeloma, which is a myelin cancer, right.

That's not a leukemia. That's a nerve sheath issue, right.

DR. LAURA GREEN: No, it's a B-cell cancer. It's an antibody-forming cancer. You're thinking of something else. Multiple myeloma is a cancer of antibody --

DR. JIM MCMANAMAN: It's the myeloid cells.

DR. KENNETH PORTIER: The myelin cells. Not myelin, myeloid. Okay. But isn't it also -- I thought multiple myeloma was more of a cancer of aged.

DR. JIM MCMANAMAN: It is.

DR. KENNY CRUMP: It particularly shows up much later in life.

DR. LAURA GREEN: Um, no.

DR. JIM MCMANAMAN: Right. That's true.

DR. LAURA GREEN: Actually, that's not true.

DR. JIM MCMANAMAN: It is true.

DR. LAURA GREEN: No, it isn't.

DR. KENNETH PORTIER: I'm pretty sure it is.

DR. LAURA GREEN: Well, we could look

it up after a break.

DR. JIM MCMANAMAN: Okay.

DR. KENNETH PORTIER: That's why I picked on age. Because I suspect you may have seen the cases where actually quite older.

DR. LAURA GREEN: No, no, no. You're misreading the table, if may say. If you look at Table 2 --

DR. KENNY CRUMP: I don't have Table 2 in front of me. I'm sorry.

DR. LAURA GREEN: Oh, I'm sorry. Okay. Well, the odds ratio of 1.1 is already age adjusted. Okay. It's already age adjusted.

DR. LIANNE SHEPPARD: I don't think it's a single parameter for age, which suggests it's in there linearly as one, but it's in there, age adjusted, yeah.

DR. JIM MCMANAMAN: That was Dr. Sheppard.

DR. KENNETH PORTIER: It is already age-adjusted.

DR. JIM MCMANAMAN: And Dr. Portier and Dr. Green.

DR. KENNETH PORTIER: Yeah, I

apologize.

DR. LAURA GREEN: And I also want to say, this is not a young cohort. I don't know why we keep saying this. 825 of these guys have prostate cancer. They are not young men. I mean, I'm sorry, it's just wrong.

DR. JIM MCMANAMAN: Okay. Let's go back to the charge question and limit our discussion, at this point, to the charge question. I think we've discussed the myeloma, but if we're veering off into prostate cancer, then we have to --

DR. LAURA GREEN: I'm sorry.

DR. JIM MCMANAMAN: So Dr. Johnson, do you have --

DR. ERIC JOHNSON: What I was going to say, because it had come up earlier in one of the presentations, this issue about age and risk; whether you should not observe risk because the cohort is young. That is not true.

You can have a young cohort and still observe a high relative risk in that young cohort. I mean, we've done studies in which we were looking at benzene exposure in supermarket workers. And we had lung cancer occurring in food workers, 100 persons of

the lung cancers were below 50. And the relative risk was like 54 for that age group.

If you look at the entire population, it would be like 1.1 something. But when you look at particular age group, the relative risk was like 54; even though it was less than 5 percent of lung cancers which were below age 50. You can still get high relative risk, even in the young population.

DR. JIM MCMANAMAN: But these are age matched, or control for age, so I think that that takes age out of the equation, as I understand it.

DR. LAURA GREEN: Yeah. I would add that as I said before, for lymphomas, the strongest risk factor known to man, besides organ transplantation, is HIV/AIDS. And those guys were 20-year-old men getting lymphoma at age 30.

DR. JIM MCMANAMAN: Okay. Dr. Zhang. Are we on myeloma?

DR. LUOPING ZHANG: Yes.

DR. JIM MCMANAMAN: Okay.

DR. LUOPING ZHANG: I forgot to mention one thing. I think from the table, the multiple myeloma, only they mentioned five studies and, Dr. Taioli, you're saying it's only four. My question is,

I think, maybe the panel need to also think, did we miss any other multiple myeloma studies in the low score?

I don't know. I mean, this is on my to do list that I should check, but I haven't got a chance to check. I just wanted to put it in just in case a panel member --

DR. JIM MCMANAMAN: Okay. We can read that issue into the docket and we can say that we'll look at that.

All right. I think we've discussed this quite a bit, and I don't know that there's a complete consensus among the panel members. But let me go to the Agency and ask if clarification is needed?

DR. MONIQUE PERRON: Not at this time. No. Thank you.

DR. JIM MCMANAMAN: Okay. Thank you. All right. Then we'll move on to Charge Question 2(d).

DR. LAURA GREEN: Actually, I don't mean to monopolize, but actually, I want to amend my statements because I've learned something. Can I do that, so that we can get a little bit more of a

consensus on the myeloma question?

DR. JIM MCMANAMAN: I don't think we need to.

DR. LAURA GREEN: Okay.

DR. JIM MCMANAMAN: I think they picked it up. Okay. Charge 2(d).

DR. ANWAR DUNBAR: Okay. This is Charge Question 2(d).

Please comment on the strengths and limitations of the available studies to inform the association between glyphosate and non-Hodgkin lymphoma (NHL). Please comment on the agency's conclusion as described in section 3.6

DR. JIM MCMANAMAN: Okay. Before I go to the next charge question, that was Dr. Green, for the transcribers. We have to remember to use our names. And that was Dr. Perron who addressed the issue about Charge Question 2(c). We're now back on track.

Okay. The lead discussant on this is Dr. Zhang. The associate discussants are doctors Crump, Green, Johnson, Sheppard, and Taioli.

Dr. Zhang.

DR. LUOPING ZHANG: Dr. Chair, if I

may, I would like to make a suggestion for Charge Question No. 2(d). If we could somehow change our discussion; because I think everybody here already know that Charge Question 2(d) is very important, regarding the association of glyphosate with non-Hodgkin lymphoma. I'd like to just make a suggestion and see if you agree.

I asked the group previously, trying to make the team -- and collecting everybody's response to the charge question 2(d); so here, what I did was reframed the question, each question, before I'm trying to do the whole thing or each one. I think the way so far, on the one hand okay, I'm leading now next.

I want to, for 2(d), at lease just for this question, I want to say here is the framed question and there is, you know, some suggestion. Could we have the member answer that first, then open to table, and then we move to the next. Otherwise, it is going to be -- because I have quite a few questions.

I just want to make it clear and it's easier to go through this discussion. Is that okay?

DR. JIM MCMANAMAN: Sure.

DR. LUOPING ZHANG: Because you also encouraged sort of discussion among the members.

DR. KENNETH PORTIER: We can take a vote.

DR. LUOPING ZHANG: Because we never got a chance, as a group, to really discuss. I think this is a good time to do it.

DR. JIM MCMANAMAN: I think that some free form is okay. But we'll try to keep it under control.

DR. LUOPING ZHANG: Okay. For 2(d); after collecting all the comments and the response from this group, including the emails and also some discussions -- just our discussion -- I have these few questions framed.

First are all studies, including original or meta-analysis selected, if it's acceptable. Here are the six original studies, we know, which is six, and the three recent meta-analysis. Right? I just want to make sure this question, as a panel, how we want to comment.

The six original, of course, the one cohort and the five case-control studies, that's what's included in the whole EPA analysis, and the

three recent meta-analysis from 2014, 2015, and 2016.

My question here, it's just I try to stimulate the discussion because this has already come here a few times. For example, Cocco (2013), you know, which is in the low category, but you also notice the two human studies in the low category, which include Cocco (2013) and the Koureas (2014), sort of in the low, but it does have some special quality, you mentioned from your presentation.

Of course, Koureas (2014) is not related with non-Hodgkin lymphoma, so we don't have to talk about it. Because that's only related to the prostate cancer, so that's out. But then Cocco (2013). It raises the question here for panel members to discuss. Should we also include that data from Cocco (2013)?

I forgot. Today, probably commented from somebody. I thought maybe Dr. Infante -- did you include in that in your analysis? That's one.

Second is also maybe from Dr. Infante's presentation, I noticed the Hohenadel (2011) somehow replaced the McDuffie (2001). That's basically how the question comes about, what studies we should include in this non-Hodgkin lymphoma study.

Here is Question number one. Let me stop here. Let's get this sorted out and then I'll move to the second question. Is that okay? Yeah.

Any comments on --

DR. JIM MCMANAMAN: Are we opening up this question about which study should be included to the entire group? I'm okay with that.

Dr. Green.

DR. LAURA GREEN: Yeah. I think the most complete list, unless I'm wrong -- correct me if I'm wrong -- is the one that Acquavella put together in their (2016) paper, Table 1. I don't know which one of you has that in front of you that can bring it up.

DR. LUOPING ZHANG: Which study?

DR. LAURA GREEN: I'm sorry. Okay. It's Acquavella, et al. (2016). It's one of those clinical reviews and toxicology papers that came out, you know, a couple of months ago. And if you look at Acquavella, et al. Table 1, this is their listing of "Relevant studies for glyphosate review: non-Hodgkin's lymphoma." They call it not Hodgkin's, which I don't like, but anyway, "non-Hodgkin's lymphoma and multiple myeloma." And they have a list of like eight or nine

studies, some of which are overlapping, that they consider to be relevant for either NHL, as a whole, or as Dr. Infante pointed out, Cocco et al. just reports on B-cell lymphoma.

Although, I think, they only report on B-cell lymphoma because that's was the only one that they found to be significant, or maybe that was, you know, because they had so few cases. I actually think that Cocco et al. has information on all non-Hodgkin lymphoma, T-cell as well as B-cell. But anyway, I would propose that we use everything that's in Table 1, unless someone feel strongly otherwise.

DR. LUOPING ZHANG: Can you give the number?

DR. LAURA GREEN: Yes. Of course.

DR. LUOPING ZHANG: Because otherwise, it's very hard to find.

DR. LAURA GREEN: Yes, I'm sorry. This is Acquavella et al. (2016) Table 1. There's like, nine rows or so.

DR. LUOPING ZHANG: No, the file name. File name. EPA-HQ --

DR. LAURA GREEN: Well, the -- oh, I can't give you the EPA name, but I'll give you the

author. It's De Roos et al. (2003). I don't know how else to do it. It's De Roos et al. (2003); Hardell et al. (2002); McDuffie et al. (2001); De Roos et al (2005) of course. Eriksson et al. (2008); Orsi et al. (2009); Hohenadel, I guess that's the way it's said, which is, as you know, an update of McDuffie. And then Cocco et al. (2013.).

DR. EMANUELA TAIOLI: Sorry. It's critical review and toxicology, the journal?

DR. LAURA GREEN: Yeah.

DR. EMANUELA TAIOLI: Okay.

DR. LAURA GREEN: Their Table 1. I think that's the most complete listing I've seen. EPA excluded Cocco et al. (201) because it was too few cases. They did not use Hohenadel et al., and instead used McDuffie et al. because as I said, I think it's because there were a lot more cases in McDuffie et al.

DR. LUOPING ZHANG: Right. Could we ask them questions?

DR. JIM MCMANAMAN: No.

DR. LUOPING ZHANG: No. Okay. No means no.

DR. JIM MCMANAMAN: It's a discussion amongst ourselves. And if there are limitations that

we need to improve on then we'll do that.

DR. LUOPING ZHANG: Okay.

DR. KENNETH PORTIER: So Orsi is included in Hodgkin lymphoma, right?

DR. LAURA GREEN: Well, no. Orsi --

DR. KENNETH PORTIER: If you look in their Table 3.4 it's --

DR. LAURA GREEN: Yeah, but Orsi also has information on both NHL and multiple myeloma.

DR. KENNETH PORTIER: So you're saying they excluded for NHL, but included it for HL?

DR. LAURA GREEN: Why they? EPA they?

DR. KENNETH PORTIER: EPA. Yeah. Table 3.4.

DR. LAURA GREEN: No, they looked at it.

DR. JIM MCMANAMAN: So can we bring this back to the strengths? I mean, what I'm getting at is that there is -- if one of the limitations of the study, or a strength of the study, is the questionability of which studies to include, then I think that we can say that. And we can comment about that in our written comments to say that you agree or disagree with what was included. Okay.

But I don't know that we need to try to resurrect the dead here in terms of which ones are going to be included and which ones are not going to be included. At this point, or we're going to be here for the rest of the day.

Let's stick to the question about the strengths and the limitations of the available studies. Okay.

DR. KENNETH PORTIER: The point I was making is that Orsi is, in Table 3.3, considered a moderate-value study. I noticed that they did use it for Hodgkin lymphoma; they didn't use it for non-Hodgkin lymphoma. I didn't see a discussion as to why it wasn't used in non-Hodgkin lymphoma. Is that in the document?

I mean, I think that's one of the things I'm trying to get at.

DR. JIM MCMANAMAN: Yes. Exactly.

DR. KENNETH PORTIER: If there isn't a justification for why it wasn't used, and it may be that -- I didn't read the article, I'm sorry. I didn't read everything.

UNIDENTIFIED FEMALE: No. It's not here.

I'm looking at the epidemiologist to say was there a justification for not using Orsi in non-Hodgkin lymphoma?

DR. LIANNE SHEPPARD: No. Orsi was used for non-Hodgkin lymphoma.

DR. JIM MCMANAMAN: Dr. Sheppard.

DR. LIANNE SHEPPARD: On page 64 of the of the issue paper in the figure, with all the effect estimates, it's the bottom one.

DR. KENNETH PORTIER: Okay. Well, then it's missing from Table 3.4.

DR. KENNY CRUMP: It's on the bottom of page 62.

DR. LAURA GREEN: Yeah, it's a completely null study. Maybe that's why --

DR. KENNETH PORTIER: I would suggest you don’t split tables like that. I'm sorry. I'm sorry.

DR. LAURA GREEN: Ken, it's a completely null study, and maybe that's why you don’t remember it.

DR. JIM MCMANAMAN: Okay. Dr. Green. Sorry.

DR. LAURA GREEN: Sorry.

DR. JIM MCMANAMAN: In regard to the number of relevant studies that were included, is there still disagreement amongst the panel members about if the appropriate studies have been included or not? And if so, if there is disagreement, then let's state the disagreement at this point. And if not, then we can move on.

DR. LUOPING ZHANG: Can I say one thing? It looks like maybe a panel member has different opinions about what study should be included. But we could maybe try to look into details, like what Dr. Green mentioned, the paper. Because we haven't even looked at the papers so we don't really know now if we should include it or not.

DR. JIM MCMANAMAN: Okay. That was Dr. Zhang. Dr. Taioli.

DR. EMANUELA TAIOLI: From a quick look, at least, since by now I know them by memory, they look like the same papers.

DR. JIM MCMANAMAN: Okay. It looks like we're including the same papers. Okay. We've taken care of that question.

DR. LIANNE SHEPPARD: The only question is, I think, is the Cocco paper, and whether it should

be included as well. I'm not sure if that was -- I haven't managed to download the Acquavella paper. But it clearly had low weight in the meta-analysis. And EPA made statements that I haven't independently looked at to form my own opinion yet, about whether it's of sufficient quality for this purpose. But I would say there's reason to consider it and it will get low weight, but there is reason to consider it.

DR. JIM MCMANAMAN: Okay. Well, it looks like there is agreement then, about the papers that were included.

Okay. Dr. Zhang.

DR. LUOPING ZHANG: Okay. My second question for the panel. Among the six studies selected, are the rating of quality scores acceptable or not?

So here we have De Roos (2005), the only cohort studies scored high. But as you heard from the discussion from the members, fellow members, the problem was this one control problem, latency issue and other limitations. So again, just to stimulate a discussion, so we should consider? That is one of the high. And Eriksson (2008) is a case-control study, also scored high. I don't know if

there is any question, but I just put it on here. Kachuri (2013) scored high, but it is non-Hodgkin lymphoma, so we don't have to discuss.

And back to what Dr. Sheppard just mentioned, Cocco (2013), even though scored low -- so basically, what I'm saying is, if some studies, specific studies interested, you know, focused on the non-Hodgkin lymphoma, should we consider or do we have a lead to think to reclassify?

DR. JIM MCMANAMAN: We're asking about the reordering or whether the rank order of these is appropriate. Okay. Since we're opening it up, I'm hoping that each discussant is going to go through this. We're going to open it up then to the entire panel.

Dr. Sheppard has her hand up first.

DR. LIANNE SHEPPARD: Well, I would definitely -- if we're going to keep the low, moderate, high -- for this purpose I would lower the rating of the Agricultural Health Study to moderate, for the reasons that, I think, have become clear from my numerous comments.

DR. JIM MCMANAMAN: Okay. Can I have a discussion about that? Is there agreement with Dr.

Sheppard's suggestion?

DR. LUOPING ZHANG: Whether you want to --

DR. JIM MCMANAMAN: To lower it to moderate?

DR. LUOPING ZHANG: Lower to moderate.

DR. EMANUELA TAIOLI: I'm one of the discussants, so you need to know my score, right? It's not about the discussion. All right.

DR. JIM MCMANAMAN: Yes.

DR. EMANUELA TAIOLI: I would lower it to moderate.

DR. LAURA GREEN: I strongly disagree. This is Dr. Green.

DR. JIM MCMANAMAN: Okay.

DR. LAURA GREEN: But again, I'm only a toxicologist. But as a toxicologist, let me reiterate why I strongly disagree: a) this is the only prospective study. It's the only one. B) this is not a young cohort. For the umpteenth time, they all got prostate cancer. C or B or three or whatever I'm up to, there are lot of cases of NHL, and three-quarters are exposed to glyphosate; d) seven years later is the follow-up, and some of them were exposed for 10 or 15

years before then.

While Dr. Sheppard is completely correct, that everyone's usage could've changed over seven years, if you think about it, a guy who started using glyphosate in 1983, and he's interviewed and rolled in 1993, he is cancer free and let's say he's 50 years old now. And seven years later, he's 57 and he's got NHL. Did he really change his use of glyphosate that much over those seven years? I don't know. You don't know. But, you know, you do what you can with what you have.

It seems to me that if person years is the right denominator, we have 2,000 incident cases of cancer, three quarters of whom are exposed to glyphosate. And we know about their glyphosate exposure seven years prior to the follow-up. So again, it hasn't been that long since they were interviewed.

We got a lot of cases, and we have, speaking as a toxicologist, the biggest potential for exposure because these are registered, licensed pesticide applicators, whose job involve spreading this crap around. Sorry, I said it again. Stuff around.

I don't see how this can be anything other than a really informative study. It's only seven years' follow-up. I'll give you that. But if a guy has been using glyphosate for 12 years and then seven years later he gets cancer, I think that's informative.

DR. JIM MCMANAMAN: Yes, Dr. Taioli.

DR. EMANUELA TAIOLI: The age of the cohort, 25 percent are above the age of 60. I now think that we can even read your statement the other way around. Did these people have cancer at much younger ages than expected, because they are all below 60?

DR. LAURA GREEN: They're all age-adjusted rates. You cannot say that. They're age-adjusted.

DR. EMANUELA TAIOLI: No, no. Hold on. Not the incidence. But the number of cases occurred at ages that are not the average age that is reported in the registry. I'm not sure that --

DR. LAURA GREEN: How do you know that?

DR. EMANUELA TAIOLI: No, I don't know. I'm saying I could read your statement the other way and we don't really know what happened. Because

unfortunately, it is not in this paper that we have in front of us now. But I'm not sure that that statement is in support of the importance of the paper.

DR. LAURA GREEN: But I still don't get why it matters. If it's an age-adjusted rate, and we're looking at the effective glyphosate exposure, and it's age-adjusted, I don't see why it matters whether the guy got it at 57 or 67. What am I missing?

DR. EMANUELA TAIOLI: So I'm not talking about the non-Hodgkin lymphoma. You were saying that there are a lot of cases of cancer in this cohort.

DR. LAURA GREEN: Two thousand.

DR. EMANUELA TAIOLI: Right. For example, there are a lot of prostate cancer. Well, we don't know if there are a lot because 54,000 x 7, I don't know if 2,000 cases are a lot or not.

DR. LAURA GREEN: There are over 800 guys with prostate cancer. There can't be 30-year-olds.

DR. JIM MCMANAMAN: I think we're talking too much about the details. That was Dr. Green and Dr. Taioli.

DR. EMANUELA TAIOLI: Yeah, we don't know.

DR. JIM MCMANAMAN: So let's get back to the charge question. And the question was, as I understand the question, this part is, whether the rank order of these studies, whether it's correct.

And it sounds like there may be some disagreement about that. And I don't know the degree of the disagreement, but can we say that there is -- I'll come to you in just a minute, Dr. Jett.

Can we come to some consensus that there is a disagreement about the degree of the rank order?

DR. LAURA GREEN: Well, I don't see why it matters because I agree with Professor Sheppard, that we ought to throw all the medium and high studies together anyway. I think what we're having is an academic argument, which we should probably stop having. I mean, all the studies have informative value, consistent with their person years at risk and their confidence intervals.

DR. JIM MCMANAMAN: Dr. Jett. That was Dr. Green.

DR. DAVID JETT: So I appreciate how

you framed this discussion. But where does it, in the question, say we have to comment on this rank?

All it says is strengths and limitations.

DR. JIM MCMANAMAN: I think what Dr. Zhang was trying to get at was that a limitation of this study was the organization of the rank.

DR. LUOPING ZHANG: Yes.

DR. JIM MCMANAMAN: And she was asking for our comments on that.

DR. LUOPING ZHANG: Because we have to discuss this and then we can really give the strengths or --

DR. JIM MCMANAMAN: I think that --

DR. LUOPING ZHANG: But could I just make one last comment?

DR. JIM MCMANAMAN: Sure.

DR. LUOPING ZHANG: Actually, Dr. Portier, actually, you mentioned -- I actually think, yes, now seems a way, as a panel, we don't really agree with the score of high, medium or low. But I think the key thing is we want to understand each study, the quality of each study. Strength and weakness, but not because we want to eliminate this

study. If we don't have that categorization to high, medium, and low, then we don't have this wall or the fighting, basically.

DR. LAURA GREEN: Well, you remember Dr. Lowit told us that they were told to rank them. Mindful of the fact that they were told to bin things into high, medium and low --

DR. JIM MCMANAMAN: The question, Dr. Green, is --

DR. LAURA GREEN: Sorry.

DR. JIM MCMANAMAN: -- are the available studies to inform the association between glyphosate and NHL. We want to talk about the limitations. And if ranking is a limitation, then we should say that ranking is a limitation, whether Dr. Lowit was told to do it or not. As a panel, we feel that it's a limitation.

DR. LAURA GREEN: Yeah, that's a good point.

DR. DAVID JETT: You're talking about the ranking itself?

DR. JIM MCMANAMAN: No. We're not commenting about the ranking itself, but whether --

DR. DAVID JETT: (Off mic).

DR. JIM MCMANAMAN: Right.

Dr. Johnson.

DR. ERIC JOHNSON: It will help because I think the most important cite is the non-Hodgkin lymphoma. I think all the other cites --

DR. JIM MCMANAMAN: Speak into the mic.

DR. ERIC JOHNSON: Sorry. The most important cite is the non-Hodgkin lymphoma. And all the other cites, I think, there is fairly good consensus among panel members.

I would suggest that if you could put that data up, the summary of the studies that count. Because I have different studies for non-Hodgkin lymphoma. I have not strong -- I have --

DR. JIM MCMANAMAN: But Dr. Johnson, I'm not sure that we really need to discuss the individual studies or to decide on whether we agree with the rankings or not. What we need to do is we need to give the agency a clear statement, an actionable statement about what we think about the limitations of using the ranking, if that's the question.

DR. ANNA LOWIT: So this is Anna Lowit. I think we're not answering our question.

DR. JIM MCMANAMAN: I don't think we are either. I'm trying to get to it, though.

DR. ANNA LOWIT: Can we get back to our question? Let me maybe restate the question. So, 2(a) of this section was about our reviews, and the quality of our assessment, and we're past that. If you have issues with our ranking, I would request that those responses go in 2(a).

2(d) is about your view of the strengths and the limitations of the studies, of the De Roos, of the Orsi, whatever the rest of them are, Eriksson. There's been a lot of talk about De Roos, but we haven't really talked at all about Eriksson and McDuffie and Orsi.

DR. JIM MCMANAMAN: Okay.

DR. LUOPING ZHANG: Yeah, we're getting there.

DR. ERIC JOHNSON: Suggestion.

DR. JIM MCMANAMAN: So wait a minute. Let's try to get this back on track again. What I think we're going to do is go back and ask each panel member to address the questions that Dr. Lowit just put on the record in terms of what is the intent of Question 2(d).

So rather than open it up to a free-for-all kind of discussion, which I think has been useful, but it may be getting a little off track, let's go back and we'll just start with Dr. Zhang and ask for your comments about that specific question.

DR. LUOPING ZHANG: Okay. Actually, that's my next question. You know, we look at the oldest studies the report included, and you know, we know you include there is no association of the glyphosate with non-Hodgkin lymphoma. That's basically your conclusion.

When we look at each study -- okay, for example, you just mentioned Eriksson (2008) and McDuffie (2001). Just using those two as an example, these two studies are also the studies, or maybe the only two studies, that show or identify the dose responses. So here is what I think to look at the dose response in the human studies, it's pretty rare. We actually see that dose response.

Actually, to me, is striking. So basically, that's why I'm also open to my fellow members and want to invite you guys to discuss the dose response, what do you think about that?

Also, positive associations, you know,

from let's say De Roos (2003), easily made it the overall odds ratio 2.1, which is statistically significant. I'm just sort of trying to balance. I'm not expressing one way or another if we should accept, but this is the data.

So as a panel, here, I mean, among the six studies, some ratio or risk is negative, but there are some positives. And how should we manage that, adjust? That's basically what I have to say. So basically, I'm focusing on the dose response or how should we deal with the positive association and positive risk, the odds ratio?

DR. JIM MCMANAMAN: Thank you, Dr. Zhang. Dr. Crump.

DR. KENNY CRUMP: I think I know where we are here. I'm not absolutely sure. We're evaluating the strengths and limitations of the studies; is that what we're doing?

DR. LAURA GREEN: Correct.

DR. KENNY CRUMP: Well, I think I agree with the limitations of the De Roos (2005), that have been pointed out. I still have an opinion that is the best study on non-Hodgkin, NHL. But it has a reasonable number of cases, 93. It's not real small.

I think the point about the cancer latency is maybe a little bit misleading. I think when these people were enrolled in the study, they had already been exposed for a number of years; I think maybe 12 or so. I'm not sure if that's right, I think that's right.

I think the latency is not all that short, it seems to me. I would rate it higher, I think, than any of the studies. Based on what I showed you this morning, I would not rate Eriksson as high because I think there is pretty convincing evidence, to me, that it's probably subject to recall bias.

Almost all of the ORs in that study were positive. In their analysis, they took out the exposed people -- exposed to any pesticide not just glyphosate, from the exposures to the unexposed. It took out people who were exposed to any pesticides from the unexposed group; and that will exasperate any effect of recall bias.

I would rate the De Roos prospective study above any of the case-control studies for that reason, for similar reasons, then the other studies.

DR. JIM MCMANAMAN: Dr. Green.

DR. LAURA GREEN: Thank you. The most informative page of the EPA document is page 64. I don't know how many of you have the EPA draft in front of you, but it's their Figure 3.2, which is called the Forest Plot by the way. Why call it the Forest Plot? Can someone teach me this? It doesn't look like a Forest.

I don't know. Whatever. Anyway. Is it named after someone named Forest? I don't know. Anyway.

DR. LUOPING ZHANG: It is.

DR. LAURA GREEN: Yeah, it is? Well, that's cool. Like a Western Plot is actually named after someone who's Western. Okay. That's cool.

DR. JIM MCMANAMAN: That's actually a Southern Plot.

DR. LAURA GREEN: Southern. Oh, right. And then western is a pun. Right. Thank you. See, I've been out of the lab too long, Dr. Chairman, or I would've remembered that.

Okay. Page 64 of the EPA draft document is their Figure 3.2, which is called -- we're now going to call it a Zhang Plot. And like, it's so informative. Frankly, I don't think we need to talk

about anything other than this picture. Like, if I'm looking at this picture, right, okay, we got six studies, right. The famous six. We can throw Cocco on here as well, if you wanted, all right, so we can make our own Figure 3.2(a).

DR. LUOPING ZHANG: You're talking about Table 3.4?

DR. LAURA GREEN: No. I'm talking about Figure 3.2, on page 64, of the EPA draft document. Everyone with me there?

Okay. We got six studies, De Roos et al. (2003) through Orsi et al. (2009), inclusive. I would argue we should put Cocco on there also, but whatever. And we got six point estimates with confidence intervals around them. And correct me if I'm wrong, but every single one of those confidence intervals overlap 1.0, meaning a null association. Now, to Dr. Sheppard's point, all of these are also consistent with positive associations that range from 1.7 to 6.2. And they're also consistent with protective effects that range from .5 to .9.

In other words, any way you slice it, it looks pretty much like a null result. And I don't care whether De Roos et al. (2005) is in there or out,

it doesn't really make much difference. And I don't know how to meta-analyze the way Dr. Infante or others do; but I know how to look at a picture. And unless I'm looking at this picture wrong, there ain't nothing here.

DR. JIM MCMANAMAN: Do you have an opinion about the strengths or the weaknesses or limitations of these studies?

DR. LAURA GREEN: Well, again, being just a simple-minded toxicologist, I think the strengths are reflected by the size of the confidence intervals, number one. To a first approximation, the McDuffie et al. result looks pretty precise. It's confidence interval is the narrowest one we got here. It goes from a protective effect, i.e. not .83 to a risk, namely 1.74, and the point estimate is 1.2.

On its face, McDuffie et al. is strong study. The strongest we have.

However, I'm mindful of what Professor Crump -- Dr. Crump -- semi-retired Dr. Crump, who has done all this work in his semi-retirement. I'm mindful of the fact that McDuffie et al. is one of the three case control studies, or four for that matter, case control studies, which for reasons completely

opaque to me, decided to define unexposed people as people unexposed not only to glyphosate, but to every other farm chemical, which is completely meshuggana. I mean, completely and totally meshuggana. Because what you're doing -- I mean, to a lab scientist, you only change one variable at a time. Okay.

What these epidemiologists are doing is changing two variables at a time. They're changing both the glyphosate variable, and they're changing the farming variable. To my simple-minded view, I don't see how you could disaggregate the effects of farming from the effects of glyphosate. I mean, it's just weird. Okay.

McDuffie et al. is now weak in my mind, because although the confidence interval is nice and tight and I like that, and it doesn't look like the tarp, you know, you put over bases at Fenwick Park, or whatever. It looks like a really precise estimate, but I feel it's a biased estimate, based on what Dr. Crump has found and what I have separately found. And let me say there are two issues. Dr. Crump is focusing on recall bias. I am focusing on something very different from recall bias. I am focusing on the fact that farmers often have lymphoma at excess rates

for reasons that probably have nothing to do with chemicals. Let me say it in a slightly different way.

If the effects that we were seeing were not for NHL, but let's say colon cancer, okay? If we saw a colon cancer risk estimate of, let's take the biggest one here, 1.85 -- it happens to have the widest confidence interval, right.

But if I saw a colon cancer risk estimate of 1.9, which isn't quite statistically significant because blah, blah, blah, I would stand up and notice. Why? Because think about it; we've already learned that glyphosate is not well absorbed, so that means it's in the gut. Okay. We know that gut flora can metabolize glyphosate, admittedly, at a rather low rate. Not to be too gross here, but imagine that you're a constipated person with a lot of glyphosate exposure and the glyphosate is sitting around in your gut for three or four days, and your gut flora are metabolizing it, okay.

That starts getting interesting to a toxicologist. And you start saying, huh, well, wouldn't that be interesting if colon cancer were elevated in some of these studies. You might start, you know, kind of having a gestalt, right.

Oh, and by the way, I don't think that, since colon cancer is not known to be elevated in farmers, we don't have the farming confounding problem. I have no idea what the recall bias is like. If you're a person who has colon cancer, are you more likely to recall that you were exposed to pesticides? I don't know. And I don't think Kenny knows either. Maybe you do.

DR. KENNY CRUMP: On a population basis I think you are.

DR. LAURA GREEN: You are. Okay.

DR. JIM MCMANAMAN: Okay.

DR. LAURA GREEN: Kenny thinks recall bias would play a part in any event. All I'm trying to say, I think, is for a whole variety of reasons, all you have to do in my mind, for the strength of the studies, is two things; you look at the width of the confidence interval, right? Because the more narrow it is, the more precise it is and therefore, to a first approximation, the more informative the study is. For example, Hardell et al. has got such a wide confidence interval, it can't possibly be an informative study, right?

DR. JIM MCMANAMAN: So you will include

in your write-up what are the various strengths and weakness of each study?

DR. LAURA GREEN: I think it's pretty simple. I mean, I'd hate to like, reduce this to such simple terms, but it's the width of the confidence interval and then it's whether you have residual, confounding or bias. I mean, right?

DR. JIM MCMANAMAN: Okay. Dr. Johnson.

DR. ERIC JOHNSON: What are we supposed to do because I'm really not quite sure.

DR. JIM MCMANAMAN: You're supposed to comment about the strengths and limitations of each of the studies related to non-Hodgkin lymphoma.

DR. ERIC JOHNSON: This is one area that I felt that we should deliberate on more intensely as a group, and unfortunately, we haven't done that. I think we really need to because that's the most important part of the entire -- yes, we all generally agree.

DR. JIM MCMANAMAN: Do you have a view about the various strengths and weaknesses about these studies?

DR. LAURA GREEN: So we'll talk about them.

DR. ERIC JOHNSON: For one thing, this is the only group in which many of the studies have elevated risk of non-Hodgkin lymphoma. And one of them, at least, was significant, clearly statistically significant.

DR. JIM MCMANAMAN: But the question is about the role of glyphosate in non-Hodgkin lymphoma, the strengths and weaknesses.

DR. ERIC JOHNSON: Right. That's what I'm saying. The risk for glyphosate were elevated in several of these studies. In one of them, it was statistically significant. I'm not sure whether I may have the wrong studies. That's why I was asking for somebody to put the studies up there because the ones I got from the table, it seems, I have -- I didn’t have McDuffie, for example.

DR. JIM MCMANAMAN: You think that there are some limitations?

DR. LAURA GREEN: No. He's saying we ought to talk about it.

DR. ERIC JOHNSON: I think -- yes.

DR. JIM MCMANAMAN: Well, we're talking about it. I want to know do you have a view about the strengths and limitations?

DR. ERIC JOHNSON: The limitations, for example, the De Roos study, for example, it's what we call a prevalent cohort. And I think Dr. Taioli appreciates that issue because she also brought it up, that it's a prevalent cohort. It's what you call a cross-sectional cohort.

And that cohort is asserted with certain biases. Unfortunately, it's difficult to predict the direction. And with that bias, all you can say is that if I observe an effect, that effect must be there. But if I don't observe an effect, it doesn't mean there is no effect.

That bothers me about that study that as a cross-sectional study. Also, the people with cancers, prior to the start of enrollment, were excluded. That's another source of bias in that cohort. Those are the little things I want, also as a group, to look at each study in detail and look at the pros and cons for each one of them. Because I think I saw more elevated risk in this group than in any of the other group.

DR. JIM MCMANAMAN: Okay. Well, then you can include that in your write-up about what the limitations are for each of the studies. Okay.

Dr. Sheppard is next.

DR. LIANNE SHEPPARD: Okay. With respect to the question about the strengths and limitations of them informing the association, and the agency's conclusion. First of all, I think the agency's conclusion is seriously flawed and needs to be strongly revised.

I think it's appropriate to say that all the selected studies inform the association, and that there are problems with interpretation with all of them. Each of them separately, is consistent with no effect for never use of glyphosate. Although, I would say that that's not completely true because I disagree with the effect estimate that was put in Figure 3.2 for the De Roos et al. (2003) study.

I want to go on record saying that the hierarchal regression analysis, while a very interesting and informative analysis in its own right, basically, is shrinking all of the estimates in that study towards the null because that's where all the estimates were in the study overall. And it's therefore not really appropriate to compare that with the other study estimates, because it's got like this other extra thing going on.

There's a standard logistic regression estimate in De Roos et al. (2003) that is adjusted for pesticides that's much more appropriate to use in a meta-regression, than the hierarchical estimate, just from the point of view of having things that are more comparable with each other in a meta-regression.

Now one can always argue about the value of doing a meta-regression. I think it's more informative than using each study alone because you basically leverage the power of all the studies. And they're potentially all flawed, but you get a more confident estimate of something that's flawed. And that, of course, is why people can argue till the cows come home about whether you should do it because of that.

DR. LAURA GREEN: Sorry, Lianne. Which number -- so you don't like the 1.6. What number do you like?

DR. LIANNE SHEPPARD: Yeah. I don't have it in front of me. I think it's 2.1.

DR. LAURA GREEN: And what's the confidence interval?

DR. LUOPING ZHANG: 1.1 and 4.

DR. LIANNE SHEPPARD: 1.1 to 4.

DR. LAURA GREEN: Can I ask you about that?

DR. JIM MCMANAMAN: No. Let's let her finish her comment.

DR. LAURA GREEN: Oh, I'm sorry. Sorry.

DR. JIM MCMANAMAN: Dr. Green. Okay.

DR. LIANNE SHEPPARD: I've already gone on at some length with the challenges of the interpretation of Agricultural Health Study, as in the De Roos et al. (2005) paper. As outstanding study as it is, and as valuable as a cohort study is, I think if you address the fit-for-purpose aspect of this, and the reason that I've already outlined, I do not consider the study to have any more weight than the also flawed, and challenged, case-control studies.

I do need to fully understand, which I didn't have time to do in the few minutes before lunch, Dr. Crump's analysis of the recall bias to understand exactly what was done and see whether I agree with that or not. And I'm looking forward to, as I've already requested, a printed copy of your slides so they can spend a little time doing that.

The understanding about the empirical

induction period, or latency period, I think is important and we got evidence from the Eriksson study that I think gives valuable insights. I think that I'm more willing to -- well, I feel like there's insight there, sort of distinct from other issues, with respect to bias in that latency analysis. And I also think that Hardell, while it talks only about -- to all herbicides is also informative for that, and suggest that induction or latency period over 10 years is most important.

I've talked about the timing of the glyphosate registration and use patterns. And while we don't know a lot about that, I think that's an important element to pay attention to with respect to the interpretation of the results. I think that the EPA's evidence assessment is highly imbalanced. It's down-weighting statistical findings and up-weighting non-statistical criteria, which I believe is inappropriate.

The non-Hodgkin lymphoma results, as I brought out earlier when we were talking with EPA, this post hoc dividing the results into bins and then saying, oh, it can't be right, is not an appropriate way to do that. The meta-risk estimate is the best

summary estimate from these studies. And it doesn't matter who does it, they all come out more or less the same. They all tell us more or less the same answers.

The findings are not contradictory. They're all separately weak, but together, there are six studies that all tell you more or less the same thing. And I think these results are suggestive of carcinogenic potential, in and of their own right.

Are there flaws? Are there concerns? Absolutely. But they are suggestive.

DR. JIM MCMANAMAN: Thank you Dr. Sheppard. Dr. Taioli, you're next.

DR. EMANUELA TAIOLI: Okay. Aside from the impression of the pictures, I'll tell you what my train of thought is. I think that because of the limitations, of both the case-control studies and the cohort study, that we went through at length, I value these studies at the same level, which is moderately informative.

In terms of the way to interpret them, this is a real classical 101 case, epidemiology 101, that the meta-analysis is very informative. Because each study is small and can be almost there and telling us something, but not enough.

I think the meta-analysis is appropriate. I think there have been three meta-analyses published, and they all came up with more or less the same results; considering that I agree with Lianne, that the first (inaudible) model should be substituted with the value of the multivariate model, which is more appropriate to compare with the other numbers.

Having looked at the three meta-analyses, there is no heterogeneity. There is no I^2 (square) value that has any meaning. That means all the studies are all very similar with each other. They may not be perfect, but very similar in their results. That's an indication that those results of the summary estimates are pretty accurate.

My suggestion is, and I would actually like to add this as one of the points, to have an extra table, because there is no meta-analysis estimated in this document. With the various meta-estimate and the sensitivity analysis, in which the cohort study has been taken out, the other studies have been classified according to criteria that we're not going through here; but they are in the papers.

And they all come up consistently with

odds ratio that are between 1.3 and 1.5, and all with confidence intervals that are 1 or more. The indications of the epidemiological studies are very consistent, and they suggest that it is an association. That's my point.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Taioli. We are running really behind time here. I'm going to open it up to the panel, but we have to be brief and to the point about this charge question. We'll start with Dr. Green, and someone else let me know if you have a comment.

DR. LAURA GREEN: All right. I'm going to try to be really succinct. I could not disagree more. I continue to fail to understand why the prospective study is not at least as informative, if not more informative, given that we do not have the bias of a retrospective design.

I mean, I don’t get it. That's just number one. Maybe it's my stupidity. I do not get it. It is a study with a lot of person years, a lot of cases, and no recall bias possible because it's prospective, number one.

Number two, I wonder, since you all know Anneclaire De Roos, why not someone asked her

about those 1,074 cases of cancer that weren't looked at. I mean, obviously, she was trying to do a prospective study, but she found in 1993, that 1,074 of those guys already had cancer. So why can't we use that data?

I mean, forget about the power of the study; let's talk about the power of her database. She's got another 1,074 cases of cancer. Okay? I'd like somebody, whether it's the agency or you all who are colleagues, and in the field, to say hey, Professor De Roos, what about those 1,074 cases?

I think there's a lot of information here that we could potentially learn something from. And obviously, again, she wanted to do a prospective study and so she didn't include them. But my God, that's a lot of data. That'd be my first point.

My second point is, I'm sorry, but odds ratios less than 2.0, for something like NHL in farmers, are just not credible. Of course, the three meta-analyses come up with the same answer, or the four or the five. They're all using the same data. I mean, duh. Okay. Everyone is going to get the same answer. But not to be crude about it, but garbage in, garbage out.

If you have biased studies, which by their very design cannot distinguish between the effects of farming on lymphoma and the effects of glyphosate on lymphoma, then you don't have squat. Okay. And if Kenny is right that Aaron Blair was wrong, to discount whether it's recall bias or the effect of farming -- he and I disagree about that -- but something is going on. Okay.

I repeat, if this was colon cancer or brain cancer or anything else that's not associated with farming, I would be with you. In fact, I'd be ahead of you. I'd be calling this an established human carcinogen. All right. I'm pretty easy. I vote Democratic. All right.

But we're talking about NHL. All right. The sixth most prevalent cancer in America, a cancer that's been associated with farming since before you and I were born -- well, I, anyway. I don’t know how old you are. But I was born in 1954, and it was already known in 1954, that farmers get NHL at excess rates, 20 years before glyphosate was even patented or whatever.

I'm sorry, but for lymphoma, for odds ratios below 2 -- I mean, let's use the

counterexample, dioxin --

DR. JIM MCMANAMAN: I think we've gone over this. I think that there's a disagreement, and that's fine. We will include that in our write-up.

Anyone else? Dr. Portier? Ken Portier.

DR. KENNETH PORTIER: Getting back to the question.

DR. JIM MCMANAMAN: Yes.

DR. KENNETH PORTIER: I looked through the EPA discussion, on the strengths and weaknesses of each of the studies, and compared them with what I can learn from Tables 3.2 and 3.4. And I think there's a couple of things missing that would help the reader be able to draw some of these conclusions for themselves. In some of the cases you tell us how many cases and controls were identified, having glyphosate exposure. I think you do that for all of them, probably in Table 3.4 somewhere.

It would be nice to know, if you can figure this out, how many parameters were estimated in the adjusted models, because most of the cases of the six studies that we looked at, well, five of the six studies, they used an adjusted model. And some of

them have very low numbers of cases and controls. For example, Hardell, eight cases, eight controls; and they did a multivariate model. They could've used up all the degrees of freedom, in that kind of comparison, that would help me understand the strength of the analysis that was done on that model.

I think, focusing on adding some information on cases, controls, sample sizes into Table 3.4, and telling us something about model size, would tell us something about the strengths and weaknesses beyond what I can just gather from what you're saying.

I don't think we have a lot to add on strengths and weaknesses over and above what you have, other than that.

DR. JIM MCMANAMAN: Okay. Dr. Zhang.

DR. LUOPING ZHANG: Okay. I should also look at what Dr. Green mentioned in that figure. I believe when you give the presentation you'll show that Figure 2, at least of the six studies, about the confidence interval.

I think, if I may, I think it's also good to have the meta from the meta risk into the same table. If you see each one, just like each one is

weak, like what Dr. Sheppard was saying, about to put it together. We could have a comparison with each individual study and compare with the meta risk. If you can list it on the same figure, could maybe help this one.

Two, Dr. Green's idea of garbage in, garbage out. My understanding is the three meta-analysis actually, they're using the same stuff, but not analysis is exactly the same, each one. In this way actually, I agree, sort of support Dr. Taioli's suggestion to make a table. Make the table very clear. Here is meta-analysis number one and what's the study?

You can click. Okay. This meta-analysis is based on this assumption because each meta-analysis, the assumption is different, then we choose this field and just start with this and that's the result. And that one was different. That's maybe much more transparent than clear.

You only mention three meta-analysis. Here is a meta risk from 1.3 to 1. whatever it is, but, you know, we should make a table to make it very clear. I think you may have misunderstood what Dr. Taioli said, but correct me if I'm wrong, what she was

saying is that there are many different ways to meta-analysis.

For example, let's say we're only focused on recall bias, case-control study. Okay. In that case, we could exclude the De Roos (2005). It's not because we have to exclude. As we said, we're only focused on case-control study. We just make meta-analysis on that one; let's look at what it is. I think that's maybe a fair way to look at the data in multiple ways, and see what we learned from this.

I don’t think we should look at it, you know, too --

DR. EMANUELA TAIOLI: But I meant not to exclude the De Roos. But some of the sensitivity analysis do only case controls, and therefore you take out the cohort, and so on. And the table should have all the various assumptions and the various stratification that have been done, and can be repeated. Now, I didn’t mean to exclude. I said at the beginning, to me, they had the same value.

DR. LAURA GREEN: No, I agree. And I think that would be very helpful.

DR. JIM MCMANAMAN: Okay. That's Dr. Taioli and Dr. Green. All right. David. Dr. Jett.

DR. DAVID JETT: This is interesting, this discussion about the farmers. Aren't the controls farmers in these studies?

DR. LAURA GREEN: No.

DR. DAVID JETT: Oh, they're not?

DR. LAURA GREEN: Well, all right. Okay. These are case control -- it's complicated and I'm going to screw it up, so everyone listen and correct me.

These are case-control studies. For Eriksson, Hardell, and I'm forgetting the third one.

DR. KENNETH PORTIER: McDuffie.

DR. LAURA GREEN: McDuffie and Cocco. Okay. In four of the case-control studies -- you know what a 2-by-2 table is, right?

Okay. Again, it's my stupid, reductive way. A proper 2-by-2 table, okay, the top row is glyphosate users. And in the columns of cases and control. The bottom row, to my simplistic mind, ought to be glyphosate nonusers' cases and controls. Right. That's the right way to set up a 2-by-2 table for case control studies. However, what Cocco, Eriksson and the others did, was the following 2-by-2 table, which is wrong, I believe. The top row is the same. Okay.

Glyphosate users, and then the first column is cases and the second column is controls. But the bottom row is glyphosate nonusers, 24D nonusers. You know, all herbicides, all pesticide, all fungicide, and all rodenticide nonusers. In other words, non-farmers. Okay.

What they're doing is changing two variables at once. They're comparing glyphosate users who are farmers with non-glyphosate, non-herbicide, essentially, nonfarmers. And because of that, to my mind, one cannot disaggregate the possible carcinogenic effects of glyphosate from the possible carcinogenic effects of everything else associated with farming. Right?

DR. JIM MCMANAMAN: That was pretty succinct. Can we make sure you include that in your write-up?

DR. LAURA GREEN: Yeah. I assume our transcriber here has got that all down.

DR. JIM MCMANAMAN: No, no. It's important to have that. And Dr. Zhang, if you can do what you just suggested, is it possible to include that in your --

DR. LUOPING ZHANG: Including a table.

DR. JIM MCMANAMAN: Right. Okay.

DR. LUOPING ZHANG: I forgot one more point. Can I say it?

DR. JIM MCMANAMAN: Okay.

DR. LUOPING ZHANG: Back to that same figure, because that six study, the risk you listed is only ever level effects, right. Estimate. But the study -- actually, they have a different way to calculate the risk. That's not actually included in there. I just want to point that out.

DR. JIM MCMANAMAN: All right. Dr. Portier.

DR. KENNETH PORTIER: This is a very minor thing. When I found the end of Table 3.4, there's a B footnote about the De Roos study that really should be in the risk and other bias column on Table 3.2. That footnote is kind of in there, but it really does affect potential biases and your understanding of the bias. If they're going to exclude people from the analysis, that's a major thing that you need to know about.

DR. LUOPING ZHANG: Do you mean De Roos (2005)?

DR. KENNETH PORTIER: De Roos '05. The

De Roos '05 study.

DR. LUOPING ZHANG: Yeah, to make it clear.

DR. KENNETH PORTIER: It doesn't -- it needs to come out of the footnote and into Table 3.2, because I think it's important.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Portier. Okay. I think that we've beat this horse to death.

DR. LUOPING ZHANG: No, we have more issues.

DR. JIM MCMANAMAN: Seriously, we have to move on. Unless Dr. Zelterman has something to say, because he's usually pretty succinct.

DR. DANIEL ZELTERMAN: No.

DR. JIM MCMANAMAN: All right. We'll go back to the Agency. Do you need clarification?

DR. LUOPING ZHANG: We haven't finished yet. I'm going to be the one to be charged in writing this.

DR. JIM MCMANAMAN: Well, I thought you were finished.

DR. LUOPING ZHANG: No. No, I'm not done yet.

DR. JIM MCMANAMAN: Okay. It's only on Question No. 3. Because I haven't even heard --

DR. JIM MCMANAMAN: We're going to have a break here as soon as we finish.

DR. LUOPING ZHANG: Okay. How about we have a break.

DR. JIM MCMANAMAN: We need to finish this.

DR. LUOPING ZHANG: Did I miss something? I'd like to hear the members about -- what do you think?

Personally, I think Eriksson (2008), McDuffie (2001), the dose response data, that's a strength. But I haven't heard anybody comment on that. Is that a strength or is that a weakness?

DR. JIM MCMANAMAN: I think we've heard various strengths and weaknesses about those.

DR. LUOPING ZHANG: Okay.

DR. LIANNE SHEPPARD: I agree, it's a strength.

DR. LAURA GREEN: No. Actually, we didn't answer her.

DR. LUOPING ZHANG: I know. That's what I needed to know, you know.

DR. LAURA GREEN: I just want to say it would be a strength if they were real, but I don't believe it.

DR. LUOPING ZHANG: See, I needed to know, right?

DR. JIM MCMANAMAN: Anybody else have a comment about the strengths and weaknesses?

DR. ERIC JOHNSON: I'm trying to determine which of the studies we are talking about. And it seems to me, the first studies in which -- when you adjust for confounders, those alterations are relative -- became nonsignificant, four of them. And only two studies we had a significant result. One was the Eriksson study, which did not control for multiple pesticides. And the other was the De Roos (2003), which did the best job controlling for other pesticides. To me, that's where the sticker is. How do we interpret this data? And it's for these two studies, to me, that we need to focus and look at what do these studies mean?

DR. JIM MCMANAMAN: Okay. Well, we have a disagreement about that amongst panel members, and I don't know that we're going to resolve those disagreements today. I mean, it's been stated pretty

clearly, the pros and cons, from each camp, related to the De Roos publication. I think there's no point in belaboring this much more. And so again, I think we can go back to the Agency and ask do you need additional clarification?

DR. LAURA GREEN: I'm sorry. Before --

DR. LUOPING ZHANG: I -- okay. Dr. Green, you go ahead.

DR. LAURA GREEN: Yeah. I think you didn't quite understand what Dr. Johnson was saying. There are two De Roos et al. papers. He was speaking of De Roos et al. (2003), not De Roos et al. (2005). Unless I'm wrong, that's precisely the one in which Professor Sheppard said, if you use the hierarchical thing, which I don't understand to save my life, you get a significant odds ratio.

DR. ERIC JOHNSON: No. Wait, wait, wait.

DR. LAURA GREEN: Oh, sorry. Well, whatever. Whatever one you like is significant. And what Dr. Johnson -- so it's De Roos et al. (2003), not De Roos et al. (2005). And I don't think we have a disagreement, necessarily, about De Roos, et al. (2003), because I don't think we've talked about De

Roos et al. (2003), unless I missed it. But I really have to go to the bathroom, so I am doing that right now.

DR. LUOPING ZHANG: But the 2003 data estimated overall -- yeah, that's --

DR. JIM MCMANAMAN: Dr. Zhang?

DR. LUOPING ZHANG: It looks like we've run out of time, but I want to put this whole thing into this 2(d) section.

What I just want to mention here is about statistical significance of the (inaudible), if it's acceptable, not adjusted, adjusted, the pairwise comparison where there is a trend test. You know, that whole thing I'm just putting on here. We can maybe have a separate group to have a discussion about that. And the latency issue was mentioned earlier, but I think here, for non-Hodgkin lymphoma, is important.

And we should also, at least, encourage my team for 2(d) to remember to consider -- you know, to get that. And the end, but definitely on the list, is how to manage or assess the bias, especially the recall bias like what, you know. This is all a very important issue for non-Hodgkin lymphoma. I just

wanted to put that in before you go over to the Agency.

DR. JIM MCMANAMAN: All right. Thank you, Dr. Zhang. Okay. Back to the agency.

DR. MONIQUE PERRON: As clear as mud.

DR. JIM MCMANAMAN: You think?

DR. ANNA LOWIT: Something like that. But it feels like we've had the same conversation for a bit, and maybe it's time to move on to the animal questions.

DR. JIM MCMANAMAN: Okay. Even if there could be a clarification, there's none needed.

DR. ANNA LOWIT: I'm not even sure what we would ask.

DR. JIM MCMANAMAN: Okay. All right. At this point, I think we should have a break for 15 minutes. So be back here at roughly 4:30 and then we'll move on to the animal question.

[WHEREAS A BREAK WAS TAKEN]

DR. JIM MCMANAMAN: All right. Is the panel present and ready to go, somewhat?

We're now on Charge Question 3.

DR. LIANNE SHEPPARD: Might I interrupt for one second, before we move on?

DR. JIM MCMANAMAN: Okay.

DR. LIANNE SHEPPARD: I just want to ask that we allow a little bit of time, at the end tomorrow, to circle back, to make sure that anything that occurs to us, that's really important, to get in the public record. There's not something about Question 2 that we might've overlooked, to make sure we get it in the public record.

DR. JIM MCMANAMAN: Well, okay. I don't think we can circle around again. I'm not sure. We can have final comments. We'll have a time for final comments about that. Dr. Portier?

DR. KENNETH PORTIER: I think one of the issues is that EPA didn't ask a question about the meta-analysis. And I think we'd like to talk about the meta-analysis. I would like to talk about the meta-analysis.

DR. LUOPING ZHANG: Thank you, Dr. Portier. It's a very important issue.

DR. KENNETH PORTIER: So they've asked us about the strengths and weaknesses of the individual studies, but --

DR. JIM MCMANAMAN: Is the fact that meta-analysis wasn't mentioned, is that a weakness?

DR. KENNETH PORTIER: Well, that's a weakness in the questions they didn't ask --

DR. JIM MCMANAMAN: Is that a weakness?

DR. LUOPING ZHANG: Maybe it's a strength for the analysis. But I totally agree. By the way, if we refer back to Charge Question 2(d) or Charge Question 2 in general?

DR. KENNETH PORTIER: Well, 2(d), though, didn't ask us about the individual studies. It didn't ask about the meta-analysis. And maybe EPA doesn't want us to comment. I mean, I'll be honest, if you don't, that's fine.

DR. JIM MCMANAMAN: Well, it seems to me that the question of whether the meta-analysis is included or not included, it comes to the question of strength or weaknesses of the studies. Maybe they should've done a meta-analysis. Well, I guess each study wouldn't have been able to do a meta-analysis, because you'd have to have all of them, right?

I'm okay with discussing that if that is not violating some sort of --

DR. ANNA LOWIT: Well, it seems that

some commenters have already discussed it at length, so if there is another opinion, I think that needs to be brought into play with the others. It's certainly not counter to the question but --

DR. JIM MCMANAMAN: Okay.

MS. DANA VOGEL: -- I think we're all getting a little bit concerned that it's now 4:30.

DR. JIM MCMANAMAN: Right. I think it would be okay asking this. If you have views about whether a meta-analysis should've been included or excluded, or can we include a meta-analysis of the data on our own and provide that to the agency --

DR. LAURA GREEN: (Off mic).

DR. KENNETH PORTIER: No. I'm volunteering about the discussion of the strengths and weaknesses of the meta-analyses that are in the report. I mean, I think that's -- part of the key question around the human data for NHL, is the one meta-analysis that IARC did, compared to the others and what does that really tell us. And I think it's important that EPA hears this panel, at least, talk a little bit about that. But I'm willing to put that to the end, as Dr. Zhang said. If we run out of time, we'll write and put our comments in.

DR. JIM MCMANAMAN: Okay.

DR. KENNETH PORTIER: I just wanted it on the table that this is an issue that I think we've missed.

DR. JIM MCMANAMAN: Okay.

DR. LAURA GREEN: Can I suggest it could come up in Question 5? Because it's sort of a weight of evidence thing, right?

DR. JIM MCMANAMAN: Right.

DR. LAURA GREEN: So we can actually address then, right?

DR. JIM MCMANAMAN: Okay.

DR. KENNETH PORTIER: And since I lead Question 5, I'll remember to bring that back up again.

DR. JIM MCMANAMAN: Okay. That was Dr. Green and Dr. Portier and Dr. McManaman who saying okay. We'll move on. All right. Charge Question 3.

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar and I'm reading Charge Question No. 3.

The Agency has followed the 2005 EPA Guidelines for Carcinogen Risk Assessment to evaluate laboratory animal carcinogenicity studies for glyphosate. As described in Sections 4.5 and 4.6, a total of nine acceptable rat and six acceptable mouse

carcinogenicity studies were evaluated and considered in the weight-of-evidence analysis.

Consistent with the 2005 Guidelines, this analysis took into consideration statistical evidence of a dose-response, the occurrence of corroborating pre-neoplastic lesions or related non-neoplastic lesions to support tumor findings, evidence of progression to malignancy, concurrent and historical control information, and statistical and biological significance of increased tumor incidence, as well as reproducibility of tumor findings.

Question 3(a) states, please comment on the agency's review and evaluation process of the relevant laboratory animal carcinogenicity studies to inform the human carcinogenic potential of glyphosate.

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The discussants on this are Dr. Ramesh, lead discussant. Dr. Ehrich, Dr. Green, Dr. McManaman, Dr. Parsons, and Dr. Sobrian.

Dr. Ramesh.

DR. ARAMANDLA RAMESH: Good afternoon, Dr. McManaman and fellow panel members. In response to this charge question, the Agency has done an excellent job of compiling information, and also

providing the necessary background material, including the proprietary information provided by the registrants to allow us to assess the findings in an impartial manner.

To that extent, the agency's review and evaluation process followed the 2005 EPA Guidelines for Carcinogen Risk Assessment, in regard to laboratory animals, the potential for glyphosates to cause tumors in these animals. From a broad perspective, the Agency used a criterion that emphasized the weight-of-evidence aspect to review animal carcinogenicity. The White Paper, Glyphosate Evaluation of Carcinogenic Potential needs to be revised, weighing to the following shortcomings in their adopted approaches:

1) the EPA arrives at the conclusion that the multiple positive tumor responses were not treatment related. At the same time, the agency fails to indicate what constitutes a positive finding or whether these are of any chance occurrence or not. And it appears that the Agency may have filtered some studies. If the study's statistically significant trend observed is not a monotonic response, the agency seems to have dismissed those studies. And especially

the statistically significant Cochran-Armitage trend test and the unadjusted pairwise comparisons. They should be considered as treatment related.

And also, the significant tumor incidences as reported, they were not reproducible in most cases, from the literature, and hence, they were thrown out. I can understand that these studies did not fulfill the Bradford Hill criteria. While this is justifiable from a regulatory standpoint, the Agency should, at least, acknowledge that the bioassays reported, they were done over a span of 40 years in different labs, using different strains. And hence, it is very difficult to replicate those studies to some extent of precision. I want them to acknowledge that in the report.

And again, some bioassays comparison was from different durations. For example, EPA used the historical controls from a 24-month-old study to compare a glyphosate treatment-related study that lasted only for 18 months. Also, if somebody with treatment duration tumor incidence, types of tumor, assessed by histopathology, needs to be included in the form of a table, in the revised White Paper.

And the reduction in weight gain in

glyphosate-treated animals, that are related to controls, observed in initial phase of the studies need to be explained for each dose. Was the reduction in tumor instance at high-dose? Could it be due to saturation of metabolic (inaudible), leading to excretion of administered glyphosate? And these aspects, like changing weight gain, (inaudible), reduced tumor instances, that needs to be discussed in the White Paper.

While glyphosate, per se, may not reduce tumors on its own, like any chemical, it is highly likely it contributes to either promotion or progression of spontaneously-occurring tumors. The background noise that we have seen in control rats, could be attributed to a species of strength-specific genetic differences.

But Wahl et al., from my evaluation of the literature provided by EPA, and the White Paper, the carcinogenicity profile fits into the category of grouping glyphosate under the weak, non-genotoxic carcinogen category. And I've received significant input from my fellow panel members, Dr. Barbara Parsons and Dr. Marion Ehrich. And I also had a few discussions with Dr. Sonya Sobrian. And hopefully,

I'd like to put final touches before it is shared with the Agency.

Now I leave it to other panel members.

DR. JIM MCMANAMAN: Thank you, Dr. Ramesh. Dr. Green.

DR. LAURA GREEN: No one will be surprised to know I disagree. I'll try to be brief. I think the Agency got it right for the wrong reasons. I'm disappointed that the agency's write-up looks -- not is -- but looks biased. I vastly prefer the analysis that the German fella presented. I'm sorry, I don't remember his name, and I don't know if he's still here. But let me tell you why.

First, I've already chewed you out on the first day for being very schizophrenic about your so-called limit dose. I mean, your carcinogen guidelines, not to mention good laboratory practice for chronic bioassays, is pretty clear. You're supposed to stress the animals to the max. Because you only have 50 animals per sex, per group, and you want to get as high as you can without really making them, frankly, sick. And because glyphosate is so non-toxic, doses of 1 gram per kilo are not maximally tolerated doses. They just aren't. You know that

from your own data. You can give these animals three, four grams per kilo for life and they are still okay. It's not right to change the rules. You are basically changing the rules.

You are saying for glyphosate, I'm going to make this artificial limit dose of 1 gram per kilo, despite the fact that it's not a maximally-tolerated dose. I mean, I'm sorry, you just can't do that, in my book. So, that's wrong.

And I don't know where this 1 gram per kilo limit dose came from. The way I read the carcinogen assessment guidelines -- admittedly, you all know much better than I do -- but the way I read them, it says you don't have to exceed 1 gram per kilo unless there are good reasons. Well, in my mind there are good reasons. That's the first issue.

I don't think that it's right to necessarily discount responses that you see at 1 gram per kilo or even 4 grams per kilo. If it's an incredibly non-toxic material, like glyphosate, and you can give the animals 4 grams per kilogram body weight for life and they're still okay, then that's what you ought to do. And those data are every bit as valid as any other high-dose dataset.

Correct me if I'm wrong, my fellow panelists, but I just think that that's weird. Because you really look like you are changing the rules for glyphosate, and you don't do that for other chemicals. That's number one.

Number two; for glyphosate, we have a situation that I've never seen in my professional career. We have like, 15 bioassays. I mean, wow. And it's really 30 bioassays because, you know, there are males and females, right. And there are like three or four dose groups. We have like this plethora of data. It's like an embarrassment of riches.

I've never seen a dataset this rich. I don't know how many millions of dollars have been spent, chronically bio-assaying the carcinogenicity of glyphosate. I mean, my God. You can like, feed a small nation on this. Okay.

Having said that, I think it is intellectually lazy not to use the data as a set. Okay. And that's where my friends, the statisticians, come in. And Danny Zelterman and Kenny Crump, and what's his name, Haseman or Haseman or however you say your name. I mean, there's a reason that they're doing these analyses. You don't need these guys, no

offense, when you've only got two bioassays, right.

I mean, a kill them and count them toxicologist, like me, can look at those data, okay. But when you've got basically 30 datasets, you need a statistician. And the reason you need a statistician is because you've got to be able to differentiate the signal from the noise. Now you all know that intuitively because you have one or two sentences in your document that says, oh, and when you look at it all together, it's kind of not consistent, so like, were not impressed.

Well, but, do it rigorously, darn it. I mean, do something that either Haseman or Zelterman or Crump know how to do. I mean, you've got statisticians. Maybe some of you sitting here are statisticians. I mean, do it the right way. And the reason to do it the right way is, as far as I can tell, and the reason I strongly feel it's not a week carcinogen but a non-carcinogen, apparently, is that when I look at what Crump has done and what Haseman had done, I'm impressed by the inconsistency among the findings.

And it looks, to this kill them and count them toxicologist, like it's all just random

noise. It looks like, you know, sometimes you see hemangiosarcoma and most of the time you don't. And sometimes you see a little malignant lymphoma, and most of the time you don't.

Now that's not the mark of a real carcinogen. I mean, let's look at the counterfactual, the positive control. If you bioassay vinyl chloride 15 times, what would you get? Every single time you get angiosarcoma of the liver. You'd get it in the mouse, you'd get it in the rat, and you'd get it in people. What happens when you bioassay dioxin a zillion times? You get a whole bunch of different tumors, but you get a lot of different tumors.

What happens when you bioassay glyphosate 15 times? Well, you get crap. Oh, I said it again. You get noise, okay. You get, you know, you get random noise.

And it looks to me, and I'm convinced, although I do not understand the statistics completely -- but I follow baseball so I do understand some statistics. It seems to me that what's happening is, you got all these hypotheses being tested, and sometimes you get a yes, and most of the time you get a no. But you don't get the same yes. Okay. And I

go back to thinking about this mechanistically and biologically.

If glyphosate is mostly in the gut, even for a couple hours, it's mostly in the gut, and to the extent that is metabolized at all, is metabolized by gut flora. Your a priori hypothesis should be, if glyphosate was a carcinogen, it should be a gut carcinogen. Okay. I mean, that's what makes sense. Most of it is not being absorbed. It's just sitting there in the gut and then being pooped out. Okay?

Why don't we see colon tumors? Well, maybe because it's not a tumorigen. Why do we randomly see these other things? And so, I just think you have this tremendous opportunity here, this incredibly rich dataset. I mean, my goodness, all those rats and mice have gone to their death for a reason, and it's for you all to do some simple statistics that I understand can be done, using either Dr. Crump's paper or somebody else's method, for multiple comparison testing; to ask yourself a simple question: if you've got 15 bioassays, two sexes, three or four dose groups, how often would you find a random positive result, whether by trend test or pairwise

comparison? And do we see that more often or less often?

And then from the biology point of view, when we see something, is it replicated? And I think we have the perfect example in that Lankas et al. paper, right. That was a low-dose study. High dose was only 30 or 31 mgs per kg. I don't know why. Like, you know, that's weird. Okay. But they found interstitial testicular cell tumors, otherwise known as Leydig cell tumors. I don't know how to say it, it's German. And everyone went, that's weird; I wonder if this is compound related.

Then they did the study again at a much higher dose level. Same strain and species, male Sprague Dawley rats, obviously male, it's testicular. Duh. Anyway, Sprague Dawley rats, much higher doses. No Leydig cell tumors. Okay. They tested the hypothesis and it turns out it was just a random hit.

I think you're right, that is not a rodent tumorigen. I feel strongly that is not a weak non-genotoxic tumorigen. Because if it was a weak non-genotoxic tumorigen, again, you'd see the same thing when you replicate the studies. And there just isn't a consistency here. And if Haseman and Crump

are right, there is actually fewer positive responses than you'd get.

I feel pretty strongly it's noise. I don't think it's a signal, whether it's a signal of genotoxicity or non-genotoxicity. I think you guys got it right, but my goodness, I don't think you did it the right way. Sorry.

DR. ARAMANDLA RAMESH: Dr. McManaman, can I request one thing. We can conduct this business in a polite way, and without offending others. There is no need to run our mouth. We can respectfully disagree. But I take strong objection to your use of certain words, with all due respect, Dr. Green.

DR. LAURA GREEN: I apologize. No disrespect was meant. I get excited. I do apologize. I meant no disrespect. I apologize.

DR. JIM MCMANAMAN: All right. Thank you. I agree with Dr. Green, largely. I think that the evaluation process was correct. You might have been able to do some additional things, but I think overall, the evaluation was correct and there's little or no carcinogenicity. I mean, as I can see it, there's no carcinogenicity for glyphosate.

But I do want to come back to Dr.

Ramesh's point, is that in the human population, it's unlikely that we're going to start with people who have not been exposed or have no previous tumors. Because you can have a tumor and you can have cancer if it goes undetected. And that might contribute to the human population.

I think one of the questions that would be important to know is whether it's a tumor promoter. Because a tumor initiator is what a carcinogen is, and a tumor promoter could be something that's entirely different. I think it's true that it's not a tumor carcinogen, but I think that all bets are off on whether it's a tumor promoter. And I think that that's an important thing that could be conducted pretty easily with animal studies. I think that's where I would draw my limitations.

We'll move on to the next commenter, Dr. Parsons.

DR. BARBARA PARSONS: My comments are somewhat extensive, but I haven't had a chance to speak very much, so please bear with me.

I disagree with the agency's approach regarding the application of the Cancer Risk Guidelines to the assessment of the glyphosate rodent

carcinogenicity data. I believe the data includes multiple positive tumor responses that the document concludes are not treatment related. One assumes that the Agency is ascribing these observations to chance. Yet, in my view, such a conclusion is not justified based on the evaluation criteria described in the cancer risk assessment guidelines.

I think I'll go into that in more detail when we talk about the statistical significance. Neither is the statistical analysis approach employed, consistent with the evaluation methods used by other authoritative bodies. At least some of the statistically significant Cochran-Armitage trend test, and unadjusted pairwise comparisons, I believe they should be considered treatment related, particularly ones that occur with P values of 0.01 or below.

I disagree with the agency’s dismissal of statistically significant trends by stating that they're not monotonic. I believe the high-dose effects on growth and survival are potentially reducing the observed significance of some of the studies that are employing very high doses as the top dose.

The document describes the lack of reproducibility of significant tumor findings across studies; without providing sufficient discussion of the technical and biological differences that make bioassays done across the world, over a 36-year period, unlikely to be replicated with any precision.

Just as an aside, you mentioned the Lankas study that was not reproduced. That was the only study that treated those animals for 26 months instead of 24 months. So how can we know that it was not those additional two months of exposure that resulted in that positive response? And there are many differences like this.

This particular charge question also asked about malignant tumors; test articles that induce malignant rodent tumors are more concerned than those that induce just benign tumors. And those that induce tumors in both sexes and multiple species and strains, also are of more concern. One comment is -- and this is something that Dr. Ramesh commented on.

One comment is that a summary table, describing the number of different types of tumors, and even the overall incidences across studies, would be very helpful in trying to understand, are they

reproducible or not. We saw examples of that in the presentations by Dr. Marques and Dr. Haseman. I think those are very helpful.

Statistically significant findings, regarding malignancies, were observed in male and female rats, Wistar and Sprague Dawley, as well as male CD-1 mice. The tumor types included mammary gland adenocarcinoma in Wistar rats. This is the Atkinson study. And the P value for the trend test was 0.003. There were inductions of lung adenocarcinoma and malignant lymphomas in male CD-1 mice. And this is the wood study. And there was a P value for the trend test for malignant lymphomas of 0.007.

There was also, not in the document, but there was a signal, I thought, for adenocarcinomas in mammary gland, in glyphosate-treated female CD-1 mice. I won't give you the incidence numbers, but I have them here. In addition, in a study of glyphosate-treated Sprague Dawley rats by Atkinson, it stated the overall number of animals with tumors was similar between groups; but the number of males in the high dose group with malignant tumors was double that observed in controls.

The study of glyphosate-treated Wistar rats by Suresh, reported the number of malignant neoplasms in the low dose males were statistically high. And the Wood study of CD-1 mice reported an overall increase in multiple malignant tumors and treated males relative to controls. Taken together, I think these data provide ample evidence that glyphosate induces malignancies in exposed rats and mice.

Regarding statistical evidence of a dose response, the document discounted four positive tumor responses, tumors with a significant Cochran-Armitage trend test. In part, because the tumor responses were considered nonmonotonic. The document discounted three additional positive tumor responses, because the dose-response was considered shallow. In my opinion, these are minor considerations, and I question whether it is appropriate to discount a significant positive trend test by using a test that favors detection of a linear response, by saying the response was not linear.

Is there statistical evidence that the perceived lack of linear dose response was, itself, significant and not just noise in the response? Also,

monotonic dose-response is not mentioned as criteria in the cancer risk assessment guidelines.

Another important consideration, in terms of analyzing dose response, is that mortality data was not factored into the statistical analysis of dose response. Review of the primary study documents indicates that glyphosate caused early and statistically-significant reductions in weight gain relative controls in multiple studies, and occasionally reduce survival in the high-dose groups.

Both of these effects of glyphosate toxicity, have the potential to reduce tumor incidences in high-dose groups. These points are not mentioned or discussed in the document. Conversely, the document does point out that in one instance -- this is Brammer -- the improved survival in the high-dose group may help explain a modestly higher incidence of age-related background tumors like liver adenomas. I find the document is not balanced in this regard.

Regarding the selection of appropriate statistical methods, the OECD test guidelines: 451, 452, and 453 state, "Selection should make provision for survival adjustments, if needed."

DR. JIM MCMANAMAN: Dr. Parsons, is this A or B? Because you'll get a chance to -- you're not on the thing for B. Go ahead.

DR. BARBARA PARSONS: Okay. Let me go ahead.

DR. JIM MCMANAMAN: That's fine. I didn't see that you weren't on the charge question B.

DR. BARBARA PARSONS: But according to FDA's Guidance, for Industry Statistical Aspects of Design, Analysis and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, the effects of differences in longevity on numbers of tumor-bearing animals can vary substantially. And so, whether or not the effects appear to be, they should be routinely corrected when presenting experimental results.

Also, the OECD guidance, document No. 116, refers to the Cochran-Armitage trend test and states, "Problems arise if there are differences in mortality between the groups. The test is sensitive to increases and treatment-related lethality, and this leads to an incorrect level of the Type 1 error, the risk of falsely rejecting null hypothesis."

I think this is really something that

should be done, systematically.

DR. JIM MCMANAMAN: If there are more comments about statistics, because you can comment about this when we get to (b). If you want to hold that --

DR. BARBARA PARSONS: Okay. I just have one more paragraph then.

DR. JIM MCMANAMAN: Okay.

DR. BARBARA PARSONS: Regarding the biological significance of the tumor data provided for evaluation. It's this reviewer's opinion, that the observed profile is exactly what you would expect for a weak non-genotoxic carcinogen, one that causes promotion or progression of spontaneously occurring lesions. This conclusion takes into account a review of the genetic toxicology data for glyphosate, which was convincingly negative.

The rodent data includes statistically significant increases in common spontaneous tumors, which are likely driven by the genetics of particular strains and substrains. This occurred at doses as low as 31 mg per kilogram per day in Sprague Dawley rat, in the Lankas study. Again, for which the P value for the trend was 0.009, establishing an important point,

I believe, or reference point for interpreting potential human risk associated with glyphosate exposure. Thank you.

DR. JIM MCMANAMAN: Thank you, Dr. Parsons. Dr. Sobrian.

DR. SONYA SOBRIAN: I haven't spoken much, but in the interest of time, I'm not going to read what wrote. Let's say, I agree with almost everything that has been said. I've come to a different conclusion -- the conclusions amongst the panelists are different.

But the issues I found where the use of the historical control, which I know will come up in another area, it seems that it was used inconsistently. That's, I think, what I find most problematic; is that the use of some inconsistent criteria, from study to study. But I thought that it should be that the use of historical controls should be made a priori, and not after you see that the incidence in the control group is small. Now, that -- I'm not sure, but it's never said that.

The other issue, I think, is brought up about the high doses and the lack of linear trend. Or when you did find linear trend, but no significant

adjusted or unadjusted pairwise comparisons? The data were just thrown out or dismissed? And I agree with what's been said. Maybe I would like to see that revisited with some of the other issues addressed.

Okay. Like I said, the issues of control groups and stats; this issue leads to the dismissal of the increases in 76.6 of the studies cited, that were listed as either having a trend or significant pairwise comparison. I just wanted to mention a couple of other issues that you might want to look at.

If you go to the source data, some of the incidences that you get, both in the incidence and in the survival, are different. And if you look at what's in the source data, from what you have in your table, it presents a different kind of stat. So maybe you just want to explain what the differences are. And why they're there.

There are also some effects in the source documents that are attributed to glyphosate. And that's never mentioned in the White Paper. I would like to see at least a discussion of that and why you dismissed it. Let's see. Oh yeah, I agree with Dr. Green about the dose.

It's interesting, in the study in which you had 4,968 something milligrams per kilogram, that in fact there was no change in survival. There was a decrease in body weight, which would've suggested maybe a decrease in tumor incidence. But what was found in that study was actually an increase in rare tumor in males. Those are things that I would have liked to have at least seen discussed in trying to reach a conclusion.

I found some inconsistencies that I think I'd like just addressed. It would make it easier to make an opinion.

DR. JIM MCMANAMAN: Thank you, Dr. Sobrian. Okay. I think we'll open this charge question up to the rest of the panel. And the charge question is to comment on the agency's review and evaluation process of relevant laboratory animal carcinogenic studies.

David Jett. Dr. Jett.

DR. DAVID JETT: Hi. I just have a real general comment, and it's sort of been covered by Sonya and others. And that is, it seems to me that if you're going to use certain specific kinds of flaws in the data, you know, not monotonic, the historical

controls, there weren't enough tumors in the controls and so forth, you're going to really have to explain that and really supported with evidence. Because without that, I tend to lean on looking at these data as something is there. It's not null.

I think you sort of, in a cursory sort of way, talked about it a couple of times in the document. But I would really, really try to increase or strengthen that argument. Because if you're going to use these, these are going to have to be supported. I forgot what the other one was, monotonic trends and a couple of other --

DR. LAURA GREEN: Historical controls.

DR. DAVID JETT: Historical controls and I forgot what the other one -- there were a couple of other things. That was just a general comment.

DR. JIM MCMANAMAN: Dr. Green.

DR. LAURA GREEN: I think everybody had very good points to make. The reason I wanted to stress the statistics and the plethora of data is, I think, a really, really important point. I want to try to state it again. Or maybe I wasn't clear.

Dr. Parsons is 100 percent correct that, if all we had were Lankas et al. (1981) on the

question of whether glyphosate causes Leydig cell tumors, she would be completely right. This is strong evidence on its face, that Leydig cell tumors are associated in a dose-dependent way with Leydig cell tumors, in the Sprague Dawley rat.

We have zero Leydig cell tumors in the untreated controls. We have 3 out of 47, which is 6 percent tumors, in the first dose group. We go from zero out of 50. The low dose is 3 tumors out of 47. The mid-dose is 1 tumor out of 49, and high dose is 6 tumors out of 44. And she could not be more correct, that if this were all we had, whether you do a pairwise comparison between the high dose group and the controls, or whether you do a trend test, this looks like a real carcinogen.

My point is a different one. The question of whether glyphosate is associated with Leydig cell tumors has been tested 15 times, nine times in the rat, and five times in the mouse. And it's only been found to be true once. The other 14 out of 15 times, it hasn't been true. You don't need to be a statistician to say to yourself, okay, if the question, does glyphosate promote Leydig cell tumors, is that true or false? It's true once and it's false

14 times.

That's my point; my point is not that individual studies are non-positive. And that's where I agree with you entirely. And that's why I was trying to castigate EPA. To call this study negative is wrong. This is not a negative study. It's a positive study. Trend test, pairwise, it's a positive study.

The reason it's uninformative is because 14 other studies disagree with it. That's my point. And that's why I don't feel it's a promoter or an initiator. And I want to speak to that initiation/promotion because I think it's a really interesting question, which I had not thought about.

But I was reminded that one of these 15 bioassays is of N-Nitroso glyphosate. Not glyphosate, but N-Nitroso glyphosate. Which, to a first approximation, if there is going to be a carcinogen out here, it's going to be the N-Nitroso compound; which was neither an initiator or a promoter, in the one bioassay.

I agree it's an open question, but it's kind of been tested a teeny bit. Not much, but a little.

DR. LUOPING ZHANG: Can I make a quick comment now?

DR. JIM MCMANAMAN: Well, wait because I think somebody else had their hands up. Dr. Sheppard did and Dr. Portier did first, I think. Can we go with Ken first?

DR. KENNETH PORTIER: When I looked at this question, I'm thinking this is related to Section 4.3 in the document, which lays out the assessment of animal carcinogenicity studies.

In the first section, there's this paragraph on dose selections. Two of the commenters, so far, have talked about the high dose. And what I found confusing is, the paragraph is maybe not clear enough.

You have two OCSPP documents that talk about not recommending the 1,000 milligrams per kilogram body weight a day, as a recommendation from a panel that has looked at animal studies in general. But I wasn't quite sure to what extent these kinds of guidance really applied to glyphosate. You kind of refer to it, but I think you could save us a lot of heartburn by kind of going into that a little bit more; into those two documents and kind of pulling out

a little bit more of the reasoning these panels had for setting that level.

And the other thing is, the difference between a maximum-tolerated dose and a limit dose. You know, toxicologists talk a lot about maximum-tolerated dose, and I think when they see a study and they look at the descriptions of what was happening in the lab, they can tell when a dose was maximally tolerated. And I see some of these in a couple of these studies; you can kind of tell they were up there. The animals had diarrhea and they lost weight, and the urinalysis was real weird, and the blood chemistry. Even two sentences that said something like that would help the reader understand it.

The limit dose, again, goes back to that 1,000 milligrams, which goes back to those two documents. I think explaining the difference between those two terms would help us a lot. And then I really think, instead of one sentence you need a paragraph that says why these two relate or don't relate to glyphosate, because I struggled with that.

The whole next section is going to focus on the maximum doses and how often you call on the limit dose argument to remove a trend effect. And

so rather than beat on the statistical test, let's go back and actually define our terms and make sure we know why you kind of were able to invoke that. And then we'll have this conversation again in the next section.

On the second section on statistical analysis to evaluate dose response and tumor incidences --

DR. JIM MCMANAMAN: Can we hold comments until we get to that section? Because we haven't actually don't it yet, so we're still on A.

DR. KENNETH PORTIER: Well, this is on the process.

DR. JIM MCMANAMAN: Okay.

DR. KENNETH PORTIER: Not on the analysis themselves, but it's on the process. And I think the discussion here lays the argument, that EPA uses a lot, between the multiple comparisons and the trend test. And they actually quote, on page 72, from the Guidelines, this paragraph about the trend test. And the key word is in the first word, in the last line of that quote, which is, "Either kind of test is sufficient."

And I think you're going to see a lot

of us keep coming back to that saying, well if either is sufficient, logically, that means if one is significant, I don't care about the other one. And what happens is, you show one's significant and one is not significant, and I chose the other one. And I think if you're going to deviate from the guidelines by a different logic, you need to set up why you can use that different logic.

And then the final point I want to make is, that in the arguments that follow, there's a lot of discussion about monotonistic dose response. Yet in this section, you don't really talk a lot about monotonic dose response. And again, if you going to use that as criteria in assessing the quality or evaluating the quality of these studies, and the results from the studies, you need to set up your argument here for why monotonicity in dose response is going to be an important criterion. It is part of the process, it's not the analysis.

DR. JIM MCMANAMAN: Okay. All right.

DR. KENNETH PORTIER: Setting up the process so that we know what the rules of the game are.

DR. JIM MCMANAMAN: Okay. Great. Dr.

Sheppard.

DR. LIANNE SHEPPARD: Yeah. I actually appreciate that I followed my colleague, Dr. Portier. Because those were excellent comments and I agree wholeheartedly with him, and I couldn't have said them as well myself.

I have to say that I spent hours, not being an expert in toxicology, but understanding something from a different panel I was on a while ago about the design of toxicology studies. I spent hours figuring out why was this limit dose important, and what was going on with it.

And of course, there's the relatively recent commentary with your brother, Chris Portier, as the first author, talking about the contract between the IARC conclusions and the European Food Safety Agency. Where they liken the limit dose to the maximum tolerated dose, which is, I think, incorrect.

That got me going even more because then I was really confused, not being a toxicologist. But I think it's important to emphasize that the limit -- as I finally think I've discerned from the guidelines, which say it's not recommended that you exceeded, because it's about the design of the

studies.

So once the studies are designed, they are what they are, and then you analyze a whole study. You don't get to change the design after the study is done. It's an experiment and the doses were chosen for a reason in an experiment. And so, the limit dose -- and most of the studies go up, plus or minus -- the limit dose is like a guideline maximum under certain conditions, is what I understood it to be. Particularly, which I believe I understand -- again, this is not my area of expertise -- with a compound where the maximum tolerated dose is really, really high. And so, then the limit dose kind of weighs into design of the study.

Once you have the design, that's your data. And you've collected the data. You don't get the throw out the high dose then. That's like, illegal.

That's really, really basic. It's really important to recognize that animal toxicology studies are designed to understand the dose-response relationship in animals, where we can't afford to study enough animals that we can find one in a million cancer. We're looking for 1 in 10. That's what we

powered the studies to do, is to detect 1 in 10 cancers, not one in a million.

For people, we care about one in a million. That's why we have the whole discipline of risk assessment as we take the hazard assessment. And once we understand what's hazardous, then we translate that to a risk assessment where we do that kind of, okay, we care about one in a million, but we know about 1 in 10 and bigger, or whatever, from animal studies. How do we do that extrapolation?

That's a whole area that's covered by risk assessment. We're not doing risk assessment. We're doing a hazard evaluation. And so, that's super important here.

The full spectrum of the doses absolutely has to be considered and are relevant to the goal of this, which is determining the cancer potential from the studies.

I just wanted to expand on that point a little bit. The other point that my colleague talked about was that monotonicity argument. And as far as I can tell, it's a completely non-statistical evaluation, and therefore, should not be done. Period. That should be dropped.

If you going to do some evaluation of monotonicity, then look for, you know, deviations from linearity, using a statistical test. It's like another degree of freedom beyond the Cochran-Armitage test. That I could accept. But this non-statistical evaluation, after you've done the statistical analysis, is completely inappropriate.

Getting back to the charge question. I interpreted as it also being Section 4.3, but also 4.2. And I have to say that, the criteria that have been laid out don't appear to be following the guidelines, which -- as we've heard, in some specific cases. And that's a problem.

And the new criteria that have been introduced, but don't follow the guidelines are not appropriate; specifically, the use of the limit dose, the lack of monotonicity, and the way the historical controls were applied. The evaluation also, was not comprehensive within endpoint.

I believe that a systematic review should be done by endpoint. And appropriate pooled analyses should be done that account for all acceptable studies that address that particular endpoint. My understanding -- and again, I'm not a

toxicologist -- but my understanding is that you not combine endpoint species and genders and pooled analyses; because not only does it violate the spirit and probably the letter of the guidelines, but also the scientific interest is in whether there's any carcinogenic potential that is relevant for humans.

And so, you need to look at each outcome and each species and, I believe, each gender separately in order to answer that question. Because my understanding is that there could be a carcinogenic effect in a rat and not in a mouse because of different species. It's not appropriate to say oh, we didn't see it in rats, but we saw it in mice. But it's not relevant because there was nothing in rats. It's relevant if you see it in mice alone.

And then with end species, there are some strain differences that I don't fully understand. I defer to my colleagues that know better about those details. And then there is clearly a lifespan consideration that's also important in these studies; whether they're 18 or 24 or 26, and that's all really important.

I did find that -- and I'll come back to this -- but I did find that some of the pooled

analyses that we saw were very valuable, with respect to answering the questions; and gave us much better insight than what we saw in the document, which picked out each tumor and study separately. That was not a useful way to do it.

DR. JIM MCMANAMAN: Thank you, Dr. Sheppard. Dr. Green.

DR. LAURA GREEN: Just to, I think, summarize, I'm not sure we have consensus, but we have more agreement than I think maybe is apparent. Focusing on the agency's review and evaluation process, I think we are all saying there is an unusual richness of data here, which could be more fairly analyzed than has been done in the draft document.

I think we're saying that -- at least I'm saying -- that the way the German guy presented it made sense because he was asking, when you test the hypothesis, do Leydig cell tumors show up in a Sprague Dawley rat; when you tested it three or four times -- there are three or four tests in the Sprague Dawley rat -- are they consistent for Leydig cell tumors or not? The answer is no. Once their positive three times they're non-positive.

And you're quite right, that it varies

by species, and string, and sex. Obviously, females have mammary gland tumors and males have testicular tumors, and never the two shall meet. Whatever.

But it's a little more complicated with regard to things like lymphoma, which you do not expect sex differences within the same strain, so it depends a little bit. But I think what we're all saying is, you all would do yourselves a favor if, rather than analyzing each, study by study, and seeming to say the same thing, which is, well it looks a little positive, but we don't believe it.

The way the German guy did it was, if it's non-positive just say it's non-positive. If it's positive, either say it's positive or say it's equivocal. And then wait till the end and then group them and see how many tests you have in the same species and strain, and sex. Or both sexes, again, if it's a solid tumor or you don't expect a sex difference, before you can come to a sensible conclusion. And if you do that, I think we all think it would be more helpful.

And if you need to go to the next level of statistical sophistication for multiple comparison testing, which is beyond my capability to do,

certainly -- I don't know whether it's beyond your group's capability to do, but it's certainly beyond my capability to do. But at a minimum, presenting the data the way the German guy did, not relying on historical controls; I think we all agreed that was post hoc and unfair. Especially for things like lymphoma that show very late in animals, when we're only talking about an 18-month study. That was really just too post hoc for any of our taste.

But I don't think you need to do that because, again, once you look at lymphoma responses across all the animals, I don't think you're going to need to bring up the historical control issue. It's not going to even raise its head.

I think we still have some differences, probably, but I think we're in agreement in most of what I just said. No?

DR. KENNETH PORTIER: Well, we're going to get to historical controls. But there was one word you said that I'd like you to strike from the record, and that's "fair." I think what we're talking about here is, clear rules and consistent application of clear rules.

DR. LAURA GREEN: That's what I meant.

DR. KENNETH PORTIER: Well, that's what you meant by "fair" but we were quite sure. And I didn't want people to feel like we feel it's been an unfair analysis. It's at most, inconsistent application of some unclear rules. That's the way I look at it.

And they can improve their process by clarifying the rules, and then consistently applying them. And then maybe summarizing them in a better way to make it clearer, of what the gestalt of all of it looks like.

DR. JIM MCMANAMAN: Dr. Ramesh.

DR. ARAMANDLA RAMESH: In the same line, the Agency never said they didn't believe in it. The term they used was inadequate. Probably that needs to be revised, reframed

DR. JIM MCMANAMAN: Thank you. Other comments. Okay. I'll go back to the Agency then -- do you need further clarification?

MS. DANA VOGEL: I think one clarification we have is we missed what you just said at the end, and we want to make sure we understood it. Could you repeat?

DR. ARAMANDLA RAMESH: Yes. Some of us

were saying that the Agency has thrown out some studies. The Agency said that you guys did not believe in it. What I said was that was not right. In one of your slide presentations, some studies were judged as "inadequate." Probably, that was keeping in line with the selection criteria the Agency had adopted to characterize the studies.

DR. KENNETH PORTIER: I think he's saying it's a pejorative here. You're kind of ruling the researchers. Probably a better term might be "not valuable" for the assessment that you're doing. I mean, that's the assessment you're really saying is, we're judging this study, that's less or not valuable to what we're trying to do here. You're not judging the researcher's doing the experiment, and saying you're an inadequate researcher.

DR. LAURA GREEN: Or maybe not probative. I mean, not probative or something.

DR. JIM MCMANAMAN: Yes. I think they get the point. That was Dr. Portier, Dr. Green, and it was Dana Vogel that asked the question.

We'll go back to the Agency.

MS. DANA VOGEL: I guess just to clarify what I heard, I did hear some differing

perspectives. I heard some things that were the same amongst the panel, but I also heard some conflicting opinions. If that could be spelled out in the report, I think that would be helpful to us.

In addition to that, in the interest of getting through this question as much as possible today, we do want to make some clarifying points about what we did and didn't do. Because it seems like there's some misunderstanding of certain analysis we did or didn't do. But I'm wondering if that might be better served either at the end or first thing tomorrow morning. Because there are just some things that were said that, I think, might be a misunderstanding of what was actually done.

DR. JIM MCMANAMAN: Maybe at the end.

MS. DANA VOGEL: Okay. We can hold them all and put them all together. That's fine with us.

DR. JIM MCMANAMAN: Sure. That's good. Okay. Thank you, Dana. All right. If we can read Charge Question 3(b).

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar with Charge Question 3(b).

For some of the available animal

studies, statistically-significant trends in tumor incidence were observed with the lack of statistically-significant pairwise comparisons, when adjusted for multiple comparisons. Please comment on the agency's methodology and interpretation of statistical analyses to evaluate a linear dose response (trend test) and increased tumor incidence as compared to controls (pairwise comparisons).

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The lead discussant on this is Dr. Zelterman. The associate discussants are doctors Crump, Portier, Ramesh, and Sheppard.

Dr. Zelterman.

DR. DANIEL ZELTERMAN: Well, there's a tremendous sense of déjà vu here that is so much of what was covered in the previous. But let me see if I can say some other things. I do have one slide. This is as if to beat to death the Lankas data. Here it is again.

This was just discussed. Dr. Dunbar presented this on Tuesday, so there's nothing new here. There's nothing new here. I'll use this as an example and keep coming back to this in the charge.

Overall, the pairwise comparisons are

going to have much lower power than the tests for trend. The published studies, if you do studies in nutrition, they'll often compare the highest and lowest quintiles, looking for differences in the extremes. However, these methods suffer from -- there's going to be a lack of power and the interpretation just flies out the window. I don't know how you interpret the very highest dose to the very, very lowest doses.

I can hear anybody trying to point to the EPA and howling with the interpretation you're trying to make from this.

DR. JIM MCMANAMAN: Dr. Zelterman, can you move your mic a little bit closer? We're having a hard time hearing.

DR. DANIEL ZELTERMAN: In the charge, you're looking for a linear trend. I don't think anybody expects a linear trend. Instead, we're looking for a monotonic trend in the unobservable underlying population. But here's a point that was just made in the previous charge. There's no reason to expect to see a monotonic response. The EPA is confusing the underlying population rates with the observed empirical rates. And these are, so help me,

on opposite sides of the wall of China. These are totally different concepts. You can't confuse these.

There are other methods that I've heard mentioned, the NOAEL and LOAEL, looking for the lowest change point in exposure from the control group. These also have very low power and I just throw them out.

What I like to see is, instead of the Cochran-Armitage test, I'd like you to also embrace the Mann-Kendall test, which is nonparametric for trends. I didn't see this anywhere. It's the probability that a higher exposure will have a higher response rate. In the formula, you look at permutations; the number of times the higher dose exhibits the higher response.

Instead, the Cochran-Armitage talks about the differences of the rates. Now, who among the epidemiologists talks about a difference? We don't. We talk about ratios, and odds ratios. So again, Cochran-Armitage doesn't have an easy interpretation. You're looking at differences of rates. I don't know how to interpret that. It's hard.

What I'm going to be coming back to is

a lot of these are the defaults and SASS. Using SASS and their defaults doesn't make you more virtuous or taller.

How about embracing logistic regression? All right. Just go full parametric. These are going to have the most power, and you also have a nice simple interpretation in terms of the dose response. I didn't see any logistic regression. But these are going to look for trends.

They're going to look for trends in terms of odds ratios. There's a nice interpretation. There is lots of power there. You have to make some assumptions, but that's okay. Nobody is going to fault you on this.

The Fisher's exact test; you know, there's a comparison of all the Fisher's exact tests. The Fisher's exact test was used to perform pairwise comparison. Simply, it enumerates all the possible combinations of responses that could have occurred in a 2 x 2 table. Using the exact text, is again, not a virtue. It doesn't make you taller or more handsome. In fact, it underestimates the effects. It's well known to have low power and underestimates the effects --

DR. LAURA GREEN: Can I ask a question about what you're doing so we can all follow you?

I don't mean to interrupt, but I just want to know whether -- I mean, maybe everyone else understand this. But in your bottom table, are you applying those tests to the data in the top table?

DR. DANIEL ZELTERMAN: That's right.

DR. LAURA GREEN: Thank you.

DR. DANIEL ZELTERMAN: Yes. There was an FDA memo, 385. I think it was -- I just listed all of the summary tables and all of the summaries statistical comparisons. And these were just extracted from that.

DR. LAURA GREEN: I'm not very quick.

DR. DANIEL ZELTERMAN: Okay.

DR. LAURA GREEN: Just so I understand, what you're walking us through, in your bottom table, are different ways of statistically analyzing, and therefore getting both raw p-values and whatever the Sidak p-value is, different ways of analyzing the same dataset. And it's the dataset that's presented above.

DR. DANIEL ZELTERMAN: That's right.

DR. LAURA GREEN: Good.

DR. DANIEL ZELTERMAN: All right.

Maybe I should've taken a minute to --

DR. LAURA GREEN: No, it's probably obvious to everyone else.

DR. DANIEL ZELTERMAN: Okay. Well, it's not obvious to me, so let me explain it.

The mice are at controls in four different doses. And in the last column, are the totals adding up all the way across, the rats. It's a Lankas study.

DR. LAURA GREEN: They are Sprague Dawley rats.

DR. DANIEL ZELTERMAN: You know better than I with this. Tails, but furry. All right.

And looking at where it says Fisher's exact, bling, bling, bling, it's comparing the control group with the lowest dose, and then the control group with the medium dose, control with the highest dose. You have three different comparisons. And Cochran-Armitage gives you one p-value for the whole, what did you say, gestalt.

DR. LAURA GREEN: And that was what the Agency used, right?

DR. DANIEL ZELTERMAN: Yes.

DR. LAURA GREEN: Got it.

DR. DANIEL ZELTERMAN: This was what the Agency used and this was a document that -- I didn't do the computing here. This was No. 385 of all the documents he sent us. This was the analysis, at the bottom, was from that document. All right. Okay.

So where was I? Fisher exacted, it doesn't make you taller or more handsome because it's called exact. Exact just enumerates everything that could happen. But it underestimates effects and the p-values are not going to be as robust and forthcoming as you would like. Use the Pearson chi-square that you learned about in grad school.

Now, for multiple comparisons, the Sidak comparison. This is used for multiple comparisons and you'll see there's a last column there for the Sidak p-value. Briefly, this is a default in SASS. It assumes the tests are independent and it's commonly compared to the Bonferroni. You may have heard of the Bonferroni correction. Okay.

And Dr. Sheppard pointed out to me, and I can verify this, that if the p-value is really, really small, it doesn't matter if you use Bonferroni or Sidak. It doesn't matter. As long as the p-value is really, really small. In fact, if you can see the

smallest one at the very bottom, it's like, three times as large, which is exactly what Bonferroni would've said. You did three tests. All right.

DR. LAURA GREEN: Wait. You lost at least me.

DR. DANIEL ZELTERMAN: So what's the last numbers? I can't read that.

DR. LAURA GREEN: You mean the 0.039?

DR. DANIEL ZELTERMAN: .013. Yeah, 13 and then 039. It's three times as big. When the p-value is really, really small, the raw p-value will be one-third the corrected value.

DR. LAURA GREEN: And that's like, some rule of thumb or something?

DR. DANIEL ZELTERMAN: No. It just happens -- I'm not going to go to the board and start writing down formulas, but it's true when the p-values are really small.

DR. LAURA GREEN: And why do we care about that?

DR. DANIEL ZELTERMAN: Because it doesn't matter whether you use the Sidak or Bonferroni --

DR. LAURA GREEN: Got it.

DR. DANIEL ZELTERMAN: -- for the really small p-values that matter. All right. So where was I? Oh, yes.

Bonferroni is going to find fewer statistically significant results. The Sidak is less stringent for the same false discovery rate. However, let us bring ourselves to the 21st century. Benjamini-Hochberg correction is now state-of-the-art. In fact, who knew, all right? But it's not the default in SASS, so it doesn't bestow virtue. All right.

When I worked at the sister agency at the FDA, across town, p-values have a very different meaning; and a lot hinges on those p-values. I've been shocked, shocked at the way the p-values have been thrown around here. I'm going to talk about this example and all the p-values here. Benjamini-Hochberg, I spoke to your programmer. Yes, I spoke to this guy and showed him how to do it. It's easy enough. And in my write-up, I'll give an exact reference that you can cite for this.

Let me cite this example. And this was a dataset that we had. And I explained the data. You're right. It's 50 rats, right? And each of four different groups. And 200 were examined by

pathologists. This is all data that we've talked about. Cochran-Armitage compares the four exposure levels. In this example, the Cochran-Armitage detects a trend, but only the most extreme of the pairwise comparisons are statistically significant.

Now we take a deep breath. The three Fisher tests are not independent. They all compare higher doses to the same control. You can't use the Sidak correction. The tests are not independent. I'm not going to go and start doing a whole lot of mathematics, but common sense would say those three tests are not independent of Cochran-Armitage either.

I have these four that is somehow related. You know, it's not obvious, maybe they're not married, but they're cousins. You know, they're related in some interesting way. All right. Should we correct for three or should we correct for four? Now it gets interesting. What are we really doing?

Let me go back to the Lankas reference. And they point out elevated tumor rates illustrated here. And sometimes they talk about it in the introduction. They said, look what we found, look what we found. And if you read the introduction, it goes on and on and they say, look what we found. And

they repeat it several times. But then you have to -- and I cite, page 2,841. That's where it gets interesting because everything up until then is talking about how much they ate and how much they pooped. All right.

There were also female rats. The rats were examined for tumors in other body parts by pathologists. I went there and I counted 32 hematology parameters, eight organ weights, 38 microscopic examinations for a total of 78. Then there were two sexes, three doses compared to controls, and overall trend for increasing dose, for a total of 624 p-values.

Now, what is the probability that the smallest p-value is statistically significant at the .05 level? We would have to use either Bonferroni or the Sidak, something like roughly one in a million. It'll be pretty darn small.

What are the chances of finding a p-value in this enormous dataset that's less than .05? Dr. Green, what was your word? I won't repeat your word, but the answer is virtually certain we will find statistically significant results with like, probability 1.

Conclusions. I've kept you so late and everybody wants to go home. Cherry-picking your p-values removes any useful interpretation you assigned to these. The P values mean nothing. Pairwise comparisons are going to have lower power than tests for trends, and are going to be more difficult to interpret. The appropriate corrections for multi-comparisons really needs to be formed in a very thoughtful manner. Not just four tests, but the hundreds of tests that actually were performed. It's not clear how many tests were performed in order to check for this.

They are not specified a priori. Again, when I worked at the FDA, they have to specify the p-values a priori, before they go out and invest a lot of money following patients to see if the drug cures cancer.

DR. LAURA GREEN: Can I ask, though, I don't really get how there's 600 tests. Let me try to reframe it. Let's say we're not interested in pairwise comparisons.

DR. DANIEL ZELTERMAN: Right.

DR. LAURA GREEN: We're just interested in trends. We would only do one trend test per sex,

per tumor type. That would only be like, let's say 100 tests, right?

DR. DANIEL ZELTERMAN: Well, it was 30 different tumor types, but then they also tested for trends in organ weights.

DR. LAURA GREEN: No, but that doesn't count.

DR. DANIEL ZELTERMAN: That doesn't count?

DR. LAURA GREEN: Okay. Because that's not cancer.

DR. DANIEL ZELTERMAN: Okay.

DR. LAURA GREEN: No. I mean, I don't think we're being completely -- that's what I'm trying to --

DR. DANIEL ZELTERMAN: Okay.

DR. LAURA GREEN: -- get to here. I don't care about organ weights. I don't care about -- if all I'm asking myself as a cancer biologist is, I did this experiment, I'm going to test each sex and tumor type for trend. I'm sorry, you said there were 38 tumor types?

DR. DANIEL ZELTERMAN: Yeah, 38 tumor types and then --

DR. LAURA GREEN: Okay. Isn't that only 76 trend tests?

DR. DANIEL ZELTERMAN: Yeah. Okay. Let's make it 100. I like 100.

DR. LAURA GREEN: No, let's do 76.

DR. DANIEL ZELTERMAN: No, 100 is going to be easier because --

DR. LAURA GREEN: Okay. Let's do 100. What do you get?

DR. DANIEL ZELTERMAN: What's .05 over 100? It's going to be .000 --

DR. LAURA GREEN: Two.

DR. DANIEL ZELTERMAN: Something.

DR. LAURA GREEN: Which way does it go? Sorry.

DR. DANIEL ZELTERMAN: So .0005, right? How many zeros?

UNIDENTIFIED SPEAKER: (Off mic.)

DR. DANIEL ZELTERMAN: Okay. It's .05 divided by 100. Take your smallest p-value.

DR. LAURA GREEN: That's five times ten, minus four, right?

DR. DANIEL ZELTERMAN: Okay. And it doesn't achieve that. All right. I rest my case,

Your Honor. It's not small enough.

DR. LAURA GREEN: Okay. I'm sorry. What you're saying is a p-value that looks significant, but is in fact only 0.039? What's the --

DR. DANIEL ZELTERMAN: No.

DR. LAURA GREEN: 0.009. That's the trend.

DR. DANIEL ZELTERMAN: Yeah. Take the guy on top and multiple him by 100. It's going to be .9. There's your smallest p-value. It's like, .9. Is that enough to write home about?

DR. LAURA GREEN: No, of course not. Oh, is that the point?

DR. DANIEL ZELTERMAN: Yeah, that's the point. We've done 100 tests. Okay. So, .009 multiplied by 78, then.

DR. LAURA GREEN: Right. By 76.

DR. DANIEL ZELTERMAN: Or 76. It's still not going to be like, .05.

DR. LAURA GREEN: Okay. Just so I understand it. The right way to do multiple comparison is you take, in this case, 76, you multiply it by the p-value, and if the p-value is way big, which it’s going to be, then the multiple comparison

test indicates that this one significant result is not significant?

DR. DANIEL ZELTERMAN: Absolutely. You got it.

DR. LAURA GREEN: Yes.

DR. DANIEL ZELTERMAN: Good. Higher math. All right. What do we got? They were not specified a priori just because SASS -- and in summary -- just because SASS uses a method and SASS is the default, it's not taken as an endorsement or the best possible method. In an earlier charge, they referred to Sujimoto, but we didn't receive that.

The fella from Germany, the nice presentation he had with the great big table of p-values, that was a very nice presentation. And it would be nice -- and here I don't have it, but this is maybe saying I've got to go home and write a paper about it. It would be nice to say here's this great big table and I want p-value for the whole table. That would be really nice. That would be so cool.

DR. LAURA GREEN: Is that doable?

DR. DANIEL ZELTERMAN: Oh, yeah. But we got to write the paper first. I mean, I don't know how to do that. I don't know how to do that.

DR. LAURA GREEN: So can I ask a related question because it was my mishegas?

Can we use your method to combine the Lankas result with the Stout, and whatever it is, the replication at the higher dose?

Remember, there were like three or four Sprague Dawley rat bioassays, all testing glyphosate. Could we do something like this multiple comparison thing across all four Sprague Dawley datasets?

DR. DANIEL ZELTERMAN: Absolutely.

DR. LAURA GREEN: And would that be meaningful?

DR. DANIEL ZELTERMAN: The easiest thing to do is multiply your p-values by four. But as in this case, you see you got to multiply them by something much bigger. But it's basically that. You multiply your p-value by the number of tests you did.

DR. LAURA GREEN: Okay. Now I just want to ask about my counterfactual or positive control.

DR. DANIEL ZELTERMAN: Bring it on.

DR. LAURA GREEN: If the compound we were looking at were vinyl chloride, and we had four tests of vinyl chloride and they all showed only one

tumor response, which was angiosarcoma of the liver, and everything else was non-positive. Wouldn't your analysis discount that?

DR. DANIEL ZELTERMAN: It would, but then, of course, you'd go out and you'd replicate and you'd see more liver cancers in other studies. And these would be replicated. This was just cherry-picked and it's totally out of context.

DR. LAURA GREEN: So --

DR. JIM MCMANAMAN: Okay. Can we --

DR. LAURA GREEN: Okay.

DR. JIM MCMANAMAN: We're getting more into an educational component than an evaluation component. All right. Dr. Zelterman, are you finished?

DR. DANIEL ZELTERMAN: Yeah, I'm finished. And Kenny is next.

DR. JIM MCMANAMAN: Okay. Dr. Crump.

DR. KENNY CRUMP: There are several questions about the analysis of the animal data. And some of these questions don't really fit the questions. I'm going to be making comments along the way. I'm not sure exactly what order to make them, but I will try to find my comments here to things

people have already addressed.

I think the biggest problem that I see in the analysis of the animal data, is we go about it from the wrong perspective. We go through tumor by tumor by tumor by tumor. Oh, here's one, here's one, here's one, here's one. And we don't get a sense of a global picture. And that's what we're missing here.

Dr. Haseman gave us some useful information in his analysis the other day. He computed the expected number of positive results you would see just by chance in a bioassay. And if you think about it, you should see roughly, anytime you analyze 20 tumor sites, you expect to see one positive even if there is nothing going on.

If you analyze 200 tumor sites, how many positives are you going to get? I mean is not quite .05, but probably less than that because of discrete things. But you're going to see a lot of things. If you don't, something's wrong. Something is wrong if you don't see a lot -- even if nothing is going on -- if you don't see a lot of significant results in analyzing these data, you got to figure out what's going wrong. You're supposed to see that, just

by chance.

I think the first thing we need to do is figure out how to handle that situation. I think Dr. Haseman had, at least, put things in perspective. He showed, due to his calculations, that the number of positive results we saw in the studies were less than a number that you would expect, if you just throw the animals with cancer into groups just by chance. And I think that's useful information.

DR. LAURA GREEN: Although, Kenny, can I ask; because Dr. Haseman also qualified it several times by saying it also depends on the strength of the positive result. Right. Isn’t it also important -- I mean, let’s just use this. If this one result, you know, gave us a really strong dose response, wouldn't that change?

DR. KENNY CRUMP: Yes. You could take that into account also. Let me finish, okay.

DR. LAURA GREEN: Okay.

DR. KENNY CRUMP: I did essentially the same thing Dr. Haseman did, except I didn’t ever get through with it. This is very tedious to do that. I need a toxicologist to pull out all the stuff I should be looking at, so I'm not looking at the wrong things.

But I looked at three studies, two rat studies and one mouse study, and computed it just like Haseman did. The expected number of positive results, less than .05, you would see in those studies, given the tumors; they just permute the tumors at random. And I got something, 4.5, I think. You expect to see about 4.5 significant results.

In that study, there were three. You got fewer than what you expect to see. I think that tells you something. And let me say, there are tests that you can use, global tests. You don't specify a result in advance. You say, what's the probability, these data show a carcinogenic effect anywhere. And you apply the test, and it has the correct false-positive rate, and you get the result. And then you can look and see if it is positive, where it occurred. There are several such tests like this, which I don't think they've ever really been applied. I don't know why.

There's one that I'm familiar with by a guy named Crump. A long time ago, Farrah and Crump (1988). There's one by Westfall (1985). There one by Brown and Fears (1981). And all of these tests, they're all very similar. You can apply them and

decide, globally, without looking at any tumor individually, what's the probability there was a significant tumor significant response anywhere in this study. I'd like to at least recommend that EPA take a look at those.

DR. LAURA GREEN: Do you need the raw data for that?

DR. KENNY CRUMP: Yeah. The problem is, one of the difficulties is you need individual animal data. Every animal -- you need to know which tumors occurred in every single animal. And then you permute animals in dose groups. It really has the same assumptions as the Fisher's exact test and the exact Cochran-Armitage test. It's conditioned on the tumor pattern you saw. That's what the Cochran-Armitage test does. That's what the Fisher's exact test does.

And just to give you an idea, we developed this test, like I said, 30 years ago, and we applied it, I think, one example for our report. We never looked at it again. But I remember in one case, a study of male mice, there was -- hepatocellular carcinoma was statistically significant, by itself, at .027.

And when we applied it as a global test, the test overall, was there any evidence on male rats, the p-value was only .15. This can make a big difference in how you interpret the data.

I think Bonferroni is another application, but I really think a test like this, that would give you an exact p-value, corrected for multiple comparisons, would even be better than using Bonferroni.

Okay. Let me go on to something else now. Oh, let me just say that although the Cochran-Armitage's trend test uses a linear dose response in its definition, it has power to detect all monotonic responses. Just because we get a significant linear trend, it doesn't mean that the dose response is linear, because it has power for all kinds of monotonic responses. We should keep that in mind.

Now, about pairwise tests or trend tests. Well, first of all, I think typically the trend tests would have greater power for detecting effects than pairwise tests. And I also think that having multiple tests for the same hypothesis just complicates things. And I also agree with what Daniel just said, that if you have three pairwise tests and

one trend test, if you're going to correct for both the comparison, you ought to throw the rend test in there to make that correction.

My recommendation is that you use one test consistently that has high power, and I think that would be a trend test. And just don't do the other tests. And your practice of down-weighting a trend test, if the pairwise tests are not significant, I think it's also against her guidelines. Someone said that it says if you get a trend test, either one, what your guidelines say is enough. You don't need to worry about the other one. But I will go further than that to say, just don't do the one. Just do the powerful trend test.

And by the way --

DR. LAURA GREEN: Kenny, wouldn't there be instances in which --

DR. JIM MCMANAMAN: Can we let him finish?

DR. LAURA GREEN: Oh, I'm sorry. I just had a clarifying question.

DR. JIM MCMANAMAN: No. We need to let him finish because there are other people that have -- and then we can clarify things at the end there.

DR. KENNY CRUMP: By the way, none of these tests that I believe were done in the EPA report were age-adjusted. And I would suggest that you should use an age-adjusted test. You should actually repeat those using an age-adjusted test. I would suggest maybe the poly-3. I'm not sure it's going to make any difference. I'm not sure there are great age differences in these tests, but I would just suggest that you just routinely adjust for age differences by using a test like the poly-3 test.

Let me see what else I have here.

I agree that throwing out dose responses that are nonmonotonic, you just shouldn't do that. That should not be a criterion at all. The true dose response can easily be linear, even though you observe dose responses -- I mean, should easily be monotonic even if the observed dose response is nonmonotonic.

And to convince myself of that I did a couple of simulations; where I took a monotonic dose response and generated data from it. I took two different cases, in both cases, the observed dose response was nonmonotonic over half the time. The idea that a dose response is nonmonotonic, it just

doesn't tell you anything.

DR. LAURA GREEN: Well, it's like this dataset.

DR. KENNY CRUMP: You shouldn’t be doing that.

DR. LAURA GREEN: I mean, this dataset is a good example, right?

DR. KENNY CRUMP: Yeah, yeah, yeah. Now, there are times, if they’re widely nonmonotonic. But even then, I just wouldn't worry about it. Just don't worry about that in conducting your test.

The EPA evaluation gives far more weight to the question of whether the observed response was monotonic than it deserves. Also, I'll comment on the use of the limit dose. It's already been commented on here. I think I agree with what other people have said about that.

First of all, I don't think what you're doing is specifically following the guidelines. When I read the guidelines, I read that for a feeding study, the limit dose was 5 percent in feed. And 5 percent is bigger than any of the doses in any of these studies.

There's a question if you're even

following the guidelines in that respect. But I do wonder -- I think it was Dr. Sheppard talking about that. I do question whether you need to have any limit dose or not. Just worry about the MTD and then if that gets something at the MTD, then you have to do a risk assessment and try to figure out what might be happening at low dose.

So just because something is significant at a really high dose, much higher than a human dose, it doesn't necessarily mean that you don't have to worry about what's happening in doses that humans are exposed to. It depends on what the dose response is. Each one of those animals is a stand-in for millions of humans. You know, we're interested in risk around one in a million sometimes.

Okay. I think that's all the comments I have right now on the analysis of the animal data. But I will have others when we talk about other issues, questions. Thank you.

DR. JIM MCMANAMAN: Thank you, Dr. Crump. Dr. Portier.

DR. KENNETH PORTIER: Hopefully, I'll be a little terser. By the way, 5 percent is 1250 milligrams per kilogram a day, and I think the

recommendation now is 4 percent, which is 1,000 milligrams. That's what those documents were kind of saying. They've lowered the limit dose. I mean the EPA Cancer Guidelines just may be behind the times on this. That's all.

DR. KENNY CRUMP: You're talking about mice or rats?

DR. KENNETH PORTIER: That was for rats. I didn't compute it for mice. I can give you that. I concur with what both of these have said. I mean, I didn't have the energy to go through and do all that analysis, and I appreciate what Dr. Haseman did, because I certainly wasn't going to do that.

The Sidak test that you used is not referenced anywhere in the document. I wasn't sure if that was Sidak or Sidak Shu (phonetic). There's a couple of Sidak multiple comparison procedures. You need to put the reference in the doc.

I would say that the Sidak test, I think you're using, is a modification of a Dunnett's procedure. It's not a full multiple comparison. It's a control vs. treatment and it modifies the P value the farther away you are in a rank order from the controls.

It may be a little bit more powerful, I guess, in some situations. It might be justified if the Dunnett test is there. But it doesn't take us away from this global experimental multiple comparison, what we call data-dredging issues. I mean, what you're trying to avoid is data dredging.

And as Daniel was talking, I was thinking, that's why researchers look at 36 tumors, right? Because you're guaranteed of getting something to publish, right? And they don't want us to do this multiple comparison procedure, because then nothing would be significant.

DR. LAURA GREEN: That's not fair. But these studies aren't published.

DR. KENNETH PORTIER: Huh?

DR. LAURA GREEN: These studies aren't published.

DR. KENNETH PORTIER: Well, the industry ones aren't, but the private university ones are, right? The issue of exact versus approximate test didn't come up; but did come up in the Haseman and Chris Portier papers. And I really think Dr. Haseman did a good job of kind of raising that issue and highlighting how important it is in doing the

test, especially with rare tumors like this. This can be very important in figuring out what's marginally significant and not significant.

On the monotonic dose response issue, there are statistical test out there to look for things like a strict inequality in dose response like a Jonquière. Jonquière test, nonparametric test. But as Dr. Zelterman mentioned, these are very weak tests.

Even if you do them, we're not quite sure -- for these samples sizes, I'm not that quite sure, in a cost/benefit analysis, it’s even worth your time to do it. I mean, if you want to say it, it just adds another test to that list of 624 tests. You'd just have another test you'd have to take into account.

The final thing I wanted to point out -- let me just make sure -- is that, you know, what we've been talking about here, in terms of answering your questions about the methodology for interpreting the analysis, is that we're arguing about false positives. And the problem is when you do these experiments, you have a high chance of coming up with a false-positive.

And the trick for you guys is figuring

out the real positives from the false positive. And I think when we get to Question 5, where we start talking about the Hill criteria and things like consistency and plausibility, is where we look at that suite of what was significant in these experiments. And we start to say, you know, is there consistent signal here?

So yeah, it might not be significant in Experiment 1, 2, or 3, but if I see liver cancer, liver cancer, liver cancer, liver cancer, that's improbable. I don't know how we'd figure that out, but, you know, most statisticians would say that's unlikely, that you would run four repeated experiments and get the cancer to come up significant in four independent experiments. Maybe even in two, it's maybe improbable.

The Cancer Guidelines that looks for things like repeated cancers in both sexes, or in multiple species, or in multiple experiments, are really trying to get at this repeatability and implausible under a randomization assumption, patterns. I think we're going to try to get to that. That's the issue of trying to get the real positives.

I think I'm going to leave it at that

because I don't really have much else to say than what these guys said.

DR. JIM MCMANAMAN: Thank you, Dr. Portier. Dr. Sheppard.

DR. LIANNE SHEPPARD: Not me.

DR. JIM MCMANAMAN: Oh, I'm sorry. Dr. Ramesh.

DR. ARAMANDLA RAMESH: I agree with my fellow panelists, who are experts in biostat. I have nothing to add.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Ramesh. Dr. Sheppard.

DR. LIANNE SHEPPARD: Now I'll take my turn. With all due respect to several of my colleagues who have spoken, I really want to put the comments into context. And to really think about the question that's being charged, the job that we have to do and the work that EPA has to do.

If the charge of our panel was to address how toxicology studies should be evaluated for use in cancer hazardous assessments, then I think a number of the considerations we've discussed in response to this charge question, about the best ways to analyze the data, are relevant. But our concern is

actually with determining the carcinogenic potential of glyphosate under existing guidelines.

We're not making up new rules, where following the existing rules. I'm really confining my consideration in what I'm responding to, to the appropriateness of the decisions and the procedures that the Agency has used within the context of the existing guidelines. And I think that is super important.

The data dredging considerations, I think this is really important that we pay attention to it. And unlike other compounds, at least my understanding, not having done this before that, you know, the database here is big. You can't ignore the multiple studies issue. I wouldn't call it a multiple testing issue because I think that's actually the wrong way to think about it. I think one of the things is, you know, really, how are we approaching the question. I think we should be likening the question here to how people approach safety studies in clinical trials. I'm not a clinical trials expert either. I'm not sure anybody else on the panel has expertise in that area.

DR. LAURA GREEN: Dan.

DR. LIANNE SHEPPARD: Dan. Well, maybe Dan can weigh in on this then. But, you know, in clinical trials when we're looking at safety, we're trying to understand any inkling that the drug is unsafe. Okay.

We're not worried about multiple testing in the same way, we're worried about any kind of signal that's out there, that tells us something that, you know, we didn't really understand before we started the study. And similarly, here, I think what we care about is whether there is compelling evidence that this compound, glyphosate, is carcinogenic in animals. That's what we care about.

The idea of pooling a whole lot of tests together and looking, you know, at lung, with lymphoma, with all the other cancer endpoints. You know, we've already discarded the weight and all that stuff. It's just not appropriate, scientifically, because that's not what we care about. Similarly, we wouldn't combine species because we care if it happens in one species. We don't care if it happens in both species. That's not the criteria. We care if there's evidence in one species.

The real question is, how do we do

that? And I think the most appropriate way to use all studies is to pool them. Pool the evidence about any particular tumor in an appropriate manner. And appropriate means that you pool -- properly taking into account things like study duration, species, gender, endpoint doses et cetera, I'll say, leaving it to the experts to determine what those things are.

And actually, I think the analyses that are in the Docket, and a spreadsheet that was updated by Christopher Portier, are actually really well on that path. I would expect that EPA, would want to redo that using their own actual criteria. And I don't want to get into the details of that, but I think that is how I would suggest approaching it.

I would not recommend adjusting for multiple comparisons. I would recommend pooling the evidence when there is an outcome where this looks important. Because we have multiple studies that are asking the same exact question, and they should be pooled.

With respect to what was done in the document, the agency's way over-weighting the pairwise comparison test. And evidence of trend is important in these small studies, if we're interested in

understanding carcinogenic potential. And furthermore, as we've already discussed, EPA's Guidelines do not state that both criteria must be met, as is clearly stated in the issue paper on page 72.

And in addition, the Agency is using additional non-statistical criteria such as monotonicity, that are neither guidelines nor sensible. There wasn't really any effort to understand why, for any given outcome, there were or were not similarly reported important trends reported in other studies.

And so, as I have already said, I think that the way to do this is to do a pooled analysis. And I would probably recommend random effects type meta-analysis, but that's maybe for a little bit more careful thought.

In my draft comments, I put in Dr. Portier's Excel spreadsheet because I think that's a really great example that we should be following. And I do want to acknowledge that ultimately, what we want to do is distinguish the false positives from the true positives. And we're all trying to figure out how to do that.

DR. JIM MCMANAMAN: Okay. We have a diversity of opinion. Dr. Zelterman, I saw you shaking your head. You were in agreement with some of what Dr. Sheppard was saying, but she was discounting the use of the multiple comparisons, and you seem to be in favor of that.

DR. DANIEL ZELTERMAN: Oh, I was mostly confused about the analogy to clinical trials. Because see, going in to talk about safety in a clinical trial, there is a lot of Bayesian evidence. That's another bad word that I apologize for using. But they already have a very good idea of what the side effects are going to be. And they know to look for them, and we plan accordingly. We know they'll be certain toxicities that we look for.

But there's a real objective, and the real objective is to find curative potential in the drug. And the side effects are something on the side that we already managed to get into account. But we don’t look for significance levels in doing many safety measurements on each patient, who is being treated for a more severe disease. It's not exactly a perfect analogy to clinical trials, but we do many, many tests.

DR. LIANNE SHEPPARD: The analogy was more in terms of the type of scientific question we were trying to answer and not the procedures that were being applied specifically. It was about the question that we're trying to answer.

DR. JIM MCMANAMAN: It seems to me, there's a lumping and a splitting here going on. Do the other statisticians agree with Dr. Sheppard that we should be just lumping all these studies together?

DR. KENNY CRUMP: I have a comment about that.

DR. JIM MCMANAMAN: Yeah.

DR. KENNY CRUMP: Well, the pooling is an intriguing idea. I'd like to know more details about it. I think the devil might be in the details. I mean, would you pool different sexes or would you pool different species? I'm thinking probably you wouldn't.

This doesn't really apply to glyphosate, but it does apply to a general type of pooling. Suppose you only had one study? There's nothing to pool, but you still got a problem with different things popping up, and you'd like to put that in some kind of comparison; and pooling, I don't

think would help you there.

DR. LAURA GREEN: Can I make some suggestions on pooling because I think it's easy --

DR. JIM MCMANAMAN: No. Let's let Dr. Sheppard respond. Because I think that this really gets down to the crux of how to provide useful information to the Agency about the approach. And I think she raised an important issue and we'll let her respond to it.

DR. LIANNE SHEPPARD: Well, first of all, we're not talking hypothetically, we're talking about the evidence that's in front of us. And you know, the guidelines seem to be more focused on the situations where you have one, or at most, two studies that you're interpreting. The guidelines don't address how to use the evidence from multiple studies, where we have here, what, on the order of 15, if I remember correctly. Although, less, if you're looking within a species.

And in terms of what you pool together, I think that's more a scientific question than it is a statistical question. I would actually defer to my colleagues across the table, who are much better prepared to answer that question than I am, about what

you would pool. But presumably, you would not pool mice with rats. In many outcomes, you would not pool genders. And then, you know, I defer to them for any more elaboration.

DR. JIM MCMANAMAN: Dr. Parsons had her hand up first.

DR. BARBARA PARSONS: I have a pretty different perspective from what we've been discussing. I do agree that of all of the reasons to downgrade the statistically significant findings, that multiple comparison is a valid issue. But I don't think it's this panel's job to invent the best statistical approach to eliminate chance observations.

In fact, this is a regulatory agency. It's a risk management decision of what level of Type 1 and Type 2 error is appropriate to accept. You would not want to use a test that's going to ensure that you never observe a false positive.

This panel is charged with evaluating the documents, which is described as evaluating the carcinogenic potential of glyphosate, based on the Cancer Risk Assessment Guidelines. We have discussed this multiple comparison issue. If you're presented with the document, what do you analyze? Do you really

do statistical test on every possible endpoint? I don't think so. It would just completely eliminate the sensitivity of your assay.

Do you cherry-pick? I don't know that that was a good idea either. Different people might approach your document in different ways. It would be subjective. Regulatory agencies come up with these decision rules. They make a broad statement that yes, the 0.5 level is too high, but if we see a lower level, this is what Dr. Bus described to us. FDA has a decision rule, and that is .025 for rare tumors, .005 for common tumors.

Now, I think it is just completely implausible that the people who wrote the cancer risk assessment guidelines did not consider this multiple comparison issue. And I believe the guidelines address this and provide -- EPA has written in here a decision rule. I don't think there's any need for us to interpret what level of significance or what adjustment for multiple comparison should be used. And that's why, in my comments before, I highlighted tumor response that occurred with the statistical significance of .01 or below.

Let me just read it to you. The

Guidelines state, "Consideration of multiple comparisons should also be taken into account. Haseman (1983), analyzed typical animal bioassays that tested both sexes of two species. And concluded that, because of multiple comparisons, a single tumor increased for a species site combination that is statistically significant at the 1 percent level for common tumors; or 5 percent level for rare tumors; corresponds to a 7 or 8 percent significant level for the study as a whole.

Therefore, animal bioassays presenting only one significant result, that falls short of the 1 percent level for a common tumor, should be treated with caution."

So perhaps I'm over-interpreting, but I turned that on its head and say this sentence describes EPA's decision rules. And that significant results that fall below that 1 percent level of significance, should not be treated with caution. Meaning, they should be accepted.

I mentioned the FDA's decision rule. The 0.025 -- well, let's just talk about for common tumors, 0.005. This is what FDA uses and this is for drugs that are considered to be therapeutic,

potentially beneficial, and the whole population is not exposed. You know, there's no potential adverse effect associated with that.

The idea that EPA Guidelines would suggest a p-value cutoff that's two-fold more conservative, I think is very consistent with the regulatory mission of the EPA. And I guess I'll just stop right there.

DR. JIM MCMANAMAN: So I think that part of the problem in some of the discussion came about, while it does revolve around so much about the p-value, what p-value should be used, it was also some of the agency's evaluation. Whether they would include pairwise in one case and a trend in another case. I think that in terms of our discussion about this, we're asked to comment on their use of these particular approaches. And to that degree, I think that it can't just be about the p-value. It has to be about the approaches too.

DR. BARBARA PARSONS: Well, I agree with what everyone else has said; that the guidelines clearly state a significance in either a trend test or the pairwise comparison, should be considered --

DR. JIM MCMANAMAN: Okay.

DR. BARBARA PARSONS: Meaning as a treatment effect.

DR. JIM MCMANAMAN: Dr. Portier.

DR. KENNETH PORTIER: Just coming back to the question, which probably should be up there. The Agency is asking us to comment on the methodology and interpretation.

DR. JIM MCMANAMAN: Right.

DR. KENNETH PORTIER: Daniel talked about methodology that he would recommend changing. And I think the three of us have talked about how you would interpret it. And then Dr. Sheppard came back and said -- and she maybe approached this with a different methodology. And I was sitting there thinking about a modeling methodology, and there's a lot to offer there. I mean, you know, that's what statisticians do, is help you put this stuff together.

Yeah, there's a lot of questions we'd have to answer before we could jump into those models. I was sitting there saying why couldn't I do that? I can't come up with a good answer of why I couldn't do it. Kenny, maybe you can come up with one.

Why we couldn't combine them, logically, but it's not EPA's normal methodology. And

I think Dr. Sheppard put her finger right on it, that the guidelines really are the typical database, which is two, maybe three studies. I've sat on this panel 50 something times. I don't think I've ever seen nine rat studies and six mouse studies that we're looking at, with a chemical that has such a weak toxicity signal. I mean, the combination is driving us crazy.

But I think that that is a mixed-effect model with an appropriate dose response curve, taking into account sample sizes. Taking into account the age at which the animals died or were sacrificed, which I think is important. Taking into account some covariates like body weight issues that we see at extreme high doses that some of those animals -- I think I saw one where within two weeks, the animals lost 20 percent body weight and never gained it. The highest dose stayed 20 percent below for the rest of their lives.

And the confounding issues, the low dose animals actually might live longer than normal dose animals; you know, giving them more time to get cancer. But I think, actually, that could be incorporated in a nice, complicated analysis. And then I thought, and what would be the end result?

Probably wouldn't change things too much. It might.

I mean, I might be surprised, but since we don't see a lot of consistent -- oh, oh, the other thing is a logical combining of tumor types. Right now, we think of those 38 tumor types as separate, but we also know something about rat and mouse physiology, and which tumors, kind of, maybe should be counted together and which ones should be separated.

I think we can, you know, logically, the EPA could reduce that. But that pulls you away from your Cancer Guidelines. Okay. We all agree that that moves you away from your current Guidelines. But it might save you bigger headaches further down the line.

But to Dr. Parson's point, though, I think what we've been pointing out is that whatever p-value you set in your guidance, there is a risk that you're taking false positives. And that risk goes up the more data you have to look at. And thinking of the FDA case, I'm sitting here thinking, well, how many safety studies for a new drug do they actually see? Maybe one, right?

One well-designed, well-managed safety study.

DR. ANWAR DUNBAR: More than that.

DR. KENNETH PORTIER: Two? Three? For a new drug?

DR. ANWAR DUNBAR: Yes, three.

DR. KENNETH PORTIER: Okay. Well, then maybe I'm wrong.

DR. JIM MCMANAMAN: Okay. Dr. Green.

DR. LAURA GREEN: I think this has been an amazing group-think exercise and, I think, we're really close to something.

I think everybody seems to be in agreement. I want to just add my toxicologic two cents worth. I really like your idea, which I gather is Chris Portier's idea, which is to look at all the data. I really like your idea of cleaving to the guidelines. That's really a good reminder. I think it's not so hard because we know that we're supposed to keep Sprague Dawleys with Sprague Dawleys and Fisher rats with Fisher rats, and CD-1 mice with CD-1 mice, and Swiss mice with Swiss mice. Hard to say, especially at 6:35 p.m.

I think this is actually a very doable exercise. Easy for me to say, I don’t have to do it. But I think it's a doable exercise. I think it would

be a noncontroversial exercise. I mean, you'd have to specify a bunch of things, but if the Agency has the raw data, or at least some raw data -- and that's a big "if" -- I do not know what the answer is. Maybe you don't have it, but maybe the NTP has it, right. I mean, somebody's got it. The industry has it.

I mean, in these 6,000 pages of things, right, there are raw animal data. I've looked at some of them from like, Kumar et al. (2001).

The raw data exists from the industry studies, animal by animal. We know what the species are. We know what the strains are. We know what the tumor endpoints are.

I have a feeling that this is all doable. And if Chris Portier has already started it, I haven't seen that spreadsheet because we seem to be in email isolation here, so I can't get it. But I mean, maybe I'm being too enthusiastic here, but I think we're all saying that this is a way to use 14 datasets in a really exciting way.

DR. JIM MCMANAMAN: Steve told me that Chris Portier's comments/approach is on the docket. We'll have that spreadsheet.

Okay. All right. I think that we've

thoroughly evaluated -- Dr. Johnson?

DR. ERIC JOHNSON: So I have a question for Dr. Trump. Dr. Crump.

DR. LAURA GREEN: Wait, is he the President? Is he the President-elect over here?

DR. ERIC JOHNSON: When we have the situation in which we have far fewer significant results than expected, like yesterday we had a situation where there were almost three times that's fewer significant results as expected. What is the interpretation of that? Is it one strong support for no effect?

Is it two, and inverse effect, or is it three, biologically implausible something along --

DR. KENNY CRUMP: I think Dr. Haseman can answer this one better than I, but I will give you some ideas. First of all, this is expected. No confidence limits were put on it, so we don't know what range would be really still consistent with the expected. You know, I really wonder sometimes if, you know, some of these studies are not done in ways that are amenable to the statistics we're assuming.

I'm not sure that they always read animals blind. And they may have a lot of

dependencies in there. And I think that might affect those kinds of things.

We assume that everything is random, but we may read slides -- I've heard they don't do it randomly. They know which dose groups they are looking at. And I've analyzed some data, I couldn't figure what was going on. And then I figured out I've had the same tumor in the control group; they gave it a different name than if it was in a high dose group. That's a possibility.

DR. JIM MCMANAMAN: Okay.

DR. LIANNE SHEPPARD: I wanted to add one more possibility; and that is when you do the multiple comparison adjustment with a whole lot of different tumors, some of which the compound has no carcinogenic effect on whatsoever, then that may also affect things. Although, you're right; the expected number should still -- false positives should show up. But this other issue is also important.

DR. JIM MCMANAMAN: Okay. I think that we've given you some suggestions and some evaluations of your approaches. I think that there is maybe some agreement, but the details may differ slightly. But I think that overall, there is a general agreement that

there were some limitations in your approaches that almost all of the commenters on this charge question had in mind.

With that, I'll go back to the Agency and ask if you need further clarification.

MS. DANA VOGEL: We don't have anything specific at this time. But again, at the end of all the questions, we'll clarify things that we hear along the way that we think are being interpreted incorrectly, about what we've done here.

DR. JIM MCMANAMAN: Okay.

MS. DANA VOGEL: Thank you.

DR. JIM MCMANAMAN: So with that, given that we are really way far behind, and we have to wrap this up tomorrow, I think that we should maybe plan on meeting at 8:00 and begin the meeting at 8:00 in the morning. I don't know who I have to clear that with. Is that okay with --

MR. STEVEN KNOTT: I concur.

DR. JIM MCMANAMAN: He concurs. Yeah, he's under the gun trying to get this finished.

DR. KENNETH PORTIER: Is Dr. Sheppard going to be awake at 8:00 in the morning, right? From Washington.

DR. LAURA GREEN: Dr. Chair, is it totally inappropriate to suggest a dinner break and another hour after dinner? Is that like, off the table?

DR. SONYA SOBRIAN: It's off the table.

DR. LAURA GREEN: Okay. It's off the table, it's off the table. Okay.

DR. JIM MCMANAMAN: Dana Vogel?

MS. DANA VOGEL: Can I ask just one question that I did forget before? I thought I heard that Dr. Ehrich was one of the lead discussants for Question 3, but we didn't hear her. Are we going to hear her comments or were they incorporated?

DR. JIM MCMANAMAN: Sure. Her comments were included in the other comments because she had to leave.

MS. DANA VOGEL: Okay. I wasn't sure. I just wanted to make sure there weren't others.

DR. LAURA GREEN: Yes. She wrote them down also.

MS. DANA VOGEL: I wasn't sure if they were incorporated in what we heard or there were additional comments to come.

DR. JIM MCMANAMAN: Thanks for that

catch.

DR. LAURA GREEN: Yeah, she provided them in writing.

MS. DANA VOGEL: Okay. Thanks.

DR. JIM MCMANAMAN: All right. Thanks, everyone, for staying late.

[WHEREAS THE MEETING WAS ADJOURNED FOR THE DAY]

DAY 4

MR. STEVEN KNOTT: Just a brief reminder, again, as I mentioned at the beginning of the meeting, you know, there were a number of public comments, and those materials will be available in the docket within the next week or so. Probably within the next few days, but certainly in the next week. And that's available on www.regulations.gov. And the docket number and the web address and everything are located on the agenda and other meeting materials.

With that, I will turn it over today to Dr. McManaman, our Chair, to introduce the panel.

Thanks.

DR. JIM MCMANAMAN: Good morning. I'm

glad to see that there are a few stalwarts that are still here, after the entertainment the other day.

I'm Jim McManaman. I'm a professor at the University of Colorado and Chair of this session. And I'll ask the other panel members to briefly introduce themselves.

DR. JOSEPH SHAW: I'm Joe Shaw. I'm a toxicologist and a permanent panel member from Indiana University.

DR. SONYA SOBRIAN: Good morning. I'm Sonya Sobrian and I'm a developmental neuropharmacologist from Howard University College of Medicine.

DR. KENNY CRUMP: I'm Kenny Crump. I'm a statistician. I'm an ad hoc member of the committee and presently unattached, professionally.

DR. LAURA GREEN: Wow. Good morning. I'm Laura Green; chemist and toxicologist with Green Toxicology, LLC. Ad hoc member, and attached to my husband.

DR. ERIC JOHNSON: Good morning. I'm Eric Johnson. I'm a professor in epidemiology at the University of Arkansas for Medical Sciences.

DR. BARBARA PARSONS: Good morning.

I'm Barbara Parsons from FDA's National Center for Toxicological Research.

DR. ARMANDLA RAMESH: Good morning. I'm Aramandla Ramesh from Meharry Medical College.

DR. KENNETH PORTIER: Ken Portier, American Cancer Society.

DR. DANIEL ZELTERMAN: Dan Zelterman, good morning. Dan Zelterman, professor of biostatistics at Yale.

DR. EMANUELA TAIOLI: Emanuela Taioli. I'm a cancer epidemiologist, professor at Mt. Sinai School of Medicine.

DR. LIANNE SHEPPARD: I'm Lianne Sheppard, a biostatistician from the University of Washington.

DR. JIM MCMANAMAN: Dr. Jett is en route, and so he'll be here shortly. I think that if we can read in Charge Question 3(c). See if we can have that read into the minutes, and we'll begin there.

DR. ANNA LOWIT: Dr. McManaman, we had one really quick clarification this morning.

DR. JIM MCMANAMAN: Okay.

DR. ANNA LOWIT: Yesterday there was

some on and off discussion about the scope of this current analysis related to the focus on the active ingredient, as opposed to the formulations. And I certainly think there is a strong consensus from all of you that we need to be looking at the formulations.

We wanted to highlight, for you, Section 7 of the issue paper. That talks about some collaborations that we have in its infancy stage with the National Toxicology Program, related to looking at a systematic analysis of the glyphosate formulations.

We're acutely aware of the issues in the literature around the formulations, but it's a very complex problem. Certainly, you've seen, in one of the appendices of our document, that we've already compiled the gene tox for all the formulations. It’s somewhat a complicated story; it's not as straightforward as the AI.

There are many, many glyphosate formulations and they all have their own different amounts of glyphosate in them. They have different surfactants. They have different amounts of surfactants and they have other stuff. It's a very complicated, complex, multi-faceted problem. That's actually why we’re collaborating with the NTP to get a

handle on the difference between the AI and the formulations. And that's going to take some time to work through, but we want you to know that we're aware of this problem. But from a regulatory point of view, we have to do registration review for glyphosate itself as an active ingredient.

We also have an inerts group and a registration division who does regulation of the individual inerts. As we work through the projects and the science analysis and the laboratory experiments on the formulations, we'll be working with our registration division and their science group who do inerts to ensure that the formulated products are safe. But it's a very complex problem and not one that can be solved quickly, and it’s going to take quite a bit of experimentation.

We want to make sure that you are aware of that. You had seen Section 7 and understood the direction that we were taking, and that we were not just ignoring what we think is an important issue.

DR. JIM MCMANAMAN: Thank you, Dr. Lowit. Any comments from the panel related to that?

DR. LAURA GREEN: Yeah, just clarification of, at least my concern. I was trying

to suggest yesterday, I think, that the middle ground be taken in the short run; which is not to look at the so-called inerts, but to look at the isopropylamine conjugate, which, again, to my mind, is known to act differently in terms of certainly physical chemistry and pH and solubility -- I guess I'm being redundant -- from the acid.

Unless I'm mistaken, that shouldn't be that difficult. I was not asking about the surfactants, et cetera.

DR. ANNA LOWIT: I think the salts issue and the different kinds of salts and their different properties is, in many ways, a separate issue than the combination of all the inerts and the active ingredient. It's a different issue.

DR. JIM MCMANAMAN: Okay. Thank you. Oh, I'm sorry. Dr. Parsons.

DR. BARBARA PARSONS: Just another quick question. Is it not possible for EPA to request data on the actual formulations from the sponsors?

DR. ANNA LOWIT: Well, we get some, but it's limited.

DR. BARBARA PARSONS: Okay. You do have that?

DR. ANNA LOWIT: We get acute lethality data that's used in worker protection safety and labeling, but that's acute lethality. We also get the three topical toxicities, skin sensitization, skin irritation and eye irritation, which are also used for worker protection to assess what kind of personal protective equipment they should wear in the field.

We also, in varying degrees, depending on the situation, do get some of that data for our ecotoxicology assessments. And on rare occasions, we will, on the human health side, get an occasional formulation study. But those are very rare and relatively infrequent.

DR. BARBARA PARSONS: But not genotoxicity data or rodent carcinogenicity data?

DR. ANNA LOWIT: Sometimes. Sometimes we do. Sometimes we do, sometimes we don't. It's not in the standard set.

DR. BARBARA PARSONS: But it seems like a huge task for EPA to undertake trying to evaluate all the formulations on your own.

DR. ANNA LOWIT: The issue is that in an average year, we get about -- in an average year in perpetuity -- because I know these numbers from

another project. In an average year, we get about 300 new formulations a year. And that's every year, and for the last decade. And will continue that way.

Companies are regularly changing the content of their formulations. The kind of testing, I think, that you're thinking about is just not feasible, given that kind of volume.

DR. BARBARA PARSONS: Thank you.

DR. JIM MCMANAMAN: All right. Thank you. If we can move on now to the charge question.

DR. ANWAR DUNBAR: Okay. This is Dr. Anwar Dunbar. I'm going to read Charge Question 3(c).

Unusually low incidences in concurrent controls in comparison with historical controls were noted in Lankas (1981), Stout, and Rueckerf (1990), and Wood et al. (2009b), and considered as part of the weight-of-evidence for tumor findings. Please comment on the agency’s use and interpretation of historical control data as a line of evidence to inform the statistical and biological significance of tumor findings for glyphosate.

DR. JIM MCMANAMAN: Thank you. The discussants on this are doctors Crump, Portier, Ramesh, and Zelterman. Dr. Crump is the lead

discussant.

DR. KENNY CRUMP: Good morning. Kenny Crump. EPA, in their document, I think invoked historical controls in three cases. And in each case, they used the data to down-weight the statistical analysis obtained, using concurrent controls.

I wonder, I guess, if that is done in an unbiased approach. You can also use historical controls in another way, but it was only using the study just to down-weight the statistical significance of the concurrent data.

I would suggest that EPA maybe established guidelines for when not to use historical control data and make it clear when they should be invoked and when they shouldn't. And in at least one case, it seems to me the interpretation of the historical data seemed questionable.

In the case of Stout and Rueckerf, the incidence of pancreatic cell tumors in the controls was lower than in the -- concurrent controls and was lower, in the historical controls. And that was used to down-weight the overall carcinogenicity rating.

But on the other hand, the rate in historical controls was below the overall rate of

tumors in the overall study; which could be interpreted to suggest that perhaps, there was a slight carcinogenic effect. Not that I would make that interpretation, but I think it's certainly could be made just as easily as the one that was made in the document.

I like to remind you that EPA Cancer Guidelines offer, I think, warnings about the use of historical control data and mandate a careful review of the historical control data to ensure that it is incomparable to the concurrent data. And this is what the EPA Guidelines say, I will quote.

"When historical control data are used, the discussion should address several issues that affect comparability of historical and concurrent control data, such as genetic drift in the laboratory strains, difference in pathology examination at different times and in different laboratories, e.g. criteria for evaluating lesions, variations and the techniques for the preparation of reading of tissue samples among laboratories and comparability of animals from different suppliers."

And I didn’t really see any evidence in the document that such a careful review was carried

out. In one case, the case of malignant lymphomas in male CD-1 mice, the Wood et al. study, I believe, the historical control data did not come from the laboratory that perform the study, relating to the possibility of non-comparability to different diagnostic criteria and different methods for preparing reading slides in the different laboratories.

Now, as the EPA Guidelines state, random assignment of animals to groups, and proper statistical procedures, provide assurance that statistically-significant results are unlikely to be due to chance alone. And I think that should be kept in mind. To me, it's not really clear that the use of historical control data, in the document, provided any valuable information over that provided by the statistical analysis of the concurrent data. And as noted above, there are questions about the appropriateness of the historical data used, and the use to which it was put.

With regard to the use of historical controls, the Cancer Guidelines state that historical control data can add to the analysis of the data, particularly by enabling of uncommon tumors or types

of high-spontaneous incidence of a tumor in a given strain. However, the historical control data were not used for either of these purposes in the document. Instead, it was just used to suggest a low-spontaneous incidence of a tumor in a given strain. I didn't see that EPA Guidelines incurs that use of historical control data.

I'd like to say, generally speaking, statistically significant increases in tumors, that's based on the concurrent data, should not be discounted simply because incidence rates and concurrent controls are somewhat lower than average. When historical control data are used, the EPA Cancer Guidelines state several issues that can affect the relevance of historical control information, and they mandate a careful review of the data.

"When historical control data are used, the discussion should address several issues that affect comparability of historical and concurrent control data, such as genetic drift in the laboratory strains, difference in pathology examinations in different laboratories, et cetera."

And the most relevant historical data come from the same laboratory and the same supplier,

and are gathered within a two or three years, one way or the other, of the study under review; other data should be used only with extreme caution. I did not detect any evidence in the document that EPA had conducted this careful review of the historical control data that is mandated in this paragraph. If such data were not available for performing such a careful review, then perhaps, that in and of itself should suggest that the historical control data should not be used.

Because of the many factors that is listed in the Cancer Guidelines that make the tumor response and historical controls unlike that in concurrent animals, historical control information should be used very cautiously, if at all. As the EPA Guidelines state -- I think this is most important -- random assignment of animals to groups and proper statistical procedures provide assurance that statistically-significant results are unlikely to be due to chance alone. I think that should be the driving force behind your evaluation.

Thank you.

DR. JIM MCMANAMAN: Thank you, Dr. Crump. Dr. Portier.

DR. KENNETH PORTIER: Thank you. I really appreciate EPA asking this question and it actually got me thinking a lot about historical controls that I haven't spent any time thinking about before. And I agree with what Dr. Crump says, in general.

First thing is, I'm going to put in my report a reference to a current publication, a 2014 publication. I guess it's Pharmaceutical Statistics 2014, on the use of historical control data for assessing treatment effects in clinical trials by V-I-E-L-E, Viele et al. It's a really nice article and it outlines six different ways that you can use historical controls in a clinical trial setting.

Now, in human studies, we don't assume human populations to have quite the genetic drift that Dr. Crump was talking about. And in fact, I talked to someone from Charles River Labs earlier in the week and we talked about that. And he says these breeding populations, even though they do a lot of work to try to keep them genetically similar, they tend to drift.

The first thing that came to my mind is that any historical controls you use need to be temporally current. Going back 10 years, the use of

historical controls sounds to me a dangerous thing, because I think that rat or mouse pool from which you drew animals has probably changed, because you're talking multiple generations already.

In this paper, the first option -- and I'm not going to go through all of them -- but the first option says don't use historical controls. It says give weight of zero to historical controls. Statisticians like this for exactly what Dr. Crump says; if you did a good random draw from the rat colony of your 300 or 400 animals from your study, and then you did a good randomization to your treatment and control groups, those sixty animals in your concurrent controls should be your best estimate of the robustness of that pool that you did that experiment on. That seems, to us, the most powerful comparison group.

Now, granted, that pool of animals in that study may be, for whatever reason, you know, more robust, fewer cancers. Less robust, more cancers. But, you would expect all 300 or 400 animals that you got in that draw to have similar characteristics, not just the 60 that you did in your concurrent controls.

And if the 60 concurrent controls are

really different than the other treatment groups, you did something in your randomization wrong. That was the first thing I started thinking about. Like, why would I go too much to historical controls? If you did your experiment right, the concurrent controls are good.

The second method is pooling. If you have three or four experiments with animals from the same lab, that have been done within say the last two years, you could actually take their historical controls and pool them with your concurrent controls and get a better estimate of the background rate.

In the situation here, where the concurrent controls were perceived to be low, and the historical control seem to be higher, when you put them together you're going to get an estimate that's below what the last two or three historical controls look like. It will bring your estimate up.

It also gives you more sample size, right. You got now, a more powerful test of controls against your treatments. And that's a situation where you give a weight of one to your historical controls. You're bringing them all in.

And then all the other four different

methods are somewhere in between where you give some weight to the historical controls and maybe more weight to your concurrent controls; and there are different ways to do it. There's using priors, which Dr. Zelterman doesn't want to hear about. But there are ways to do shrinkage estimators. That's the first issue.

I think you need to look at that and think about, you know, in your discussion, how you've used it. The second thing is the way you've used it in this document seemed wrong to me, when I started thinking about it. You looked at the variability in historical controls and then you looked at the point estimate for the treatment and you compared the point estimate for the treatment to the distribution in historical controls.

In fact, the historical controls should be your best estimate of long-term population standards. That should be thought of as a point estimate and the variabilities in your treatment group.

You're kind of doing a one sample T-test where your treatment group has the variability. That's the sample. And your historical control rate

is your best guess of where the population centers. I would think doing you test the other way around would be more statistically supported, to say okay, 8 percent is my historical, what's the likelihood that Treatment 1 significantly differs from 8 percent, given the variability I've gotten?

I think you did -- even though they didn't do a formal, they should've done it the other way around. Okay. And I think that's the other stuff Dr. Crump mentioned, that I've already mentioned, so I don't need to go into that.

DR. JIM MCMANAMAN: Thank you, Dr. Portier. Dr. Ramesh.

DR. ARMANDLA RAMESH: I agree with Dr. Crump and Dr. Portier. With regard to using concurrent controls and historical controls, if we face a situation when the tumor instance in concurrent controls is lower than that of historical controls, how are we going to interpret the results from a biologically significant test, 10 point? That is an issue that needs to be taken into consideration by EPA.

DR. JIM MCMANAMAN: Thank you, Dr. Ramesh. Dr. Zelterman.

DR. DANIEL ZELTERMAN: Let me say I do agree with Dr. Portier, and I'm going to go even more extreme than Bayesian. We frequently use historic controls in clinical trials where it's very expensive. And we are using them when you actually design a study.

In order to estimate what are the appropriate exposure levels, you are thinking, well, what's the background rate? And even more importantly than using the historic controls, were actually using Bayesian methods. We're saying, well we've seen studies like this before, with maybe compounds like this before, and what did we do the last time we saw this.

Well, these are the doses we used. All right. We are actually Bayesians behind, perhaps not admitting it, that we're using a lot of Bayesian methods. Yes, they're sometimes subjective, but as Dr. Portier points out, you can often view them as say, there's a number of virtual controls that we don't have where we give the controls a different kind of weighting.

You're going to use the prior knowledge of the studies when you sign the doses. If you don't,

let's take an extreme case, we're not going to use historic controls. We're not going to think about anything that happened before. We're going to reinvent the wheel. We're going to pretend we've never done mouse studies before. That seems absurd. You're not going to talk like that. You are going to use historic controls.

There was an enormous study, Dr. Green and I were talking about, the big Megamouse study. This was something that was done in the '70s, involved tens of thousands of mice. Okay. Dr. Portier, it's not concurrent, but these are tens of thousands of mice and they were looking for unusual cancers.

They were looking for all sorts of unusual things that don't occur very often, and you do need tens of thousands of mice to see this background rate. Are we going to throw all that away? No. You really are using historical controls, but we have to admit it.

Now I want you to go a little bit further and use some Bayesian methods to include and incorporate the historic controls.

DR. JIM MCMANAMAN: Thank you, Dr. Zelterman. Okay. This charge question is open to the

rest of the panel. Dr. Green.

DR. LAURA GREEN: In response to the charge question language, please comment on your use and interpretation. I would urge you not to use the historical control data in any of these three instances; for important biological and then ultimately statistical reasons. Biologically, of course, the Lankas bioassay and the Stout and Rueckerf bioassays used the Sprague Dawley rat, which of course is an outbred species. It's the reason we don't use it anymore in cancer bioassays. It's a good reason.

Now obviously, people are outbred species too, so in some sense, the data are reliable in that sense, but obviously, you don't want to use old data from outbred groups. I mean, that's just really playing with fire.

I'd also say your use of them, when you're dealing with individual studies, strikes me as just plain unnecessary. Because as we've been urging you -- since we have this unusually fortuitous circumstance where we have any experiments including in the same species and strain -- we have been urging you to simply, when you report each study, just report the data. Do not interpret it beyond statistics.

Following what Dr. Parsons was saying, just file statistical guidelines and use the trend test, and the P value is going to be the P value using the concurrent controls. It seems to us, given the opportunity to have replicate experiments, it is when you combine those replicates, it is then that you may want to comment on what the datasets, as a whole, looks like.

For example, it is only once Stout and Rueckerf use much higher doses of glyphosate than Lankas had used, and failed to find Leydig cell tumor increases, that then obviates your need to even bring up historical controls in Lankas. Because the only reason you brought him up is the data looked a little positive. In fact, it looked very positive. the trend test was not .009, as I recall. Although I don't know if it was the right trend test.

But the point is, once it replicated at massively higher doses instead of 31 mg per kilogram, the high dose was over a gram per kilogram, and you don't see anything; well, then, the second test failed to replicate the first findings so you're done. It seems to us it only gets you into trouble and it's unnecessary. Or, at least, it seems to me.

DR. JIM MCMANAMAN: Thank you, Dr. Green. Dr. Crump.

DR. KENNY CRUMP: I had a follow-up question for Dr. Zelterman. I'm not really clear on the example you presented in human data it's quite analogous to what we have here. It's my understanding the reason -- you did not have a control data, so you have to use historical controls. I understand that was probably to save money, that you did not have concurrent controls.

But suppose you did have enough money, and suppose you did have a proper concurrent control group, would you continue to use historic controls? And how would you use them?

DR. DANIEL ZELTERMAN: Well, you're presupposing I had more money. How much more do I have?

DR. KENNY CRUMP: Enough to get a control group equally as large or larger than your exposed group.

DR. DANIEL ZELTERMAN: Okay. I did. Here's the data. Here's the data. But isn't it bothering you a little bit that those controls don't look like the controls we saw a year ago, in another

study? Does that bother you that those controls have a very different rate?

DR. KENNY CRUMP: Well, I'm not sure. But I'm asking a little bit of a different question. Suppose you had developed a concurrent control group, how would you use, or would you use, historical controls and how would you use them?

DR. DANIEL ZELTERMAN: Oh. Very easily. Here's how a good Bayesian would do it. You have your controls, but then you have, if you like virtual controls, say something is the background rate of say, 1 percent. You can say I have a virtual set of 100 mice, of which one developed a tumor in the control group. And then I would take these 100 virtual mice and add that to the dataset and that's the Bayesian analysis. That's all there is to it. You just said I had a virtual set of 100 mice.

Now somebody may say, well, the real way to do that, well, is, I don't really have 100. I'm not that sure of 100. Maybe I only have 50 mice and then counted as, so help me, half a tumor. And just run the mathematics through. There were 50 mice and half a tumor, or I could do 10 mice and one tenth of a tumor.

You realize when I'm adding this, I'm not changing things very much. I could've said one mouse and one hundredth of a tumor and nobody would argue that that's going to change the analysis at all. I mean, that's the interpretation. That's the way it would be done. Unless Dr. Portier has a better way.

DR. KENNETH PORTIER: No. I was just sitting there thinking, you know, we focus on controls, but I'm more interested in the treatment groups and what all this says about the treatment groups. And I understand the Bayesian example, that's beautiful, actually. It's a great way to think about how you would pool in additional data.

But would you do that for the other groups or do you assume they're okay? They actually do follow the population group. And it's only randomization produced a slightly weird control group. Is that what you're kind of worried about?

I mean, when you say I worry that the concurrent controls are low, what are you really kind of concluding there about the experimental design? You're just saying fate was against me when I randomize these and I got all 60 zeros, when I should've seen at least one or two, right?

DR. DANIEL ZELTERMAN: Yes.

DR. KENNETH PORTIER: That's kind of what you're thinking of.

DR. DANIEL ZELTERMAN: That's right.

DR. KENNETH PORTIER: So let me throw a wrench into this. Let's take these 300 animals that you got from Charles River, you assigned them random groups and by fate you got 60 controls that got zeros. Suppose there's no treatment?

Now, from those 300 animals and say the background was 10 percent, I should've seen 30 tumors. Now, none of those 30 tumors are in control, right?

DR. DANIEL ZELTERMAN: Right.

DR. KENNETH PORTIER: So they're in the other treatment groups. That means my expectation is that all these other treatment groups are going to be higher than control, right. Because I've now got 30 tumors spread over 180 animals, or whatever it was, 240 animals; whereas before it was 30 tumors over 300. I took the 60 controls out. This is what was driving me crazy. Like, well, what does that mean for our tests? Had you thought about that?

DR. DANIEL ZELTERMAN: Well, yeah, that's hard. And yes, it's unfortunately, academic.

The chances of that happening are small. In a lifetime, an agency's lifetime of examining one study after another, the chances of this happening are pretty small. That's where statistics works in our advantage. Whereas, you're going to be looking at many, many studies and this sort of thing won't happen very often. There you're saved.

DR. KENNETH PORTIER: So still playing the devil's advocate. So now what we're saying is that batch that came really has a lower rate, right. So instead of seeing 30, I probably might've seen 15. But the problem is still there. You've kind of raised the historical control rate that these things are still -- I don't know. I haven't figured it all the way through.

This is why we don't want to go there. You know, the more I think about it, why I don't want to go too far into really thinking hard about historical control, is because they mess up your statistical thinking about how valid these tests are when you say I'm going to deal with the 300 animals.

There are 300 animals coming from one population. And the differences I see are due to the treatments because I randomize everything else. I'm

good. You know, statistically, I'm happy and I like the results. But the minute you start messing around with one group versus the other group, a lot of the inference tends to fall apart. And Dr. Sheppard, you kind of agree with that?

DR. DANIEL ZELTERMAN: Yeah, I think they're saying yes.

DR. JIM MCMANAMAN: Okay. That was Dr. Portier and Dr. Zelterman, a discussion between those two, since they didn't identify themselves. And if any of the panel members have a disagreement with the consensus that you shouldn't use historical controls, please speak up. If not, then I think we'll move on to the next charge question.

Dr. Johnson. On topic.

DR. ERIC JOHNSON: Yes. What I would like to know is when historical controls are used, whether there is data on the historical controls that can be used to compare the current controls to see whether these controls are different in characteristics like body weight or other parameters.

That would certainly help.

DR. JIM MCMANAMAN: Yeah. That would provide some validation for the use of historic

controls.

DR. KENNETH PORTIER: That's Method No. 4: Test and Pool.

DR. JIM MCMANAMAN: Right.

DR. KENNETH PORTIER: You test and then you say well, if it doesn't look like they're that different, let's go ahead and pool them to get a better estimate. I feel slightly better about that approach.

DR. JIM MCMANAMAN: All right. Okay. Any further clarification?

DR. ANNA LOWIT: No. We heard consensus.

DR. JIM MCMANAMAN: Okay. All right. Charge 3(d).

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar. I'll be reading Charge Question 3(d). Please comment on the agency’s conclusion that there is an absence of corroborating preneoplastic lesions or related non-neoplastic lesions. Please also comment on the agency’s conclusion that there is a lack of progression to malignancy to support tumor findings.

DR. JIM MCMANAMAN: Okay. The discussants on this are doctors Parsons, Ehrich,

Ramesh and Sobrian. Dr. Parsons is the lead.

DR. BARBARA PARSONS: So let me start by saying Dr. Ehrich is not here, and she gave me her comments to read on this. I could either read them right now or you need to remind me at the end because I will forget.

DR. JIM MCMANAMAN: Okay. Well, I'll remind you. Why don't you give your comments first?

DR. BARBARA PARSONS: Okay. I think the document didn't adequately describe the process that was used for the evaluation of pre and non-neoplastic findings. I would've liked to see, you know, some written description of the approaches --

DR. JIM MCMANAMAN: Dr. Parsons, your soft voice is making it hard for us.

DR. BARBARA PARSONS: Sorry. I would've liked to have seen some written, you know, detailed description of what that analysis entailed. And that would've made it easier for us to go and look at the same study documents and, you know, reproduce your findings or not.

In order to provide informed comment on the potential relevance of preneoplastic lesions, as is requested by this charge question, as well to

investigate bioassay reproducibility, myself and Dr. Sobrian analyzed the primary study documents. But questions remain as to the procedures that were used to evaluate preneoplastic lesions.

Did the EPA consider only lesions mentioned in the summary reports, or was there a predetermined process to go through the individual -- I mean, because the study reports have, you know, hundreds of descriptions and counts of preneoplastic lesions. There's lots of ways to approach it and it just would be helpful to know what was done.

Generally, the report says there were -- that's not correct. For the most part, when the document describes or refers to preneoplastic lesions, it's in the context of downgrading specific significant responses, and it gives the overall impression that no preneoplastic lesions were observed. No statistically significant increases in preneoplastic lesions are contained in these documents. That's the impression that I got from reading it. And I think that's not entirely correct.

The Brammer study of Wistar rats, for example, "observe changes in liver, which comprised of treatment-related increased incidence of hepatitis and

increased" -- this is a quote from, I guess, the study document. "-- increased incidence of hepatitis and increased incidence, but not severity, of proliferative cholangitis in males apparent at 12 months as well as at the end of the study." And I won't read the rest.

There was a significant increase in lymphocytic hypoplasia of the thymus, observed in female Sprague Dawley rats, exposed to 11 and 34 mg per kilogram per day, relative to control. And that is from the Lankas study. There are increases in lymphoid hyperplasia observed in female CD-1 mice. I have the numbers here. Apparently, that was pulled from the primary study report. This is in the study of Atkins on CD-1 mice.

And one study reported both significant induction of a lymphoid hyperplasia and malignant lymphoma in the same study. Specifically, a significant lymphoid hyperplasia was observed at the low and mid doses in male CD-1 mice. That 71 and 234 mg per kilogram per day, in a study where malignant lymphomas were significantly induced that 810 milligrams per kilogram body weight per day. That's the Wood study, which had a trend test for malignant

lymphomas of 0.007.

I would also like to point out that in at least two studies, there seems to be an inverse relationship between dose and the incidence of preneoplastic lesions. The Atkins study of Sprague Dawley rats, for instance, there was a significant decrease in kidney hyperplasia observed in female rats. And in the Knezevich and Hogan study of CD-1 mice, there was actually -- and then this is a quote:

"There was actually a decrease in renal tubular epithelia changes, basophilia and hyperplasia in males. And although there was a dose-related increases in these changes in females, no tubular neoplasms were observed in females." I think this quote may come from Greim.

As I said, EPA document gives the impression that no treatment-related induction of preneoplastic lesions were observed. They were, but overall, I do agree that there does seem to be a dearth of preneoplastic findings in the studies in which there were significant tumor responses. I believe this is consistent with interpretation that glyphosate is non-genotoxic and does not cause de novo preneoplastic lesions during treatment.

This conclusion doesn't contradict the hypothesis that glyphosate could be a weak monogenic toxic carcinogen; one that causes the outgrowth of pre-existing spontaneous lesions. To me, it makes some biological sense that there may be observations of dose-related increases of preneoplastic lesions in some studies, and dose-related decreases in preneoplastic lesions in studies where there is a significant tumor response.

Do people understand what I'm getting at here?

DR. JIM MCMANAMAN: Do you have any additional --

DR. BARBARA PARSONS: Yes. I think I will stop there.

DR. JIM MCMANAMAN: Thank you, Dr. Parsons. Dr. Ramesh.

DR. ARMANDLA RAMESH: I agree with what Dr. Parsons had mentioned. The absence of preneoplastic lesions when compared to the tumor responses, it supports the view that glyphosate is not a carcinogen or compound of considerable carcinogenic potential, because we did not see any treatment-related lesions.

In some cases, it may have contributed to the progression of pre-existing lesions, but that frequency is very low. I agree with the interpretation of the Agency with regard to preneoplastic lesions.

DR. JIM MCMANAMAN: Thank you, Dr. Ramesh. Dr. Sobrian.

DR. SONYA SOBRIAN: I agree with what has been said, but to directly answer the question, "Please comment on the agency's conclusion that there is an absence of corroborating neoplastic lesions or related non-neoplastic lesions," it's not clear what data the Agency used to come to this conclusion. There are no summary tables in the White Paper. And that really would've been helpful.

That meant that we had to go through the source documents, which we did. First of all, it was unclear what we're looking for, so most of us chose hyperplasia. And there are five -- from going through the source documents -- I found five rat studies, and they're all listed in here, in which there was a significant change in hyperplasia. But in only one study, Suresh's (1996) did the hyperplasia goes on in the same tissue to produce a tumor.

Okay. There isn't a lot of evidence from the rat studies. And with the mouse studies, there are only two that found significant increases in hyperplasia, and none of those were in the same tissue. While it's difficult to tell what the Agency based its conclusion on, if you go through the source data, there's very little evidence for a progression from neoplastic to tumors.

DR. JIM MCMANAMAN: Thank you, Dr. Sobrian. Dr. Parsons is now going to read in Dr. Ehrich's comments.

DR. BARBARA PARSONS: "With human exposure, less than 7 mg per kilogram per day, and animal test with greater than 1,000 mg per kilogram per day, toxicity data in the high dose animals lacks real-world relevance."

Wait a minute. It's the wrong one.

DR. JIM MCMANAMAN: Yeah.

DR. BARBARA PARSONS: She circled it. Okay. I'm sorry. 3(e), right?

DR. JIM MCMANAMAN: 3(d).

DR. BARBARA PARSONS: Oh, okay. 3(d) is at the bottom after (f).

DR. JIM MCMANAMAN: That's how Marion

thinks.

DR. BARBARA PARSONS: I'm sorry. "The Agency did due diligence in review of available information. Studies were done that included histopathological examination of laboratory animals before the end of long-term experiments. Preneoplastic lesions should've been noted then, and in animals whose tissues were collected at the end, especially when some in the group had neoplastic lesions."

DR. JIM MCMANAMAN: Okay. Thank you. I'll open this charge question to the rest of the panel. Yes, Dr. Taioli.

DR. EMANUELA TAIOLI: I think this aspect of being a promoter instead of genotoxic, it has to be reviewed by the epidemiologist as well. Because if that's the train of thought, then a lot of our discussions about adjusting for other pesticides, or smoking, it's really less relevant. Because if it's a promoter on some other genotoxic agents, then we should look at interactions among a genotoxic exposure and this exposure.

We need to give this aspect some weight in our thinking, because it may change a lot of the

focus, at least in my mind, of what we are thinking about with the epi studies.

DR. JIM MCMANAMAN: Thank you, Dr. Taioli. Other comments?

Dr. Portier.

DR. KENNETH PORTIER: Well, I just wanted to make very clear that that's what we're saying because this is a big part of the biological plausibility argument when we get to Question 5. What I'm hearing is that what you're seeing, the signal you're seeing, in the preneoplastic data, or lack thereof, makes it biologically plausible that this is less an initiator cancer and more of a promoting agent. I mean, that's what I heard. I just wanted to confirm that. Do you guys agree to that?

DR. JIM MCMANAMAN: That was Dr. Portier. Yes, Dr. Parsons?

DR. BARBARA PARSONS: If I may, you know, the study documents do make the point that what they are seeing are increases in common spontaneous tumors. Spontaneous mutations are fairly frequent. And your chemical, if it's a promoter, it's going to grow those out, they're going to develop and tumors. It's going to occur at different rates depending on

the genetic susceptibility of the rodents. But is not going to be inducing more preneoplastic lesions constantly during the treatment.

It's not what you would expect to see for genotoxic carcinogen. I mean, that's what you would expect to see for genotoxic carcinogen.

DR. JIM MCMANAMAN: Thank you, Dr. Parsons. Dr. Taioli.

DR. EMANUELA TAIOLI: Not really maybe for now, but what about the in vitro studies were promotion? Because we only look at genotoxic, so that's for later.

DR. JIM MCMANAMAN: Well, as far as I know they weren't conducted. They weren't presented, at least. For now, I think we can come back to this general question when we come to Question 5, and come back and explore this a little deeper there. But for now, related to Question Charge 3(d), I think that we have to stay on this question.

Dr. Johnson.

DR. ERIC JOHNSON: So the issue of whether glyphosate causes cancer by means other than through a genotoxic effect, was of some concern. However, in the absence of two-stage experimental data

on initiation and promoter, first, I know, those experiments have not been done. And if they've not been don, I don't think we should consider glyphosate as a promoter in interpreting our data.

DR. JIM MCMANAMAN: Thank you, Dr. Johnson. Dr. Parsons, did you have a comment in response to that?

DR. BARBARA PARSONS: Just that I believe there was one initiation promotion study done in rodents. And I believe it was one of those removed from evaluation by the Agency because it was inadequate. I don't remember any details beyond that, except that it was positive.

DR. JIM MCMANAMAN: So perhaps, when we get to Charge Question 5, we can come back to that and make a recommendation that we look into that.

Okay. Any other comments related to this charge question?

Okay. Hearing none, I'll go back to the Agency.

DR. MONIQUE PERRON: Nothing at this time. This is Monique Perron. Thank you.

DR. JIM MCMANAMAN: All right. Thank you. Okay. Charge Question 3(e).

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar. I'm going to read Charge Question 3(e). In the case of glyphosate, there are multiple carcinogenicity studies available for the evaluation of carcinogenic potential.

The Agency looked across all of the studies and found that tumor findings were not consistent or reproduced in other studies conducted in the same species and strain at similar or higher doses. Please comment on the interpretation of conflicting evidence and reproducibility for these studies.

DR. JIM MCMANAMAN: Okay. The discussants on this are doctors Green, Ehrich, Parsons, Portier, Ramesh, and Zelterman. I don’t know why the rest of us weren’t asked.

I think we'll start with Dr. Green as the lead discussant.

DR. LAURA GREEN: Thank you. Just following up on the last question, Dr. Parsons, the study to which you allude is George et al. (2010). That's titled, "Studies on Glyphosate-Induced Carcinogenicity in Mouse Skin: A Proteomic Approach. And it's in J. Proteomic, Volume 73, pages 951-964.

And you're quite correct, the Agency discuss it in passing and what they said -- and I have not looked at George et al. myself, so I do not know whether the Agency summary is adequate or not. What the Agency says on page 70 of its document is, "An initiation promotion study, George, et al. (2010), in male Swiss mice that tested a commercial formulation of glyphosate (41 percent), on the skin." Oh, that's not a full sentence. Well, whatever.

"Study deficiencies included a small number (20) of animals tested, only males, and a lack of histopathological examination. Well, so a), I don't quite understand the sentences, but b) the Agency did look at it. They don't note whether those small number of animals showed positive results or not. I would caution the obvious, which is if the small number of animal, nonetheless, showed a positive response, it's still a meaningful study.

If the small number of animals showed a non-positive response, obviously, its probative value is limited by its small size. At a minimum, this reader -- who by the way, did not read page 70 prior to right now -- this reader would've liked the Agency to add an additional sentence to talk about whether

the study was apparently positive or apparently non-positive.

DR. JIM MCMANAMAN: Thank you, Dr. Green. I guess we have Dr. Ehrich's comments. We'll save those until the end.

Dr. Parsons.

DR. MARION EHRICH: Yeah, I'm on the phone, Jim.

DR. JIM MCMANAMAN: Oh, okay. Well, sorry, Marion.

DR. MARION EHRICH: I'm on the phone. On this one, having worked with pathologists a lot, they did due diligence and they did do these histopathological lesions. Preneoplastic lesions should've been seen during the time courses of some of those experiments that are in the end, in some of the animals. And the sample size is very small. It's really not unusual, especially in longer-term studies as the animals age, to actually have occasional lesions that are just background noise.

When EPA kind of discounted them, I thought that was actually appropriate.

DR. JIM MCMANAMAN: Is that it, Marion?

DR. MARION EHRICH: Yeah, that's it. I

only have short comments.

DR. JIM MCMANAMAN: All right. Thanks, Marion.

Dr. Parsons. We're on 3(e).

DR. LAURA GREEN: No, I was finishing up on (d), I hadn't actually started on (e) yet.

DR. JIM MCMANAMAN: But we have to be on 3(e) or there's complete confusion on what's going on.

DR. LAURA GREEN: Right. I'm about to talk about 3(e); I just haven't done it yet.

DR. KENNETH PORTIER: We understood it, Jim, you didn't.

DR. JIM MCMANAMAN: Well, I thought we ended 3(d). Okay. So, 3(e). If we can stay on topic, that would be very helpful in keeping the poor transcribers -- okay. So, 3(e), Dr. Green.

DR. LAURA GREEN: Yes. Sorry. I meant only to say that I had something else to say about 3(d), which I had just finished saying.

On 3(e), I think you've already heard our answer. We would very much prefer if you would present each study individually, without much interpretation beyond just the standard statistics.

And then when you get to combining the studies, we would recommend that you combine the studies according to species and strain; noting any differences, such as which studies went only for 18 months and which one for 24 months and which one for 26 months.

I mean, there are details, but nonetheless, we recommend that at the end of discussing each of the 15 studies, you have tables or graphs, whatever you like, that show at once, the results in the Sprague Dawley rat, the Fisher rat, the Swiss mouse, the CD mouse, et cetera. And it seems to us, based on what the statisticians have been saying, principally, that when you do that, you will find overall that the study replicates failed to find the same positive results.

You will find that your overall conclusion, which is taken as a whole, the evidence as a whole, from the 15 bioassays, fails to confirm carcinogenicity. We believe that you will, in fact, corroborate your conclusion in a more systematic way.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Green. Dr. Parsons.

DR. BARBARA PARSONS: No, Dr. Ehrich.

DR. JIM MCMANAMAN: Dr. Ehrich has

already -- she was commenting on 3(e).

DR. BARBARA PARSONS: No. I think she was commenting on 3(d).

DR. JIM MCMANAMAN: Oh, really? How can we end something and then still have comments going backwards?

I'm sorry. I hope that the transcribers figured that out because Steve and I were completely flummoxed by this. Okay. Marion, do you have something to say on 3(e)?

DR. MARION EHRICH: 3(e)?

DR. JIM MCMANAMAN: Yes.

DR. MARION EHRICH: Yes. It's difficult to deal with conflicting evidence and reproducibility. They did not ignore such evidence as it was presented. But it's hard to draw a conclusion so they said the data are inadequate, and seems appropriate. And that's all I have to say on this.

DR. JIM MCMANAMAN: All right. Thank you, Marion. Dr. Parsons, are you ready now?

DR. BARBARA PARSONS: I am. I think the document ascribes equal weight to the 15 acceptable rodent carcinogenicity studies. It states that tumors seen in individual rat or mouse studies

were not reproduced in other studies conducted in the same animal species and strain at similar or higher doses.

But in order to judge whether or not this conclusion is valid, and the lack of reproducibility should be given more weight than the positive tumor findings, one has to consider whether the studies were of similar quality. Did they employ rodents with equivalent tumor sensitivities; and whether equivalent tumor incidence data were analyzed in a consistent manner.

My review of the primary study document suggests that the studies varied greatly with respect to these criteria. A major concern regarding the conclusion that tumor findings are not consistent, relates to the fact that the studies vary in terms of design and quality in ways that are expected to impact their sensitivity.

For example, the study by Lankas treated rats for 26 months, which to my mind, could very well explain why they detected a tumor response that was not detected in other studies, which only treated rats for 24 months. I don't see how someone can rule out that possibility. The Stout and Rueckerf

study, generated statistically significant responses for three different tumor types.

This study may have had greater sensitivity than the others because it employed 60 rats for treatment group compared to 50 in most of the study. And just as an aside, the glyphosate document itself says other observations can strengthen or lessen the significance of tumor findings in carcinogenicity studies, such factors include -- and one of those factors is tumors at multiple sites. I think that weighs into the weight-of-evidence for the Stout and Rueckerf study.

Across mouse studies, mice were exposed through the diet for between 16 and 24 months. The mouse study by Rayner and Gordon sacrificed males after 16 months and females after 18 months. And most importantly -- I've checked this a few times -- it included histopathological analyses on only 10 mice per dose group. This study really has much less sensitivity than the rest. I think it's not appropriate to really even group it with the rest and say, you know, there are 15 studies that disagreed with each other.

Clearly, this study should not be

weighted as heavily as those where there are these histopathology results from 50 animals per sex dose. Some of the studies had low survival at terminal sacrifice, less than 20 animals per group, which is also expected to reduce the sensitivity.

The study by Pavkov and Wyand and the study by Pavkov and Turnier, they employed sulfonate and propylene glycol as a vehicle. These two studies used different test article. Are they reproductions of these other studies? To my mind, they are not.

And again, in the Pavkov and Turnier study, the males in the zero-ppm treatment group were sacrificed at 89 weeks of treatment, whereas the other treatment groups were sacrificed after 95 weeks. I mean, these are small things, but there are a lot of these. Or maybe they're not small things.

Again, I struggle with -- it’s not clear to me how the tumor responses were systematically examined by EPA. But I think I'll just skip over this point. It's not clear whether histopathological examinations were performed in an equivalent manner across studies. The rat bioassay, by Suresh, did not include histopathological analyses on all the low and mid-dose rats at terminal

sacrifice. And it also reported that autolysis precludes its evaluation of many samples.

Thus, there are many differences in the study quality that could account for the lack of consistent statistical significance in the bioassay results. And these should at least be discussed in the document because they weigh against the argument that the significant, but irreproducible, tumor responses must be due to chance rather than glyphosate treatment.

And I'd like to take a little time to make a point about how much genetic variability there is across the same strain of rodent, used in these different studies. I did this to educate myself, but I'd like to share it with you.

Rodent strains maintained in a separate breeding colonies for extended period of times, as we've heard from Dr. Portier, do not necessarily have the same spontaneous tumor profiles. I have a reference here, King-Herbert and Thayer. King-Herbert and Thayer -- toxilogical pathology (2006).

This is the basis of the OCED recommendation that only studies performed within five years in the same laboratory should be considered as

historical controls. In an attempt to get a sense of the amount of variability among the rodents used across the studies that we're evaluating, I just pick the incidence of a single tumor type and compared it across studies.

I read somewhere that pituitary tumors were a common, spontaneous tumor in these rodents. And it was not a tumor that was implicated as potentially having a glyphosate response, so I just picked that one pretty much at random.

I'm going to give you, for control Sprague Dawley male rats, the frequency of pituitary tumors in some of these studies were 40, 56, 58, 70, and 52. So that range there was 40 to 70 percent. I have all the numbers, but I'm just going to give you that range for the rest.

In control female Sprague Dawley rats, the range was 76 to 94 percent. Control Wistar rats, the range is between 6 and 34 percent. In females, it’s 16 and 80 percent. In control CD-1 mice, pituitary tumors range between zero and 64 percent. That was for the males. And it's actually the same for females, zero and 64 percent.

This suggests that even within

particular rodent species, there can be relatively large differences in background tumor incidences, which are likely to impact the detection of statistically significant findings. If you start out with a high background level spontaneous mutations, your chemical -- no one is saying that it is a strong promoter, not even a strong promoter, a weak promoter. But we're talking about the increased incidence of relatively small numbers of tumors. If you have a higher background, you're just not to be able to see that.

The other point is that when I reviewed the study documents, the toxicological findings themselves are really quite different in these reports. I think if you put these in front of me and mix them with others, I couldn't tell you which one were the glyphosate ones. They really read quite different.

These also varied across different tumor bioassays and provide additional evidence, that biological or mythological variability in the studies conducted in the US, the UK, Japan and India between 1973 in 2009, they're just going to have a lot of variability.

I believe the combination of rodent genetics, bioassay methodologies, including the number of rodents analyzed, statistical analyses, what specific data was analyzed and toxicity, which is going to vary determined on what doses were selected in a particular study, those are all expected to contribute to the lack of consistently significant findings across studies. I don't give this much weight, the lack of consistent findings in in my evaluation of carcinogenic potential.

But that's one side of the argument. The other side of the argument, well, how much reproducibility was there in the findings? I completely agree with the idea that we need a table that provides groups, the findings that were observed across studies. Okay.

So again, to inform myself as to reproducibility, I tried to collect information on not only -- so I started out with which targets had evidence of a statistically significant response. And then I looked across studies, did those studies have similar, but nonsimilar responses that didn't reach the level of statistical significance?

And I'll just say that this also added

to my confidence that there is some reproducibility there. For example, for lung, I found that there were six studies in which all glyphosate-treated group have an equal or greater tumor incidence above the concurrent control for at least one type of tumor in one sex. And the highest observed incidence is twice the control level; a similar finding for liver, where I thought there were five studies, and for lymphatic and thyroid tumors, where there were three studies.

And we did see an earlier presentation, there is, at least, agreement that there were three, I guess they call them equivocal, significant responses in terms of malignant lymphoma. I'll stop there.

DR. JIM MCMANAMAN: Thank you, Dr. Parsons. Dr. Ramesh.

Dr. Portier. I was on the wrong one.

DR. KENNETH PORTIER: I'm not touching that. That was great. Sorry. I can't add anything to that discussion.

DR. JIM MCMANAMAN: Okay. Great.

Dr. Ramesh.

DR. ARMANDLA RAMESH: Dr. Parsons made our job very easy. I don’t have anything to add other than some small statement. Even though EPA used

stringent criteria for picking up studies for comparison purposes, we all know that strain specific differences exist, and differences exist in the study design and all.

In that context, even if the tumor responses are statistically significant, they may be of a chance occurrence rather than glyphosate treatment. With all seriousness, if the studies are not reproducible, we need not worry about those; because at the end of the day, we need to make right decisions on the basis of sound science. I don't want to lose sleep over this.

DR. JIM MCMANAMAN: Thank you, Dr. Ramesh. Dr. Zelterman.

DR. DANIEL ZELTERMAN: I agree with the very thoughtful comments from Dr. Parsons.

DR. JIM MCMANAMAN: Thank you, Dr. Zelterman. The question is now open to the rest of the panel.

Okay. Dr. Jett.

DR. DAVID JETT: I guess my quick thought on this, I mean, we all know how difficult it is to replicate a study. It's almost impossible, if you've ever tried it. But I'm wondering if the

question is more related to reproducing a result, than replicating a study. I just wanted to just throw that in, but I absolutely agree with all of Dr. Parsons' comments.

DR. JIM MCMANAMAN: Does anyone want to respond to Dr. Jett's -- Dr. Green.

DR. LAURA GREEN: Dr. Zhang, did you want to --

DR. LUOPING ZHANG: I have a quick comment.

DR. JIM MCMANAMAN: If there's not a response to Dr. Jett's suggestion, then --

DR. LAURA GREEN: Oh. Actually, I do.

DR. LUOPING ZHANG: Oh, no. Sorry.

DR. JIM MCMANAMAN: Okay. Dr. Green then.

DR. LAURA GREEN: I agree that the question is whether the specific result is replicable. I agree with Dr. Parsons that individual studies obviously have great differences in terms of the quality. I want to make an important point, I think, though, which is within a critical study with regard to hemangiosarcoma in male mice, which I believe was a central finding in the IARC declaration that

glyphosate is as established rodent carcinogen, I think it's really, really important to point out that although it is absolutely the case, that in male mice in that study, there was a very strong trend for hemangiosarcoma of the liver. Zero in the controls, zero in the low dose, zero in the mid-dose and four out of 50 in the high-dose. It's pretty impressive. But what is very important is that the same study using females, who obviously have pretty similar livers, there was no dose response relationship at all.

And in particular, zero hemangiosarcoma of the liver in female controls, two in the low dose and all the denominators are 50 here. It goes zero, two in the low dose, zero in the mid-dose, one in the high dose. And high-dose here is a gram per kilogram. It is absolutely true that across studies one has to be a little careful, but I would say within a study, especially with organ like the liver, to see such disparate results, I think is significant.

DR. JIM MCMANAMAN: Dr. Parsons.

DR. BARBARA PARSONS: This has been mentioned a few times, but it is absolutely clear that male and female rats and mice have different incidence

of spontaneous tumors for different organs.

DR. LAURA GREEN: Of the liver?

DR. BARBARA PARSONS: I think so. I think male are more susceptible.

DR. JIM MCMANAMAN: Yeah. I've heard that males and females have different hormones.

DR. LAURA GREEN: We're talking about the liver here.

DR. JIM MCMANAMAN: Yeah. But in point of fact that there are a lot of incidences where in females, their livers respond differently than the males.

DR. BARBARA PARSONS: Yes. And they have underlying differences in levels of spontaneous mutation.

DR. LAURA GREEN: But the control groups for both the males and the females were zero. I mean, just looking at the concurrent controls. The male response is strong and positive; the female response is completely non-positive, and there's no background rate problem here because the controls have no liver tumors.

We're not talking about B63F1 mice here. I mean, were we talking B63F1 mice, I couldn’t

agree with you more. They get a lot of spontaneous liver tumors. It's a real pain in the neck to look at them, but we are looking at CD-1 mice here, which are not hyper-susceptible as evidenced both by the concurrent controls. And to my knowledge, there's no sex difference in CD-1 mouse livers. I could be wrong. I would love a pathologist to weigh in on this, but to my knowledge, there is no such sex difference. And certainly, in the concurrent controls, it's zero in both cases.

DR. JIM MCMANAMAN: Wait a minute. Dr. Sheppard was first. Then I'll go to you, Kenny.

DR. LIANNE SHEPPARD: I want to say, first of all, that I really appreciated the very deep thought and important comments that Dr. Parsons made. They resonate very strongly with me. I think that's been an extremely valuable contribution.

I wanted to say that one of the things I noticed, when I reviewed this document, is a summary of the rat data on page 82, it's about paragraph. And the summary of the mouse data, on page 90, also about a paragraph, are almost identical in their format and content. This, as a reviewer of scientific evidence, made me very concerned, because it almost felt like --

well, it didn't feel like it drew from the evidence, but almost like it came about in some other way.

I also want to say that one of the values -- in spite of the potential heterogeneity between studies that Dr. Parsons talked about -- one of the values of pooling data is that you get more evidence when you combine information than you do from a bunch of small studies, and there's a tremendous amount of value.

Not only are you not ignoring the studies that show, on their face value, negative or equivocal results, but you're also, you know, you're combining everything together. If there is some evidence in the multiplicity of studies, you can find it pretty clearly. And, you know, the nice, again, somebody needs to go and understand the details, and probably do it again according to all the EPA's criteria, and make sure all the studies are the ones the Agency has full access to the data for.

But the spreadsheet that's on the docket, that was provided by Chris Portier, shows very clearly that for mice, when you combine all the experiments together -- and this is for one, two, three, four, five different studies -- there is a very

clear evidence regardless of how you do the testing for renal tumors. To me, that suggests there's pretty strong evidence in one species, and one cancer outcome, that there is an impact of this compound.

DR. JIM MCMANAMAN: Thank you, Dr. Sheppard. Dr. Crump.

DR. KENNY CRUMP: I agree with a lot of what has been said about this issue. But I do think that true carcinogenic responses should be reproducible to be real. I mean, we can debate about why they may not appear to be reproduced in certain situations, but I do think they should be reproducible in order to be concluded to be real.

EPA noted the lack of reproducibility of statistically significant responses, but this was, as it’s been pointed out, it’s only stated kind of as a boilerplate statement at the end of the summary. I would have liked to have seen, as other people have looked at, maybe tables of something you think is statistically significant; and look at the response that was seen in all of the studies so we can make some determinations. Do we think there is a reproducibility or not? I would encourage the Agency to put more information out there for us to look so we

could determine that in a better way.

I tried to go through, in fact, I did go through, all of the studies and looked at each one that was determined statistically significant. And I pulled out all the data from all the other studies, on that particular endpoint, and compared them. And I summarized it in my earlier submission. I do have the original raw data that I could also provide if anyone was interested. But I didn't really detect much evidence, at least, of reproducibility. I considered the strains, the sexes, species, and the dose rates. In retrospect, I could've also considered the duration of exposure, but I did not do that.

But I would like to mention the one case that Dr. Parsons mentioned, and that is lymphoma in mice. And that is the one case where there was a statistically significant result in two studies of the same endpoint and the same species and the same sex. This is the Wood et al. (2009) study. And the Sujimoto (1997) study. And Wood et al., it was 0, 1, 2 and 5. And in Sujimoto, there was 2, 2, 0, and 6, both of those were statistically significant .05 level.

But if you look at those really

closely, they don't really seem to match up that well. Sujimoto had much higher doses than Wood et al. And in fact, the high dose in Wood, where you got 5, which that was the cause of the statistical significance, there was almost a comparable dose in Sujimoto, 838, where there were not tumors.

Although it's interesting that they both occurred in the same species, same sex, I didn't see them as being quite comparable. And in addition, Hogan and Knezevich also had the higher dose in either of these studies, and they did not detect any evidence of significant effect of malignant lymphoma in their study.

In fact, the response in the high dose was equal to the response and controls. That's the closest thing to comparability that I detected, but I don't think -- maybe with all of these studies we've got and all the things we've looked at, I'm not sure how much strength we should give to that. But I do have the data that I pulled out for all the studies. I'd be glad to include that if we think it's important.

In summary, my review of the data show that the positive responses were not produced in other

studies. In fact, in many cases, there were significant or near significant negative trends in the same tumor categories as those in which significant positive trends were identified.

With so many tumor categories recorded in these studies, as we've talked before, a true significant positive trend and significant negative trends would be expected, even if treatment has no effect on tumor rates. And I did see about as many significant negative trends as I saw significant positive trends. We should also think about that as well.

But I would go on to say the multiple comparison problem is particularly acute in the case of glyphosate because we've got so many studies. It's very unique. It's a particularly acute problem in the case of the glyphosate data. And it appears that the positive responses observed are no greater than what would be expected just by chance. So overall, these results appear, to me, to be best interpreted as the results of random assignment of animals to dose groups, rather than due to any carcinogenic effect of treatment.

DR. JIM MCMANAMAN: Thank you, Dr.

Crump. This seems to be a different view than what was expressed. Does anyone have any comments about how, potentially, the two views could be reconciled?

Dr. Sheppard.

DR. LIANNE SHEPPARD: I think the way to reconcile it is by pooling the data instead of counting the number of statistically significant tests in one direction or another. The data should be pooled. That way you can ask the question on the large database as opposed to a lot of separate studies. All these studies are small and there's natural variation, particularly with small numbers. And distinguishing, you know, a count of zero and a count of 5 and studies that are done differently; you know, there's a lot behind that. The pooling allows you to get a better sense of it.

DR. JIM MCMANAMAN: Is that what Dr. Chris Portier did for the renal tumors?

DR. LIANNE SHEPPARD: He did it for several tumors in the mouse data. I'm not exactly sure how he pooled, because he didn't document that and there's devils in those details. But yes. It seems like it was done appropriately, in general. But specifically, the Agency might want to tweak some

details.

DR. JIM MCMANAMAN: Let me ask a question. Given the low animal numbers that we have, is this kind of variability or kind of hence of one thing or another, is this what we would expect for something that would be a weak tumor promoter? Is that we were to get this kind -- and that we really need more animals or greater power in the studies to evaluate this? Or is it something that would not be consistent with that possibility?

DR. BARBARA PARSONS: I think that's right. I think that if you had a weak tumor promoter, and the magnitude of effect is small, that this tumor profile is what you would expect to see.

DR. JIM MCMANAMAN: Dr. Green.

DR. LAURA GREEN: I agree with everything that's been said, but I want to amend something I thought before. We've all been talking about tabulating the data. But what Kenny just said made me realize, we should graph the data because there are very different dose groups. We ought to just make a simple x/y plot, right. We've got six mouse studies -- by the way, I don't know why Chris Portier only has five because there's six of them.

But we ought to just make an x/y plot.

And on the x-axis are doses of glyphosate acid; and on the y-axis are percent response. And just see what the data look like, right? I think that would be better than a table because it would allow us to see this dose variation and it would be super informative, I think.

DR. JIM MCMANAMAN: That might be a good idea, except for Dr. Ramesh pointed out why that might not work, given that we're at high doses already.

DR. ARMANDLA RAMESH: Are we talking about a particular species or strain?

DR. LAURA GREEN: Yeah. For example, the CD-1 mouse has been tested five or six times, look at the renal tumors. And there's different doses and they're slightly different, you know, time courses. And the Wood study I think is the one where it was terminated 18 months. There are few details.

But for the most part, there's enough similarity that if we do it by species and strain -- and I would argue for plotting the males and females on the same chart. Although obviously, for things like testicular cancers and mammary gland tumors,

that's not a good idea, but I would argue for others it would be. Or if you'd like, two different charts.

I mean, the details don't matter. But what I realize, listening to everyone, is because there are such different dose ranges, a table is not completely informative.

DR. ARMANDLA RAMESH: I have a problem with comparing with the female animals because I don't know how many of them were normalized with regard to the cyclicity. It's through cycle changes and all, because most of these chemicals are under hormonal influence also.

DR. JIM MCMANAMAN: Yeah, but these were long-term studies, so I wouldn't think that that would make any difference.

DR. ARMANDLA RAMESH: Yeah, but I think instead of saying it is, I don't want still to say it is a re-carcinogen. It may be, but for that matter any chemical that's the same. And glyphosate is no different from the other chemicals that have a lesser carcinogenic potential.

DR. JIM MCMANAMAN: Okay. Thank you. That was Dr. Ramesh. Dr. Crump.

DR. KENNY CRUMP: Yeah, a couple of

points. The idea that this data is consistent with a small, but nongenotoxic effect, I think that's probably true. But I think we can't rule out it's also consistent with what you expect by random, is assignment of animals to dose groups. I think that's still true. Maybe both are true.

With regard to the suggestion that we should be pooling animals, I haven't seen any details on that. Sorry, I haven't read Dr. Portier's paper yet. But I'd like to know more about that before we would recommend something like that.

I'm not sure what we're pooling here. It seems like we're only pooling, correct me, but we're pooling responses of the same type in different studies. But I don't really see how that would address the multiple comparison problem when we have so many tumors in different sites completely, anyway. It might help a little bit. But I'd like to know more about the pooling, and how we would do it and how we would interpret it.

DR. LIANNE SHEPPARD: Well, the scientific question is whether there's carcinogenic potential. And I don't think that means potential in all sites, it means in any site. And therefore, it's

not -- my scientific interpretation is, it's not appropriate to put together different sites and to consider them equally. You need to take each site in turn. Because if this compound is carcinogenic in a single site, it's still -- according to my understanding of reading the guidelines, it still has carcinogenic potential.

And so therefore, the multiple comparisons question is not about all sites, it's about any one site. And the best way, in my mind, is not to say oh, what is the P value that we expect in a really small study; but, what is the evidence in the body of studies?

And that's why the pooling is more appropriate in my mind, then the multiple comparison adjustment. Because the pooling allows us to get at the deeper and much more important question, which is, what is the evidence in the data that we have, that there's carcinogenic potential? And so then we just need to go about trying to answer that as technically well as we can.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Sheppard. Dr. Johnson, do you have --

DR. ERIC JOHNSON: Yes. From what I've

heard, I seem to hear much more concern about this animal carcinogenicity study than the flavor I got from reading the EPA's Summary of Conclusions.

I wish our colleagues could highlight these studies, which are not so obvious when we read the EPA conclusion in the report. Because really, I mean, there is room for different thoughts when you hear all the details, which Dr. Parsons' was really elegant.

DR. JIM MCMANAMAN: Okay. Thank you. I think that we probably -- Dr. Zhang, do you have a quick -- I see your light is on.

DR. LUOPING ZHANG: Oh. Quick comment. I hurry, you know. I think if I could make a suggestion. I think the document the Agency provided, I think it's a little bit difficult to really, for me at least, get the most important information. What I'd like to suggest is when we had the first public comment from EFSA, see, they make the table. It just shows you the example for the lymphoma in mice. They put the other study, and the male/female and the dose, so everything in one table.

I heard how to present the data would be easier to do a comparison. I think that would

maybe be a good way to do it. Because I thought there are some studies, what she presented, we didn't have. But finally, actually, I found it from, you know, somewhere. You actually included it, but excluded it from the write-up; but in your table, it was actually still there. But it was just very difficult to get the data. That's just a suggestion.

DR. JIM MCMANAMAN: All right. Thank you, Dr. Zhang. Dr. Crump.

DR. KENNY CRUMP: One more comment about how we might display the data. The way I did it, I thought it was revealing to me. I did it, first of all, in a given sex and strain, and listed all the studies one below another, giving the doses and responses, that we could look at. And did the same thing in the other sex in those same studies. And then I went to other strains of the same species to look at those.

And finally, I went to the other strain of rats to see if there was any corroboration in there. And I found that way to organize the data to be revealing, at least to me.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Crump. I think that we've discussed this pretty

thoroughly. I'll go back to the Agency and ask if there is further clarification needed.

DR. ANNA LOWIT: So we've heard a large number of suggestions that vary in their complexity. We would hope that the report represents that broad spectrum of suggestions; not only of complexity, but of different points of view. We're hearing, to some degree, I think, conflicting advice, which is fine, that the studies differ in many ways. And then we're hearing advice to then pool them.

That's two different ways to look at the information. We would hope that all of those views are represented.

DR. JIM MCMANAMAN: That was Dr. Lowit. Let me encourage the panel members, when you do your write-ups, if, for instance, Dr. Sheppard is in favor of the pooling, please provide good recommendations about the approach and what should be done in terms of pooling, in your view, so that we have details about that.

Would that be helpful?

DR. ANNA LOWIT: Yes, but I don't want it to become -- I don't want to drown out all the other suggestions about figures and tables.

DR. JIM MCMANAMAN: No, no, no. I'm just using that as an example. If you have a specific point of view about how to present this, or how to evaluate this, then really, please include as much detail as possible in the report.

DR. ANNA LOWIT: And all the suggestions as well.

DR. JIM MCMANAMAN: Yes. Okay. Do we want to take a break now, maybe a 15-minute break? So be back at five after 10:00.

[WHEREAS A BREAK WAS TAKEN]

DR. JIM MCMANAMAN: I think we're at 3(f). If we could read that into the docket.

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar. I'm going to read Charge Question 3(f). As described in Section 1.4, high-end estimates of exposure based on the currently registered uses for glyphosate in the United States have been calculated as 0.47 mg per kg per day and 7 mg per kg per day for potential residential and occupational exposures, respectively.

As a result, the Agency concluded that

tumors observed at high doses, those approaching or exceeding 1000 mg per kg per day, following glyphosate administration, are not relevant for human health risk assessment.

Please comment on the conclusions regarding the relevance of high-dose tumors to the human health risk assessment for glyphosate.

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The discussants on this are Dr. Parsons, Green, and Ramesh. Dr. Parsons is lead.

DR. BARBARA PARSONS: First, I wanted to echo a comment that was made, during the open comment period, regarding what I perceived as the dilemma set up in the EPA document. On one hand, the document downgrade studies that don't use doses as high as 1000 mg per kilogram per day; and at the same time, makes the argument that doses above 1000 mg per kilogram per day are not relevant to human exposure. I'll just mention that.

Certainly, I think it's clear to all of us, the tumors induced only at very high doses are less of a safety concern than those induced at doses within the range of human exposure. Chemically induced modes of action occurring at high doses, which

have the potential to overwhelm homeostatic mechanisms, may not occur at lower doses.

However, in regards to this charge question, what I would like to point out is that there were significant, potentially carcinogenic effects observed at doses lower than 1000 mg per kilogram body weight per day. Significant induction of lymphocytic hyperplasia was observed at 11 mg per kilogram body weight per day. And that was Lankas.

Significant lymphoid hyperplasia was observed at low and mid-doses in male CD-1 mice. That's 71 and 234 mg per kilogram body weight per day, in a study where malignant lymphomas were significantly induced at 810 mg per kilogram body weight per day. That occurred with the trend test of 0.007. And I explained yesterday why I think the Cancer Guidelines are suggesting that it would be something we should pay attention to.

Male Sprague Dawley rats in the Lankas study demonstrate a significant trend, and a significant pairwise comparison between control and high-dose for testicular interstitial tumors, when the high dose was 31 mg per kilogram body weight per day. Also, with a P value of 0.009. I think the Agency

should consider these glyphosate concentrations below 1000 mg per kilogram body weight per day, which produced, what I assume, our carcinogenic effects in rodents, consider them when establishing acceptable levels of glyphosate exposure.

I conclude that carcinogenicity was observed with rodent lifetime exposures as low as 31 mg per kilogram body weight per day. I don't think this generates concern for dietary or residential exposures to glyphosate. But this is only about fivefold greater level than EPA's upper limit estimate for glyphosate exposure in the occupational setting.

Therefore, I disagree with the conclusion in the document that says 7 mg per kilogram per day is well below -- this quote -- "Well below the doses necessary to elicit the effects seen in these animal carcinogenicity and genotoxicity studies."

I would add that if glyphosate causes progression of spontaneously arising lesions -- and by this, I mean cells carrying cancer driver or other mutations -- then humans are potentially at risk of glyphosate-induced carcinogenicity; and the longer human lifespan is expected to contribute to that risk.

In terms of selecting appropriate

uncertainty factors for ensuring public health, there are a number of factors that I would recommend EPA consider.

First, it should recognize that the much longer human lifespan, relative to the rodent, is likely to result in human tissues accumulating more spontaneous cancer driver mutation than rodents. Here, I'm talking about mutations that confer a tissue-specific selective advantage to mutant cells. The risk associated with chemical exposures, capable of causing progression of pre-existing spontaneous lesions, are potentially significant in human.

The use of glyphosate, which I believe is likely a high-dosed rodent tumor promoter, within formulations in which other chemical entities possess any genotoxic potential, would be a significant public health concern. But to balance that, I want to say that it should also be recognized that the potential replacement of glyphosate, a well-characterized herbicide with potentially well-characterized or potentially less safe herbicides, would also carry a risk.

And this is pretty much an aside, but in some of the comments that we heard, I just want to

mention that since we're -- well, never mind. I'll just leave off.

DR. JIM MCMANAMAN: Thank you, Dr. Parsons. Dr. Green.

DR. LAURA GREEN: In response to the charge question, it is, in my experience, unusual to a priori disregard doses of gram per kilo risk -- well, let me say it in two ways.

If the responses that Dr. Parsons points out are true positives, then the draft document's treatment of the data is not health protective. Regardless of whether they are true positives or false positives -- and by "they" I mean, the findings of Leydig cell tumors at 31 mg per kg in Lankas et al. study, which I've made clear, I think it's a false positive.

But regardless, it is not Agency policy, in my experience, to make what seems to me a bit of an arbitrary decision here, especially since, as we have mentioned, a gram per keg day is not the maximally tolerated dose. There is no evidence that important systemic or organ-level or tissue-level damage is occurring at a gram per kg day. I know of no reason to discount the findings at a gram per day,

and higher for that matter, up to 4000 mgs per kg day or 4 grams per kg day.

I find the agency's decision here to be counter to what it does for lots of other chemicals in lots of other settings and programs within the Agency. I would also note that, in my experience, the only times that the Agency discounts wholesale high-dose response, is if it has strong belief that the mechanism of action, by which the putative carcinogenic events are happening, is well-known and displays a hockey-stick like shape in its dose response relationship.

I hesitate to say the word "threshold," but certainly for chemicals such as chloroform in drinking water, the Agency struggled long and hard before it finally determined that there was enough science on how chloroform induces cancers and tumors. And that it has an apparent threshold below which tumorgenicity risk is essentially zero. And only after years of discussion and thought did the Agency decided that for a chemical like chloroform, one could disregard high doses.

I am disturbed by this. I would not recommend it. It turns out to be academic because, as

I've made clear, I think the tumor findings are false positives anyway. But if they were true positives, I think this is an incautious approach, which I think it's counter to Agency policy, except in very rare circumstances.

DR. JIM MCMANAMAN: Thank you, Dr. Green. Dr. Ramesh.

DR. ARMANDLA RAMESH: I agree with the Agency conclusions because no matter whatever amount of glyphosate is taken in, only 30 percent was found to be observed. The rest of it is excreted largely through feces and urine.

The net amount going to the tissues to cause any mutations or any perturbation seems low. However, in the revised White Paper, they may want to emphasize the point raised by Dr. Parsons. The likelihood of glyphosate contributing to the progression of a pre-existing lesions or mutations. That aspect needs to be mentioned as a qualifying statement.

Other than that, by and large, I am in agreement of the conclusions, that at high doses, the findings are not of any toxicological or carcinogenicity consequence.

DR. JIM MCMANAMAN: Okay. I'll open this question up to the rest of the panel. We've heard differing views. Dr. Johnson.

DR. ERIC JOHNSON: Well, I would just like to point out that if we use the dioxin example, EPA used in its risk assessment, the occupational cohort studies from NIOSH. And that cohort had exposures that were up to over 10,000 times what you'll find in the general population.

I don't see why, in this case, we should limit consideration of exposures greater than 1,000 mg per kg, especially when there's no toxicity observed at that dose. Over 10,000 times, the exposure will experience the occupational cohort, compared to the general population. And whether dioxin was going to be classified as carcinogen or not, it was going to be based on those data. There is no limit on that.

DR. JIM MCMANAMAN: Thank you, Dr. Johnson. Other comments? All right.

DR. KENNY CRUMP: I have a comment.

DR. JIM MCMANAMAN: Dr. Crump.

DR. KENNY CRUMP: Well, I'm thinking one of you has pointed this out, but I think EPA needs

to clarify its position on result on exposures that exceed 1000 mg per kg per day. In some places the document appears to suggest that none of his responses are related to treatment. But in other places, it seems to indicate that these responses are related to treatment, but they're simply being discounted by the Agency. I have some examples of that wording in my fuller submission. I think it's really important for the Agency to clarify that point. Are you just disregarding them because they're high? Do you think they are due to treatment or not?

DR. JIM MCMANAMAN: Thank you, Dr. Crump. Other comments?

Dr. Sheppard.

DR. LIANNE SHEPPARD: Thank you. The first point I would like to make is while the charge question focuses on risk assessment, the document that were evaluating is about hazard assessment. The dose considerations in a hazard assessment are really different from those in a risk assessment. And the goal of a hazard assessment is determined hazard potential, not exposure potential.

As I mentioned yesterday, in order to inform the dose response evidence from small studies,

it's important to study high enough doses where the effects can be anticipated in the small samples if indeed effects exist. Now that is not to set aside the scientific considerations of problems with high doses that Dr. Parsons talked about, but that evidence needs to be made clear if there's any reason to be concerned with that. And presumably, that is taken into account in the design. That's the point of the guidelines for these studies, is to take that into account in the design and to not study too high doses where there's going to be problems.

Again, as I stated yesterday or earlier this week, from a human point of view, we care about increased cancer incidence on the order of one in a million. We can't do an animal study of a million animals. As we heard, just a few minutes ago, nor do they live long enough to necessarily show the endpoints that we care about.

A small toxicological study will never have enough power to provide evidence for such small increase risk. We have to base the analyses and our determination of the evidence on the experiments as their designed, and infer from the entire dose spectrum that is studied.

It's inappropriate, after the studies are completed, to discount the high dose results. Because it's the high doses that help us understand and give us the sufficient power, in small sample sizes, to allow insights to be inferred from lower doses. It's the role of risk assessment to do that extrapolation to lower doses. It's not the role of hazard assessment.

DR. JIM MCMANAMAN: Okay. Other comments? I think that Dr. Sheppard makes some very cogent points related to this. And if the other panelists can weigh in on her points, relative to the other assessments, I think it might be helpful.

Dr. Portier.

DR. KENNETH PORTIER: So, you know, I had kind of the same feeling. Every time they say the hazard statement, they tack on, in the report, at human relevant doses. The discussion of the high doses is extremely important because of that translation.

Where I do have problems with high doses, and I wish would be done in the report, is actually tell us when the high dose seemed to produce conditions in the animals that would raise concern,

that what we're seeing is not related to the carcinogenic potential of the chemical, but its toxic potential at high doses. When you start seeing real big changes in blood and urine chemistry, when you see extreme body weight conditions. I mean, that's when I start to get worried.

The problem with glyphosate, and I was trying to figure out why would they take a mouse study up to 4100 milligrams, which is what 13, 14 percent of expected adult body weight. And I think the early of researchers were saying we don't think there's a toxic effect here; we can just give them high doses of this stuff. But nowhere in the document did they go to the original studies and look through the notes and say, where are there health issues at the high doses.

For a few of them, we did note body weight drops immediately; that that particular high dose never quite caught up. Which has some implications on its carcinogenicity, but I didn't see a lot of the additional biological conditions that would tell me, well, maybe I shouldn’t be considering that high dose. I'm kind of left uncertain. For me, it's almost study-by-study, they should've gone in and said, at the high dose, nothing was seen; at the high

dose, something was seen. Okay, maybe I dropped it here. I don't drop it there. I'm on the fence, right. I'm in between.

DR. JIM MCMANAMAN: It sounds like you were leaning towards Dr. Sheppard's point of view, though.

DR. KENNETH PORTIER: Well, you know, I think globally, in the document, they're mixing, to me, risk assessment and hazard. And I think it comes down to this statement that they keep tacking at the end, not at human relevant doses. And they haven't done the full exposure assessment, although we had some discussion on that.

And I'm sorry I missed the first day because I think there was a lot more discussion on exposure then. But I would've liked a more clean hazard assessment myself. And I think when we get to Question 5, some of that discussion is going to relate more to using the Bradford Hill criteria to assess hazard than to assess risk.

Although we're talking about dose response, but we didn't do modeling and all that other stuff that goes with risk assessment. This is somewhere an in between report. It's in between a

hazard assessment and a full risk assessment.

DR. JIM MCMANAMAN: Neither fish nor fowl. Okay. Dr. Green, did you have a comment?

DR. LAURA GREEN: Yeah. I wanted to agree with everything that was said. Dr. Sheppard is exactly right; the point of doing high-dose studies is to make up for the fact that you've only got 50 or 60 animals per group.

By the way, you know, two years in a rat pretty much is a human 70 or 80-year lifetime. That's not so much problem, but obviously, 50 animals per group is not a great stand-in for 300 and however many million Americans we have, not to mention 7 billion people on the planet. Dr. Sheppard is completely right.

I just want to remind us that toxicologically, this is a very unusual compound. It's not toxic per se, except at, you know 5 grams per kilogram or higher levels, which is pretty non-toxic. It's not metabolized at all by the liver or any other human enzyme system that we know of. It's metabolized a teeny bit in the gut, depending, I imagine, on exactly what microflora are they are and how long the stuff is in the gut. It's not an electrophile, it's

not a nucleophile.

I mean, the things that we worry about with high doses have either to do with saturating detoxification systems or other, you know, sort of toxicologically significant differences. As far as we can tell, there are no toxicologic significant differences between a low dose of glyphosate and a sublethal dose of glyphosate.

I mean, it's just non-toxic until there's so much of it that it kills you for pretty much nonspecific reasons. And by "you" of course I mean rodents. And by the way, that's actually seen in human clinical writeups of people who have attempted to commit suicide by drinking lots of Roundup or their equivalents in Japan. I don’t know what it's called Japan.

It turns out to be really hard to kill yourself drinking Roundup. And when you get into trouble, it turns out to be mostly because of the surfactants and other things. I mean, glyphosate is super non-toxic and it's not metabolized and therefore, I don't -- by humans and other mammals -- therefore, I really don't see why one would discount a gram per kg. It does not fit in the paradigm.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Green. Dr. Crump.

DR. KENNY CRUMP: I'd like to say that I totally agree with what Dr. Sheppard said. I think, I'm not sure if anyone said this is this discussion, but from my look at the EPA Cancer Guidelines, 1000 mg per kilograms per day is not what they recommend as a top dose. It's 5 percent in diet for feeding studies. They have that problem also.

DR. JIM MCMANAMAN: Okay. Dr. Jett.

DR. DAVID JETT: I'm an organophosate expert and I'm thinking about drinking Roundup. I think, I'm probably mostly leaning towards Dr. Sheppard's position. What I do at NIH mostly is translational research so we do a lot of preclinical safety studies and things like that. And usually when we can, we try to do these studies where we have a dose where we know we're going to have a positive effect. And it may be really high, but it's almost like that internal control so that we know that we have the proper dose range.

Given the fact that we do know that there are some levels of Roundup that will produce these effects, and it may be really high, I probably

would lean on looking at studies that included that dose.

Now, the significance of the tumors is another story. But to discard studies simply because they only see anything at the high tumors, I think, probably is not the way to go.

DR. JIM MCMANAMAN: Okay. Thank you. I think we've heard a pretty good discussion about this. I'll go back to the Agency and ask if there's any additional clarification.

DR. ANNA LOWIT: No additional clarification questions, per se. I just want to remind all of you that the U.S. works under the OECD mutual acceptance of data, what people call the MAD. Which means that, under the mutual acceptance of data, the OECD guideline limit dose of 1,000 would be the maximum tested in the studies that we receive.

If this panel was to suggest that we routinely start asking for our less potent chemicals to test up to 5 percent of body weight, it would be in conflict with the OECD, and we would be in conflict with our other international partners.

DR. JIM MCMANAMAN: Okay. Dr. Sheppard.

DR. LIANNE SHEPPARD: Yeah. I just wanted to say, we're not asking that you change anything about what you're asking for; we're only asking you to use the data that you have to its fullest.

DR. ANNA LOWIT: I think there's a semantics thing that we're hearing. That there's a belief on the panel that we have discarded information. And in fact, had we discarded it, it would not have been in the paper.

I guess to some degree I would ask some of you to think about your use of certain words because they are, in my view, inaccurate to the paper. It may be a reasonable criticism that you have on our phrasing of how the limit dose effects were looked at, but we do take issue with the comments about information being discarded, because nothing was discarded.

DR. JIM MCMANAMAN: Okay. I think that the issue here is relevancy. And I think the comments should be made towards the relevancy of these high doses. If we could elaborate in using the term "relevancy."

Okay. I think then we'll move on to

Charge Question 3(g).

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar. I'll be reading Charge Question 3(g).

Please comment on the strengths and uncertainties associated with the agency's overall weight-of-evidence and conclusions based on the available animal carcinogenicity studies as described in Section 4.8.

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The discussants on this are doctors Ramesh, Crump, Parsons and Portier. Dr. Ramesh is the lead discussant.

DR. ARMANDLA RAMESH: I am in agreement with the agency's interpretation, with a little bit of reservation. I find that the strengths or the weight of approach is considered adequate, and the qualifying criteria EPA adopted for selecting studies that's appropriate. The weaknesses are, in the document it was mentioned the observed tumor responses are unrelated to glyphosate treatment. That conclusion needs to be revised a little bit, saying that yes, the observed tumor responses are unrelated to glyphosate treatment, going by the literature reports and data.

However, the contribution of glyphosate

to either promotion or progression of spontaneously-induced lesions, cannot be ruled out. With that qualifying statement, the document is okay.

DR. JIM MCMANAMAN: Thank you, Dr. Ramesh. Dr. Crump. 3(g). Yes, overall weight-of-evidence. Question G.

DR. KENNY CRUMP: I have a different number.

DR. JIM MCMANAMAN: It's the last one on the slide. Yes, it's 3(g).

DR. KENNY CRUMP: I'm sorry. Okay. I summarized some of the thing I've said before, but I considered the weight-of-evidence evaluation gives excessive weight to several factors in the weight-of-evidence evaluation. And those are monotone dose responses, historical tumor rates, lack of statistical significance of pairwise comparisons when they're a significant trend, and disregarding or giving low weight to what results to exposures greater than 1000 mg per kg per day.

On the other hand, I think EPA's weight-of-evaluation do not take proper account of the serious multiple comparison problem caused by focusing attention on the most extreme tumor responses out of a

large number of responses. And I'll just briefly go through each of those shortcomings and make further comments about them.

First of all, the monotonicity; the fact that an observed dose response is not monotone provides essentially no evidence that the underlying true response is nonmonotone. That's not part of the EPA guidelines. And I think it just absolutely needs to be dropped. In fact, I did a simulation that showed. I took two monotone dose responses and simulated the data. There were more nonmonotone responses than monotone in every case.

Historical control rates; in cases in which EPA relied on historical control rates, it was used to suggest that the tumor response is not dose-related. If this is true then all the tumor responses observed in all dose groups are incidental, so it would be reasonable to compare the historical tumor rates with all the tumors and not just the ones in the control group. The EPA Cancer Guidelines properly recommend caution in the use of historical control data. And I'll repeat this one more time. I think I've already repeated it twice.

"Generally speaking, statistically

significant increases in tumors should not be discounted simply because incidence rates in treated groups are within the range of historical controls or because incidence rates in concurrent controls are somewhat lower than average." That's a direct quote from the EPA Guidelines.

I think the reliance on the use of historical control data in the report was overdone a bit and not in keeping with EPA Guidelines. Pairwise tests; in several cases, EPA used the nonsignificance of pairwise tests to down weight a significant trend test. And this is contrary to EPA Guidelines, as has been pointed out by me and others just this week; which says, "However, the EPA Cancer Guidelines states that significance in either a trend test or a pairwise test is sufficient to reject the hypothesis that chance accounts for the results."

And so, in my opinion the EPA analysis would be on a sounder and more easily-interpreted footing if it avoided a battery of pairwise tests, and instead, conducted a single powerful test for carcinogenicity, namely an age-adjusted trend test. One test for carcinogenicity for each endpoint. I think that would be a much better approach.

Disregarding of exposures greater than 1000 milligrams per kilogram per day. I mentioned just a few moments ago, that is at odds with the EPA Guidelines, which suggested 5 percent of test substance -- above 5 percent would be the cutoff. And there were no exposures in any of the studies that exceeded 5 percent in the feed.

I see no reason for disregarding results from exposures greater than 1000 mg per kg per day, as long as the dose does not exceed the maximum tolerated dose. I also do not agree that such doses necessarily have no relevance for human risk.

Strict reliance on significance of individual tumor responses at the 5 percent level. All the shortcomings, I mentioned previously, are in the direction of making a conclusion of no carcinogenic effect, when there is a carcinogenic effect. However, it seems to me that these shortcomings are more than compensated by focus on the statistical significance of tumor type, showing more extreme dose responses among a very large number of tumor types for which data are available. With such a large number of tumor types available for statistical evaluation, you have a terrible multiple comparison

problem as really exacerbated in the case of glyphosate because there are so many studies.

This statement has been stated before; a number of statistically significant responses would be expected to occur simply by chance when evaluating such a large number of tumor types. In fact, the meta-analysis that Dr. Haseman did, as well as the one that I did, suggests that the number that we were seeing in these studies were about what you'd expect to see by chance.

In addition to the issues concerning the evaluation of the animal data presented above, I think it's still important to note that none of the statistically significant tumor responses were fully supported in other studies of the same sex and species and strains. I'd also like to point out that none of the statistically significant responses were particularly strong. In fact, if you make a reassignment of one or, at most, two animals in any study, you would change the result from significant to nonsignificant. All I'm saying from that is these responses, we're saying they're statistically significant, they're not strong responses at all. Thank you.

DR. JIM MCMANAMAN: Thank you, Dr. Crump. Dr. Parsons.

DR. BARBARA PARSONS: First, I'd like to say, I totally agree with that. The magnitude of the effects that we're talking about are small. Regarding this charge question, the document concluded that the observed tumor responses correspond to common, spontaneous tumor types, and are unrelated to glyphosate treatment. In my opinion there is sufficient evidence to conclude glyphosate is a weak rodent carcinogen at high-doses. And in my opinion, 31 mg per kilogram per day is still a high dose. I'm going to throw out one more example of why I think this of the five mouse studies, and I discount one because they only had 10 animals.

DR. LAURA GREEN: Fair enough.

DR. BARBARA PARSONS: Two found increases in lymphocytic hyperplasia and three found increases in lymphoma. I Interpret the totality of the tumor data, as supporting the hypothesis, that glyphosate causes the promotion or progression of common, spontaneous lesions.

Regarding uncertainties associated with the agency’s overall weight-of-evidence, to my mind,

the lack of correction for survival also factored into my evaluation of the potential significance of the observed tumor responses. Because I think that they may become more significant if you correct for decreased survival. Even though it may not have been statistically significant decrease survival, I think, in some cases there was decreased survival in the high-dose groups. But in any case, I think that's the data that we should be looking at. That's all I have.

DR. JIM MCMANAMAN: Thank you, Dr. Parsons. Dr. Portier.

DR. KENNETH PORTIER: Thank you. You know, when I first looked at this question, I didn't write anything down, because I suspected the answer to this question would come out of the earlier discussion. I think that's what I'm looking at.

When you look at this section, it has like six paragraphs. I don't have a problem with paragraph one. Paragraphs 2 and 3, you have a lot of discussion. The report has a lot of discussion on the pairwise statistical significance, the lack of monotonic dose response, the historical control information. And I think the panelists weighed in on all of those things. For example, pairwise tests

significance, we really think if the trend test is significant, that's sufficient. And that's in your guidance and you should run by these rules.

We don't see the guidance talking about monotonic responses. We're not sure that argument fits in here unless you're going to do this in a more formal way. And then we just had the discussion on historical controls; and I think the panel is kind of leaning towards being extremely conservative in how you use historical controls.

I think there's some issues -- even if you use historical controls, you potentially use them in the wrong statistical way in this document, you'd have to turn that around.

And parts of paragraph 5 follow paragraph 2 and 3 in the discussion on testicular tumors. You also have this mentioned.

In paragraph 4, the last sentence says, "In the mouse, the increase in the incidence of renal tumor, hemangiosarcoma, lung adenomas, malignant lymphomas and hemangiomas were reported only in a single study; and findings were not seen in the four other studies conducted in CD-1 mice at similar or higher doses."

I think we heard in Dr. Parsons presentation, just a little while ago, that I think she would disagree with that statement for lymphomas, right. There are five studies in the CD-1 male mice and we see tumors in three of them. And then she reported that the other two studies had premalignant lesions in the study discussion. I think we're going to have to disagree with that statement as well.

And then in paragraph 5, there's kind of a two-part paragraph. If you move the discussion on testicular tumors out, you're left with this beginning of a discussion of risk assessment. I think the discussion in the last section, we kind of concluded that the high doses are maybe relevant for hazard considerations, but they don't have to be relevant in dose response.

Once you make a hazard declaration and you move to dose response, when you're actually doing the modeling to find a point of departure and all the stuff, you don't have to pay any attention to the highest dose, because you can argue that it is way outside human relevance at that point, right? And fit your dose-response model to the more relevant doses to get your point of departure for your cancer slope

factor, or whatever.

I think that section, you need to think about what's going on there because again, you're missing a risk -- you're kind of putting a risk assessment statement in with a hazard discussion. And in the last paragraph, it's three sentences. I think, from what I've heard, the panel kind of disagrees with the first sentence and agrees with the last two sentences.

We kind of disagree that based on the weight-of-evidence, the Agency has determined any tumor findings observe, for glyphosate, are not considered treatment-related. I think we've been arguing that some of them are -- even at the high doses, we're not willing to throw them out.

But that tumor findings observed at the highest dose were also not replicated, reproduced in studies, and some animal strains or higher doses. And that's a matter of the data. There are situations where it shows up in one high dose and doesn't show up in another study.

And then the last statement, "Even if the high dose tumors were considered treatment-related, these findings are not considered relevant

for human risk assessment based on use pattern and potential exposures." And that would be part of the risk assessment, not a hazard assessment. And I'll try to write all that down. I got most of it written.

DR. JIM MCMANAMAN: Thank you, Dr. Portier. Dr. Green.

DR. LAURA GREEN: I'd like to give some specific recommendations, please, to, I think, the same page that Dr. Portier was just alluding to. It's page 96 of your document, the first full paragraph that's starts, "When looking across the studies." if I can just help a little bit.

Starting on the third line there, "With the exception of testicular tumors in SD rats." First, you shouldn't say testicular tumors. That's too vague a phrase. It's actually the interstitial tumors or Leydig cell tumors. You can use either phrase, but testicular tumors is too broad and potentially misleading; because there are some types of testicular tumors that are, in fact, of significance, but these are not them.

Second, you give four reasons here for considering them to be less relevant, and I would suggest you may want to rewrite these. "First, you

say that testicular..." -- and again, you should say interstitial testicular or Leydig cell -- "...tumor data do not show monotonic dose response." Please eliminate that. As Dr. Crump and others have said, that's not a meaningful reason to discount a finding.

Your second reason, you say, "The concurrent controls appear to be unusually low for this tumor." That's correct, but -- well, you can leave that in. That's correct.

Next, you say, "There were no neoplastic or related nonneoplastic lesions." Again, I'm not sure that that's relevant for Leydig cell tumors. I would not include that as a reason to discount it.

Then you say, "And this tumor type was not seen in other studies at doses up to 35-fold higher in the same strain of rat." Obviously, that's critical and I would recommend you keep that in.

I would also recommend that you cite the work by pathologists such as Gary Boorman, B-O-O-R-M-A-N, who wrote in the 1980s, I believe. And there are many others who have cited him and followed on his work.

With regard to the specific pathology

of finding, Leydig cell tumors in the aged Sprague Dawley rat -- and I would remind you that, as Dr. Parsons pointed out, which I had not noticed, Lankas et al. ran their study for 26 months, which is very unusual and highly likely the reason that these Leydig cell tumors appeared in excess.

The pathologist, like Dr. Boorman, have shown, using thousands of control untreated Sprague Dawley rats, that it is extremely difficult to differentiate pathologically between hyperplasia in interstitial spaces in the male Sprague Dawley aged rat. It is extremely difficult to distinguish between hyperplasia and bona fide tumors, especially with small lesions.

And in fact, a rule of thumb, among pathologists and cancer biologists, is bona fide carcinogens. If they in fact are testicular tumorigens in the rat, you should look in the Fisher rat, the F344 in particular, which is a more reliable indicator of testicular tumorigenesis than the Sprague Dawley. I would urge you to cite at least a Boorman et al. or others, because there's a very rich pathology literature on this specific tumor, in this specific outbred strain of rat.

I would say one more thing. I would like to apologize to Dr. Lowit and the rest of EPA, for my ignorance, at least, on OECD Guidelines for carcinogen bioassays. I was completely ignorant of those. And now you mention it, I did remember that the German fella, and the French gal, both mentioned the limit dose of the gram per kg.

I was actually confused by that. I would continue to argue as a scientist, especially with regard to a non-toxic compound like glyphosate, that that limit dose makes no scientific sense. But I was unaware that you were bound by a policy decision made by the Europeans. I would add, maybe this is why toxicologists in Britain maybe voted for Brexit.

DR. JIM MCMANAMAN: Thank you, Dr. Green. Other comments?

Okay. Dr. Sheppard.

DR. LIANNE SHEPPARD: I just wanted to add my voice to this. As we've heard, I think most eloquently stated by Dr. Trump, the weight-of-evidence analysis --

DR. JIM MCMANAMAN: I think that that's Dr. Crump.

DR. LIANNE SHEPPARD: Now I'm doing it

too.

DR. KENNY CRUMP: I'm getting used to this. I think there may be ways to use it to my benefit.

DR. LIANNE SHEPPARD: My apologies, Dr. Crump. The weight-of-analysis evidence inappropriately discounts high doses and did not take into account the full spectrum of results in all the studies reporting on a specific outcome species and gender. We didn't see, in the document, any of the other study results for any particular outcome, other than the ones that popped out as significant, and that's problematic. We've made suggestions about addressing that.

The analysis inappropriately uses historical controls and takes into account nonstatistical criterion for monotonicity. It inappropriately discounts trend tests when pairwise tests don't inform the conclusions. Multiple aspects of the analysis do not appropriately reflect the guidelines.

The strength of the evidence assessment should either follow the guidelines that the evidence, of even one outcome in one study, in one species, is

evidence of carcinogenic potential; or it should explicitly recognize the large number of studies for this compound and combine them to provide the best possible evidence from the large number of studies.

And I want to acknowledge that, as I think we've said earlier, this is kind of new ground for you guys. The guidelines are for a body of evidence where you have one or two studies. And so here you're faced with a whole lot of them. You can't, in the same way, I think, rely on the guidelines. I think you either fall back on them and take them at face value, which means, as I said, one study, one outcome, that's enough. Or you do what is statistically more valid, which would be to take all the evidence from all the studies that ask a specific question, which is within a species and probably within a gender, and certainly within a health outcome, a specific cancer, and then you pool them.

And if there's meaningful heterogeneity between the studies, you know, there are ways to deal with that appropriately. There's not a difference of opinion, I think, or different recommendation. There's no conflict by Dr. Parsons saying oh, there's a fair amount of heterogeneity in these studies due to

this, that and the other thing, as she said earlier.

And my recommendation is that you pool them in statistical, you know, tools for meta-analysis, which is one of the ways you pool them. You can explicitly account for heterogeneity with, for instance, a random effect. There are ways to deal with that appropriately that should be done.

I also note that looking ahead to a risk assessment, there's another value in doing that. Because a pooled analysis would give you a much more stable estimate of dose-response than you're getting from any one study of 200 animals. That's another reason to do the pooling, because that's what you really care about, is the dose response. And you need to figure out how to get down to the low end and what the point of departure is. If you can get that function well estimated, then you have a much better ability to figure that out in the risk assessment.

With respect to details in the text, a couple of things I wanted to make sure that we mention is, you know, there are never any explicit weights given for the weight-of-evidence analysis. We don't really know what's a high weight thing and what's a low weight thing. And that, I think, is problematic.

And I think statements of evidence -- I quoted part of a sentence -- "Appear to be unusually low." Those should either be removed or backed up with a P value as statistical evidence. I don't think it's appropriate to, in a conclusion, say this appears something with no way to really understand what that means, statistically. And I also think that evidence regarding human exposure is not evidence that should be used for determining whether animal data gives evidence of a hazard.

And finally, I think the last sentence -- and I'm saying this more directly than my colleague Dr. Portier did. The last sentence in Section 4.8 should be struck from the document because it is not relevant for hazard assessment.

DR. JIM MCMANAMAN: Thank you, Dr. Sheppard. I think you've heard a full discussion of this charge question. I'll go back to the Agency and see if there are any clarifying issues that need to be considered.

DR. ANNA LOWIT: This is Anna Lowit. No clarifying issues. Thank you.

DR. JIM MCMANAMAN: All right. Thank you. Okay. With this, we'll move on to Charge

Question 4. And if we can have that read in.

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar and I'm going to read Charge Question 4.

As part of its analysis, the Agency has considered almost 200 assays investigating the genotoxic potential of glyphosate. Of these, 107 were performed with the active ingredient glyphosate. These included in vitro and in vivo studies from the open literature, as well as studies submitted to the agency that were conducted according to the Office of Chemical Safety and Pollution Prevention/Organization for Economic Cooperation and Development Guidelines.

Non-mammalian studies were excluded from this analysis unless the assays were generally recognized to inform the human carcinogenic potential of glyphosate, in general, bacterial reverse mutation assays. Studies evaluated genotoxic endpoints, such as gene mutations in bacteria and mammalian cells, chromosomal aberrations, micronuclei formation, and other assays measuring DNA damage.

Question (a) reads as follows: Please comment on the agency’s review and evaluation process of relevant genotoxicity studies to inform the human carcinogenic potential of glyphosate, including the

decision to exclude non-mammalian studies, such as those in reptiles, plants, worms, or fish, and except those generally recognized to inform human carcinogenic potential.

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The discussants on this are doctors Parsons, Shaw, and Zhang. Dr. Parsons is lead.

DR. BARBARA PARSONS: So Dr. Shaw had to leave, but he read my comments and then he gave me his comments to add to those. I'll be giving those. I believe the rodent data supports the conclusion that, at high-dose, dietary exposure to glyphosate can cause promotion progressing of pre-existing spontaneous lesions.

Studies in non-mammalian species would be of interest in terms of understanding potential underlying mechanisms of promotion or progression. Clearly, such studies should be given less weight in the determination of whether or not glyphosate is likely to be genotoxic in humans. Those were my comment. And as I said, these were shared with Dr. Shaw and actually, his comments are more extensive.

He says, "I agree and have only little to add. I think the review and evaluation process of

genotoxicity studies is sufficient, given the limits of the accepted assays. I do want to make one comment, and admittedly, it likely doesn't add value to your process, but highlights what I see as a deficiency in the assays that are available to you.

I don't think any of the assays employed provide an unbiased measure of structural mutations, especially smaller ones, i.e. insertions, deletions and rearrangements that give rise to copy number variants, which require sequence-based approaches to resolve. I raise this issue for five reasons.

1) the mutational classes mentioned in the first paragraph of Section 5 of the draft report as a type of mutation that will be evaluated..." perhaps this should be described better.

I think it talks about detecting insertions, deletions and rearrangements. He thinks that the tests that were described don't fully measure the types of damage mentioned in that paragraph. And I'm reading this into the record and he will, you know, provide a more cogent description of his arguments in the report. Copy number variations which arise -- this is point number two. "Copy number

variation which arise both mitotically and somatically are now known to form at rates much higher than other types of mutations."

3) "these are formed by mechanisms that differ from base substitution, including inhibition of replication, which some studies have reported for glyphosate." That's why he thinks this is relevant.

4) "structural mutations contribute at least as much, and likely more, to human variation as base pair substitution mutations, including reported strong associations of copy number variations with many cancers, cancer risk factors and also mechanisms for promotion.

5) there seems to be some evidence that structural mutations contribute to response to glyphosate exposure." Here he's talking about plants and amphibians that develop resistance to glyphosate. I think his point is often that the mechanism for that is amplification copy number variation. That was the end of his comments on this particular question.

DR. JIM MCMANAMAN: Thank you, Dr. Parsons. Dr. Zhang.

DR. LUOPING ZHANG: Yes. I actually, totally agree with Dr. Parsons and Dr. Shaw's

comments. I had an immense discussion and conversation with Dr. Shaw last night. And if I can elaborate a little bit more about that. After the intro in that section, you describe the mutation. You include everything about what the mutation is about, deletion, duplication, amplification, whatever. But with the data we have for glyphosate and mutation, it's only -- actually, the data we have is only like an M test. I don't even know if you have HBRT.

It's not the 21st Century mutation we actually talked about. That's why Dr. Shaw wants to really put that. You either have to specifically say what's the mutation you're including. You actually say, oh, you gave a spectrum of everything and then you elaborate on that. I'm just trying to clarify, if I may.

DR. BARBARA PARSONS: I think they're studies -- not HBRT.

DR. LUOPING ZHANG: Yeah. TK, that's actually. Sort of.

DR. JIM MCMANAMAN: That was Dr. Parsons.

DR. LUOPING ZHANG: Okay. Also, another point that you really like to make is maybe

where -- currently we lack the data for the mutation because it is, you know, the mutation he mentions is highly sequencing a base technology. But what we didn't know is now there. That's question number one.

Now, question number two; from his view, he saw glyphosate actually could cause a duplication or amplification, which could cause copy number variation that's already seen and readily reported in species. That could be as a potential mechanism of action, you know, the Agency should consider. So basically, I just tried to elaborate a little bit more about what Dr. Shaw was writing here.

Now back to my own comment, I totally agree with my panel members, but I would like to add, at the least, to question 4, the rest of our members and the Agency to think about two other studies from human monitoring studies; it's on the Bonassi (2009), which I think, actually is a pretty good study. I mean, both: Bonassi (2009) and Curasi (phonetic) (2014). It seems to have two studies kind of ignored from the genotoxicity. So Bonassi (2009) measures binucleated micronuclei in the Columbian farmers.

But what they really did, I think the beauty of this study, is that they're using farmers

themselves as control. Before they apply the glyphosate products, you know, taking the blood and measuring the micronuclear level, and then five days after, and following up four months after. You are your own controls. I actually think for the human monitoring, that's pretty good data. They did actually measure the increase of the micronuclei frequency after the farmers are exposed to glyphosate.

I think this is kind of valuable data. I just think we should consider. At least, I'm raising the question for other panel members to think. This is one.

And also, to me, when I look at Table 3, I think, maybe I forget exactly the number for this study, also they see the trend. You know, in some area, you know, after five days, you see the increase, the significant increase of micronuclei compare with them before they're exposed. And then four months after, you know, some groups, they increase it even more. But some other group, they didn’t see the consistent increase after four months. But I have a biological explanation for that.

Micronuclei, if you have a single micronuclei, but when cells go to the next division,

you may lose the micronuclei. It really depends on each person's response about how long the micronuclei recycle in your cells. It could be if you wait long enough, you may not see, you know, consistent increase. I think it's still okay.

But anyway, if you look at the data analysis from four months, compared with before they applied the glyphosate, it's still a significant increase. I feel this piece is maybe the only human data we should heavily consider. That's one study.

Second is Curasi (2014). This study, they measure the genotoxicity as 8-hydroxy deoxyguanosine as the DNA damage. It looks like they also see the increase of the level 8-hydroxy deoxyguanosine from glyphosate, one or more applications compared with no applications. Relative risk is 1.47, but, you know, it's not statistically significant because 95 percent confidence interval is from .78 to 2.77. But I still think that human monitoring data is not easy to obtain. I still think that it's important information to be included. We can discuss how we should interpret the human data, but I just don’t think that we should discard it.

That's all my comment.

DR. JIM MCMANAMAN: Thank you, Dr. Zhang. Comments from other panel members?

Dr. Taioli.

DR. EMANUELA TAIOLI: Go back to the previous sections, are there in vitro studies showing -- I mean, looking at promotion? Because you guys are all talking about genotoxicity because it's oxidative stress or micronuclei, right. There is nothing looking at tumor promotion in the in vitro model?

DR. BARBARA PARSONS: I don't think there is such a test for promotion in vitro.

DR. LAURA GREEN: Yeah, that's right. Remember, though, there is that one skin bioassay with 20 animals that we want more information from the Agency on. Or one of us should just go read George et al., whatever year it was.

DR. JIM MCMANAMAN: Okay. Other comments? If not, thank you, Dr. Zhang. I think you raised some very important points, especially related to the human data, though. I hope you'll be able to cite those references in your write-up. I'll go back to the Agency then.

DR. GREG ACKERMAN: This is Greg Ackerman. No clarifying questions.

DR. JIM MCMANAMAN: Thank you.

DR. ANNA LOWIT: This is Anna Lowit. I wanted to make two quick comments. That the George paper that came up a couple times, remember, it's in a formulation; it's not the active ingredient. The interpretation of the George study is complicated by all the other things in that formulation.

DR. LAURA GREEN: But was it positive or negative?

DR. ANNA LOWIT: I don't know.

DR. BARBARA PARSONS: I think it was positive, but as Marion pointed out on the phone, again, the small number of histopath, she, I think, agreed with us that it shouldn't be considered, because it's just not reliable information based on how the study design was set up. That you would need another study to really get at the promotor speculation that's been kind of running around.

DR. ANNA LOWIT: So I want to speak to the speculation issue.

One of the distinct differences between the regulatory science arena and the academic science arena, is that we have to deal with the data we have in front of us. We have to be honest about the

uncertainties that we have. But if you can all be cognizant that we cannot fill our documents with hypotheses and speculation. That if there are tangible logical next steps that can be taken, that's useful feedback; but throwing out hypotheses, for which there are no data, is not that useful for us.

There's a fine line between being honest about your uncertainties in helping us take the next step, and what those steps are, and crossing over into making speculative comments. So, if you can be careful with that.

DR. JIM MCMANAMAN: I want to make sure that this is clear to the panelists. Dr. Taioli.

DR. EMANUELA TAIOLI: I think you are right. On the other side, I want to have on the record that we look at this George. Because when there is only one study, we have to be very careful with this regard for some reason. We have to evaluate very carefully because it's the only thing we have. The same with Bulanasi.

DR. LAURA GREEN: Can I ask Steve Knott to possibly provide the George study during the lunch break?

MR. STEVEN KNOTT: Sure.

DR. LAURA GREEN: Thank you.

DR. JIM MCMANAMAN: You can ask anything.

DR. MARION EHRICH: Can I make a comment? It's Marion Ehrich on the phone.

DR. JIM MCMANAMAN: Marion? Okay. Go ahead.

DR. MARION EHRICH: I heard the EPA. That's really true about their documents. We can note that they noted the deficiencies of the data and I think that came through in the document that they wrote, the White Paper that we all read. But they're not in the position to do something about it or make judgments, you know, hypothesis, I would agree with that statement.

You know, sometimes there's limited data and we have to deal with it. And I think they've done a really good job of noting such when they wrote the White Paper.

DR. JIM MCMANAMAN: Thanks, Marion.

DR. LUOPING ZHANG: Yes. Actually, I discussed it with Dr. Shaw about this because sometimes we don’t have data, you can't do anything about it. But what he would say, if that's the case,

under the intro section you should redefine, or specifically define, your mutation. That's the thing I think you can do.

But another thing is now because where in the genotoxicity section for Charge Question No. 4, I think it would still be useful to have a paragraph to say, okay, here, you know, maybe genotoxicity is not the measure. I think it's still good to have other potential mechanism. At least it should have a statement to say other potential mechanism of action not tested yet, but it could be possible. That's basically one thing.

And also, I forgot to mention one more thing about Bonassi (2009) study. I also think I was showing the data to my neighbor and actually, the data looks like somebody with a biostatistics background should also look at the trend test. The data, to me, you know, somebody should do, either Agency or any biostatistician on the panel, to look in a little bit of detail in Bonassi (2009) study in which they didn't do the trend test.

DR. JIM MCMANAMAN: Thanks, Dr. Zhang.

Okay. I think that with that, we can move on to the next charge question, 4(b).

DR. LAURA GREEN: This is not open to the other panel members?

DR. JIM MCMANAMAN: This is open to the panel members. The panel members have been discussing this for quite a while.

DR. LAURA GREEN: Yeah. I actually had a question and this is going to show my ignorance. My vague understanding of the utility of non-mammalian species includes often the zebra fish, which I understand is a model for carcinogenicity in many settings.

And I want to ask both the panel and EPA whether there are any tests of glyphosate in zebrafish; and if so, if those were examined.

DR. JIM MCMANAMAN: I don't remember hearing that presented.

DR. GREG ACKERMAN: Well, we didn't present that. There may be one or it may be with the formulation. I'm not really sure. I can't remember off the top of my head.

DR. LAURA GREEN: (Off mic).

DR. GREG ACKERMAN: No.

DR. LAURA GREEN: (Off mic).

DR. GREG ACKERMAN: Yeah, because we

didn't consider the nonmammalian --

DR. LAURA GREEN: Am I wrong that researchers believe that the zebra fish can be a reliable model for human tumor genecity?

DR. GREG ACKERMAN: Yeah. I mean, I've seen it used for models for so many things, but I'm not sure.

DR. JIM MCMANAMAN: Okay. I thought we concluded this and went back to the Agency for clarification, and then we had additional discussion. I think it's coming on me to go back to the Agency to ask if anything has been unclarified then --

DR. ANNA LOWIT: No. Let's keep moving.

DR. JIM MCMANAMAN: Okay. Good deal. All right. So, 4(b).

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar. I'm going to read Charge Question 4(b).

Consistent with the OECD guidance, in vivo findings in genetic toxicology testing are considered as having a greater relevance to humans than in vitro findings. Consistent with 2005 Cancer Guidelines, all available data were considered in the weight-of-evidence evaluation of the genotoxic

potential for glyphosate. The relevant studies are summarized in tables 5.1 to 5.7. Please comment on the agency's approach for evaluating the genotoxicity data.

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The discussants on this are doctors Parsons, Shaw, and Zhang. Dr. Parsons is lead.

DR. BARBARA PARSONS: So my comments on this is, the Agency has assembled and evaluated relevant genotoxicity data in an appropriate manner. Full stop.

And I have Dr. Shaw's common as well. And his is, "Agreed with the already noted limits mentioned to Question 4(a)."

DR. JIM MCMANAMAN: Thank you. Dr. Zhang.

DR. LUOPING ZHANG: One word: agreed.

DR. JIM MCMANAMAN: Thank you, Dr. Zhang. Now, let me make sure; the question is now open to the remainder of the panel for discussion if anyone has any comments. Dr. Portier.

DR. KENNETH PORTIER: This is interesting reading.

DR. JIM MCMANAMAN: Yeah.

DR. KENNETH PORTIER: I just want to point out the discussion earlier on multiple comparisons. We must have what is it, 600 tests here, and so finding two or three significant tests shouldn't raise any big concerns. I mean, they just point to something, but I don't see any big patterns in this. I just wanted to point that out.

DR. JIM MCMANAMAN: Thank you, Dr. Portier. Other comments?

If not, then we'll go back to the Agency if you need additional clarification.

DR. ANNA LOWIT: No. All is good. Keep going.

DR. JIM MCMANAMAN: That was Dr. Lowit. Okay. So now we're on Charge Question 4(c).

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar. I'm going to read Charge Question 4(c).

As described in section 1.4, oral exposure is considered the primary route of concern for glyphosate and high-end estimates of exposure ranged from 0.47 to 7 mg/kg/day. Please comment on the human health relevance of the genotoxicity findings with respect to the doses where effects were observed and the route of administration.

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The discussants on this are doctors Parsons, Shaw and Zhang. Dr. Parsons is lead.

DR. BARBARA PARSONS: The genotoxicity studies were conducted at sufficiently high doses; and there are a sufficient number of negative studies were glyphosate was administered through the oral route to support the agency's conclusion that glyphosate is not genotoxic. Positive findings in a few very high dose IP studies may represent secondary effects of high-dose toxicity, which would not have human health relevance.

I shared this response with Dr. Shaw, who agreed and indicated he had no additional comment.

DR. JIM MCMANAMAN: Thank you. Dr. Zhang.

DR. LUOPING ZHANG: Again, one word: agreed.

DR. JIM MCMANAMAN: Thank you, Dr. Zhang.

DR. LUOPING ZHANG: Actually, I wrote I strongly support Dr. Parsons comments.

DR. JIM MCMANAMAN: Okay. This is now open for comments by the panelists.

Okay. Seeing none, then -- oh. Dr. Portier.

DR. KENNETH PORTIER: Yeah, I'm not sleeping back here.

DR. JIM MCMANAMAN: Okay.

DR. KENNETH PORTIER: Just because it's geno, it doesn't mean -- if I remember correctly, in some of the public presentations there was discussion about the mechanisms of action for which -- like IARC considers cancer program -- mechanisms that drive cancer, one of which was the oxidative stress. And this whole section is genotoxicity, but do we have anywhere any data that would discuss some of these other mechanisms like inflammation or oxidative stress?

DR. LUOPING ZHANG: The oxidative stress actually, I think, IARC really included. It is the human monitoring data your agency didn't include? Yeah, that's what I think.

The human data, when they measured the 8-hydroxy deoxyguanosine, that's an indicator for the oxidative DNA damage.

DR. KENNETH PORTIER: And that was positive or a negative?

DR. LUOPING ZHANG: It is increased regulatory risk, but nonsignificant. But from the measure, the level of 8-hydroxy deoxyguanosine -- I was just looking at -- it's basically double the amount from -- okay, I can give you an exact. It's increased from 27.9 percent from long-term glyphosate users to 43.8 in one or more times of using the glyphosate. That's their actual amount. But I actually think that could be IRAC conclusion for oxidative stress.

I don't know how much the animal data -- I don't see that they have the animal data. That's why I thought it was a human monitor data.

DR. LAURA GREEN: Can I add --

DR. JIM MCMANAMAN: Wait a minute. That was Dr. Zhang and Dr. Portier. This is now Dr. Green.

DR. LAURA GREEN: Sorry. The EPA document actually discusses this very point. And I believe this is a point in which NTP has been asked to weigh in because they know a lot about various oxidative stress assays. I mean, much more than I do. And I think the NTP group told EPA that the evidence was equivocal and they were going to think about it

some more. Am I sort of right about that?

DR. BARBARA PARSONS: Yes. If you look in Section 7, about our NTP collaboration, they do have experts in oxidative stress and felt that the existing database on that issue is not robust.

DR. JIM MCMANAMAN: Okay. Dr. Jett.

DR. DAVID JETT: I was just going to say, I asked this question when I think you weren't here in the beginning, and it's just not a whole lot of data was the answer, I think. And so, it wasn't really included as evidence.

Well, in general, that whole mechanistic evidence stream wasn't really included in the analysis. And you might be able to correct me or update me.

DR. JIM MCMANAMAN: Dr. Parsons.

DR. BARBARA PARSONS: I just agree that that is the case, but the reason is because the document concludes that glyphosate has no carcinogenic potential, and so there was really no -- I'm assuming that it.

DR. LUOPING ZHANG: One more. If I remember correctly, the first day when you presented the genotoxicity data, basically, it's saying if you

only measure 8-deoxyguanosine that doesn't really reflect the real oxidative for stress. That's my intake from what you presented.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Zhang. Other comments related to this?

If not, then I'll go back to the Agency.

DR. ANNA LOWIT: We don't have any clarification, but just to answer Dr. Parsons question that she asked to us. We maintain an active literature search on glyphosate and its formulations. And there is just a paucity of systematic and reliable mechanistic kind of information that you can put together. It's not that we ignored it because remember, we're going to also be doing non-cancer assessment at the same time for reg review. And so many of those studies would be relevant for non-cancer, too. We didn't ignore anything because it didn't relate to what we're doing today.

DR. JIM MCMANAMAN: That was Dr. Lowit. Thank you. I think we'll go to the next Charge Question, 4(d).

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar and I'll be reading Charge Question 4(d).

Please comment on the strengths and uncertainties associated with the agency's overall weight-of-evidence and conclusions based on the available genotoxicity studies, as described in Section 5.7.

DR. JIM MCMANAMAN: Thank you, Dr. Dunbar. The discussants on this are doctors Parsons, Shaw and Zhang. Dr. Parsons is lead.

DR. BARBARA PARSONS: The agency's conclusion that the overall weight-of-evidence indicates there is no convincing evidence that glyphosate induces mutations in vivo, via the oral route, is sound. Areas of remaining uncertainty are related to the potential for glyphosate-induced inflammation, DNA damage, genotoxic effect secondary toxicity caused by high dose exposures.

For example, glyphosate-induced oxidative stress 8-Oxo-dG and sister chromatid exchange, and whether the glyphosate containing formulations have any genotoxic potential.

Let me see. And Dr. Shaw said, "I have nothing to add to the response to the charge question."

DR. JIM MCMANAMAN: Thank you, Dr.

Parsons. Dr. Zhang.

DR. LUOPING ZHANG: Yes, I agree with what Dr. Parsons just said. But I also, again, I mean, I already mentioned this. I put a question, if we still should mention some other potential genotoxic relations. If the Agency doesn't want to hear, we can eliminate that because we don't have data yet. But here is Dr. Shaw's response to my question.

"This seems to be somewhat addressed with my comment on the copy number variation." In some way, I think Dr. Shaw and I are thinking in kind of a similar direction. No data doesn't mean it's negative data. Anyway, one thing I would like to mention -- actually, Steve, can we mention the studies just accepted? It hasn't been published yet.

Let's do this. I'd like to use some example. Glyphosate looks like it's not strong. Maybe nongenotoxic compound. But I think, definitely, we couldn't exclude the other potential mechanism of action. There is a study from Berkley, and it's from my colleague, Dr. Daniel Nemiroff's (phonetic) group.

What they did is they applied the active base, the protein profiling assay, a function assay, to map the reactivity of glyphosate metabolite.

And glyoxylate is an aldehyde known to react with nucleophilic amino acids on protein targets.

For example, assisting or nesting in the in vivo. The in vivo in mice. They also show that glyphosate can be metabolized, the in vivo to glyoxylate, that will react with several cysteines across many protein targets in mouse liver.

What they actually conclude is really not my area, but this paper is going to be coming out very soon. And I already sent the paper to Steve and also our group. I haven't shared it with everybody. But I want to just put this into the record.

Their conclusion is glyphosate exposure can lead to inhibition of several fatty acid oxidation enzymes. And second, glyphosate exposure can also increase in the levels of several lipid metabolizing, including trichlosaris (phonetic) and some other yeast. I can't even say the chemical word. Sorry.

And then the third, glyphosate exposure can't maintain the body temperature in their treated mice. That's their major findings. The paper is going to come out in the cell series, the chemical biology. I just want to put it there.

I don't know what's the cut off of the

literature we should include or not include. But I'm using this as an example. That could be a non-genotoxic mechanism for glyphosate.

DR. JIM MCMANAMAN: We can have that come into the record. But in regards to the charge question, about the weight-of-evidence --

DR. LUOPING ZHANG: I did say I agreed.

DR. JIM MCMANAMAN: Okay. Great. All right. Well, then I'll open it up to other panel members for this charge question.

Okay. Seeing none --

DR. LAURA GREEN: Can I just say I agree with the agency's view of this? And I would like to reiterate, to the extent that relevant mechanistic information would be on immunotoxicity, in my mind, not genotoxicity, I would again like the Agency to include the strengths and uncertainties in weight-of-evidence, with regard to the immunotoxicity of this compound.

DR. JIM MCMANAMAN: Thank you, Dr. Green. Okay. Unless other panel members have a comment? Then I'll go back to the Agency.

DR. ANNA LOWIT: No, it's clear. And if possible, can we just keep moving?

DR. JIM MCMANAMAN: Yes.

DR. ANWAR DUNBAR: Okay. That ends 3(d). At this point -- 4(d), sorry. 4(d). We're going backwards. We have some additional information that Steve wants to read into the record.

MR. STEVEN KNOTT: Okay. This is just a brief announcement. During the public comment period yesterday, Dr. Marion Ehrich had a question of one of the public commenters about the methodologies used, and it's the analytical methodology for testing levels of glyphosate in food products. This was during the Moms Across America comment.

They didn't have the answer, and actually, another commenter responded that they thought it was the ELISA methods. We just received a note that that was incorrect. The method is actually the LC-MS/MS. I just wanted to put that into the record. And the written comment will be included in the public docket.

DR. JIM MCMANAMAN: Okay. We're now at the last charge question, Charge Question 5. If I could have that read into the record.

DR. ANWAR DUNBAR: This is Dr. Anwar Dunbar, and I'm going to read Charge Question No. 5.

The modified Bradford Hill criteria were used to evaluate multiple lines of evidence using such concepts as strength, consistency, dose response, temporal concordance, and biological plausibility. In accordance with 2005 Cancer Guidelines, the agency used weight-of-evidence analysis to characterize the human carcinogenic potential of glyphosate and determine which cancer descriptor is supported by the data.

The Agency has described the strengths and uncertainties associated with the choice of various cancer descriptors with a focus on “suggestive evidence of carcinogenic potential” and “not likely to be carcinogenic to humans.”

Please comment on the completeness, transparency, and scientific quality of the agency’s characterization of the carcinogenic potential.

DR. JIM MCMANAMAN: Thank you. Dr. Dunbar. The discussants on this are doctors Portier, Green, Parson, Taioli, and Zelterman. And Dr. Portier is the lead.

DR. KENNETH PORTIER: Mr. Chairman, I have about four pages of comments to read and it is a quarter to 12:00, and we started at 8:00. And this is

the crucial question. I wanted to propose whether we wanted to break early for lunch and come back a quarter to 1:00, which would give us an hour and 15 minutes to complete this question.

DR. JIM MCMANAMAN: Well, normally I would agree with that, but given the fact that there are some early plane flights that panel members have to catch, I'm hoping that we can go ahead with this. And then maybe if we can finish up, then we can have lunch. It's an incentive.

DR. KENNETH PORTIER: Okay. When we break at 2:00 for lunch, I'm going to say I told you so. Okay. I just thought I'd lay that on the table. I see the panel is not interested. Okay.

Okay this is Question 5. Okay. Question 5 asked the panel to comment on the completeness, transparency, and scientific quality of the argument presented in the issue paper, leading to the conclusion, which is in the issue paper, page 141, that the strongest support is for not likely to be carcinogenic to humans at doses relevant to human health assessment.

The issue paper's goal is to describe the agency's comprehensive analysis of available data

from submitted guidelines studies and the open literature. Hence, we're being asked to globally address the completeness, transparency, and scientific quality of the overall report as it's related to the final classification recommendation of glyphosate. First note that the conclusion of glyphosate carcinogenicity offered in the issue paper has two parts. And we've talked about this before.

The first part is a hazard statement; the second part is a risk characterization statement. Since the issue paper is not a for-all risk assessment of technical glyphosate, as outlined in the 2005 guidelines for carcinogen risk assessment, the issue paper conclusion must be assessed as stated. We're going to try to tackle that statement as you've made it.

The issue paper is conceptually driven by the 2005 guidelines for carcinogen risk assessment which, in turn, incorporates the modified Bradford Hill criteria to evaluate strength, consistency dose response, temporal concordance and biological plausibility of multiple lines of evidence in a weight-of-evidence analysis. The issue paper also draws on the 2010 EPA OPP draft framework for

incorporating human epidemiologic and incidence data in human health assessment, which also utilizes a modified Bradford Hill criteria as applied specifically to epidemiologic data.

In the question of completeness of the agency's carcinogenic potential characterization. For the epidemiology studies, the Agency followed this peer-reviewed guidelines on evaluation and use of epidemiology studies in risk assessment and reviewed -- and I have six bullets here -- the study design, including study sample size and power to detect effects under consideration, the quality exposure assessment in epi studies, the potential for differential and non-differential misclassification of effects or outcomes, the measurement and utilization of or not of potential confounders, potential biases, and their impacts on observed associations and the associated statistical analysis.

That's what you commented on. The panel made a lot of comments around how this could be improved.

For the animal studies, the issue paper reviewed, followed standard practice and considered study design, sample size, adherence to quality

guidelines, statistical analysis, the use of trend in multiple comparison testing procedures. Concurrence with historical control rates where available, evidence of carcinogenicity through tumor magnitude, occurrence of multiple sites, multiple strains or species, their progression latency, and dose-response, and absence of tumors in well-conducted, long-term animal studies.

And we just had a long discussion about how that section could be improved. And we're going to come back to -- I'm talking about completeness right now. For the genotoxicity studies the issue paper also followed standard practice and considered test type an objective, substance tested, the quality and implementation of the study, the adherence to standard study design, sample size dose and use of positive and negative controls. Conditions under which the study was performed; for example, solubility pH osmolarity, cytotoxicity, and also a degree of binding and evaluation of outcomes, and consistency among findings in support for particular MOA/AOP.

By any criteria, this list suggests a complete review. I think discussed here and, in my own thinking, missing was study data and results for

workers engaged in manufacturing glyphosate. We assume because there's none in the report, there's probably no data available there.

And then other human incidence data, such as reports on acute accidental exposures. The 2010 EPA OPP draft framework for incorporating human epidemiology and incidence data in health risk assessment, discusses the utility of other incidence data. While incidence data have little direct relevance to cancer outcomes, time trend suggesting increasing incidence and acute exposures can also be suggestive of increases in overall exposure over time, which can, in turn, impact inferences about the quality and biases in the human epidemiology studies.

We didn't hear anything about drinking glyphosate to try to kill yourself, but it would've been nice to see some of that in there. And seeing an increasing trend in that, I think, would've affected our thinking about exposure.

On the issue of transparency, which I parenthetically say, honestly and openness of the agencies carcinogenic potential characterization, with this report in the documents provided for the meeting on the public docket, agency has succeeded in being

highly transparent. It's clear that the panel is not at any major issues following the agency's assessment as described in the report.

Supplemental documents provided on the meeting docket have allowed panel members to duplicate most analyses and verify most report claims, or at least find where these claims originated. While the panel has indicated some areas where it disagrees with the agency's assessment, we have not found areas where we've been unable to determine where the agency's conclusions come from or arose.

Section 6.6 of the issue paper is clear in laying out the agency's argument for its final classification, so you're transparent. Scientific quality of the agency's carcinogenic potential characterization. I asked the question what is scientific quality? Quality science is reproducible, free from distortion, credible, built on what is known or on sound science, follows logical inferences, and is honest about what's achievable within the limits of the available design data.

I asked the question, does the study have clearly formulated question? Yes. Does the study follow logical inference? Yes. I should say

the report, build on sound science. I think so. Are the report authors honest in the limits to available data and information? I think so. Have the report authors carefully assessed the research literature and understand the current state of the science? Yes

Can others replicate what the report scientists have done? Yes. Is the study free from biases and distortions? And I put maybe not totally free, but at least honest about where biases and distortions might have an impact on study conclusions. And I suspect this is going to be a topic that others in the panel will address.

Is the study adequately comprehensive as to avoid biases by exclusion? And I'd say yes, but only if you remember that the objective of the study is an assessment of the carcinogenicity of technical high-grade glyphosate, and not some other mixture of glyphosate with other substances included. In this we can conclude that the report represents quality science.

And now we're going to move on to thinking about the characterization. For the epi data, the issue paper concludes, based on the weight-of-evidence, the Agency cannot exclude chance and/or

bias as an explanation for observed associations in the database. “Due to study limitations, and contradictory results across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and risk of NHL cannot be determined based on the available data.” That's a quote from page 68 in the report.

Note that this conclusion does not mean that these are null studies; that is, they're well-conducted studies that report no association between exposure. The epi studies are not null. They do report things, it's just the conclusion is that they have study limitations in contradictory results.

The 2005 guidelines state, on page A2, "When cancer affects are not found in an exposed human population, this information by itself is not generally sufficient to conclude that the agent poses no carcinogenic hazard to this or other populations of potentially exposed humans, including susceptible subpopulations or life stages." The findings in the epi data by themselves don't say this is not a carcinogen. The epi data by itself is insufficient to support the conclusion of not likely to be carcinogenetic in humans.

The 2005 guidelines state, on page A4, "When cancer effects are not found in well-conducted animal cancer studies in two or more appropriate species, and other information does not support the carcinogenic potential of the agent, these data provide a basis for concluding that the agent is not likely to possess human carcinogenic potential in the absence of human data to the contrary."

The 2005 Guidelines also state, page A3, "The default option is that positive effects in animal cancer studies indicate that the agent under study can have carcinogenic potential in human." I shifted some stuff around, so I want to make sure.

For the animal carcinogenicity assay data, the issue paper concludes, on page 96, "Based on the weight-of-evidence, the Agency has determined that any tumor findings observed in the rat and mouse carcinogenicity studies for glyphosate, are not considered treatment-related. Tumor findings observed in the highest doses tested, were not reproduced in studies in the same animal strain at higher doses."

We're going to come back to this issue. For the genotoxicity studies, the issue paper concludes, page 128, "The overall weight-of-evidence

indicates that there is no convincing evidence that glyphosate induces mutations in vivo, via the oral route. And while there is limited evidence of genotoxicity for effects in some, in vitro experiments, in vivo effects were given more weight than in vitro effects, particularly when the same genetic endpoint was measured, which is consistent with current OECD guidance. The only positive findings reported in vivo, were seen at relatively high doses that were not relevant for human risk assessment."

All this comes down to whether the limited evidence of genotoxicity at relative high doses, and the limited evidence of a potential dose response relationship in some cancers, and the uncertainty in the epidemiology study findings around an association between glyphosate exposure and the risk of NHL, are sufficient to change the EPA findings of not likely to be carcinogenic in humans without the modifier at human relevant doses, to inadequate information to assess carcinogenic potential or even suggested evidence of carcinogenic potential.

The issue paper's argument for concluding a classification of not likely to be

carcinogenic to humans, rests on the descriptor convincing evidence the carcinogenic effects are not likely below a defined dose range where the data are robust for deciding there is no basis for human hazard concern.

I'm going to read this last paragraph, but then I think we're going to open it up. Because I don't get to everything and I think we're going to need more panel discussion.

"The inability to propose a scientifically supported MOA/AOP for glyphosate and precursor events of action for glyphosate, along with reproducible negative genotoxicity findings, or a very weak signal from the epidemiology evidence..." I basically said no signal from the epidemiology evidence and weak signal from the animal data lead me, myself, Ken Portier, to agree with the agency's weight-of-evidence assessment of not likely to be carcinogenic at human relevant doses.

I think at this point we need to open it up for others on the panel to conclude. I do have some comments, if we want to get back and actually go through all the Bradford Hill criteria, because we did have some discussion around a number of these. Part

of the agency's argument has to do with -- especially with the animal data -- is around the issue of consistency of findings. And we just had a discussion that basically said that variability in study and measurement conditions makes assessment difficult.

I think we all agreed to that. And lack of consistent findings is kind of expected in this many animal studies. And the combination makes it very hard to give a lot of weight to inconsistent findings. The consistency argument from the discussion we had this morning seems to kind of down weigh that aspect of the Bradford Hill and we spent a lot of time with the dose-response question.

To me, the biological plausibility component is a big part. I don't think we spent too much time on temporal concurrence and coherence, but I don't think those are issues that we're worried about here. The issue is more the dose response, the biological plausibility, and then a lot of the uncertainties that remain after we look at what's relatively a huge database for herbicide. I mean, this is, like somebody pointed out, 30 years of study on this chemical and I'm surprised we're still at this level of uncertainty at that point.

I think with that, I'll turn it over to others to add their comments and then we'll come back.

DR. JIM MCMANAMAN: Thank you, Dr. Portier. Did I hear the words -- was it the Bradford Hill's wording that it has to be robust data that is negative?

DR. KENNETH PORTIER: No. The Bradford Hill criteria is just a framework we're thinking through all of these studies.

DR. JIM MCMANAMAN: Right. You used the word "robust" and so I'm wondering about is -- because I think there is an issue with the robustness of the animal data. And I don't remember whether you used it in terms of the epidemiology data or the animal data.

DR. KENNETH PORTIER: And I think I was saying robust in the sense of a lot of studies. Not robust in the sense of a robust finding.

DR. JIM MCMANAMAN: Conclusiveness. Okay. Got you.

DR. KENNETH PORTIER: There's just a huge dataset here, compared to most things we've ever seen before this panel.

DR. JIM MCMANAMAN: Thank you. All right. We'll open it up. Dr. Johnson.

DR. ERIC JOHNSON: Before we start the discussion, please make this clarification; we can make a decision based on just one tumor type? Because there are many, many tumor types, even for the human studies, many, many cancers that were investigated.

DR. JIM MCMANAMAN: So let's go back to the wording there because I think this is --

DR. KENNETH PORTIER: That's why I kind of read through those quotes from the Cancer Guidelines. From page A4 in the Cancer Guidelines, "When cancer effects are not found in well-conducted animal cancer studies, in two or more species, and other information does not support the carcinogenic potential of the agent, these data provide a basis for concluding that the agent is not likely to possess carcinogenic potential in the absence of human data to the contrary."

Human data trumps, right? And then you're looking for consistency across two species, it's usually something in rats and something in mice, right?

The guidelines also state, on page A3,

"The default option is that positive affects in animal cancer studies indicate that the agent under study can have carcinogenic potential."

If you find it -- and these guys might correct me on this -- but I think if you conclude it occurs in one species, a tumor occurs in one species, that might be enough to change it from no evidence to suggestive evidence. You'd need two species, and probably in one sex, to be able to say something beyond that, right?

DR. ERIC JOHNSON: But within the human data, we only need one tumor type to make a decision.

DR. LAURA GREEN: Right.

DR. KENNETH PORTIER: Yeah. Yeah, the human data trumps everything. If you conclude that there's signal in the epi data of cancer, then they can't say it's not carcinogenic. They have to deal with it as if it's a carcinogenic agent.

That's why the discussion yesterday was so very important.

DR. JIM MCMANAMAN: Why don't we begin with that? Why don't we begin with whether there's is any --

DR. KENNETH PORTIER: Well, there's

other people on here that may have prepared the other piece.

DR. JIM MCMANAMAN: Oh. I thought you were opening it up. Sorry. You wanted to open it up. And I was following your lead, which is okay with me.

I mean, we can do it where we can open it up to other panel members at this point.

DR. KENNETH PORTIER: Dr. Green, Dr. Parsons.

DR. JIM MCMANAMAN: Let's just go through with the other discussants. Dr. Green.

DR. LAURA GREEN: Okay. I'm mindful of what Thurgood Marshall said at his retirement interview, which was, "I'd like to be remembered for doing the best I could with what I had," which I thought was a very useful thing to keep in mind.

I do believe the agency did a good job with what it had. I think we've given you suggestions over the last couple days for doing a better job, but I do think you did a good job with what you had.

I'd like to return to the NTP guidelines, which I don't have in front of me; but my strong recollection is that for the rodent data, NTP has carved out for itself a characterization called

equivocal. And it defines that -- and again, I'm doing this from memory -- but it defines that as the characterization. It gives the results of a single bioassay when it sees statistically significant increases in one or more dose groups, that cannot determine whether those are treatment-related or not.

I think I have that right. Obviously, some of us disagree about whether the positive findings are all false positives or maybe some false positives and true positives. But I think that disagreement is expected because obviously, Chris Portier and others put more weight on the animal data. Some of us put less weight on the animal data. I think that's exactly what the word "equivocal" means. You see increases, you can't tell whether their treatment-related.

I don't know if EPA has the ability to use the NTP language in its characterization of these 15 bioassays, but I would like it to at least consider that. And that's separate from how and whether you group the data or lump the data or split the data. It comes to, in my mind, how you ultimately characterize your weight-of-evidence.

I mean, weighing the evidence from 15

bioassays, you have three choices; you can either find reliable evidence of a signal of carcinogenicity. You can find unreliable evidence of a signal of carcinogenicity, which I take to be equivocal, or roughly. Or you can find strong evidence of non-carcinogenicity. The problem is strong evidence of non-carcinogenicity is obvious. Science marches on, you know, if there were a mega mouse study done of glyphosate and, you know, you found -- I don't -- let's call it hemangiosarcoma to the liver. You know, I'd be the first person to say, "Wow, that looks interesting."

This comes to a problem that we have and maybe you're stuck with. And I again, talked about it a few days ago, and Dr. Trump and I have been wrestling with this -- oh, Jesus.

DR. KENNY CRUMP: Dr. Trump. She did it again.

DR. LAURA GREEN: President-elect Crump and I have been struggling with this. The problem with the phrasing not likely to be carcinogenic in humans strikes us as sort of unscientific. It presumes in level of omniscience that none of us on earth has. But if you're stuck with it, you're stuck

with it.

If your only alternative is that or suggestive evidence, to this reviewer at least, "suggestive" is wrong. Because it means that you kind of believe that the positives in the rodent data are true positives, and they're two true positives, and they're not outweighed by the lack of replicability, if that's a word. I don't like suggestive.

I would like to say that, with regard to the completeness of your assessment, not to repeat myself, I want to see more on immunotoxicity. And the reason is because my esteemed colleagues are worried about NHL; I am not.

But to the extent that others disagree with me, I would like a discussion in your document about why you think it's implausible that NHL is glyphosate-related. I mean, it's equally important to speak about biological plausibility, but let's not get carried away. I mean, as a society, we once thought it was plausible that the witches in Salem were responsible for bad stuff. And it was plausible that women shouldn't vote because we have uteruses and small brains. Just to pick two examples. I could go on, but you get the point.

I don't think we should be in love with our own notions of biological plausibility because they're limited to what we know in a 21st Century.

But we do know something about implausibility, right? And to my mind, again, for a tumor-like NHL, for which the odds ratios are routinely between one and two, but not three or five or ten, we know about NHL that immunodeficiency is a strong risk factor, i.e. AIDS in organ transplant patients, having massive odds ratios on the order of 10 to 100.

We know that there's strong genetic determinants of our own immunocompetence. Everyone sitting around this table, depending on our genetics and our age, has different state of immunocompetence. To the extent that observational epidemiology, by definition, is nonrandom -- and again, I may be using the terms wrong. But to the extent that observational epidemiology is nonrandom, when you have at most a small signal, whether it's odds ratio -- you know, whether the low confidence interval is above or below one. But if it's a weak signal -- statistical significance aside -- if it's a weak signal, and you're talking about a tumor which is so dependent on

the immune system, which is so different among groups, I'm not convinced that the data can be relied on.

I mean, what if a couple of pesticide applicators also had AIDS? What if a couple of pesticide applicators also had an organ transplant? I mean, the epidemiologist can't possibly ask all these questions. But again, uniquely for NHL in farmers -- and as Professor Johnson has study for much of his lifetime -- the farm environment with viruses in animals that are established causes of leukemia and lymphomas, I would like to see your discussion of the Bradford Hill criteria explained to the reader if you think it's true; why you think it's implausible that a small signal of NHL is meaningful. Maybe you don't. I do.

And as I said it's a counterfactual here. If there were six case-control studies on colon cancer, and we had the same weak but statistically significant meta-estimates, okay -- if there were statistically significant meta-estimate of, let's say, 1.8 with a lower bound of 1.1 even, for colon cancer, I'd be singing a different tune, okay. Why? Because of your weight-of-evidence. It's in the gut. It's barely metabolized, but when it's metabolized it's in

the gut. It would be nice if any of the animal tumor data, by the way, showed colon cancer, which it doesn't.

I guess I'm urging you to think a little more holistically. I reluctantly agree that if you have to choose between suggestive and not likely, not likely is a better choice. But if in some future date your agency can rewrite these characterizations, to this observer at least, I think a more scientifically reliable designation would be something like, the weight-of-evidence fails to provide reliable evidence of carcinogenicity.

And by the way, I think it's true in rodents and in people. I think it's true at all doses. I don't think you have to modify it at human relevant doses because, as Kenny has pointed out, -- if I call you Kenny, I don't get the wrong last name. As Dr. Kenny has pointed out, if even the responses at a gram per kilo are not treatment-related, then I don't think you have to, you know, modify it by dose. But anyway, that's my gestalt.

DR. KENNETH PORTIER: You know, Laura. It's interesting because if you look at this statement "not likely," that's a probabilistic statement. It

just says it's unlikely. And you've asked them to address implausibility which kind the parallels that unlikeliness kind of concept. I like what you picked up on there.

DR. JIM MCMANAMAN: Thank you, Dr. Portier and Dr. Green. Dr. Parsons.

DR. BARBARA PARSONS: I would like to echo Dr. Portier's statements about completeness and transparency. I did not try to evaluate the human epi data. I'm frankly not qualified to do that.

I think it's clear that glyphosate is not a genotoxic chemical. I am hung up on the rodent carcinogenicity data. I have to say, I do not support the conclusion that glyphosate is not likely to be carcinogenic to humans as an appropriate descriptor of the carcinogenic potential of glyphosate, because I don't think the criteria statements that go along with that descriptor apply.

The first criteria given in the Cancer Risk Assessment Guidelines are animal evidence demonstrates lack of carcinogenic effects in both sexes, in well-designed and well-conducted studies, in at least two appropriate animal species in absence of other animal or human data, suggesting a potential for

cancer effects. The animal data demonstrates lack of carcinogenic effects.

That's not how I characterize the data. At most, it's equivocal. It doesn't demonstrate there is no carcinogenic effect. And rather, I believe there is sufficient evidence to conclude glyphosate in the high dose rodent carcinogen.

Second descriptor is, there's convincing and extensive experimental evidence showing that the only carcinogenic effects observed in animals are not relevant to humans. If glyphosate causes progression of pre-existing lesions, or cells carrying spontaneous cancer driver mutations -- and I believe this is the only option, assuming that it is not genotoxic -- then there is reason to expect that humans -- maybe I'm missing a word here -- that is relevant to humans, who could be as or more susceptible than rodents to equivalent doses, depending on age. I don't think that applies. The third descriptor is convincing evidence that carcinogenic effects are not likely by a particular exposure group.

The rodent carcinogenicity studies were conducted via the appropriate oral dose route that's

applicable to humans. And so, this statement doesn't apply.

The last statement, I believe, that there's convincing evidence that carcinogenic effects are not likely below a defined dose range, might apply. But the fact that the high-end estimate of occupational exposure, 7 mg per kilogram body weight per day, and the lowest dose that generated a significant rodent tumor response, in my opinion, 31 mg per kilogram body weight per day, are within a five-fold range -- and again, to my mind, that is a cause for regulatory concern -- I believe that suggestive evidence of carcinogenic potential is the most appropriate cancer descriptor, based on the rodent carcinogenicity data.

DR. JIM MCMANAMAN: Thank you, Dr. Parsons. Dr. Taioli.

DR. EMANUELA TAIOLI: Okay. The human study as we discussed before, are kind of central to this point of discussion and all these evaluations. And I think we went through all the limitations and the advantages of the studies yesterday. We don't have to cover everything again.

I think it's positive that we kind of

all agree with that 6/7 studies that have been considered. We are all on the same area. And we have a cohort study and six case-control studies for non-Hodgkin lymphoma, which was the center of the discussion. I'm not so surprised that there are so many case-control studies because that's what you do when you have a rare disease under study. I'm not so surprised that there are so many case-control studies.

Now, the evidence of both the cohort and case-control study for non-Hodgkin lymphoma, which is the central -- then I'll go to multiple myeloma in a minute -- are all the same direction, are all within the same range of association at the point that the summary estimate has no heterogeneity, basically, which is a very unusual situation for epidemiologists.

And even with sensitivity analysis, trying to reduce the number of studies to studies that are more homogeneous among themselves, for example, restricting to case-control studies; restricting to studies that have no proxy responders. They always bring up odds ratio that go between 1.3 and 1.5, 1.6, which for epidemiology, is actually an odds ratio that somebody estimated we expect.

And I just have the curiosity now and

went back to look at the odds ratio for a women study for estrogen and breast-cancer. Post-menopausal estrogen was 1.22, one confidence interval and 1.4. That's what we, unfortunately, deal with on a daily basis. To discount this result and saying that it's the unlikely attribute, to me, it's basically not reflecting the results of those studies.

In addition to that, the multiple myeloma data are equivocal, they're not that straightforward as no association. For all of these reasons I'm more in favor of the suggestive than the non-likely. If I could use equivocal, I agree, I would be very happy. But apparently, we can't.

DR. ANNA LOWIT: Dr. McManaman, this is really important. I have a clarification for Dr. Parsons before it gets lost.

DR. JIM MCMANAMAN: Okay.

DR. ANNA LOWIT: Okay. Dr. Parsons, I appreciate your very logical and systematic go through the Cancer Guidelines; I really appreciate that thoughtfulness. Your last point I just wanted to make sure it is clear to us.

You got to the last one about the, above a certain dose. And then what you did was

compare that dose to the human exposure that you've been shown. In our world, that is crossing the line from science to risk management. The relative proximity of those two things does not play in the cancer qualification because what that is as it is a risk management call of, let's say hypothetically, that margin is small. And even you said yourself, it gave you pause or looked risky, which moved you down to thoughtful to move down to suggestive.

The agency's job is to decide that magnitude and whether rates need to go down or workers need to be better protected. It shouldn't play in the cancer classification.

DR. BARBARA PARSONS: I appreciate that. I totally understand that that is a risk management decision, and I'm not saying that a good risk management decision cannot be made here. But statement is, there is convincing evidence that carcinogenic effects are not likely below a defined dose range. I don't think that applies. And I gave the reason why I don't think it applies.

I'm not saying that these are the numbers that you must use. I'm not trying to get into -- believe me, deciding whether or not is it

carcinogen or not is enough. I don't want to get into what is a safe level.

DR. JIM MCMANAMAN: I think we should move on, in terms of the panel. Thank you, Dr. Taioli.

Dr. Zelterman.

DR. DANIEL ZELTERMAN: Well, I'll be brief. I certainly can't add to many of the comments that have already been made. I can comment on the completeness and transparency of the process. We may not agree on the outcome, but we should agree on the quality of the agency's work in putting together such a panel and thank them for convening.

I couldn't help but think that maybe there's really an elephant in the room, and that we're looking for carcinogenic effect, and maybe glyphosate has an effect in many other health matters. And I kept wondering maybe there's a birth defect, like thalidomide or maybe there are many other health effects that we're just glossing over. And I saw no mention of this because so much of what we're talking about is just carcinogenic.

DR. JIM MCMANAMAN: Thank you, Dr. Zelterman. We've had all of the discussants on this

question weigh in. I think we can open it up to the rest of the panel. I'd like to direct us a little bit. I don't want to inhibit anybody from saying things, but I would like to start with Dr. Sheppard because I'd like to hear her thoughts related to the human carcinogenicity and whether -- because Dr. Taioli certainly has a viewpoint that seems to suggest that there might be.

DR. LIANNE SHEPPARD: Yes. And I actually agree with Dr. Taioli on this. And I wanted to say that my perspective is not only as a statistician, which complements Dr. Taioli's perspective, but looks at the data a little bit more at face value than bringing in the incredibly valuable insights from the science that are also very, very important.

I have to say that most of my work is in air pollution epidemiology. And the evidence base there for health effects, not specifically cancer, but the evidence base there developed from epidemiology. It developed from epidemiology and time series studies where the relative risk estimates were on the order of 1.01 to 1.05. You know, those are the kinds of risk estimates that epidemiologists typically dismiss out-

of-hand. But that is the evidence base that developed. And then, in cohort studies, the affect estimates are on the order of 1.2, 1.3.

In air pollution epidemiology, where we actually have the advantage, relatively speaking, of quantifying exposure much better than we do in almost any other environmental exposure, including glyphosate. You know, we've been able to advance our understanding and make huge changes, through the Clean Air Act, to protect public health with very, very small risk estimates that were, for a long time, not supported by mechanisms or even by animal toxicology. But the epidemiology was used to basically trump the rest of the evidence.

Eventually the mechanistic evidence has started to catch up. And so, the bench science has begun to elucidate the mechanisms. But it was the epidemiology that led to policy statements and action that has indeed changed the air pollution exposure. And it has been documented, for instance, at looking at changes in life expectancy over 20 years, to be associated with changes in the trends in air pollution.

I think based on the non-Hodgkin

lymphoma results alone, and affirming what Dr. Taioli said about the meta-risk estimates and the lack of heterogeneity, personally, I think that's suggestive. Does that mean that it's clear that more evidence, as it accumulates, might not change that conclusion? No. I mean, it's too early to say. But clearly, it's suggestive to me, and it's the most public health appropriate conclusion to reach, is that because of that human data, the evidence is suggestive.

I also think -- which is not what you asked me to talk about, but I want to continue -- to say that we also have seen evidence in the animal studies for some outcomes in at least one species. And my reading of the guidelines is, that's enough right there. The epi evidence, in some sense, doesn't matter other than to strengthen the conclusion. The animal evidence alone is enough.

And you know, I really appreciate the perspective that Dr. Parsons has brought, that it's a weak promoter. Because it seems to me that a lot of the evidence base isn't really well-aligned with that promoter aspect and that may be my lack of understanding of all the different pieces of the bench science that went into that. But my sense from the

way she was able to pull that conclusion out of the data she saw, but it hasn't come out on any of the other documents or work or bodies that have reviewed this, suggests to me that there's still some understanding to be developed there.

I feel pretty strongly that the evidence is suggestive. You know, it would be interesting to reflect on whether I would come down to equivocal instead of suggestive, if that were category. But since we're not in the realm of making up new categories, I am not going there.

It's clear to me that we can't conclude, as the Agency has done, that it's not a carcinogen. That's just completely inappropriate based on their criteria.

I appreciate Dr. Parsons going through some of the details on that. We can't do that. And there is too much data to say that it's inadequate. It has to be suggestive.

DR. JIM MCMANAMAN: Okay. I'd like to stay with the human as much as possible for right now. We'll go with Dr. Crump and Dr. Johnson because you both weighed in on this pretty heavily during the time.

Dr. Crump, if that's the name you're going by now.

DR. KENNY CRUMP: I'm really not minding being called Trump. I'm trying to think of ways to take advantage of that. Kind of like Obama saying he liked Obamacare.

With regard to human data, the case-control data, I made a presentation yesterday that highly suggests, I think, that these results could easily be due to recall bias. And in the studies, I mean, if you look overall, people say, oh yes, they're recall bias. Yes, recall bias is a problem.

I don't see any references in any of these studies that deal with that issue. But McDuffie and Eriksson had almost all of their ORs -- they didn't do this just for glyphosate, they did it for a whole bunch of pesticides. Almost all of them, all the ORs are bigger than one in those studies. That's what you expect, if there's recall bias, for driving it.

Plus, in those two studies, they did something -- I can't quite understand why they did it. I can think of one reason, but basically, I don't think it's should've been done. They replaced -- they

threw some data out of their unexposed, so they used unexposed -- not just unexposed to glyphosate, but unexposed to any pesticide. And if there is recall bias operating, that would exacerbate it and make it worse. To me, all of this data are consistent with recall bias. That's what I have to say.

DR. JIM MCMANAMAN: Dr. Taioli made the point that -- especially with NHL -- that there seems to be consistent trends. And if that seems to be the major consideration, that is making suggestive epidemiology evidence, I mean, do you have a feeling about her analysis of that?

Because I mean, I think we're throwing out some of the data, as you pointed out, but her points are the trends.

DR. KENNY CRUMP: Well, you know, if have bias like this, you have only three doses, I mean, the chances of a trend is quite high. I would think that could easily just be an incidental finding.

DR. JIM MCMANAMAN: Dr. Taioli.

DR. EMANUELA TAIOLI: One thing is that -- then why there are case-controls studies in the world? I mean, you can't discount all the case-control studies because they all have recall bias.

That's part of the design. Same as the cohort studies have to go on for 30 years to show something. In this case, the agriculture only went on for seven. Every study has, in its design, inherent problems. And that's one thing.

In terms of the association with the adult pesticides, I think it's important to go back to the animal studies because really, if it's a promoter, that would explain why you cannot adjust or see association with the other pesticides. You will see an interaction. And so, all of them could be significant, but then interacting with each other. Then there will be more analysis if that venue is the correct venue, which frankly, I don't know because it's not my area. It sounds appropriate and logical, but then really, the association for each individual pesticide won't really mean that there is recall bias. It would mean that there is a biological reason behind it, in my view.

DR. KENNY CRUMP: Can I respond to that?

DR. ERIC JOHNSON: Can I respond?

DR. JIM MCMANAMAN: Wait a minute, let him respond to this. We'll bring you in, just a

minute.

DR. KENNY CRUMP: I don't think that really relates to the question of the possibility of recall bias. But I think you were saying, why are people doing all the studies all these years of there's a problem.

DR. EMANUELA TAIOLI: In general.

DR. KENNY CRUMP: There's not a problem with all case-control studies. It would only be a problem with those where they determined exposure by asking cases and controls together -- asking cases and controls about their previous exposures. That would be the only issue where there would be a recall bias problem.

DR. EMANUELA TAIOLI: But that's how case controls are about. If you have breast cancer, they ask you if you had menarche at 14 or 13, 50 years before. That's how the case control is designed; and everybody will recall differently. And that problem is in all of the case-control studies. That's the limitation of case-control studies, unless there is a marker of something that happened 50 years before, which is very unlikely, in general.

DR. KENNY CRUMP: Let me say, I know,

they do these studies a lot. We got a lot of them here. That doesn't mean they're valid studies. Read the literature, everybody says -- well, not everybody. I read two instances where people said there are problems with control bias. I just read what Chris Portier said about control bias. He asked if there was a problem.

DR. LAURA GREEN: Recall bias.

DR. KENNY CRUMP: Recall bias. Thank you. I want to say control bias. Chris said, he was asked, is there a problem with control bias or something like that. And his answer was, yes, I agree; there's a problem with control bias.

DR. EMANEULA TAIOLI: We agree that that's the limitation of case-control studies. But that doesn't mean -- first of all, it's for all case-control studies, not just this specific six. And it doesn't mean you throw them away. You know that's a limitation. Cohort studies have a limitation of being, in general, too short. And it's the case here, for example. We're not throwing it away; we are keeping it with its limitations.

I don't think this is a reason to disregard what the literature, especially for a rare

disease where case-control studies are the elected design, like non-Hodgkin lymphoma, multiple myeloma, those rare diseases. The case-control is the elective study design, in order to have enough cases.

DR. KENNY CRUMP: I agree that would be the study design. But it may be, despite epidemiologist's best efforts, they can't overcome this problem. I haven't seen any data that indicate they've done anything about this problem. They don't even discuss it. I think we're the same place we were 35 years ago, in the study that I quoted by Preslow and Day. He says it's a big problem.

I haven't seen any movement from that. All I've seen it's still a problem, but we just don't want to talk about it anymore. That's what I see in these studies.

DR. JIM MCMANAMAN: Dr. Sheppard had her hand up first.

DR. LIANNE SHEPPARD: I think this is the time that I want to make sure we read into the record my response to Dr. Crump's analysis of recall bias yesterday.

While I agree with you and Dr. Taioli, and I think every other epidemiologist in the room,

that recall bias is a feature of case-control studies, it doesn't necessarily mean that they should be disregarded. And I also want to say that I think your concern is particularly acute for pesticides, at least be somewhat I heard.

And in fact, the Blair and Zahm 1993 paper that you provided an analysis of yesterday, has some evidence about whether there's any -- well, you could decide whether you want to call it recall bias based on the careful work they did to do surveying and then go in and do additional probing.

And you provided a very interesting analysis yesterday about that, and I was concerned about it, so I asked for the details, and spent some time last night thinking about what was appropriate. And your analysis looked at exposure by outcome, case control status, comparisons of pesticide exposure. And the simplest case, which is the one I focused on is an ever/never reporting of pesticide use, meaning zero versus one or more.

And you showed two tables; one with evidence -- oh, he's bringing it up. In the interest of time, I'm going to continue to read this and then people can look at the evidence when it comes up on

screen.

So there two tables; one for evidence based on the pure self-report, i.e. what was volunteered. And the second one based on evidence based on self-report plus deeper probing.

And as you would expect, more probing resulted in more reporting of pesticides. I think we would all agree that that's what you would expect. And this turned out to result in greater odds of an effective of exposure after probing than was estimated before the probing.

And the question is whether that is evidence of recall bias or just the result of a better estimate of the odds ratio, which is the exposure effect of interest, due to less measurement error in the exposure. And I suggest that the analysis, that Dr. Crump provided yesterday, was the latter. It was evidence that more probing leads to less measurement error and therefore bigger odds ratios due to less measurement error, less attenuation towards the null.

I took the same exact data, the herbicide reporting data, and looked at it differently, as a pair data for cases and control separately. And so, the tables that you see on the

screen are set up with volunteered as columns and volunteered, plus probed, as rows. They're labeled, "probed" as rows. And the classifications are "never," that's minus, or "ever," that's plus, which means one or more herbicides, reported. And an individual either reports the same both times or they change their reporting.

Now, because the probing elicited more pesticides, nobody reported fewer pesticides with additional probing. The cell that's volunteer positive and probe negative is zero. That basically, if you have a positive -- more pesticides that you probe -- excuse me, when you don't probe, you're not going to then give no pesticides when you do probe. Those are the tables below that you can derive from Table 9 of Blair and Zahm, if you would like to do the analysis yourself.

And so, then the question is, is there a differential response in terms of the effect of probing in the cases versus controls. And there were two ways that I looked at that; one is that I took the ratio of the number that changed over the number the state the same. And the other way I did it was take the ratio of the change over the total.

The ratio of the change to staying the same is close to 23 for both cases and controls. And the ratio of the change to total is about 19 percent for both. And so, this is what I would call passing the inner-ocular test. That means it hits you between the eyes. That means you don't need a statistician to tell you that there's no difference, the numbers are essentially the same.

I conclude quite strongly that there's no evidence of recall bias due to additional probing about pesticides in this Blair and Zahm paper. And this is only one piece of evidence and it can't rule out the presence or potential for recall bias, but I think it does give us the best evidence that we have at hand this suggest that there's no differential memory about pesticides, when you probe for cases and controls.

DR. ERIC JOHNSON: Can I respond?

DR. JIM MCMANAMAN: Yes. We'll get to you, Dr. Johnson, in just a minute.

DR. ERIC JOHNSON: It’s on this issue.

DR. JIM MCMANAMAN: I know, but he needs to respond to this, I think; because this is an important point.

DR. KENNY CRUMP: Well, I have to admit, Dr. Sheppard, that I don't fully understand what's you've done here yet. I have to talk to you about it and get it worked out in my mind. Maybe because my brain is kind of frazzled at the end of the week. But what I do understand, I think you may have misinterpreted what I was saying.

The probing, in comparison with the unprobing, in my mind, has nothing really to do with the aspects of recall bias. You could think of those -- I just presented them just because they were in the paper. But you can think of this as two separate ways to question. You do it, the first way just with a volunteer, or you could it the second way. We do the volunteer and then you probe. That's the second way of getting the information.

Basically, you have two ways of getting the information. I don't see that the difference between the two is important as far as control bias is concerned. You could look at either one individually and those ORs that I reported yesterday, are the ORs that you get when you do that, you can look at either one separately. I'm not sure the differences are really important. Let me finish.

But all of those ORs were the ORs you would you get suggesting control bias. They were all greater than one and some of them were statistically significant. But I would also point out that this is an old study, and it's the only study that I found, in the literature, that had quantitative information on control bias. And so, that suggests to me that his issue has certainly not be studied to any great extent and not studied enough.

DR. JIM MCMANAMAN: Rather than get into a further back and forth about this, I think what my goal was is to try to -- because this was an important -- this was critical to the evaluation of the epidemiology study. And so, I wanted to get two lines of thought. I'm coming to Dr. Johnson. But I've been asked about the possibility of the break.

If we can have Dr. Johnson with a brief comment related to this and then we'll take a break.

DR. ERIC JOHNSON: Yes. I do appreciate Dr. Crump's concern for recall bias, which is always an issue in any case-control study. We have a way of dealing with recall bias in case-control studies. And that is, for example, if we didn't with cancer cases, we would also choose -- in addition to

non-cancer cases as controls, we would choose cancer controls. And that takes care of recall bias usually in epi studies.

The other point we have to make is that, each epi study is a questionnaire of sometimes hundreds of questions. My questionnaire, which I'm using, believe it or not, has about 600 primary questions and 3,000 secondary questions. There are a lot of questions.

And even if recall bias is an issue, what you usually find is that it may be an issue for certain questions. For example, there is not going to be much recall bias in asking the question, does this person smoke cigarettes or not. There's not going to be much recall bias with that. It's the absolute method which you're using to just discard all this that I'm against.

So even in practice, it doesn't work that way. It's only specific questions within studies that you would be worried about recall bias. There are certain questions that are so straightforward that there is no recall about it at all.

Thirdly, if you look at the pesticide study, if recall bias was an issue, for every single

pesticide, we should see an overestimate of risk. If it was that bad, we should see for every single question, for every single pesticide, we should see an odds ratio that's greater than one, and we don't see that. It's a concern, but for you to just knock out all these studies, I think that's too extreme.

DR. ANNA LOWIT: So Dr. McManaman, this is Anna Lowit. I just want to make sure that we're answering the agency's question.

DR. JIM MCMANAMAN: I think we are. The whole idea is that Dr. Portier -- according to the guidelines, I guess, as I understood what Dr. Portier was saying, is that if there's epidemiology data that suggests that there's a link to cancer, then that ends the game right there.

Because I know there was a disagreement, I was trying to get that brought out about the legitimacy of that claim. Because if as a consensus, the panel agrees that there is epidemiology data to link glyphosate with human cancers, then I think that we can go home right now, right?

DR. ANNA LOWIT: The panel does not have to be in consensus.

DR. JIM MCMANAMAN: I know. I agree.

But I was just trying to get --

DR. ANNA LOWIT: I'm just concerned that Dr. Crump actually didn't even get his opinion on the record, if he was suggestive or not likely. I just want to make sure that individuals are getting their opinion on the record and that we're not redoing the discussion that we had over the last couple of days.

DR. JIM MCMANAMAN: Okay. Well, we can -- let's do this. Let's take a break and we can come back and make sure that everyone gets their opinion on the record. Just a bathroom break. A bile break. Five minutes.

[WHEREAS A BREAK WAS TAKEN]

DR. JIM MCMANAMAN: So what we want to do -- where is Ken Portier?

He's out. Okay. We're trying to open this. I think there are critical questions, so I'm trying to get the discussion going on. But each person will have a chance to say yay or nay on what their views are. But I just wanted to address the major considerations in terms of this charge question.

That's the method in my madness.

Dr. Crump wanted to have a couple of responses. I really don't want to go into the validity, but I just wanted to try to address the concerns, the statistical concerns or the epidemiological concerns, that would inform the evidence that there may be some human data suggesting that there is a link.

DR. KENNY CRUMP: Well, first of all, Dr. Johnson, said some things that made me stop and think a while ago. Maybe I overstated before, but I don't think this recall bias applies to all case-control studies; and not even case-control studies where they assess exposures by polling the cases and controls. It may be that it only happens in cases like this of pesticides, which it's very difficult to remember the pesticides you're exposed to.

I don't mean to imply that all case-control studies have this bias, but I think they could all have it in these cases where you have these pesticides. You have to remember what you had in the past.

I would like to say one more thing about what Dr. Sheppard presented, which I'm still

trying to understand exactly what's the point she's making. But that's my fault, I'll work on that.

I would like to point out that the only reason I presented this data from this old study -- first of all, it's the only study I could find that even tried to evaluate recall bias. It's a real old study. I don't think this issue has been studied very completely. In fact, when I analyzed the data, I got something very different from what the authors concluded, which, by the way, they concluded without any sophisticated analysis, like Dr. Sheppard has presented. I thought it was worth presenting it.

But my main point in my presentation was the table that I presented that dealt with the evidence for control recall bias in these glyphosate studies. I think that's what we need to, perhaps, focus on. I saw that the data that I presented, I thought, is just what you expect to see if recall bias could explain all of the results. And there are other problems, of course, with these studies, but I think possibly, recall bias could explain all of those findings in those studies. And I think that table I presented, at least, is consistent with that.

DR. JIM MCMANAMAN: So that would be a

discount of that information. Before we go to Dr. Green, Dr. Zelterman told me that he disagreed with Dr. Sheppard's analysis and that he had mathematical proof.

DR. DANIEL ZELTERMAN: No, no, no, it's quick. If we measure everybody twice, which is essentially what's going on here, you look at the concordant pairs, you look at the discordant pairs. In the first table, everybody is asked were you exposed?

DR. JIM MCMANAMAN: Dr. Zelterman, get closer to your microphone.

DR. DANIEL ZELTERMAN: The people who change their minds at 17 and zero, all right, it's the discordant pairs; the people who said one thing on one survey and then something else on the other survey. And then if we look at the second table, it's 32 and zero, the discordant pairs. This is what we do when we have a lot of epidemiologic studies. We look at only the discordant pairs.

Okay. Of those who change it's invariably -- the first hypothesis is that invariably, it's upon probing those who initially said they weren't exposed, said that they would be exposed. We

can only really go in one direction. That's hypothesis number one; and there's your intraocular 17 and zero, 32 and zero. It's intraocular, as Dr. Sheppard calls it.

Now, of those who are at risk for changing their mind. Who is at risk, again, the epidemiologic term? In the first table, there's only 35 who said no, as they're volunteering their risk, and 84 volunteering the risk. So how many individuals at risk for changing their mind? Music.

Okay. In the first table, it's 17 out of 35 and in the second table, it's 32 out of 84, which work out to, among the cases, it's almost 49 percent are going to change their mind. And among the controls in the second table, it's 38 percent.

In other words, among the cases, they are much more likely to say that they were exposed upon the second probing of finding out. In other words, those who are already cases, the effect is going to be bigger because now the cases are saying that they were more likely to be exposed. There's more likely to be a change in the first table than in the second table. This is going to increase the effect size.

DR. LIANNE SHEPPARD: I don't agree with saying that you're not at risk of changing your mind on further probing unless you had zero pesticides.

I think everybody who was interviewed a second time, which is 91 for cases and 172 for controls, is at risk for changing their mind. And therefore, if you if you want to do it by at risk, then I think you should use the changeover total estimate in the table. I don't think it's appropriate to also condition on their response.

DR. JIM MCMANAMAN: Yes, Dr. Taioli.

DR. EMANUELA TAIOLI: Yes. I don't think I would restrict recall bias to this case; it's a problem of case-control studies. Limitation is recall bias, no matter what, because you're always asked what was your weight when you were 18? What was your height last month? Whatever. Even things that don't change, you know, how many kids you had? And believe it or not, there are people, it happened to me, who don't remember how many kids they had.

DR. JIM MCMANAMAN: Right. This is a detail that is not --

DR. EMANUELA TAIOLI: No, but it's the

problem of this studies.

DR. JIM MCMANAMAN: Yeah. The question is, it's the validity of your opinion that this is a real link. And so, there are two schools of thought; one is that that opinion may be biased by people changing their mind because of recall bias. And the other is, as Dr. Sheppard is championing, is that there really isn't that, so it tends to validate that point of view.

Without going into any more detail about the two schools of thought, I think we've established that -- let me go back. Okay. This is Dr. Johnson.

DR. ERIC JOHNSON: I really don't think we should pursue this further because then the issue of interview bias come into play.

DR. JIM MCMANAMAN: Yes.

DR. ERIC JOHNSON: So we might be able to distinguish between interview bias and recall bias.

DR. JIM MCMANAMAN: You're right. We have some idea of the spectrum of abuse.

DR. ERIC JOHNSON: But I think it's also sufficient to say recall bias may be a problem. That's it.

DR. JIM MCMANAMAN: Okay. Dr. Portier.

DR. KENNETH PORTIER: I was going to slightly changed the topic. One of the things that Dr. Taioli mentioned is the fact that all of the odds ratios are above one. The point estimates are above one. Now, the confidence intervals, right, drop below one, on all of them. And to my way of thinking, that's where the meta-analysis was supposed to come in, right. It's supposed to come in and say when we take the totality of the understanding of these studies and we put them together, what do we got?

And to me, that was a good part of the report, was they went there, they went into that and try to discuss it. And the thing that got me is that the lower bound on that was like 1.03, right. It's above one, but oh, my gosh, it's very little above one right.

DR. EMANUEL TAIOLI: But look at the I^2 (square); the heterogeneity is zero. That means they're really drawn from the same population. It's very rare, as you know better than I do; that usually, when you have 25 percent of the heterogeneity you are happy because it's kind of low. This is zero.

And the other thing is that a lot of

public health decisions, such as removing the treatment of post-menopausal estrogen, have been based on odds ratio that were much lower than this.

This is a valuable number.

DR. KENNETH PORTIER: I agree. And I looked at this. I was going to say, when I saw this, I had the same reaction, you know. My stomach kind of turns over and I say yeah, they are not significant, but they're all above one. And then I looked at the meta-analysis and said okay. And I saw the I^2 (square) and I said okay, yeah.

Then I took it to my epidemiologist. You know, I have two epidemiologists with 30 plus years of cancer epidemiology; and I showed them Figure 3.2 and they said oh, yeah, I don't see a signal. They were not impressed with 1.2 or 1.0 or 1.3. I think they were looking at the upper-end of the confidence bound, something we're not looking at, and say these bands are pretty wide on the other end. That indicates that individually, the studies weren't well-estimated.

I mean, you're right; they're estimating the same odds ratio. They're no getting around that. But they were not particularly impressed

with either the size of the average odds ratio or the meta-analysis. And that's why I stopped thinking about it beyond that.

DR. JIM MCMANAMAN: Okay. Thank you, Dr. Portier. Dr. Johnson.

DR. ERIC JOHNSON: So I don't think we should delve into this too much because I think we have so few studies to worry about. For example, the non-Hodgkin lymphoma, that we can examine each of those studies specifically for not only recall bias, but for other types of biases.

There is one study I remember looking at in which every single odds ratio, whether it was for fungicide, insecticides, and subgroups of those, all of them were below one, which got me worried. How could all of these odds ratios be below one?

One of the studies which I got -- I'll pull it up. There are issues with individual studies, and we just have to focus on the ones which are important for this evaluation.

DR. JIM MCMANAMAN: Thank you, Dr. Johnson. Dr. Green.

DR. LAURA GREEN: I wanted to add something which I think would be helpful for the

Agency. It is responsive to the charge question and I think it would actually allow more consensus than maybe is apparent; although, Dr. Sheppard is going to add something, I believe.

Strength of association is an important characteristic in any causation assessment. And it's important characteristic when you're trying to worry about residual confounding biasing things, either away from the null or toward the null. I believe that Dr. Crump's concerns about recall bias, my concerns about confounding by the biological and antigenic stimulations on farms, would be obviated, were the estimates either from individual studies or the meta-analysis larger with tighter confidence intervals?

And I don't even really care about the tightness of the confidence interval, I'm talking about the strength of the association.

I have at least two concerns about biasing away from the null. Professor Sheppard has a concern about biasing toward the null. But the truth is, these confounders can only account for excess or less odds ratios of like, .5 or something, right? I mean, no amount of recall bias is going to account for an odds ratio of 10 or five, or even four. And when

you speak, Professor Taioli -- and I think you're exactly right -- when you speak about true positives in either air pollution or women's health, when you speak of a true positive with odds ratio of only 1.2 or even 1.02, yeah, this is very significant.

But the reason that it's different here is that we have pretty good confidence that the estrogen heart disease in women thing is reasonably unconfounded; although understand there are socioeconomic issues, blah, blah, blah. But I guess my point is, again, uniquely for lymphoma, which has been associated with farming since before I was born, anything that covaries with farming is going to covary with risk of lymphoma.

We are stuck with this, which is why Professor Johnson and I and all of us, and Dr. Zhang, are hoping that in the future there will be data on glyphosate-exposed workers who are not farmers. And we can finally get to the issue of glyphosate alone, whether in formulation or not, not confounded by exposure problems because we don't know how much, you know, what a pesticide applicator is really exposed to. Look at their ranges; they span like two orders of magnitude in range estimates, for what a pesticide

applicator is exposed to.

If we had factory studies, like in the old days with benzene and leukemia, where we knew the exposure, where we did not feel there was important confounding by other causes of leukemia -- like working in factory is not leukemogenic, as far as we know -- but for benzene, right.

The real problem here, it seems to me, is that the strength of the association is small. Yes, it's often larger than one, which is why we worry about whether there's a systematic bias away from the null. And we have explained, I feel, why there are systematic biases away from the null. These are farmers exposed to antigenic stimuli; and antigenic stimuli and lymphoma are hand-in-hand, right. People who have tuberculosis and malaria, for example, chronically get lymphoma at three or four times above normal.

There are many reasons to be concerned. And I want to ask Dr. Sheppard to talk about why she's concerned in the opposite direction. But I think what it comes down to, for your causation assessment and the weight of the evidence, is the strength of the association. We would all be in agreement if the

association was stronger.

DR. JIM MCMANAMAN: If it was black and white there would be no discussion. I will give Dr. Sheppard one chance to respond and then we're going to move on to the others.

DR. LIANNE SHEPPARD: Yeah. I would agree with both of those. With respect to what you were eliciting from me, measurement error bias is actually pretty important, particularly in this kind of recall kind of situation. And in fact, Dr. Crump's analysis yesterday, from the Blair and Zahm paper, showed really pretty good evidence of when you reduce measurement error you see a bigger effect, a case-control effect, which is related to the pesticide exposure. It was a nice example, in general, of that impact, I think, other than the highest group where there were really small numbers that was seen in that analysis.

I also wanted to say that our difference of opinion about the epi data is, I think, consistent with my understanding of what IRAC concluded with respect to the epi data, that there's some inkling of something there, but for lots of reasons, you're worried about it. And we've heard

around the table, lots of reasons why were worried about it; but it shouldn't be ignored. But perhaps more of the evidence base should be based on the animal data where the signal is a lot clearer.

DR. JIM MCMANAMAN: With that, let's move to the annual data. Dr. Parsons had some very cogent concepts and comments about the validity of the animal data.

DR. LUOPING ZHANG: Before we go to animal data, could I address some human data? My light was on forever.

DR. JIM MCMANAMAN: Sure.

DR. LUOPING ZHANG: You're trying to ignore me, but it's okay because my last name is Z. But anyway.

DR. JIM MCMANAMAN: Dr. Zhang.

DR. LUOPING ZHANG: I actually appreciate, Dr. Chairman, really focusing, for the final conclusion, the human data is important for the human study. And now we're actually sort of -- all the past discussion was focused on non-Hodgkin lymphoma. I would like to, back to before the Charge Question 2(d), which actually, I think we didn’t get to that 2(d). One of them is to comment on the

conclusion of the agents. Let me just try to see this.

EPA conclusions is here. I just read. "NHL based on the weight-of-evidence, the Agency cannot exclude chance and/or bias as an explanation for observed associations in the database. Due to study limitations and the contradictory results across studies of at least equal quality, a conclusion regarding the association between glyphosate exposure and the risk for non-Hodgkin lymphoma cannot be determined based on the available data." That's the EPA conclusion.

Actually, I think yesterday when we got to 2(d), we didn't really, you know, elaborate on that. I would like to pull it back.

I'm actually thinking, I only express myself, opinion now to the 2(d) team. Because I haven't discussed this with my team yet, even though I had a long meeting last night.

But I think we should think about it and re-address the key question. I think the key question for 2(d) would be whether or not there is a potential of glyphosate associated non-Hodgkin lymphoma risk in exposed humans.

If a question is addressed this way, I would say, based on the weight-of-evidence, from old data, that was obstructed from old qualified and available human studies, for example, now, from 24 and then subtracted to six. I actually would say, I cannot exclude the possibility and/or the likelihood of a preserve with a positive association between glyphosate exposure and the risk of non-Hodgkin lymphoma, even though study limitations and contradictory results across the studies remained.

I don't know. My consent is why the Agency has said, cannot exclude the chance and the bias, why we cannot address it? We cannot exclude the possibility and the likelihood, right? Back to the EPA, 2005, the (inaudible). If we look at the suggestive evidence of the carcinogenic potential, you're only need a single positive cancer results, if I understand it correctly.

I think for the human data, again, six of them toward one, right? And this is a question I got confused from Dr. Portier's comments on the meta-analysis. From what I hear from you yesterday, meta-analysis is useful, especially in this situation, six studies, very tight. And even though small increase

the of relative risk, but if you combine them together, that's significant. Significant is significant.

You increase 20 percent or 30 percent. But what we want to address is, can we really exclude the likelihood or possibility from the human data? That's actually, unless it's my consent, I'm from public health, and actually, I did -- one more thing I wanted to -- I didn't plan to, but I put on here. On my report, the first thing I quoted is, quoted from EPA, ethics training. Public service is public trust. To serve with honor. Here is what we're here for.

We follow the precautionary principle to protect the public health. That's why I think we should think, how should we really frame our key questions to protect the public health. Okay. Back to you. Your question is, is meta-analysis --

DR. ANNA LOWIT: Okay. Dr. McManaman, we have 30 minutes until the adjournment of the meeting. And I appreciate Dr. Zhang's comment of suggested, because it's answering our question. I will take offense to the suggestion that we're not being good public servants, on behalf of my team. That we do take offense to that suggestion.

We still haven't heard Dr. Crump's answer the question; and nor have we heard a number of other panelists, including Dr. Ehrich on the phone. We would like to hear from a plethora of viewpoints.

DR. JIM MCMANAMAN: Dr. Zhang, are you --

DR. LUOPING ZHANG: I haven't finished. Because I want to also echo what Dr. Green said earlier about how to systematically look at the data. To me actually, I think human NHL data we shouldn't exclude; and should consider carefully and scientifically, and fairly.

But also, I want to bring the next point is -- for example, Dr. Green brought up benzene. Benzene is a human leukemogen, but there is no animal data. There's no animal model to test if benzene can cause leukemia in any animal model.

But I think here, for glyphosate -- this is another thing I wanted to add -- for the rodent carcinogenicity test, especially for lymphoma, I think the agency's only, including Wood (2009) studies, but the European one, they include five more. Actually, I thought the Agency didn't have the paper, but now I find out you that you do have it.

I think we should look at the lymphoma results in the mice model a little bit more carefully as well. In a way, I actually felt, is that a coincidence or is it a real potential or likelihood for glyphosate. Could it possibly cause lymphoma? Because we see human data and it's suggestive with the animal data. I feel that's something we maybe needed to think systematically or holistically.

But unfortunately, I think, I want to also say again, immunotoxicity data was kind of missing and the one we have is really not good. But the new study I brought in today actually would be possible to suggest, you know, that -- if the glyphosate involved in metabolic pathways or fatty acids pathways, that's all linked into these regulation of the immuno-response. There is some holistic response to lymphoma. That's my comment.

DR. JIM MCMANAMAN: Okay. Let's open it up to some of the other panel members. Marion, are you still on the line?

DR. MARION EHRICH: I am. I just had it on mute.

DR. JIM MCMANAMAN: Okay.

DR. MARION EHRICH: Did you want my

comment? I didn't think there was this controversy about this White Paper. I thought it was pretty clear as it was written. I'm a little surprised to see that there was this much controversy, because I thought the EPA did a pretty good job of going through everything. You know, I just didn't think it was going to be as controversial as it's turning out to be. I guess that's my biggest comment right there.

DR. JIM MCMANAMAN: Okay. You would agree with it's not likely?

DR. MARION EHRICH: I would agree with it's not likely because that's what the EPA says.

DR. JIM MCMANAMAN: Okay.

DR. MARION EHRICH: I looked at their data and I looked at how they looked at everything and there just isn't enough there. It's just not enough. It's going to be reviewed again in another, what --

DR. EMANUELA TAIOLI: Not enough is not "not likely." Those are two different things. If your idea is not enough, it's a different concept. That is different.

DR. KENNETH PORTIER: I think I've captured the epi discussion and the disagreement and I think we'll be able to address that under the issue of

consistency of signal, and plausibility, and under uncertainty. I mean, we'll kind of address those three things under the epi discussion.

You know, if I would, I'd like to take it back to Dr. Parsons for just one minute --

DR. JIM MCMANAMAN: I agree.

DR. KENNETH PORTIER: -- on the animal stuff. Because I was thinking about your justification for thinking that the lowest dose of which a cancer was observed. But if you look at that study, actually, if you take the exact test, there isn't a significant trend. And the multiple comparisons don't show any differences among the group. And the lowest dose is right at the historical control; although it would be nice to know how old the historical controls are.

It's hard to go that far down to whatever it was, 3.05 milligrams as a lowest observable effect level. And I would kind of say significant. Most of us would look at that and say, that's probably still randomness down that low.

I'd ask you to comment against that. I'm going to pushback on that in terms of --

DR. BARBARA PARSONS: Okay. I don't

understand --

DR. KENNETH PORTIER: -- my statistics --

DR. BARBARA PARSONS: I don't understand. It's not an exact test. This P value --

DR. KENNETH PORTIER: Right. The test they did were approximate tests. And the things that Joe Haseman showed is that doing an exact test takes it from like .04 up to a .065; which at .05 level, you would say that's not a significant trend test. I think that was right. I have to go look it up. Almost all the trend tests were not significant.

DR. JIM MCMANAMAN: Dr. Parsons. Let's let Dr. Parsons --

DR. KENNETH PORTIER: Under the exact tests, almost all the trend tests disappear.

DR. ERIC JOHNSON: Just a point of order, I'm a little bit confused. I thought we were discussing the epidemiological.

DR. JIM MCMANAMAN: No. We finished with that.

DR. ERIC JOHNSON: No. No. Because you did not give us a chance -- I mean, there are --

DR. JIM MCMANAMAN: Well, no, you'll get a chance to --

DR. ERIC JOHNSON: No, no. You did not give me a chance. I only addressed Dr. --

DR. JIM MCMANAMAN: Oh. I thought you addressed that.

DR. ERIC JOHNSON: No, no. Only Dr. Crump's issue of recall bias. You did not ask us to tell you our overall evaluation of the data.

DR. JIM MCMANAMAN: Okay. All right. Go ahead.

DR. ERIC JOHNSON: So the first thing is that, I think, the last descriptor, which say discussions with no evidence -- the last one. What was it now?

DR. LAURA GREEN: Not likely.

DR. ERIC JOHNSON: Not likely to be carcinogen to humans. That descriptor, I have difficulty with this. I think it's directed against the animal studies, not epi studies. If you look at all four criteria, it either directly addresses them or implies animal studies. There is no guidance there for epidemiologic studies.

I go to the next criterion, which is

the one suggestive of evidence and, again, two of those four guidelines are directly animal, of the animal studies. Of the first two, one simply says -- let me read what it says. And that's the only one that applies to epi studies. I wish they would put these things up for us when we discuss them. That would be some help.

Suggestive evidence. It says, "If a small and possibly not statistically significant increase in tumor incidence is observed in a single animal or human study." There is only one human study. If you observe possibly not statistically significant increase, that does not reach the weight of evidence for the description of likely to be carcinogenic to humans. That is enough to be classified as suggestive.

DR. LAURA GREEN: No, but you need to read the next sentence.

DR. ERIC JOHNSON: Okay. "The study generally would not be contradicted by other studies of equal equality in the same population group or experimental system."

Now, that statement, to me, when we look at non-Hodgkin lymphoma, we do have, not only in

one study, an elevated non-statistically significant result, but consistently, I think in five of the six studies, they were all elevated above twofold. And in one of them, it was actually statistically significant. And in fact, in two of them, it was actually statistically significant. And in one of those, they did control for all the multitude of pesticides, which is the strongest adjustment you could make, and the other one they did not control.

That group, the non-Hodgkin lymphoma, to me, if I use that single criterion, makes it just logically that a conclusion has to be this criterion. Bearing in mind that the fourth criterion, of not likely to be carcinogenic, does not seem to apply to human studies to me.

DR. LUOPING ZHANG: Can I add one more? Plus, the dose response.

DR. JIM MCMANAMAN: Thank you, Dr. Johnson.

DR. LUOPING ZHANG: Plus the dose response, also, detected in that study.

DR. JIM MCMANAMAN: Thank you, Dr. Zhang. Okay. Well, let's finish up this. Dr. Crump, what's your overall view about the relevance of the

human data?

I thought I heard you, but maybe I didn't. There's concern that you didn't express your views about the epidemiology data related to humans. I thought I heard you, but maybe not. Do you want to reiterate that?

DR. KENNY CRUMP: I think I've stated it several times. I don't think we can rule out the possibility that these findings are all related to recall bias. I thought the table I presented the other day certainly suggested. That's exactly what you'd expect to see if there was a problem with a control bias.

And I can't use these data in any positive way to suggest an effect on non-Hodgkin lymphoma because of that problem. And there are other problems with the studies too. But I think, in my view, recall bias could be responsible for all those results.

DR. JIM MCMANAMAN: Okay. Thank you. We want to finish up with the animal data, if we can. We're open now to the question about whether there's data in the animal literature that is suggestive of a link. We'll go back to Dr. Parsons or Dr. Ramesh or

anybody who wants to add into this.

DR. BARBARA PARSONS: Do you want me to answer the question that Dr. Portier posed?

DR. KENNETH PORTIER: You're the one that kind of strongly came out that said, you know, you see a signal in the animal data.

DR. BARBARA PARSONS: I did.

DR. KENNETH PORTIER: And I think the rest of us do have to kind of chime in on that.

DR. BARBARA PARSONS: My guiding principle was to adhere to what the guidelines are directing us to do, how to evaluate the data. I think this is critically important for a situation where there are competing public interests. There is a difficult risk management decision ahead. I totally see that; and because that's what we were asked to do. We were asked to evaluate how EPA evaluated the data, based on what is prescribed in the cancer risk assessment guidelines.

As I explained in my remarks, my reading of the guidelines is that a significant trend test, with the P value below 0.01, should be accepted as evidence of a carcinogenic response. In my mind, there is no reason to discount that. And I have given

my argument for why I don't accept some of the reasons that EA has argued that those should be discounted.

Now, I'm not absolutely wedded to this 31 mg per kilogram per day being the most critical low dose number. If someone -- I'm not a statistician -- if you can give me a reason why that should not be used, okay. But my reading of how we're supposed to evaluate the data, based on the guidelines, I'm just not comfortable with -- I'm not going to say discarding -- but discounting significant effects, particularly, just because they may be due to chance.

There is a public health issue here where our job is not to come to our conclusion based on the criteria that we can accept no false positives. I don't think that's our job.

DR. LAURA GREEN: But, Dr. Parsons, here's the central reason that this night is different from all other nights, if I can put a little Judaism in here. As we've said ad nauseam, this is not a situation where we have one or two bioassays and nothing else.

We have 15 bioassays or so, depending on how you count. The guidelines that EPA plays by very specifically say the study generally -- meaning,

let's take Lankas et al., let's take the Leydig cell tumor response at 31.5 mg per kg. The study, Lankas, generally would not be contradicted by other studies of equal quality in a same experimental system.

We have nine rat studies, three of them in the Sprague Dawley. We have three, maybe four, but at least three I can think of, three tests of the question, does glyphosate cause Leydig cell tumors? One test says yes. At 31.5 mg per kg, with a significant trend test. And by the way, Ken, I didn't understand what you said before because I think it is a significant trend test I think that's what Professor Zelterman said, it's not .009.

Dr. Parsons is 100 percent correct, that if we had that bioassay result and nothing contradicting it, I would be with you. Okay? But first of all, it's the 1981 study in an outbred animal that went for 26 months. And as I've mentioned, Dr. Boorman and others discount that for very good pathological reasons.

Regardless, Stout and Rueckerf, using the same Sprague Dawley animals, repeated the assay, not 31 mg per kg, but all the way up to 1 gram per kg, and failed to find any Leydig cell tumor response. No

suggestive, but nothing. Bupkis. And then it was done another set of Sprague Dawley rats.

It seems to me, given EPA's Guidelines, which say when you have contradictory evidence you should stop and think about it, given the pathologic problems of diagnosing Leydig cell tumors in aged Sprague Dawley rats, I just do not see how one can hang one's hat on that response, per their own guidelines and frankly, per what I understand to be the pathology of this tumor.

DR. LIANNE SHEPPARD: Can I say something?

DR. JIM MCMANAMAN: Yes.

DR. LIANNE SHEPPARD: I mean, one of the problems is that counting tests doesn't really help us navigate this multiple testing problem. We really need to help the EPA move forward, I think, with a recommendation that helps them consolidate the evidence in a more thorough and balance way that includes all the negative and positive studies in one analysis.

DR. JIM MCMANAMAN: Dr. Crump? That was Dr. Sheppard.

DR. KENNY CRUMP: I want to say I

appreciate the careful thought that Dr. Parsons has given to all these issues and I've enjoyed her comments very much. But I do want to comment on the testes tumors in the Sprague Dawley rats.

First of all, I think the rule in the guidelines, that it should be less than 1 percent in a common tumor and 5 percent in a rare tumor. I think that's just a rule of thumb that was developed many years ago, and I don't think we should think it applies as an overall. I think we can do something better than that. I don't agree that we should always apply that particular rule as a hard and fast rule, particularly with so much data. They were thinking of applying it to a single study.

It seems to me the testes tumors in male Dawley rats, if there's ever a case for ruling that as being incidental, I think this should be it. The high dose was very low. It was an old study. In fact, Greim et al. says we shouldn't consider that study because the doses were too low.

And there have been four other studies in the same species, same strain, the same sex, and none of them show any evidence of an effect in this kind of tumor. One of the studies have a negative

dose response. Not significant but negative.

In male Wistar rats, there are two studies there. They all give negative dose responses. Again, not significant, but they are all negative. I think if there was ever a case we could consider that this was an incidental finding, it would have to be this case. There's been so much evidence against that being a real effect.

DR. JIM MCMANAMAN: Dr. Ramesh.

DR. ARMANDLA RAMESH: I think part of the problem we are breaking our heads is lack of literature on glyphosate. Part of the reason is there are not that many publications from academia. Being a researcher from academia, the trend is we are not that much fascinated, not toward glyphosate. For that matter, not towards any chemical if no one dies, if no one becomes important, if it doesn't pose a significant health issue enough for us to write a grant application and request for funding.

And our resources do not permit to embark studies of this on our own and spend our resources. The very fact that no farmer or his spouse became important, no one has died of cancer or no one has any significant health issue, it stresses the

point that no amount of whatever dose you use, either for an animal or human, lesser proportion of it gets into the body to disrupt cellular homeostasis or to affect the cellular macromolecules and to bring out any adverse health effect.

The Agency has to go with the kind of studies that they have. Well, probably, after hearing all of our deliberations, we suggested that they revise their White Paper, clarifying some of the issues raised. But that is not going to change the notion that it is not likely to be carcinogenic to humans. That's what my personal take from this is.

DR. JIM MCMANAMAN: Thank you, Dr. Ramesh. Dr. Sobrian.

DR. SONYA SOBRIAN: After what I've heard when we discussed Question 3, I'm a little surprised at what I'm hearing now. I think everybody's focusing on the on the first study in rat, which may or may not be the one to focus on. You're forgetting that there are 15 studies. And if you look at the table, which you don't have now, that was presented by Dr. Niemen, as you called the German fella.

Anyway, if you look at what you see in

mice, you see a really different story. If look at a malignant lymphoma, he's got equivocal for three of the five studies. If you look at kidney tumors, he's got equivocal for, again, three of the five studies and for hemangioma and sarcoma, he's got at least two equivocal. There's some signal there.

I think during the discussion of Question 3, we pointed out where some of the -- I don't want to call it shortcomings, but some of differences in the way that the panel versus EPA looked at the data that were presented.

I mean, we had difference in opinions about the use of historical controls, which a lot of people spoke to. We had differences in opinion about what kind of statistics to use and if trend were enough or if you needed pairwise comparison. There were a lot of issues.

I think we're ignoring that and getting stuck on Lankas. And also, we've talked -- or you've talked about -- transparency. And I'm not saying that the agency's not transparent, but how many academics can get the data that's 10G? There is an issue with transparency.

The other issue I brought up was when

we were asked to do Question 3(d), about how the Agency look that preneoplastic lesions. But that's not to say that people are not transparent, they're just issues.

But I think there is a signal. I mean, from all the discussion that people seem to be backing away from now, which I find really interesting, that there is a signal. There's something going on. To say that it's the last -- whatever -- I mean, I think it may be suggestive. I like Dr. Green's equivocal but since we can't use that, I think there is something going on in the animal data that I would find that hard to just, out of hand, ignore.

DR. JIM MCMANAMAN: Well, one minute. Coming back, the question is please comment on the completeness, transparency and scientific quality of the agency's characterization of the carcinogenic potential of glyphosate. And Dr. Portier set the stage for us for this discussion by going through those systematically.

And I think that there would be little -- I haven't heard anyone say that they disagreed with his assessment that it has been complete. That it was relatively transparent, although, maybe, Dr. Sobrian

saying there may be some issues here. It's a scientific quality, I think, that the questions are revolving around right now.

And I think the discussions have brought out the limitations of what the panel's understanding is about the scientific quality of both the human epidemiological studies and the animal studies. And I think that as a panel we don't have to agree, but I think that the discussions have addressed the -- unless someone wants to say that they disagree with Dr. Portier's initial assessment, I think the panel pretty much agrees with his first three points. And it's the scientific quality that I think that we're struggling with.

I'd like to hear from the panel if they have a problem with the transparentness or the completeness. Other than that, I think we're appropriate to focus on the scientific quality, because that's where it really hinges. There is a dearth of quality studies.

Dr. Portier.

DR. KENNETH PORTIER: I was going to say for the notes, I see your point about transparency. You're absolutely right. We can see

the responses, but the public can't go into the study designs and look at non-neoplastic lesions and make their own assessment of that kind of thing. I made a note of it.

DR. JIM MCMANAMAN: Okay.

DR. SONYA SOBRIAN: That's not a reflection on the Agency. That's a reflection on the --

DR. JIM MCMANAMAN: On the process. Yeah. Dr. Ramesh.

DR. ARMANDLA RAMESH: I think the Agency in their presentations on first day, clearly outline what are the study quality conservations, study designs and how they made the exposure assessment and outcome assessment. And they also discussed about the confounding controls. They have made it clear in their transparent way, what are the filters that they have taken into consideration for coming up with the White Paper and assessment of the studies. I'm fine with it.

DR. JIM MCMANAMAN: Okay. Other comments? That was Dr. Ramesh. I thought I introduced him. Dr. Johnson.

DR. ERIC JOHNSON: Quick clarification.

Let's take the benzene situation in which for a long time it was only the human data that we had to declare benzene as carcinogenic. It was later on that they found that benzene caused cancer in animals as well.

In our evaluation here, if we find suggestive evidence of carcinogenicity in human studies, shouldn't that override -- because the ultimate target population is the human population. Does the conclusion for the human study trump that of the animal study, when it seems to me the consensus is that there is suggestive evidence in humans, based on the criteria we were given? Because if it was left to me, I may have a different criterion, but this was the criteria that was given. I think all of us agree that it's suggestive evidence for the non-Hodgkin lymphoma.

Now, given that, when the animal data is under general toxicity and they are all included, should they end off concluding that there's no evidence that this thing causes cancer?

DR. JIM MCMANAMAN: I'm going to punt that because I think that Dr. Portier discussed that in his initial setting up of this problem. I'll go back to Ken.

DR. KENNETH PORTIER: I think when we

write-up this section, what I'm looking at under the quality is the logical inferences. And so, what we're going to do, is we're going to point out for the epi data that the that some of the panel didn't agree with EPA's logic that led them to a conclusion. We'll try to point out the positives and the negatives and the things we've talked about. And then we'll do the same thing with the animal studies.

We don't have too much concern with the genotox, but, you know, the animal studies, we're not fully convinced with the logic and there's no consensus. I mean, I think we'll just point out both sides and try to be fair in that discussion; and that's all they're asking us to do.

They're not asking us to make a carcinogenic decision, that's their job. Our job is just to say, you know, we agree with your logic, we don't agree with your logic; or we don't agree, and here's where we don't agree, or where we think you need to shore up your logic shore up your argument.

DR. JIM MCMANAMAN: Strength of evidence.

DR. ARMANDLA RAMESH: I think we need to add a little bit in that sentence, something like

given the few number of studies available.

DR. JIM MCMANAMAN: That was Dr. Ramesh. Dr. Parsons.

DR. BARBARA PARSONS: So following on what Dr. Portier just said, it may be useful to focus on the animal data, or the area that has the strongest signal, which would be the malignant lymphomas.

DR. KENNETH PORTIER: And again, this is why I was coming back to the consistency and plausibility. Because, I think, you know, as I read this, I was saying well, you know, we're seeing something in the epi and the lymphoma, and then I'm looking in the animal data. And I was listening very carefully to what you guys were saying about the quality of the animal data and the lymphoma and the myelomas.

And so, we've kind of got to bring that in and look at that coherence there. How do these things stick together? And again, we're not all in agreement on that, but we're just trying to help the Agency look through that, again that logic, but now it's the combined logic of the two.

DR. JIM MCMANAMAN: Okay. I think that we're at our deadline hour. I don't know that we can

go much beyond what we've discussed. At this point, let me go back to the Agency to ask, there was some issues about clarification that they were going to hold until the end. We'll ask Dana Vogel to -- I see Anna Lowit bailed.

MS. DANA VOGEL: She had a family obligation.

DR. JIM MCMANAMAN: Okay.

MS. DANA VOGEL: So just one thing. I heard some different opinions, especially in the weight of evidence at the end. It would be helpful, especially considering that a few members had to leave and are no longer here, for all the opinions to be captured in the report, just so we have a full understanding of what everyone think.

Because I think it, you know, from my perspective, it's very important for us to understand both sides of it and exactly what you're recommending. I think because there's no consensus, that's going to be the most important thing that gets written up in the report for all section, including the weight of evidence. That's it.

DR. JIM MCMANAMAN: Okay. All right. At this point, the panel has one last

opportunity to make statements and express their views about this session and about the presentations.

With that, I'd like to start by saying I really appreciate the wealth of discussion and the diversity of views that the panelists have expressed with this. In some respects, it seems like a very simple problem because it's not a really particularly toxic compound. But it just goes to show you that, you know, sometimes what seems pretty simple on the surface is more complex when you look at it in detail.

And I really appreciate the level of thought and work and effort that the Agency has put into this. It's an incredible amount of work. I mean, there's just so much data. I think the panelists are saying, oh, my God, we're swimming in data here. Too bad we don't have several weeks to really fully get into this, because it is a lot of data. And you guys had to provided it to us. I really appreciate your efforts going into providing the data.

I particularly appreciate also the comments from the public speakers. We had really, quite a diverse group of public speakers. And in some respects, an entertaining group of public speakers.

And so, this has made this really an eventful meeting.

I appreciate the thought that the group from Monsanto, particularly, put into the analysis of this problem. I think it was very helpful, as well some of the public -- I don't remember particularly who it was, I don't see him here -- I can't remember whether it was the Natural Resources Defense Council -- but one of the guys, he put a lot of thought into this, too. I really appreciate the other side of the issue.

And finally, I'd like to express my really sincere compliments and gratitude to the staff for getting this all together, especially Steve Knott and Tamue Gibson, for pulling all this together. This is an incredible amount. And Laura Bailey for keeping them organized and getting this all done. And Laura's staff. This is great. And the stenographers. I mean, she's back here -- you guys can't see it, but she's got really long arms. She back here poking me saying, "Will you get this under control?"

With that, I'll turn it over to Sonya. I'm getting tired.

DR. SONYA SOBRIAN: It's getting late.

DR. JIM MCMANAMAN: Yeah.

DR. SONYA SOBRIAN: First of all, I'm really sorry Anna's not here because I'd really like to compliment EPA on all the work that they've done on this. It's an amazing amount of work. And even though we might disagree, we still do appreciate -- I appreciate, I'm sure the rest of us do -- how much work you put into getting this White Paper together.

It's been a most incredible three or four days. I missed the public comments, so I missed some of the entertainment. But this is a very dichotomous issue and I think we've put a lot of time into this. And I'm looking forward to seeing which of the many recommendations you'll be able to take. And I look forward to reading the next iteration of this White Paper.

I'm finished.

DR. JIM MCMANAMAN: Kenny.

DR. KENNY CRUMP: Is this a good time to give my bottom line appraisal?

DR. JIM MCMANAMAN: Sure.

DR. KENNY CRUMP: I just thought of one thing that you might want to think about. We have all this huge amount of data, but we focus attention on the lymphoma in the mice. And I'm just thinking of

how ironic it would be if that drove our decision with all the massive amount of data we have on this issue, assuming that it's not compound related.

If two animals had been reassigned to the control group rather than high-dose group in those studies, we would not be discussing it at all because noting would be significant. I just think that's ironic if that would be something that would drive our decision.

My bottom line, if I had to choose one of those descriptors that EPA has thrown out, I think I would go with not likely to be carcinogenic in humans. I personally don't like that descriptor. I really don't like "equivocal" either because surely, we scientists can do more with all these data than just say something is equivocal. I think that would lead us to a lot of criticism and possibly even some laughter, if that's all we can say with all this data.

But I don’t like the, “not likely to be carcinogenic in humans” because it sort of suggests that we can prove a negative. I mean, we haven’t tested glyphosate in all possible configurations. And even if it had been, there's always a chance there's a small carcinogenic effect that we would overlook. I

would prefer a descriptor such as no credible evidence that glyphosate is carcinogenic in humans. That's it.

DR. JIM MCMANAMAN: Next.

DR. LAURA GREEN: I just want to say thank you.

DR. ERIC JOHNSON: Again, I appreciate all the hard work in which EPA has done. Really, it's a lot of work and I really appreciate that amount of effort. I mean, I want to thank them for putting all the work together.

I have to say that -- and this is a dream and hope that we can have a better relationship with industry when it comes to studying human populations. We really need industry.

I've been in this business for quite a number of years, and industry sees academia and other independent research institutes as a fool, really. And I hope there can be a change in the future in which they do not see us as a fool. That we're all trying to protect the human population, and collaborate with us. Of course, we're all affected. Even they, themselves, they're children are affected.

I really hope to see some change. Some leadership in industry, to participate more and be

more cooperative and transparent, and help us to deal with most of this. There are thousands and thousands -- in fact, it's going to be even more important in the future because there are thousands and thousands more chemicals being introduced into the environment. It's never going to be possible for us to evaluate these chemicals without collaboration from industry. Period.

DR. BARBARA PARSONS: This is Barbara Parsons. I'm just going to say I appreciate having the opportunity to express my opinions on this topic. Thank you.

DR. ARMANDLA RAMESH: This is Ramesh. Thank you, Mr. Knott, and other EPA staff, and also the scientists of the EPA, for sharing their viewpoint. The White Paper is not an easy document. It takes a lot of effort and discussion with a lot of people. Coming to that document as a guidance or a reference point, made our job easier.

I also thank the industry representative for giving their version of the story. And also, the public speakers for educating us, providing the ill-effects from a common man's standpoint. Overall, it was a worthwhile experience,

serving on this panel, and I thank my fellow participants for their cooperation.

DR. KENNETH PORTIER: It's Ken Portier. For those of you who have done this for the first time, I have to tell you, I've have done a lot of these and rarely does the panel disagree as much as this one has. And I don't want you to think that this is normal. I think this is the situation; it's a lot of data. And then I was sitting here thinking, the last time this happened, the epidemiologists were at the table too.

I think there's something about epidemiology, and that EPA really needs to get that 2010 Guidance tightened up and move from draft into something that's real guidance so it'll help us with these conversations. I'm not saying it's the epidemiologists; it the topic.

DR. LAURA GREEN: I have a friend who is an epidemiologist at Boston University. He defines epidemiology as, the arguing with other epidemiologists.

DR. LUOPING ZHANG: I really would like to thank you, Mr. Knott, and your team. You know, really, to organize this, is actually difficult, the

most controversial chemicals we have to evaluate. Also, I'd really like to thank, you know, all the EPA scientist. I do think you have done the best you can.

I want to take this chance, I think, maybe the one doctor who just left, maybe misunderstood my comment, why I was quoting from my EPA ethics training; probably it's always, it's public trust. It's not what I mean to you guys; I mean for our panel members. As we come, that's our job, you know.

But also, I do really appreciate this chance where, you know, I was on this committee. I learned a lot. I learned a lot from the topic. I also learned a lot from, you know, my panel members. Like recall bias and all the biostatisticians too. And those are issues maybe, of my own, I don't consider that heavily. But I think now, you know, it's a chance also for me to learn from EPA scientists, and also for me to learn from everybody on the panel.

Thank you all.

DR. DANIEL ZELTERMAN: This is Dan's Zelterman. I have nothing to add. No, wait. No, wait.

The Agency, you guys may be demonized in the popular press, but I'm a big fan. I really appreciate all that you've done in putting all this information together. And then I was told this is only the beginning, that you have additional panels that have to consider this compound, and many other compounds. It's already Friday afternoon and your work is just beginning.

As for my fellow panelists, some of you I'm seeing now for the second time and I really appreciate everything, the heated discussions, especially.

I learned a lot and I look forward to ever crossing your paths again. This will be a lot of fun. Thank you.

DR. EMANUELA TAIOLI: Thank you for your work because it was amazing. Thank you for the Chair and the friends I made. And I have to echo Dr. Portier, this was the least boring SAP I have been in my life.

DR. LIANNE SHEPPARD: Well, I want to echo the thanks of everybody around the table; and also, comment a little bit, stepping back.

As a member of the Clean Air Scientific

Advisory Committee, and having been on a couple of IRA's panels. I've seen this process in a number of different manifestations. There's clearly some differences in how the realized process happened here, from what I'm used to. But in general, they all fall under the same umbrella, and the same principle of public participation, and transparency, and openness and good scientific exchange.

Ultimately, I think all of us are here because we're interested in the public good. EPA and its mandate is doing its job. And while sometimes it seems a little adversarial when we challenge EPA, I think it's ultimately incredibly valuable and supportive of your mission to have scientists on the other side of the table scrutinizing deeply, everything you do. Because that allows you to rely on our expertise to strengthen your work.

As we move forward, I guess we're all mindful that that will be even more challenging for you in the days ahead. I hope this process, from your point of view, has also helped you do the best job you can. Whatever we have done to challenge or question you is all in the spirit of what we're all for, which is the public good.

DR. ERIC JOHNSON: Yes. I would like to specifically thank our Chairman for the way he directed us throughout these four days. He really did a very good job.

DR. KENNY PORTIER: Except that he didn't give us lunch. Right?

DR. JIM MCMANAMAN: It seems, Ken, that one time when you were Chair we didn't get lunch either. It's Friday. We can go have a beer now.

Before we take off and go our separate ways, we have a post-meeting, meeting in our room, to discuss how we put together the final document.

Okay. Wait a minute.

MS. DANA VOGEL: Just really quickly, I also wanted to thank all the panel members for the lively discussion and the thoughtful deliberations. We do appreciate all of your comments.

I want to thank the Chair. As everyone has said, this is probably the most eventful SAP I've been in over the years. I feel for the people who are trying to do the transcription, especially what happened during the public comment.

But we really do appreciate all your feedback, all your input. And lastly, I would be

remiss if I didn't thank my team of scientists who gave up at least six months of their lives, weekends, nights in addition to working every day on every other thing that they do, to, in my mind, pull off one of the best scientific analysis. And they are some of the best scientists I've ever worked with. I just want to appreciate my team as well.

DR. JIM MCMANAMAN: We have Steve Knott.

DR. MARION EHRICH: Am I on the line?

DR. JIM MCMANAMAN: Yes, Marion. We forgot about you. Out of sight, out of mind. Okay. We have Marion, please.

DR. MARION EHRICH: Okay. I've been trying to say something since you made your comment.

DR. JIM MCMANAMAN: But I can't see you wave your hand.

DR. MARION EHRICH: I've enjoyed being on a panel with so much give and take and I appreciate everything. Sorry I can't be there today, but that's the way it goes. Best of luck as we try to write this up with all the little controversies I wasn't expecting.

Okay. I'm done.

MR. STEVEN KNOTT: Well, I want to add my appreciation, along with everyone else. I would like to thank Dr. McManaman for chairing this weeks' meeting, and all of the members. I mean, this was really a heavy lift. There were a lot of public comments and a lot of information to go through and I really appreciate everybody's effort.

I definitely want to thank OPP Science, Dana, Anna, Monique, Greg, Anwar and Jeff for your presentations, and being available to provide clarifications. The presentations were very clear, very helpful to the proceedings.

And I want to thank all the public commenters who, I think, are no longer in the room, but may be online, for all the really good feedback that the panel received, and information that they received.

And again, I'll add my thanks to my colleagues on the SAP staff, Laura, Tamue, Joyce and Don, who is out front, and our transcribers. I think that covers everyone, but I don't think we can say it enough. Thank you. We really appreciate everyone's efforts. And with that, the meeting is now closed.

[WHEREAS THE MEETING WAS ADJOURNED]

* * * * *