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U.S. ENVIRONMENTAL PROTECTION AGENCY (EPA)

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FEDERAL INSECTICIDE, FUNGICIDE AND

RODENTICIDE ACT SCIENTIFIC ADVISORY PANEL
(FIFRA SAP)

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OPEN MEETING TO CONSIDER AND REVIEW DRAFT FRAMEWORK AND CASE STUDIES ON ATRAZINE,

HUMAN INCIDENTS AND THE AGRICULTURAL HEALTH STUDY: INCORPORATION OF EPIDEMIOLOGY AND HUMAN INCIDENT DATA INTO HUMAN HEALTH RISK ASSESSMENT

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DOCKET NO.: EPA-HQ-OPP-2009-0851

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TUESDAY,
FEBRUARY 2, 2010

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The Panel convened, at 8:30 a.m., in the Lobby Level Conference Center, of the U.S. Environmental Protection Agency, located at One Potomac Yard, 2777 Crystal Drive, Arlington, Virginia, Steven G. Heeringa, Ph.D., Chair, presiding.

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FIFRA SAP CHAIR PRESENT:

STEVEN G. HEERINGA, Ph.D.

DESIGNATED FEDERAL OFFICIAL PRESENT:

MYRTA R. CHRISTIAN, M.S.

FIFRA SAP MEMBERS PRESENT:

JOHN R. BUCHER, Ph.D., DABT
JANICE E. CHAMBERS, Ph.D., DABT, A.T.S.
GERALD A. LeBLANC, Ph.D.
KENNETH M. PORTIER, Ph.D.

FQPA SCIENCE REVIEW BOARD MEMBERS PRESENT:

JOHN C. BAILAR, III, M.D., Ph.D.
FRANK J. BOVE, Sc.D.

RICHARD GREENWOOD, Ph.D.

ELLEN B. GOLD, Ph.D.

SHELLEY A. HARRIS, Ph.D.

WILLIAM L. HAYTON, Ph.D.

CHENSHENG LU, Ph.D.

BETTE MEEK, Ph.D.

NU-MAY RUBY REED, Ph.D., DABT

JOHN S. REIF, D.V.M., M.Sc.

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C-O-N-T-E-N-T-S

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C-O-N-T-E-N-T-S (CONTINUED)

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C-O-N-T-E-N-T-S (CONTINUED)

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C-O-N-T-E-N-T-S (CONTINUED)

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P-R-O-C-E-E-D-I-N-G-S

8:46 a.m.

MS. CHRISTIAN: Good morning and welcome.

Sorry for the delay, but we are going to start. If anything happens, then we will deal with that at that point.

I am Myrta Christian, and I will be serving as the Designated Federal Official to the FIFRA Scientific Advisory Panel for this meeting.

I want to thank Dr. Heeringa for agreeing to serve as Chair of the FIFRA Scientific Advisory Panel for this meeting.

I also want to thank both the members of the Panel and the public for attending this important meeting of the FIFRA SAP "to consider the Draft Framework and Case Studies on Atrazine, Human Incidents and the Agricultural Health Study: Incorporation of Epidemiology and Human Incident Data into Human Health Risk Assessment".

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We appreciate the time and effort of the Panel members in preparing for this meeting, taking in consideration their busy schedules.

The FIFRA SAP is a federal advisory committee that provides independent scientific peer review and advice to the agency on pesticides and pesticides-related issues regarding the impact of proposed regulatory issues on human health and the environment.

The FIFRA SAP only provides advice and recommendations to EPA. Decisionmaking and implementation authority remains with the agency.

As a vehicle for this meeting, I serve as a liaison between the Panel and the agency. I am also responsible for ensuring that all provisions of the Federal Advisory Committee Act are met.

As the Designated Federal Official for this meeting, a critical responsibility is

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to work with the appropriate agency officials to ensure that all appropriate ethics regulations are satisfied. In that capacity, Panel members are briefed with the provisions of the 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 Prevention, Pesticides, and Toxic Substances, and in consultation with the Office of General Counsel, have reviewed these forms to ensure all ethics requirements are met.

For members of the public requesting time to make a public comment, please limit your comments to five minutes unless prior arrangements have been made. For those that have not pre-registered, please notify either myself or another member of the SAP staff if you want to make any comments.

For presenters, Panel members, and

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the public commenters, please identify yourself into the microphone provided, since this meeting is being recorded.

There is a public docket for this meeting. All background material, questions posed to the Panel by the agency, and other documents related to this SAP meeting are available in the EPA docket. The slides of this week's presentations will be available in the docket within two days, and the agenda lists contact information for such documents.

At the conclusion of the meeting, the SAP will prepare a report as a response to questions posed by the agency, background material, presentations, and public comments. The report serves as meeting minutes. We anticipate the report will be completed in approximately 90 minutes, or 90 days after the meeting, not 90 minutes.

(Laughter.)

Again, I wish to thank the Panel for their participation. I am looking forward

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to both a challenging and interesting discussion over the next few days.

At this point, I would like to introduce Dr. Steve Heeringa, Chair of the FIFRA Scientific Advisory Panel.

CHAIR HEERINGA: (presiding) Thank you very much, Myrta.

And welcome to everyone, staff and scientists from the EPA, and to the general public.

We look forward to the next few days and, hopefully, a very interesting and productive set of discussions on the topic that has been assigned to us.

I want to, before I get underway, do a few special introductions. As many of you probably know, the FIFRA SAP has a permanent panel of individuals who provide continuity to the process, and then ad hoc specialists are brought in to address specific issues, to make sure that we have proper coverage of all the scientific expertise that

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is required.

But on the permanent panel, I want to recognize a new member, Dr. Gerald LeBlanc of North Carolina State University. Gerry has worked with us as an ad hoc member on the Panel, and we are very pleased to have him and his expertise join us.

So thank you, Gerry.

And other members of the permanent panel will introduce themselves as we make general introductions.

Dr. Carey Pope from Oklahoma State will be joining us tomorrow morning, and Dr. Dan Schlenk is not here for this particular meeting, but along with the other individuals here who introduce themselves, this is the permanent panel for the FIFRA SAP.

As Myrta said, I am Steve Heeringa of the University of Michigan. I am currently Chair of the FIFRA Science Advisory Panel. My responsibility during these proceedings is to help with the running of the meeting and the

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flow of the meeting.

I am a statistician with expertise in population-based studies, some of which may be relevant in this discussion. But, otherwise, I am here to help to facilitate the process.

I will turn to the other experts to introduce themselves.

Ken?

DR. PORTIER: Good morning.

I am Ken Portier, Director of Statistics at the American Cancer Society in Atlanta. I am a biostatistician and a member of the permanent panel.

DR. CHAMBERS: I am Jan Chambers. I'm a Professor in the College of Veterinary Medicine at Mississippi State University. My expertise is in pesticide toxicology, and I am also a member of the permanent panel.

DR. BUCHER: I am John Bucher. I am the Associate Director of the National Toxicology Program at NIEHS. I am a

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toxicologist by training and a member of the permanent panel.

DR. BAILAR: John Bailar. I'm Professor Emeritus, University of Chicago, and for some years have been a scholar-in-residence at the National Academies here. I am a physician, statistician, and probably most relevant here, an epidemiologist.

DR. MEEK: Good morning.

I am Bette Meek. I am the Associate Director of Chemical Assessment at the McLaughlin Centre out of the University of Ottawa. I am on interchange from Health Canada, where I have managed a number of chemical risk assessment programs. My background is in risk assessment and toxicology.

DR. GREENWOOD: I am Richard Greenwood from the University of Portsmouth in the UK. I am a Professor of Environmental Science there. I have got experience and expertise in mode of action of pesticides and

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in environmental monitoring.

DR. HARRIS: Good morning.

I am Shelley Harris from the University of Toronto, and I am also a scientist at Cancer Care Ontario. I am an epidemiologist with a background in exposure assessment and toxicology.

DR. BOVE: My name is Frank Bove. I am a Senior Epidemiologist at the Agency for Toxic Substances and Disease Registry, which is part of the Centers for Disease Control. My research interests are in drinking water contamination and birth defects and cancers. This is the third SAP meeting on atrazine I have been on.

DR. LU: Good morning.

This is Alex Lu. I am faculty on the Harvard School of Public Health. I do pesticide exposure and research.

DR. GOLD: I am Ellen Gold. I am Professor and Chair of the Department of Public Health Sciences and Chief of

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Epidemiology at UC Davis.

DR. HAYTON: I am William Hayton. I am Professor of Pharmacy at the Ohio State University. My area of expertise is pharmacokinetics, which deals with pesticides absorption, distribution, elimination, and that would bear on issues of exposure.

DR. REED: My name is Nu-may Ruby Reed. I am a toxicologist with the California Environmental Protection Agency. I do pesticide risk assessment and address risk assessment issues for our group of toxicologists.

DR. REIF: I am John Reif. I am a Professor in the Department of Environmental and Radiological Health Sciences at Colorado State University. I am an environmental Epidemiologist.

DR. LeBLANC: And I'm Gerry LeBlanc, Professor and Department Head at the Department of Environmental and Molecular Toxicology, North Carolina State University,

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and am a new permanent SAP member.

CHAIR HEERINGA: Well, thank you to everyone who has joined us as a member of this Science Advisory Panel. It is a busy time of year, particularly in academics, and I assume elsewhere as well. We appreciate you taking time out of your schedules to participate in the process.

As I am sure we will learn this morning, this is the launch of a very important year, I think. We were given an introduction to this late last fall in terms of the goals and expectations for the coming year for the Science Advisory Panel.

At this point in time, I would like, in fact, to turn to Dr. Steven Bradbury, who is the Acting Director of the Office of Pesticide Programs, for some introductory remarks.

Steve?

DR. BRADBURY: Thank you, Dr. Heeringa.

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I would also like to welcome the Science Advisory Panel to this week's meeting. I would mention that at all these meetings that we have we greatly appreciate all the hard effort that members of the Panel put in prior to a meeting in reviewing all the materials that we provide, and, of course, the time and effort while you are here, and then preparing the reports after the meeting is done.

The work of the Science Advisory Panel is just fundamental to the business of our program and ensuring that we have the best quality science and scientific input from our peers, as we move forward in sometimes very complex activities that we are undertaking.

Having the input from the scientific community to this Panel is instrumental in ensuring the scientific integrity of the work we do and, through a public process like this, ensuring that there is transparency in the activities that we

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undertake, and how we are evaluating different scientific approaches, be they generic methods or information about a specific chemical and a specific decision that we need to make.

You may be well aware that the President and Administrator Jackson feel that, and they have made it very clear that, scientific integrity and transparency are a fundamental aspect of the business of the Environmental Protection Agency, and the role of the SAP is very fundamental to meeting the objectives of the leadership in our organization. So, in advance, thanks for all the effort you will be putting in over the next week and beyond, and the efforts you have already put in.

I would also like to thank the team members that will be giving the presentations in a bit. Dr. Tina Levine will be introducing our colleagues.

In addition to scientists in our Health Effects Division, who have been

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involved in preparing for this Science Advisory Panel, there's also been contributions from our colleagues in the Office of Research and Development, as well as colleagues in the National Cancer Institute and the National Institute of Environmental Health Sciences.

They will be working with us over the coming years for aspects of what we will be starting today as well. So I just wanted to not only thank the individuals in our program, but also make it very clear that the activities that we are undertaking, not necessarily unique for this set of questions, there's usually activities that we undertake in collaboration and partnership with other scientists in the agency and outside the agency as well.

Let me spend just a few minutes providing some context for today's or this week's Science Advisory Panel meeting.

There's really two themes to what

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we are undertaking this week. One of them is very broad in terms of large areas of effort that we are undertaking, and then one aspect of this week's review will be focusing on a specific issue, but that issue actually helps transcend across other activities that we are undertaking.

So some context in terms of the regulatory program: one aspect of the pesticide program is to ensure that on a regular basis, as set out by statute, that we reevaluate the scientific information around pesticides that are currently registered in the United States, as well as taking a look at current policy issues. So we want to ensure that on a regular basis every pesticide is being reevaluated in terms of the science and ultimately the decisions in terms of protecting human health and the environment.

We just finished in 2006 and 2008 one cycle of that reevaluation process, which we called the Re-registration Program. Over

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the last year or so, we have initiated the second 15-year cycle of reevaluating all the pesticides that are currently registered in the U.S. That program is called the Registration Review Program.

A very important aspect of this Registration Review Program is embracing agency guidelines as well as NRC recommendations in terms of problem formulation, if we are using words that ecological risk assessors use, or scoping and analysis planning, if we are using words that human health risk assessors tend to use. That is a very important aspect as we go into this registration review cycle.

Related to that, one of our goals was to ensure that we are taking advantage and analyzing all the best available information as we go forward, but not just laboratory toxicology studies, but also ensuring that we are taking full advantage of analyses of incidence data that may be available for a

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given compound, as well as starting to increasingly figure out how to incorporate epidemiology data, not only into problem formulation at the beginning of a risk assessment process, but also how we can be using epidemiology as we move through risk assessment and risk characterization.

So that we are pulling together all of the lines of evidence and the weight-of-evidence analysis to understand the mechanisms of chemicals, understand dose response relationships, understand adverse outcomes, and how to integrate information not only for the chemical, but across chemicals or other life history attributes.

So this SAP reflects getting started in that process of ensuring and getting feedback on how to go about using incidence data, how to go about using epidemiology data, how to evaluate the characteristics of those kinds of studies, and to give us some feedback into how to integrate

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that information as we begin a risk assessment process and as we move through risk assessment, ultimately, to the risk characterization stage.

As we go forward and get input from all of you, it gets back to the point of scientific integrity and transparency. As we move forward and start to refine, adapt, evolve our processes with incidence data and epidemiology data, we want to get feedback from you and ensure that, as we go forward, through your reports and our response to those reports, the public can see how we are going to start to incorporate this new kind of information.

Related to the epidemiology aspect of today's SAP and SAPs down the road, one of the areas of collaboration over the last several years has been with the NCI and NIEHS in terms of the Agricultural Health Study, which is a very sort of state-of-the-art, state-of-the-science, prospective epidemiology

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study that EPA has been working in collaboration with NIH.

Those studies are starting to come online, many of them published, and many of the chemicals that are associated in that study are the same chemicals that we will be starting to come through registration review in the coming years.

So one aspect of this SAP and future SAPs is to get feedback from all of you in terms of how to go about integrating that very platinum-level study, if you want to call it that, that will start to be available to us to start to use as we go forward.

Now there is a dual purpose to this SAP, as well as sort of these broad issues that we will be getting feedback in terms of a framework we are starting to develop as well as some case studies, but a dual purpose in this SAP is also to get some feedback on some of our initial steps in reevaluating the scientific information with

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regard to atrazine, and in particular, atrazine in terms of human health protection.

As we indicated back in November, when we met with you, and with the documents that are going up in our dockets and on our web pages, over the course of 2010, we will have a series of three Scientific Advisory Panels looking at various issues about the underlying information associated with atrazine. This SAP is a piece of that or part of that process.

And in particular, and consistent with the broad perspective of this SAP, it is getting feedback on how to take a look at some classes of epidemiology studies that are associated with atrazine that were published since our last human health risk assessment. In particular, getting feedback on how to interpret some retrospective epidemiology studies that have been published in the last several years, as well as some epidemiology studies that have an ecologic design

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associated with them.

As we get some feedback in terms of how to evaluate studies of those types, how to take a look at those studies and begin thinking about how those studies can be used in problem formulation and perhaps risk characterization, this SAP, not only dealing with the broad context, will also deal with some initial input as we start this science review process for atrazine.

As we move into the spring, in April we will have another SAP in atrazine. That one will focus specifically on laboratory toxicology information, in particular, looking at non-cancer effects associated with atrazine.

Then, in September, we will be meeting again with the Science Advisory Panel and pulling it all together, both laboratory toxicology studies as well as epidemiology studies, both cancer and non-cancer, and then integrating that information. The scientists

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will be sharing with you how they have gone about integrating that information.

So, clearly, this meeting is a very important stepping stone as we move through the spring and ultimately into the fall, because we hope that this SAP will provide us input on the framework that you will be hearing about and using some case studies to illustrate that framework, which, again, will not only help us more broadly across our reevaluation program as a whole, but also some specific feedback, as we get started with the atrazine reassessment.

So, with that, I will close. I just want to thank you again for the input that you will be providing us in the coming days.

And if it is okay with the Chair, I think I will turn it over to Dr. Tina Levine, who can provide a little more context.

CHAIR HEERINGA: Yes, Dr. Levine is Director of the Health Effects Division.

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Good morning, Tina.

DR. LEVINE: Thank you very much.

We are all heaving a sigh of relief because Anna is here now. So I will try to be briefer than maybe I would have to be if she hadn't been sitting there.

But I would also like to add my welcome and reiterate Steve's appreciation to the SAP for your time and your efforts. As you know, your feedback is an important component of improving the scientific foundation for our regulatory decisions.

I would like to introduce the OPP team. Some of them are at the table and will be speaking today, but all of whom were very involved in preparing the information that is going to be presented today.

To my right, Anna Lowit, Aaron Niman, Shalu Shelat, also Jeff Dawson, Jonathan Becker, Matthew Lloyd, Sarah Winfield, Mary Manibusan, and Carol Christensen. I think they are all here in the

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room.

I would also like to thank the Ag Health Study Executive Committee. We are proud to be working together on an understanding of the differences between the Ag Health Study and EPA's exposure assessment approaches as we move toward integrating Ag Health Study results into our risk assessment.

We would like to acknowledge the important contribution of Dr. Kent Thomas of EPA's National Exposure Research Laboratory, who is EPA's representative on the Ag Health Ex Committee, and he was unable to attend the meeting this week, unfortunately.

As Steve discussed, we have an immediate need for a transparent, scientifically-supportable tool for integrating epidemiology and human incident data into our human health risk assessment.

Many of you were present in September of 2008 when we presented a draft science issue paper on the organophosphate

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pesticide chlorpyrifos to the Panel. One of the recommendations from the 2008 SAP was to perform a weight-of-evidence analysis integrating in vivo and in vitro animal experimental studies with findings from several epidemiological studies. We expect the weight-of-evidence analysis for chlorpyrifos to be completed this year, as we work toward a new risk assessment late in the summer.

Steve also discussed our ongoing reevaluation of the human health effects of atrazine, including evaluating epidemiological data. Atrazine and chlorpyrifos are only two of the chemicals where epidemiology and/or other human data may be important to fully understanding risk. As Steve mentioned, we are undergoing registration review, which is a 15-year review cycle. We are aware that there are a number of big epidemiology studies that are likely to have bearing on our evaluation.

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Later today, you will hear about the Ag Health Study, a collaborative effort between NCI, NIEHS, and EPA. The Ag Health Study is a large, prospective cohort of close to 90,000 people in North Carolina and Iowa. This study has already generated over 100 publications.

There are other prospective epidemiological studies which involve research on pesticide chemicals that may be of interest in our risk assessment. For example, the NIH/EPA Children's Centers have published a number of studies on the association between pesticide exposure and birth and neurodevelopmental outcome. We believe some of these studies can provide important information on the effects of pesticides on children.

Not all epidemiologic studies are as robust as those from the Ag Health Study or the Children's Centers. It is not unusual for ecologic or retrospective studies to be

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published in the open literature. We often struggle with the most appropriate approach to integrating these less robust studies into risk assessments, and are interested in your feedback on approaches for doing that.

Ultimately, as we develop risk assessments under registration review, our goal is to use more systematic, transparent, and scientifically-robust approaches to evaluating and using the human incident data that we have used as well as the epidemiological data in the literature.

So, as I conclude my remarks, I would like to restate my appreciation to the Panel for your time and effort this week. I know you have a very busy year ahead of you, and this is just the beginning.

We are genuinely interested in your feedback and input on the most scientifically-supportable approaches to integrating epidemiology and human incident data in our risk assessment. I am looking

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forward to listening to the discussions over the next few days.

Now I would like to introduce Dr. Anna Lowit, a Senior Scientist within HED. Anna received her Master's and Ph.D. at the University of Tennessee in environmental toxicology. She is the lead author of the draft framework and is also the team leader on the atrazine human health reevaluation that we are doing this year.

She is going to provide an overview of the draft framework and provide some context for the case studies we are going to be presenting to you today.

Thank you.

CHAIR HEERINGA: Thank you, Dr. Levine.

Dr. Lowit, it is good to see you.

DR. LOWIT: Just enough time to catch my breath. People who know me well know that I have bad time karma.

(Laughter.)

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I got up at 4:45 this morning. On the GW, if you know the area, the George Washington Parkway, I went a mile over an hour and a half period, including turning my car off for about 45 minutes, as ambulance after ambulance kept passing. I was going, oh, no. But, hopefully, whoever that is will be safe with all those people coming to their rescue.

And thank goodness for the BlackBerry. I actually found the log-in and called into the number and was cheering Steve on as I sat at that light saying, "Talk, Steve, keep talking, keep talking, keep talking," in hopes of being able to sit down and collect my thoughts for a second.

(Laughter.)

So I apologize to all of you. Some things sometimes just happen.

So I am just going to take a few minutes to get the technical presentation started and really focus on the -- we have a series of presentations today. I will give an

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overview of the framework, focusing primarily on the weight-of-the-evidence analysis.

After what I would expect to be some questions and answers, we will pass to Lieutenant Aaron Niman, who sits to my right, who will discuss the retrospective and ecologic atrazine studies.

Following that, we will have a pair of complementary presentations, one from Dr. Michael Alavania and Shalu Shelat, who works in our program.

Then, finally, we will round out with Sarah Winfield, who is representative of our human incident team.

We have a number of presentations to go through this morning. In order to not be duplicative of the presentations you will hear from Aaron and Shalu and Sarah, I am going to focus almost entirely on the weight-of-the-evidence analysis from the draft framework.

We decided it made a lot more

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sense to talk about the context of an epidemiology study or the context of human incident with the case studies, as they made a nicer picture, instead of going back and forth.

So I am going to talk almost primarily on the weight-of-the-evidence analysis, and hopefully, maybe tee-up some of the major issues for the three of them, plus Dr. Alavanja.

But before I get started on the weight of the evidence, I thought I would just take a minute and let you know, since we are in the middle of heavy preparations for the April meeting, for the atrazine April meeting, I thought I would just take one minute and let you know where those things are.

As you may realize, about two months ago, we provided the Panel with basically a bibliography memo of a list of references. We hope to get a similar bibliography memo for the April meeting out.

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The goal was the end of this week. Maybe the beginning of next week is probably a little bit more realistic, but in the next week or so that will come probably through Joe Daly, I assume. So that will be about two months before the April meeting, which is basically what we have done for this meeting.

Our materials are due to this Panel the beginning of March, and it looks like we are fairly hopeful that we will make the beginning of March. It has been a pretty daunting analysis, several hundred literature studies to go through.

We did make a choice to stop our literature review as of this weekend. You may have noticed from the memo from a couple of months ago that we, basically, said things, as of January 30th, we would hold until September, and we are sticking to that.

It is largely logistics. We now have a very short period of time to finish our paper and take all those studies and put them

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in a nice analysis. Things that show up three days before we are due to you don't do anyone justice, doesn't do us justice or you, or even the new data. So that choice was made, and we are sticking to it.

We think we have, actually, a very nice, solid, comprehensive evaluation of what is available as of this weekend, and things did show up over the weekend, by the way.

Okay. So, with that, I will just get going.

The concepts in the draft framework are largely, if not almost entirely, already peer-reviewed and what we believe are fairly robust. Certainly, the application of the modified Bradford Hill criteria, as used in what we call the mode-of-action framework, has been peer-reviewed within the U.S. several times and throughout the world.

The pesticide program actually has fairly extensive experience in applying that. I will give you an example in a little bit.

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But what we are trying to do, as we move forward, is to embellish, not embellish -- it's the wrong word -- to improve the existing frameworks by bringing in concepts from two of the recent NRC reports about the 2007 "Toxicity Testing in the 21st Century", and the newer one, "Science and Decisions: Advancing Risk Assessment". I am not going to talk about those in detail, just barely some of the concepts that I think are important to the dose discussion.

One of the things that we really like about the mode-of-action framework is it is extremely flexible and allows incorporation of data from many different sources. What we really like about it is it is a very transparent tool for organizing, reviewing, and interpreting information. It is not under any circumstances a checklist or a strict recipe book for how to do a weight-of-the-evidence or mode-of-action analysis, for that matter. It is simply a way to organize and

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review information that is transparent, that puts things in a very nice order.

So, historically, we have used the NAS 4-step paradigm, where you have hazard assessment, leading to dose response, and exposure assessment to risk characterization. And largely, we still follow this. But the 2007 21st Century Tox Testing Report sends that 4-step process in a slightly somewhat important, different direction. I am not going to spend a whole lot of time on this because some of you probably know this better than I do.

But what we are going to talk about today is really focused on this center area, where we talk about, where we think about weight of the evidence across biological perturbation, think about pathways of toxicity, thinking about what to do with in vitro studies, and finally, dose response.

Another important concept, as we move forward in our program to improving our

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risk assessment process, is really bringing in the idea of problem formulation. Our colleagues in the Environmental Fate and Effects Division have been doing more formal problem formulations than we have in the Health Effects Division for a number of years now. But we are steadily improving our use of these problem formulations.

Like, for example, in our risk assessments being done for registration review, we are actually doing an initial step in all of those analyses of what we call scoping document, which is a document done very early in the process and shared to describe the existing database, the old risk assessment, how we see things changing with new policies.

We think that, with respect to including epidemiology and improving our use of human incidence, this sort of thinking is a very logical way to go. In fact, you may have noticed in our case study on the

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Agricultural Health Study we are actually proposing for the analysis, the side-by-side analysis, on the exposure metrics to be, basically, problem-formulation analysis.

The step one piece of that, you will hear Shelley talk about later, is almost exactly suited for this sort of analysis, that you take two complex sorts of information and you do a side-by-side to look to see where your strengths and your weaknesses are, where your similarities and your differences are. We plan to actually do that analysis as a problem formulation.

So, as I said a minute ago, we are proposing to use modified Bradford Hill criteria like that used in what the agency calls the mode-of-action framework as a major tool for organizing, reviewing, and interpreting data.

So this is a graph straight out of the framework. It is largely adapted from another plot from the NRC report in 2007. I

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took one of those figures and made a new one, and added a few extra circles to make it a little bit more robust for our needs for this purpose. But it is a really nice context to think about source to effects.

It is a very nice way to organize information, that you start with the chemical and everything you know about it, as it moves into the body. So you have pharmacokinetics, absorption distribution, everything you know about those sorts of parameters. You get to the molecular target and the pathway of toxicity. Then each level is a higher level of organization.

The agency is very largely still working on how to bring this whole process into our risk assessments, but we are working on it. We will get there. But today we are really just going to focus on these right two circles, the human incidence and then epidemiology. But, clearly, they are important parts of the whole process.

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We believe the mode-of-action framework is really the best starting point for doing this kind of weight-of-the-evidence analysis, largely because it is a tested tool and it is very effective. It is a tested tool that we have used very -- it is a wonderful way to take information like that in the slide before and organize it in a very transparent, logical way.

It is a great way to think about species and dose response extrapolation, whether it is animal up to human or high to low. It is a way to organize information on in vitro and in vivo, and also from human data. By organizing it according to the framework, it becomes a very transparent tool, and transparency is a critical component of our work.

Some of you know this just as well, if not better, than I do. But, briefly, what we define as the modified Bradford Hill criteria and the mode-of-action framework is

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you start with a postulated mode of action. We have a postulated set of what we call key events, leading from that initial absorption all the way through to the ultimate health outcome.

Two of the most important components here are the dose response concordance and the temporal concordance, so that you can align the different key events by dose response and time, to make sure that A leads to B leads to C, and that those things fit together and they make a nice order.

Clearly, thinking about biological plausibility and coherence are critical pieces of this. You want to evaluate the degree to which the entire database makes sense together, and in the context of epidemiology, to what degree do the results of epidemiology study fit with what is known about the chemical array.

One of the important parts of the mode-of-action framework is an explicit

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description of uncertainties. So areas where you are strong, where the database is weak, what can be done to fill those in, or if that is even something that is necessary.

This is a graph I took from a recent paper by Boobis, et al. I think it is a very nice picture way of looking at the generics of the key events and mode-of-action analysis. This largely follows, although the words are different, it very much largely follows the source-to-outcome pathway from the 2007 NRC, where you begin with here you talk about external dose.

You think about absorption and distribution processes that bring the chemical to the target tissue, and then you think about the actual interaction of that target tissue with the chemical, ultimately, leading to some sort of perturbation, whether that is an adverse perturbation or just a perturbation, ultimately leading to some sort of pathological change, and then the tox endpoint

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of interest.

So, for those of you who haven't seen a mode-of-action analysis and the way that we put them together, I thought I would just take a minute and show you picturally where you can use information, human information, because I think some people think, when the agency talks about this sort of mode-of-action analysis, the assumption that it is all animals, that it is all animal data, that is not necessarily the way it is.

So, if we just start with the basics, with in vitro studies, you can think about using in vitro studies for a number of steps here. In vitro steps are critical in developing parameters, let's say for a pharmacokinetic model or kinetic parameters of a metabolism.

You can use in vitro studies to think about pharmacodynamic effects of an interaction of a chemical with its target tissue in vitro. And you can also think about

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biological perturbations, like the example I will show in a few minutes. We have some cytotoxicity data in the blood or epithelial.

There are cases occasionally where we have delivered dose studies in humans. Just as an aside, before we use any such study, it is reviewed by the Human Studies Review Board for both ethics and science.

But, just generically, assuming that whatever the study is, there is a positive review from that Board, those kinds of studies can provide information on a variety of things. Some of them are very pharmacokinetic-focused, the metabolism studies where you can look at blood or urine metabolites.

You can also see we have a number of those kinds of studies that have blood metrics, let's say cholinesterase, for example, which would be, whether that is a perturbation or something else, it is probably a personal view. And obviously a tox effect,

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a concern, you can see clinical signs in those studies sometimes.

We see data from biomonitoring studies, whether they are large-scale or small-scale. Let's say a worker biomonitoring study. You can have large-scale studies, like NHANES, for example.

So I have got the arrow pointing primarily toward absorption distribution, thinking largely about urine and blood metrics. There is a dotted line there towards biological perturbation because cholinesterase in metrics, for example, can be considered biomarkers. So that would be a perturbation.

And lastly, what we are going to talk about today would be the final outcome of concern. We think largely epidemiology study in human incidents provides information toward the end of this pathway, although certainly there are some here and there that provide some biomonitoring information or they can be really a blend of types of information. But,

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really, in a generic way, epidemiology and human incidents help us understand the final outcome in humans.

So, as you saw in the documents, we have actually not yet completed a weight of the evidence using epidemiology data, but using the framework that you have, we have over the years used epidemiology data in our risk assessments. And certainly some of our sister offices have done this a lot more than we have.

But we haven't followed the framework per se yet. Obviously, with the atrazine work going on, we will be doing that. There are a couple more actions that you heard from Tina that we are working on that will also do that.

So what I thought would be helpful, particularly for those of you who are not necessarily familiar with how we apply the mode-of-action framework, to show you a hypothetical example. And it is hypothetical

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only in that the epidemiology data that I don't really show is not real. Everything else about the example is real.

There is a herbicide that we did the mode-of-action analysis for several years ago. This is work that Vicki DeMarco and I did together.

A couple of you will very easily recognize the example because that we use in a lot of training programs, and it is also one that a couple of you served on the Review Panel for. So you may recognize it.

So the animal component of this has actually been reviewed by the SAB in a joint review that was done with ourselves, the Office of Water, and ORD NCF, back around 2005.

This color is not looking good.

Okay, so the chemical here, it is a herbicide, and it is a herbicide used primarily on cotton and turf. The way this chemical works is that the parent chemical is

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a pentavalent compound that has to be activated to the trivalent active metabolite. It is that active metabolite that causes toxicity of the bladder epithelial. And if that is sustained, if that toxicity is sustained over a long period of time, you see regenerative proliferation, and eventually, that proliferation leads to hyperplasia. That, in time, leads to urinary bladders.

In this case, this is actually a wonderful dataset. We have those response data for each of these five key events. There is dose response data for the activation of the pentavalent to the trivalent and how much of the trivalent is urinated in the rats.

We have very nice in vivo and in vitro data of the urothelial, and we have proliferation data in rats, hyperplasia, and it is human data. The real dataset, the rest of it is all in the rats.

So this is a really nice way to organize this kind of information. What you

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have at the top here are the major key events discussed, the amount of active metabolite in the urine, a metric of toxicity, a metric of the proliferation, the hyperplasia, and then, ultimately, the carcinomas.

This is a very qualitative table, simply because there's only so much you can put on one slide. But, for each of these, we actually have quantitative dose response, and in some cases we have two or three datasets in each case. Like, for example, there are two bioassays that have the cancers. We have proliferation data. I believe it is in two datasets.

This dataset is actually a mix of things under the literature and things that were submitted as part of the final registration process.

So, if you just skim it just with your eyes, the pluses, as you go down in dose responses, the pluses, meaning a positive response, become more obvious. This is

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clearly a non-linear event. This cancer is clearly a non-linear event.

Okay. So, how do you interpret that? What can you do with it? What sort of other information can you even take from it?

This is a concordance table, as you would think about in a human relevance concordance analysis. So it is separated by qualitative and quantitative concordance. And we have got it split here between the qualitative in the animals and the humans, and then information about how strong that information is.

So we will just sort of talk through it. So we have the presence of the active metabolite in the urine that is really the first key event. Without that activation metabolism, you are not going to get the cancers. So we know we have it in animals. We have a great dose response.

We do know there is an analog to this herbicide that has two fewer methyl

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groups than this herbicide does. We know from the analog that you can get production of the trivalent metabolite in the analog. So the assumption is, if you can get it in the analog, you can also get it in the dimethyl parent compound.

There is also, but it wasn't shown here, a direct dose in human study. We have never put a lot of weight on that study, simply because it was done a couple of decades ago, before the analytical techniques were improved and you couldn't pick up the trivalent metabolite in the urine. So it doesn't provide a lot of information on what is pentavalent and what is trivalent.

So what we think here is that we have considerable evidence in animals over the active metabolite, but it is limited in humans. But what we do have quantitatively is there is a PBPK model, a physiologically-based pharmacokinetic model, developed by our colleagues at NORD down in North Carolina, who

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developed the PBPK model for both the analog compound and this dimethyl parent.

Through in vitro work that they have done to scale-up the rat model to the human, they believe that qualitatively that you could get the trivalent metabolite, although there's some significant absorption issues there. But, quantitatively, we really can't get a good handle on it.

Okay. So that is the really important step. If you don't get the trivalent, you don't get anything else.

So, as we move down, the next piece would be you have to sustain the urothelial toxicity that would lead you to the regenerative proliferation. So, clearly, in the animals we have a strong dataset. I believe there is more than one study; I didn't look this morning.

So, in humans, it is really unknown if we would get enough metabolite to get the cytotoxicity. And if you don't get

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the cytotoxicity, you are not going to get the proliferation.

But we just say, basically, that since it happens in animals, we think it is plausible in humans, but we don't have any information.

So, in the real database, we think about the tumors. Do we have tumors in animals? Yes, we do. Do we have tumors in humans? We don't have the epi data to say that, but we think it is possible. If you had enough of the trivalent metabolite and sustained the urothelial damage for long enough, it is possible. So we think that this mode of action is plausible in humans.

There's another piece to this that shows sort of some ways that you can use the newer technologies in in vitro data. Part of what came out of the SAB review of this mode-of-action analysis back in 2005 was that the Board suggested to the agency that we believe that we could actually assemble a case, the

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toxicodynamic equivalency for this compound. So that what we mean by that is that, if you were able to achieve the same levels of the trivalent metabolite at the site of action in the human as you could with the rat, that the latter epithelial would actually respond similarly.

The reason for that is three different studies, one of them in an in vitro sort of toxicity study that showed that the in vitro 50 percent concentration for cytotoxicity was identical in human tissues as it was in rat tissues in a bladder cell line.

There are also two microarray studies that were done by EPA's ORD lab that complement one another. Basically, those two studies together show that the genes up-regulated in the human tissue were similar to those up-regulated in the rat tissue, and that, interestingly, actually, the rat cell line was more sensitive compared to the human cell line.

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There are some issues with absorption of this compound. There may be reasons that the rat, actually, absorbs more than do the humans.

So, based on the combination of these three things, and what we were able to learn from the PBPK modeling that complements this, we determined that we thought that rats and humans would respond pharmacodynamically similar at the target site. So, as you think about weaving that kind of information in the totality of the weight of the evidence, and how you would implement that in a risk assessment.

So what if we knew more about humans, about Herbicide X, just hypothetically? So what is different here is I have added two new squares. One would be a biomonitoring square, and the other one would be an epidemiology square.

As I mentioned a few minutes ago, there is human-delivered dosing data for this

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compound, but it is very dated because of the analytical methods, and it is not very helpful.

There is some large-scale biomonitoring data for the analog chemical, for which we think you could have the trivalent, but it doesn't help us with the absorption issues for the parent compound. So that is where biomonitoring data for that parent active ingredient would be helpful. Because if you could predict how much active metabolite, you would get a better prediction of the quantitative metric for the tumors.

Also, let's say, hypothetically, there was some epidemiology data for our parent compound, our herbicide, that could provide either some qualitative or quantitative characterization of the plausibility of the rat bladder tumors. We do know that the analog chemical does cause bladder tumors in humans. There's a pretty extensive database for that.

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So, just qualitatively, that connection, we still think that those tumors are plausible in humans, but there is a quantitative component that we can't get to because of the problem of the dimethyl and the absorption. So the epidemiology data would provide a key piece of characterization there.

So how would it fit into my 2x2 table of all of the key events? Well, the key events would largely stay the same because those are strong datasets, and they stay the same. The question would be, well, how would the human epidemiology data fit into that? Would it provide information to better quantify the risk of the compound? Would it send us in a new direction?

Hypothetically, there are some issues with uptake of the dimethyl form of the compound that may or may not change its pharmacokinetic properties leading to different target tissue. Those are just questions that we wouldn't know without those

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data. In the absence of that, we assume that the bladder tumors are positive.

So there is the concordance table again. The only thing that is different here is the bottom. I added, hypothetically, if we had some epidemiology data, you could better fill in these boxes, the documents, and do a better job of describing the quantitative component of that concordance.

So I think I've got just one or two more slides to go.

So we really think the mode-of-action framework is really a strong place for us to be. It is not, under any circumstance, I will restate from earlier, a checklist, a set of criteria, a recipe to follow. Largely, it is a chemical-by-chemical analysis.

The framework is a tool. It is a tool for organizing information, for doing that in an explicit way, to discuss uncertainties and strengths, places where you can improve the database, places where you

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talk about where animals and humans are different. It is also a great place to bring in new information that we have never used before, whether it is epidemiology or the new high through-put stuff.

But we would be remiss without bringing up one of Hill's quotes that basically says that, even if you don't have a big, fancy, mode-of-action analysis, if there is enough to convince people that there is a problem, that you don't postpone action and that you would act on that.

So, if that is one of the questions you are thinking, what happens if you don't have a lot of animal mode-of-action data, if there is a convincing case, we will act on that. There is no question.

So this, I believe, is my last slide. It is just bringing you back to the organization of where we are going to be today, the organization of the framework. I think that is my last one. Yes.

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CHAIR HEERINGA: Thank you very much, Dr. Lowit.

At this point, are there any questions of clarification of Dr. Lowit from Panel members?

(No response.)

I think we are ready, then, to move on to the presentation.

DR. LEVINE: Let me introduce our next speaker from HED, Lieutenant Aaron Niman, who received his Master's degree in public health from the Rollins School of Public Health at Emory University and has a bachelor's from the University of Michigan.

Aaron is an industrial hygienist whose expertise is in evaluating biomonitoring surveillance data. And as a member of the atrazine team, he has reviewed some epidemiology studies on birth outcomes which he will discuss today.

CHAIR HEERINGA: Members, if you want to follow along, the slides are in the

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black notebook, obviously.

LTJG NIMAN: As Dr. Levine mentioned, I am going to be presenting Case Study A, which was an evaluation of several recent epidemiologic studies on atrazine and its association with birth outcomes.

Before I go into the specific case study, I am going to provide some additional background or context that relates the case study more closely to the draft framework and discuss some of the study features that are talked about in the framework. Then I will go into more detail about the actual atrazine case study.

But just to emphasize upfront, the case study really had two dual objectives. First, to illustrate the range of factors that need to be evaluating when incorporating epidemiologic findings in risk assessment, and two is the more specific objective which relates to the 2010 evaluation of atrazine. So, obviously, the SAP's input will provide

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guidance more broadly and also more specifically for the atrazine reevaluation.

Just to start with the background, the draft framework provides some general guidelines for evaluating epi. It highlights a number of key study features which are listed right here.

Most broadly, when we are trying to understand an epi study finding in the context of a risk assessment or its research goals, and try to understand, given its strengths and weaknesses, is it really focused more on generating a hypothesis or does it really provide or demonstrate causality? So trying to distinguish between studies that may be more useful in the problem-formulation stages of risk assessment or causality and might have greater influence on a weight-of-evidence analysis.

And one important component of that is the study population; what are the key characteristics of that study population? And

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how do those factors relate to trying to generalize the results to other populations which might be a particular focus of a risk assessment, be it children or another specific population?

Exposure assessment is always a key aspect of any epidemiologic study, just given the challenges of trying to characterize environmental exposure. So it is just particularly important to figure out why the approach was used. Was it based on a questionnaire or an indirect approach, or was there some attempt to use personal monitoring or biomonitoring, which provide more direct estimates of exposure? And all these different tools have their own strengths and weaknesses, and they will influence both the validity of the study as well as its overall research goals and scope.

And related to that is the data source used to determine health outcome. So we are, obviously, interested in what data

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sources were used as well as their strengths and limitations, and accurately characterizing disease burden in the study population.

Then, finally, it is always important to consider how data was collected and how that could potentially bias the results or influence the findings. Then, it is always important to consider the statistical approach used, and what is the approach used and could it potentially influence the results?

Then, finally, with any epidemiologic study, it is always important to consider confounding. So what potential sources of confounding are there? And how did the investigators consider those and consider how they could influence their study results?

These are sort of the general features that we think are important to focus in on when we begin evaluating epidemiologic studies.

I will now go more specifically

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into the actual atrazine case study, which you guys all received. While there is a broader literature out there on atrazine, this case study focused on six particular studies, five of which were reviewed in the actual document. We thought it would be useful to use these five studies to illustrate the types of epidemiologic studies that are often published in the literature, including studies that use other retrospective or ecologic designs, usually because they focus on relatively rare health outcomes that are challenging to study. And they also have similar challenges in exposure assessment.

So we felt these five particular studies would illustrate a number of points, and these are the sort of things that we try to understand when we evaluate studies more generally.

Another reason we focused on these particular studies is they shared many design features. I already mentioned the

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retrospective or ecologic design, but they also focused specifically on adverse birth outcomes. They are all based on similar health outcome data, specifically birth registry data. They, also, all focused on environmental exposures rather than occupational exposures, so low-dose exposures that people would be exposed to from the general environment.

While they did have these similarities, there are a number of key differences. Sort of the purpose of the case study was to illustrate the important factors of the epidemiologic studies based on these differences. I am going to go into more detail in the rest of my presentation on each of these things, but I am going to focus on the level of study design and how that helps us understand whether a study is better for hypothesis generation, problem formulation, or provides more direct information to establish a causal relationship.

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I will then focus on exposure assessment because it is always a particular important source of uncertainty in environmental epidemiology. Then, finally, I will talk a little bit about confounding.

So, as I mentioned, the five studies that were reviewed used either ecologic or individual-level design. Many of you, I am sure, are aware of what these things mean. But, in an ecologic study, the unit of analysis is at the group level. For example, exposure would be aggregated to a geographic boundary, and the same with incidence or prevalence of disease.

Then, just conversely, with an individual-level study, it is, obviously, focused on the individual study participants. So, in this type of study, you would be able to have personal estimates of exposure for each study participant and identify each study participant's disease status.

So, as discussed in the case

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study, ecologic designs do have some nice benefits. They are typically less resource-intensive, and they typically leverage existing data.

The example of the studies that are discussed in the case study are the first two studies which used USGS surface water monitoring data. So that was data that is actively collected by USGS. So it is relatively easy to just access that data and this type of analysis without too much cost.

So it is particularly useful in hypothesis generation or problem formulation, as I had mentioned. But there is a limitation, typically, just called the ecologic fallacy, where you don't know which individuals were exposed to which levels of the chemical.

So, just using the first study as an example, which was based on the USGS surface water data, you don't know if the mothers who had children with birth defects

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were truly the ones that were elevated or exposed to elevated levels of atrazine or other chemicals. So, because of that disconnect and that challenge, to go from population-level estimates to individual-level, it is difficult to use the results to establish causality or provide evidence of causality.

In contrast, individual-level designs, because they are focused on characterizing exposures for each individual, they can be more resource-intensive, depending on the data source. And often, you can have greater confidence in the results because for the very reason that you are giving each individual in the study population an exposure level. So they can be useful in hypothesis generation, but they are, also, potentially of greater relevance in other weight-of-the-evidence analysis or risk assessment, depending on the other study features.

A lot of this I mentioned already,

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and it is discussed in the actual case study. But the USGS surface water is an example of ecologic measure, which provides just national-level estimates of surface water concentrations. So it is very difficult to extrapolate that down to an individual level.

In contrast, Study C in the case study used maternal address to assign individual levels of exposure based on proximity to soy and cornfields. So that is an example where they were able to use existing data to try to get at individual-level exposures.

And the other, Study D and Study E were both based on municipal drinking water data, but that data varied in overall quality. So one of these is probably, you could only consider it ecologic in nature, which was the Villanueva study conducted in France.

And the final study had high-resolution data. So I think you can make a stronger case that it represents individual-

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level exposures.

The next key feature I am going to talk about is exposure assessment. Anytime I think you are reviewing an environmental epidemiology study, it is an important source of uncertainty, just due to the nature of complex exposure pathways. This can be anything because of human behavior patterns, which are complex, the presence of multiple chemicals in the environment. So there is always the potential for exposure to mixtures as well as correlation between a number of different risk factors. There's all these factors to consider in exposure assessment that make it less straightforward and challenging.

A couple of key features to evaluate, when trying to understand exposure assessment, the first that I will talk about is specificity. This is the degree with which you can attribute an exposure measure to a specific chemical agent or a source. This is

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particularly important for risk assessment purposes because we often focus on either a specific chemical or a group of chemicals that share a common mechanism of action. So it is important that a measure be able to be attributable to a specific chemical.

And just considering the three general types of data that were used in the studies we reviewed in Case Study A, one was national surface water, one was proximity to corn and soyfields, and the third was municipal drinking water.

And you could probably make a case, national surface water and municipal drinking water, because they actually measured true levels of atrazine in those sources, you have good information on atrazine. In contrast, with proximity to corn and soybean fields, all you know, you don't know much information about the true level of atrazine exposure, and there's a number of other factors that could also be correlated with

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corn and soybean fields via other agrichemicals, such as nitrates or fertilizers or other potential risk factors. So, in that case, when it is a surrogate of exposure, it is real difficult to tease out what would be attributable to atrazine or another chemical or other risk factors.

The next factor related to that is spatial resolution. This also relates to my previous points about ecologic versus individual-level studies. Often, environmental epidemiology, it is based on some source of environmental data. These are all examples right here.

It is particularly challenging to take any sort of national estimate of exposure and try to use that at a higher spatial level, such as via a state or even a county or individual-level exposure. It is challenging to go from that national level to an individual level.

In contrast, when you have

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something like municipal drinking water, you have very good confidence that the person is going to be given at least their home drinking water source from a specific system. So you can have greater confidence in the resolution to estimate individual-level of exposure.

And the other thing, I guess, related to spatial resolution is being able to attribute different sources, sources of exposure. With proximity to corn and soybean fields, while the focus is on one specific source, when there is another potential source, specifically drinking water, it doesn't capture that. So it is important to consider different sources as well.

The last feature I will talk about for exposure assessment is temporal resolution. There's two important things to consider. The first, which isn't specifically talking about it in the case study, but the window of susceptibility. I dare you to have a measure of exposure that is relevant to the

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health outcome that is included in this study. So it is important for the measure of exposure to be biologically relevant.

Again, using the studies as an example, the Indiana study that focused on municipal drinking water, it was able to focus on specific trimesters of pregnancy in specific periods of time. So that gets a little better focus on particular windows of susceptibility, whereas a lot of the other studies maybe had a single measurement in time, usually time of conception.

And another separate issue, but also related to temporal resolution, is longitudinal variability. The same thing, where a lot of these studies use a single measure over time. So how well does that single measurement represent longer periods of exposure? So just things to consider when trying to understand exposure assessment.

Then one other thing is variation in exposure. In order to establish a

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relationship in an epidemiologic study, there has to be biologically-meaningful differences in exposure. So it is important, when using categorical variables to characterize exposure, it is important to consider whether there are true biological meaningful differences in their exposure levels. So is the high group truly exposed to higher levels of atrazine?

Similarly, when it is a direct quantitative measure, such as the examples listed here, the Villanueva and the Ochoa-Acuna study, is there sufficient variability in a population between the different categories?

One thing that was highlighted in the case study, the Villanueva study, there is very small differences between the different exposure groups, which would make it difficult to see associations, if they exist. It would reduce statistical power. In contrast, the other studies had better variability and

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larger differences between the different exposure categories.

This just basically summarizes a lot of the things I just mentioned. So I won't go into this table in much detail.

Then, finally, with any epidemiology study, it is always important to consider confounding because these are factors that can change the magnitude of direction of the association that is observed in a study. And I am sure you all know the definition of confounder, but it is considered something that is associated with both the disease and exposure.

In the reviewed atrazine studies, most of the studies did a reasonable job controlling for common confounders. Some of the things that were included in the studies were maternal risk factors, such as alcohol or tobacco use, demographic factors such as age of mother, sex of infant, education status, as well as prenatal care. So they considered a

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number of common confounders, which was, I think, a good aspect of the studies.

There is, however, always potential for confounding from less common sources or demographic sources that aren't captured as easily. One of the examples that is raised in the case study is this issue of seasonality.

From the studies based on the USGS data, which showed longitudinal trends and birth defect rates over time, it showed a highly seasonable pattern. So this could certainly be attributable to atrazine, but it could also be attributable to other covariates that fall in the same seasonal patterns. So some of those things can be difficult to tease out, such as an example of a less conventional, I guess, confounder that could be important to consider.

This just summarizes the confounders that were included in the studies. Study B was the only one that didn't consider

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any confounders. The one unique aspect of Study E, which was the Indiana study focused on drinking water system monitoring data, is that it also considered season of year in their statistical models. They did try to attempt to control for seasonality.

Now that I have talked about sort of our thought process and what we have thought about when evaluating studies, I will go into the specific detail of the strengths and limitations. These are things that are summarized in the actual document.

Study A was the one that focused on USGS surface water data and natality data collected by Indiana CDC. This was an ecologic study, and its strength is that it provides sort of an overall snapshot in trends in both birth defects and atrazine levels in the environment. For this reason, it is useful in hypothesis generation, but for the same reasons, it can only be used to demonstrate correlation. This is because of

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its ecologic design and also because the measure of exposure, it is unlikely that it would reflect true levels of exposure at the individual level.

This is because of the nature of the USGS surface water program; not all the sources are drinking water. Some of them can be small streams. Some of them can be large bodies of water. So they are not necessarily representative of what people are actually drinking out of their tap.

The second study, basically, used the same sources of data to characterize exposure and outcome and actually included some of the same coauthors. So it is basically the same strengths and limitations, and I won't repeat those now.

Study C focused on maternal proximity to corn and soybean fields. A key strength of this study, as I mentioned before, was its ability to characterize or estimate individual-level exposures, which was a key

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benefit of the study. And also, it focused on the specific period when atrazine was used most commonly. So this also helps control for potential seasonality because you only focus on a specific time of the year.

However, although proximity to corn and soyfields has some strengths, it is also a surrogate of exposure. So it is very difficult to attribute that directly to atrazine, and there could be other sources of exposure that aren't specifically from the nearby corn and soyfields; particularly drinking water is the primary source of exposure.

And other limitation, well, it is good that they focused on a specific period of a year. The results might only be, it only provides information on that time, and it only provides information on births in rural areas. So it is difficult, it may be difficult to extrapolate the results to other populations and, more broadly, to the entire year.

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Study D was the first of the studies reviewed to focus on municipal drinking water, which is a more direct measure of exposure, because it is what people are actually going to consume. So this was a benefit of the study, as well as its focus on specific trimesters during the pregnancy. So that gets at that issue of window of susceptibility and focusing on specific time periods.

There were some limitations, however, in the actual data, and they had limited data to develop a time series of exposure. They had a single measurement for each municipality. They didn't have a measurement over time that could be matched to a trimester, for example.

And another big limitation of the study is that there were relatively small differences in exposures between the groups. So there was limited variability in the study.

And then finally, Study E, which

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was probably the strongest of the studies, just due to its exposure data. It was able to utilize multiple sources of drinking water which had been collected in Indiana over time. So they were able to develop time series of exposure to each individual that was included in the study or identified through birth registries.

Also, they were able to consider a number of confounders and, as I mentioned before, they attempted to control for seasonality in their statistical model.

There are some limitations to the study. One that is mentioned in the actual case study is that there wasn't any information in the publication about how the different data sources, which represented different municipalities, compared. So that would have been helpful.

Also, the study results are driven by a single community water system, which represented about 70 percent of all the births

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in the study. So just limitations to consider.

So this concludes the atrazine case study. Moving forward with the atrazine reevaluation, there will be a much more comprehensive review of the epidemiologic data. So this certainly isn't meant to represent the agency's review of all epi data, just to sort of kick things off and make sure that the approach we are using for understanding these studies is grounded by good science. So good guidance from the SAP will help OPP to develop a more systematic approach.

Thank you.

CHAIR HEERINGA: Thank you, Lieutenant Niman.

And I would just turn to the Panel briefly to see if there are questions of clarification on this overview of sort of definition and standing constructs in these different studies.

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Dr. Bailar?

DR. BAILAR: I have two questions. First, has anybody looked at the seasonal patterns in areas where there is little or no exposure to atrazine?

And let me ask the second question because it is parallel. Has anybody looked at these areas that show the cycle prior to the time atrazine was used in substantial quantity?

LTJG NIMAN: Offhand, I don't have a good answer to that. I don't know.

DR. BAILAR: I think it would be important to look at those things. My guess is that you will find seasonal patterns.

Forty-five years ago, in the mid-sixties, I published a review paper on congenital malformations and month or season of birth. There was already enough in the literature to show that there were cycles for three specific malformations.

CHAIR HEERINGA: Thank you very

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much, Dr. Bailar. I think, too, when we get to our question two this afternoon, those types of insights are appreciated.

Dr. Bove?

DR. BOVE: I will ask a quick question. There are other studies that have looked at birth defects, including studies in Iowa that used population-based birth defect registries, which none of these studies have. So, are you going to include those?

I know, of course, there are other epidemiologic studies looking at atrazine, for example, in occupational cohorts and cancers, and so on. But just focusing on adverse birth outcomes, are we going to get the entire universe, because this isn't?

LTJG NIMAN: Yes, and this wasn't really intended to reflect the entire universe. So, yes, the actual atrazine evaluation will consider the entire literature.

So, if there are specific studies

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that you want to submit to us, I think you can.

CHAIR HEERINGA: Dr. Reed? Dr. Lowit first.

DR. LOWIT: Just to follow up on what Lieutenant Niman said, as we keep the atrazine train on the track, the April meeting will focus on experimental toxicology studies in vitro in primarily mammals. It is the September meeting where we will bring all of the epi, whether it is birth outcome or cancer, and all of those studies, and the full weight of the evidence.

CHAIR HEERINGA: Dr. Reif?

DR. REIF: Just to follow up just a bit as a comment regarding the suite or array of studies that have been chosen for the case study, the issue I think is not only with respect to the completeness of the body of epidemiologic literature that applies to atrazine, which you are going to incorporate in a future meeting. The issue is for us to

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appreciate the variety of study designs that are used in epidemiology to bring them into the context of the risk assessment framework.

So, it would be very helpful to consider other designs, for example, case control studies or studies whereby monitoring has been used in epidemiology to answer the questions that you raised about the usefulness of epidemiology in the risk assessment process, specifically in the mode-of-action model that you are using.

So the unfortunate consequence of a limited array of studies that are primarily ecologic in design and don't incorporate, for example, cross-sectional approaches to biomonitoring and looking at an outcome or case control studies is that we are going to be a little bit limited in our ability to answer your questions regarding the application to the MOA framework.

CHAIR HEERINGA: Dr. Reed?

DR. REED: I was wondering if in

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any of these epi studies that the coexistence of other triazines and their metabolites have been looked into? Or is it all about only focusing on the atrazine?

LTJG NIMAN: Not all those studies specifically measured a chemical drug, but for the ones that did, it was atrazine only. Some of them also included measurements of nitrates. And I am thinking of the USGS studies. They also had another category. They had a category called just other chemicals, but they didn't specifically focus on the other triazines.

CHAIR HEERINGA: Dr. Lowit, your light was on. Were you going to respond to Dr. Reif?

DR. LOWIT: Yes. We are going to appear a little sort of double today, and I apologize for that.

In response to your question about the challenge of thinking about these atrazine studies in the context of the mode of action,

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and in the absence of the other birth outcomes data and everything else, if you can look at this from two hats, one would be the atrazine piece. One of it is this is actually not an uncommon situation for us, that a study of the nature that Lieutenant Niman described for a chemical for which we don't know a lot about the mode of action, and it is necessary for us to think about how that study fits in the totality of the risk characterization.

So I acknowledge that it is an incomplete atrazine piece, but it is actually not an uncommon problem from a generic standpoint. If you can, some feedback along the generic piece of that would be very helpful.

CHAIR HEERINGA: Okay, we are at 10:15, and I apologize, I apparently have a failing battery in my watch. So I can't look at the clocks here because I am totally confused. The man with two watches never knows what time it is.

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So we are going to take a 15-minute break, and we will reconvene at 10:30. We will use that clock as our standard for the day.

Thank you.

(Whereupon, the foregoing matter went off the record at 10:15 a.m. and went back on the record at 10:30 a.m.)

CHAIR HEERINGA: Welcome back, everyone, to the second half of our first morning session of the EPA Science Advisory Panel, discussing the topic of the "draft framework and case studies on atrazine, human incidents and the Agricultural Health Study: the incorporation of epidemiology and human incident data into human health risk assessment".

At this point, we are in mid-point in the scientific presentations and overview from the EPA staff.

Dr. Levine, would you like to --

DR. LEVINE: I would like to

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introduce Dr. Michael Alavanja, who is the principal investigator on the Agricultural Health Study. Dr. Alavanja has a Doctor of Public Health from Columbia University, and I guess over 150 publications. He is retired from the Public Health Service, but he is still continuing to serve as a Senior Scientist at the National Cancer Institute.

So, with that.

DR. ALAVANJA: Good morning, everyone.

I had the idea of doing the Agricultural Health Study in about 1991 and convinced the internal review groups in 1992, and we actually got into the field in 1993.

Since that time, a number of other federal agencies have come onboard and refined and advanced the Agricultural Health Study in a number of different ways. Those include the National Institutes for Environmental Health Science, which is focusing largely on the non-cancer endpoints, and the U.S. Environmental

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Protection Agency, and the National Institutes for Occupational Safety and Health. Their focus is on the exposure assessment, which is a crucial aspect of the Ag Health Study.

I would like to talk about briefly the background, purpose, and scope of the Agricultural Health Study, then talk about the study design, talk about exposure assessment, and in one slide summarize how I think there is a commonality between what we are attempting to do in our methodology and the Bradford Hill criteria in the mode-of-action framework that has been discussed this morning, and then answer any questions that you might have.

So, first, the background, purpose, and scope: the basic background information was that there is a worldwide occupational and non-occupational exposure to pesticides. It is estimated that over 1 billion people worldwide are occupationally-exposed, and to some degree almost everyone,

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certainly almost everyone in the United States is exposed non-occupationally to pesticides, either by using it in home and garden or indirectly through being bystanders, consumers of food or water that is contaminated to some degree.

The literature review back in 1993, and maybe to the present, would suggest that previous health studies are characterized as having inadequate exposure assessment. We know that exposure or misclassification can result from inadequate exposure assessment. So one of the things, clearly, that we had to do was to improve upon that.

But exposure misclassification can reduce our ability to identify agents responsible for disease because there is a general trend toward a bias toward the null. That is, if you are misclassifying people on exposure, you will tend to miss a signal of effect, even if it is there.

A lot of the previous studies are

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out of case control studies. Although case control studies are excellent, they have been criticized when applied to pesticides because the exposure assessment was done after the disease onset. So some case recall bias is a possibility under those circumstances.

So the purpose of the Ag Health Study is to study a wide range of health effects of agricultural exposures in farmers and their families, and, too, the research, hopefully, will be generalizable to a much wider population worldwide. I will touch upon that as we move through the presentation.

The scope of the Ag Health Study, the major exposures include pesticides, of course, but it is also exposure to animals, engine exhaust, solvents, and organic and inorganic dust. So we have been working on all of those in the Ag Health Study.

The health effects under study, certainly cancer, but, also, respiratory health, reproductive health, neurologic

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diseases, and even workplace injuries, through a collaboration with extramural investigators.

What does epidemiology and maybe what does epidemiology from the Agricultural Health Study contribute to the situation? What are some of the characteristics?

Well, first, there is no extrapolation of results from a lab animal to a human. So I think we are focused on the right species, if we do this work correctly. There is no extrapolation from high exposure in animal testing to lower exposure in the human experience because we are looking at the human experience for workers that use these pesticides.

The results are generalizable for the chemical evaluated. I say that because we are looking at a large population in two geographic areas, Iowa and North Carolina. The only caveat I would add to that is that we can only generalize within the range of exposures of the study. So we have a fairly

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broad range of exposures in the study, but we can only make conclusions within that area of exposure.

The comprehensive exposure assessment that we are doing tends to minimize misclassification, but the endpoint of what we are doing is rank-ordering exposures. So that is an important point. Although we are making some measurements in the field, basically, we are trying to correctly and accurately rank-order exposures, individually ascertained, and put them into proper rank order by chemical.

It is a prospective study, so that tends to minimize information bias. There is no case recall bias because the exposure assessment was done prior to the onset of any cancer.

We control for confounders to obtain valid risk estimates. I will expand on that point a little later in the presentation.

We have been generating biologic results to assess biologic plausibility and

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modes of action, and to identify susceptible subpopulations. That aspect of the study has a later start, but, in fact, we are actively working on that as this year we started, actually toward the end of 2008, doing that work in 2009 and we will continue.

The epidemiologic design is the next item that I would like to talk about. So it is a prospective design. That is, the exposure was discussed prior to the cancer onset. So all of my comments today are directed at cancer because there's slight differences for other disease endpoints.

We have approximately 52,000 private applicators, and private applicators are farmers and nursery operators. We have 32,000 spouses of farmers in the study, and that is really important because many of those spouses really represent more of our own experience here; that is, people who are not occupationally-exposed, but get indirect exposures. I am not going to focus on that.

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It is a topic for another time, but I think it is a very important topic.

We also have approximately 5,000 commercial applicators, and these are folks who do pesticide application for hire.

We have two important agriculture states as the focus of the study, Iowa and North Carolina. Corn and soybean and hog production turn out to be important for both states, but then North Carolina has a more varied agricultural economy. So there are exposures there associated with growing fruits, vegetables, tobacco, and cotton.

The target population are licensed pesticide applicators, as I mentioned, both private and commercial. But the reason this is the strength of the study, actually, is that they are regularly exposed to the pesticides, although they are not exposed every day, as one would experience in a manufacturing plant.

They are also knowledgeable about

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the chemicals they use. That is because they actually have to purchase these chemicals, keep records of their effectiveness, and there are some tax advantages. So there are records for those purposes. So they are very knowledgeable.

And farmers tend not to move their residence. So it is easier to follow up, and we have a low lost to followup, as you will see, with regard to cancer incidents.

We have a comprehensive exposure assessment plan in place. We administered the initial questionnaire, which was self-administered, between 1993 and 1997. The enrollment questionnaire was administered at pesticide licensing examinations or classes, and we had 82 percent participation of the target population. So that was a successful enrollment process.

We also had a take-home questionnaire for the applicators that provided additional information, and we also

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had the spouse enrollment through a take-home questionnaire.

Since then, we also had two subsequent phases, what we are calling Phase II and Phase III. Phase II was between 1999 and 2003. There was a second questionnaire, updated exposures, updated some of the confounding factors. That was followed up yet another time between 2005 and 2010, again, updating exposures and other information of interest.

We also made field measurements of pesticides on a sample of the study subjects. So, clearly, the questionnaires are something that we could do for everyone in the cohort, but the field measurements were done on a sample.

So, in the EPA field study, we had 69 folks who applied 2,4-D using various methods, and we had 17 apply chlorpyrifos. This was basically for both the 2,4-D and the chlorpyrifos on field crops.

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NIOSH is also working with us. They looked at 74 applicators that used captan. This was in orchards in both Iowa and North Carolina. So there were different application methods used there.

The questionnaire content, in brief, we have lifetime pesticide exposure for over 50 pesticides. The focus of the questionnaire was for 50 pesticides, but we had write-ins and we have about 30 where there was sufficient numbers of write-ins that we can use that information.

Basically, we are trying to get the number of days per year a specific pesticide was used and also the total number of years that pesticide was used.

We go into exposure determinants. We want to know the pesticide application method that they used with these pesticides, whether or not they repaired the equipment themselves, the pesticide application equipment themselves, and whether or not they

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mixed and/or applied the pesticides, and what personal protective equipment did they use.

So these are the exposure determinants that we have and we can apply to each of those pesticides.

We also looked at other farm activities and non-farm occupations because these might be considered potential confounders. So we have that information.

We have lifestyle factors, including smoking, diet, alcohol consumption, but also physical activity and a number of other characteristics.

We have the medical history of these individuals to learn about other conditions that they may have, and we have a family cancer history. Basically, we try to get this updated each time we gave a questionnaire in the three phases of the study.

There's been little lost to cancer incidents followup, less than 2 percent in

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total when we have been following the population. One of the reasons we have been somewhat successful in this regard is that we went to states that had population-based cancer registries, and farmers tend not to move very much. So those cancer registries tended to work for us.

We monitored the date the study subject moved from the state by various means, but, also, with the aid of the Internal Revenue Service, which we can use because we are working with the National Institutes for Occupational Safety and Health.

And we are following mortality for everyone and haven't lost anyone because of the National Death Index.

We have over 1 million person-years of followup at the current time. So our ability to look at rarer cancers is increasing with time and rarer exposures. We have buccal cells collected as a source of DNA on over 35,000 people, and we are actively analyzing

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that to see if there are genetic susceptibility factors. This year and next, we will be able to publish a number of those papers, I am quite sure.

So, basically, what I said was that there was an enrollment phase from 1993 to 1997, a Phase II, where we did a followup with telephone interviews to get the exposure history over the five-year period that elapsed since enrollment. We collected buccal cells from about 35,000 people. We administered a dietary questionnaire, a rather lengthy dietary questionnaire. In Phase II, 2005 to the present, we are just essentially finishing that up now. We have a five-year follow-up telephone interview that has been completed. All along, we have been following up cancer and mortality followup.

So there's a possibility, then, that there could be confounding associated with this. As Aaron and others have mentioned, in order for a variable to be a

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confounder, it has to be associated both with the exposure and the disease. So the confounders that come to mind, there could be certainly the concurrent pesticide exposure. So, if we are studying chemical 1, there is the possibility that the other 50 or more pesticides that the farmer is likely to use could confound the situation.

But, fortunately, by collecting all the information, we can put those other chemicals into the model and determine whether or not there's confounding present. So that is a strength of the Agricultural Health Study, that we can do this on an individual basis.

But there is also the possibility that pesticide exposures confound with other occupational exposures. So there are non-farming occupations that are potential confounders. We have information on the most frequent occupations other than farming. Many farmers have to supplement their income, and

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so this is a possibility.

But there's also other farm exposures, and these have to be taken into consideration. We have done that in the Agricultural Health Study to a large degree.

Of course, all of our questionnaires are online, so they can be examined by anyone with an interest to do so.

Then, thirdly, there is the possibility of confounding through lifestyle factors. So we have tobacco use, alcohol, diet, and physical activity that we have used somewhat routinely in looking to see if there is confounding.

As it turns out, there hasn't been much of an influence of the potential confounders on our risk estimates. We have looked at those carefully, and there tend not to be serious issues with confounding that we can detect.

So, the overall research strategy, we have two states and two license types. So

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what we are looking for are the exposure response associations in both states. We sort of take things seriously when we see that there is this consistency between the two states, and if we have a lot of data, also, within the two license types.

We have done this now for over 25 individual chemicals, and those have been published. But we consider those, even though we have certain strengths, we still consider those hypothesis-generating papers because what we would like to do is reevaluate later in time. We are starting to do the reevaluations later in time this year. So, there, we would, then, look to see if we continued to have the geographic consistency and the consistency in time.

Then, finally, whenever possible, we don't believe that we can do this in all instances, but we are certainly looking for the biologic evidence that would suggest maybe a mode of action. So that table completely

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filled out would lead us to believe that we have a chemical that should be of interest to the International Agency for Research on Cancer and to the EPA and other regulatory bodies.

We, of course, are just generating the science as best we can. We will never be in a position to conclude that something is a carcinogen or not, although we hope the evidence we provide helps in that effort.

With regard to exposure assessment, as I mentioned before, we are getting at the duration of use. We have that for each of the pesticides, the frequency of use. So, if you multiply those first two together, you get an estimate of the total days of application for that specific pesticide in a lifetime. And we have attempted to verify that that information is accurate, and I will mention that in a moment.

But, then, there is also an intensity weighting factor that I will speak

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to you about at a little bit greater length. So, there, we look at the application method, whether or not the chemical was mixed by the person under study, whether or not they repaired their own application equipment, and what personal protective equipment items were they using.

Then, as you will see, we looked to see in a sort of natural experiment that we had in our study whether or not the information about exposure assessment was repeatable and whether or not the information about the duration of exposure was valid. I will mention that in a moment.

Then we compared the questionnaire data to field measurements of pesticides. I will show you how we did that as well.

So, in the first instance, we found that farmers in the Ag Health Study provided reproducible results. My colleague, Aaron Blair, published a paper in 2002, and we took advantage of a natural experiment. We

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simply gave certain individuals a questionnaire in each of two subsequent years. We didn't intend to do that, but we did that to over 2,000 people. So we wanted to see how consistent the results were. I will share that with you.

But, essentially, what we found was that the specific chemicals and application methods were highly reproducible. The agreement was between 80 and 95 percent for "ever" versus "never" use of that chemical. So we took advantage of that natural experiment.

But we also, then, compared the information on duration of use with when did the chemical come onto the market. So we compared the registration date and data with when the farmer said they were using the chemical. That corresponded very well. Most applicators provided complete information on the lifetime use of the pesticide.

This is some of the data that

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Aaron Blair generated. You see here that, for 2,921 Iowa farmers that were given the same questionnaire two times apart, we had exact agreement of atrazine, 86 percent glyphosphate, 82 percent 2,4-D, 87 percent as exact matches. So this tended to give us confidence that the questionnaire was, in fact, getting it right with regard to reproducible results.

But then we have, in addition to the estimate of total days of exposure, we have various metrics. So the first metric that we have for each of the pesticides is lifetime exposure days for that specific pesticide. As I mentioned, it is a multiple of the years of application of that specific pesticide times the days of application per year. So we have that for all of the 50 pesticides, and then for those write-ins as well, so for about 80 pesticides.

But we also wanted to go beyond that because one day of exposure for me, who

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may be dressed up in a spacesuit and completely protected from the outside environment, would be different for another person applying the same chemical for the whole day without any protective gloves or any other protective equipment. So we want to be able to distinguish that as well.

So we introduced, my colleague Mustafa Dosemeci came up with an intensity of exposure algorithm to weight the days, so we could differentiate days of potential high exposure from days of potential low exposure.

The third item is lifetime days of exposure, all pesticides. Some of our first papers were criticized because they said, well, yes, you are adjusting for all these pesticides, but what about the total insult of all pesticides? So we had that information in the questionnaire. So we have that available as an adjustment factor.

And then another thing that I would like to talk to you about on another

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day, we also have this factor, a high pesticide event, which is not getting at the chronic exposure, but it is particular events when you have an unusually high exposure.

As it turns out, this has proven to be a very important exposure characteristic for some diseases, not yet for cancer. We have been looking, but it doesn't show up yet. But for macular degeneration, for certain neurologic endpoints, high pesticide exposure events are, in fact, an important exposure.

So the exposure algorithm that we are using is listed, let's see, right there. Intensity, so do you mix, do you apply? What is the application method? What is the repair? And multiplying that by the personal protective equipment you use.

So the information from the questionnaire is administered to everyone, is used to get information on these factors. We also use the information from monitoring studies, such as the Pesticide Handlers'

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Exposure Database, the PHED. So that was another source of information that Mustafa used in order to come up with this algorithm and the weighting factors associated with it.

The assessment of the algorithm was made with field measurements. I will show you some of the results of those. And the assessment of the algorithm was made by comparing the results to outside sources. A study in Canada used our questionnaire to assess exposures by questionnaire, but, then, also made certain measurements. So we studied that situation to see how well our questionnaire did under those circumstances.

So, briefly, to illustrate the algorithm, the first item might be if you mix. If you don't mix the chemical, you get a zero for the score. If you always mix, you get a nine.

Now this is just an illustration. This table would be much more lengthy for all of the possibilities. So you imagine, if you

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mixed some of the time, you would get a score between zero and nine.

Then, applying the pesticide, there are various application methods. A banded application is one where you are dropping the pesticide off in back of a tractor into a row between the crops. For that, there is relatively low pesticide exposure potential. You get a score of two. Broadcast spray, there would be a little bit more. That would be a three. But if you are hand-spraying, you would get a score of nine.

Now these relative weights are based on the literature and where actual measurements were done. This was all put into place prior to the onset of the study. So we didn't have any information that we generated ourselves to base this on when we started.

If you repaired your own chemical application equipment, you would get a score of two, and if you did not, a score of zero.

For personal protective equipment,

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it is a little more complicated because you can be wearing various pesticide protective equipment. But if you look at the top, where a person is wearing chemically-resistant gloves, the person is also wearing some type of respiratory protection, wears a face shield or fabric or leather gloves, which are not recommended, but is doing all of that, they would get a protective score of .1. So that is the number of days would be multiplied by .1. So it would be reducing the score to 10 percent of the original.

And you see there are various combinations. If you say no to rubber gloves, no to the respirator, no to the face shield, the goggles, yes to the fact that you don't use any personal protective equipment, you would simply get a one. So you would get the full impact of those days of exposure. So that is what the algorithm would do.

And it is illustrated here. So I have been given a score, let's say, and I mix

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the pesticide. I get a nine for that. The application method, I hand-spray. I get a nine for that. I repair my own equipment when it gets clogged, and I contaminated when I do it. I get a score of two for that. Then, the personal protective equipment, I wear chemically-resistant gloves and boots, and so the score of protective factor is .4. So my intensity score is a 7.6.

So this, then, helps put things on an ordinal arrangement, but this is what we do for each of the chemicals, for each of the people in this study.

So now what we have here is a study led by Kent Thomas from the EPA, where he had 69 individuals that used 2,4-D, and the categories 1, 2, and 3 are based on the exposure algorithm score. So, in this particular evaluation, the category 1 was 5.5, was the median score, based on our questionnaires; 9.4 for category 2, and 15.2 for category 3. But this was the

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concentration of 2,4-D, the geometric mean in micrograms per liter in the urine.

So what we saw here, then, was, in fact, there was a correlation. Our high correlated with high urines; our medium group with medium urines, and our low group with low urines.

So this is our basic attempt. When the data become more plentiful, we actually divide into finer groups, so that category 3 may be split into the sort of lower end of the high and the higher end of the high. So we can expand this study.

Joe Coble took the same exposure algorithm and did it on the basis of the urinary measurements made in this Canadian study to see, outside the study, how well it did. So you see that the same pattern occurs, that as the 2,4-D increased by our evaluation, based on questionnaires, it also was found to increase in the urine of the individuals that were measured.

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Then, this was done again for another chemical, the same study and a different chemical, a herbicide, MCPA. So you see a similar pattern for increasing urinary concentration with increasing algorithm score.

Okay. So, in summary, I think I only have two slides left, possibly three. So what we found is that the AHS exposure algorithm scores were consistent with pesticide exposure measurements in urine, and if I elaborated on this a bit more, actually, even with the dermal exposure.

Then, the second point, this I didn't present the data for, but this is also, I think, important. The algorithm for the AHS was more closely related to measured urinary levels than any individual exposure determinant.

Some other studies have been able to look at the acres applied or the pounds of active ingredient applied. When we looked at those independently, there was a correlation,

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but when you put it all together in an algorithm, we had a better correlation. So we believe that the algorithm should reduce this classification even better than using any one of those determinants alone.

But there's also a continued refinement of the algorithm that is necessary. The weighting factors could be adjusted as more data become available. When some of the data from the orchard studies came in, it was found that there maybe the weighting factors have to be adjusted slightly because different application methods were used. So that is an ongoing process.

Okay. Finally, this is sort of the last slide. I wanted to relate this to what the EPA has presented in their packet. They talk about a modified Bradford Hill criteria in the mode-of-action framework. This really applies to, how do you evaluate the totality of the information that you have, not from one study, but from all of the

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studies?

But, nonetheless, since there is a multifaceted nature to the Agricultural Health Study, I thought I would relate how I see what we are generating fitting in.

First, there is the notion of a dose response. We can't generate dose response information from the Ag Health Study, but we can do exposure response. You are aware of the difference, of course, between the two.

We are doing rank order. We believe we are doing it pretty accurately, but it is an exposure response. We have total lifetime days of exposure to specific pesticides. We have, then, the intensity-weighted lifetime days, which I think is an improvement over simply doing the lifetime days. Then we have verified exposure by comparing questionnaire data to field measurements. So I think that would be part of our contribution.

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The temporal concordance is something that we have because the exposure was done prospectively. We have information about exposure prior to the onset of the cancer. So that is there.

But when we start doing our molecular studies, I would like to also say that that is also what we can do. We will have exposure information prior to the onset of some of these intermediate endpoints that we will be generating.

With regard to biologic plausibility, biomarker studies of exposure and effect, or toxicity pathway studies, we are working on those right now. We have some sources of blood. We have published one paper on a precursor to multiple myeloma. That was MGAS. We found that MGAS was, in fact, elevated in the Agricultural Health Study and related to particular pesticide exposures.

Then, we are also doing a very large genetic susceptibility effort, and some

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of those studies will be published this year.

Coherence, well, coherence within the Ag Health Study, we always compare results whenever we can, when we have sufficient numbers, between Iowa and North Carolina. We would expect, if you are using the same chemical under the same application conditions, we should be getting the same results. So we compare that for consistency. And if the study is very large, which some of ours have been, we compare the private to the commercial.

The weak point there is that the commercial applications, there's only 5,000 of those in the study, but certainly the number of person-years is building up, and we will be able to do that.

Then, I would just say that all of our papers and our methodology and questionnaires are online. So we have, I think, now 110 peer-reviewed manuscripts from the Ag Health Study. Those can be found at

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that website. They are listed under methods, exposure, assessments, health outcomes, diet, and injury. So I invite you to take a look at that.

This study, obviously, is one where there is a large intramural team and actively working on this study. So it is a large group of very talented people that are working on this study.

And lastly, I open myself to questions.

CHAIR HEERINGA: Thank you very much, Dr. Alavanja. That is a very interesting presentation.

One thing, the Panel is suffering from missing data, and it has a periodicity which I suspect that we got the odd pages and not the even pages. I think some of the even pages have some critical information on them. So we will try to -- sorry about that.

In any case, let's move on to some questions for clarification for Dr. Alavanja.

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Dr. Portier?

DR. PORTIER: Ken Portier.

In your slides showing the categories, your rank-ordered categories, is it safe to assume that the definition of those categories is thirds of the distribution? So that, when n=69, there's probably, oh, there were 22 in category 1? Or is there some other mechanism for creating your rank-ordered category?

DR. ALAVANJA: Usually, it would be tertiles of exposure. So that it is arbitrary. What we have done is, when the data permits, we very often split the upper categories, so we have tertiles, with the upper tertile being divided into, and so we can look to maximize the range of exposures that we are looking at.

CHAIR HEERINGA: Dr. LeBlanc?

DR. LeBLANC: In your table relating to research strategy, your last column was biological evidence in humans. I

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was wondering if biological evidence referred to the types of endpoints you had in a latter slide on biological plausibility, or is it more related to just simply precedence for cancer in humans, or both?

DR. ALAVANJA: I think it is safe to say it would be both. Okay? So the evidence, we have some blood samples and we are looking at, for example, DNA methylation patterns as part of its own epigenetic phenomena. We are also looking at telomere shortening, an endpoint, and as with the epigenetic phenomena, that have been associated with cancers.

We are doing that, and we have an expanding list of things that we are looking at. But, then, we are also using -- those were from blood samples. We are looking at, and I have a new effort that is looking at, MGAS, this condition that is a precursor to multiple myeloma, but we will also be looking at NBL, which is a precursor condition to

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chronic lymphocytic leukemia. So we are doing that as well.

And, then, with buccal cell samples, where we have lots and lots of that available for study, we are looking into genetic susceptibility, and our first look was on prostate cancer. So we are doing a lot of work with prostate cancer.

CHAIR HEERINGA: Dr. Chambers?

DR. CHAMBERS: Jan Chambers.

Impressive study. I have a couple of questions to clarify in my mind what you are doing. You said you were using solvents as one of the things that you were looking at. Is that the solvents that are used in the pesticide mixes or independent of agriculture?

DR. ALAVANJA: It's not independent of agriculture, but, well, independent of the pesticide applications. So it is largely solvents, cutting oils and things that are used in ancillary processes associated with the farm and farming.

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DR. CHAMBERS: You talked about the initial questionnaire going in from 1993 to 1997. So were they commenting from that point forward or were they also trying to recall what they had used? It was talking about lifetime exposures. So are they trying to recall what they had used prior to that point as well?

DR. ALAVANJA: I'm sorry that I didn't make that clear. Yes, they are. We, in the first questionnaire, attempted to recreate an exposure history up until that point. For some individuals, that was one year, but for others it was 30 years. But, in all instances, it was prior to any report of cancer.

DR. CHAMBERS: Would there not still be some recall bias of something that was that many years ago in those cases, though?

DR. ALAVANJA: Not in the sense of case recall bias. You know, if we are looking

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for an association both with the chemical and the disease, that kind of bias, which is some might say the ones that you would be most worried about, that couldn't occur because there was no cancer at that point.

There could be what might be considered random misclassification. That is, you have a better memory than I do. So you can recall what you did, let's say, five years ago, and I simply don't have a good recollection of that. But it wouldn't be a bias, a confounding bias, because disease or cancer would not yet be on the scene.

DR. CHAMBERS: Thank you.

When you are doing your intensity weighting, if a person's activities change over time and all, is that taken into account? Or do you just get one overall number for each individual for the intensity rating?

DR. ALAVANJA: In the enrollment questionnaire, which goes to the history of the applicator prior to the enrollment, that

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is one number. But now we have Phase II and Phase III questionnaires, which focus on the next five-year periods. So what we are doing in our reevaluations is to incorporate the information over time and how the exposure would change over time, based on, most often, more protective equipment being used.

DR. CHAMBERS: And you talked about commercial applicators. Are those just commercial applicators in agriculture or this is not talking about residential-type things? It is just strictly agriculture?

DR. ALAVANJA: No, it does include residential applications as well. So, in the State of Iowa -- the commercial applicators were limited to the State of Iowa, and that is just because of the way they administer the examinations in North Carolina, it was difficult to get to the places.

But, in North Carolina, commercial applicators, a large fraction of them were agricultural applicators, but others were the

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Orkin Man and, you know, the lawn-and-garden applications as well.

DR. CHAMBERS: Almost through. The medical histories, are those self-reports or are those on medical records?

DR. ALAVANJA: The medical histories are self-reports, as I indicated, but for special studies, NIEHS has gone back and verified particular conditions by going back to medical records. So they have done that with asthma, you know, certain other diseases where they have actually gone back and verified those.

DR. CHAMBERS: One last one. Have you tried to do any sorting by chemical class within the pesticides of things that are acting by the same mode of action that are already known? You are sorting that way, too?

DR. ALAVANJA: Yes, and the lesson, I believe the genetics is actually showing that this is consistent. But I found in a prostate cancer evaluation that there

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were six chemicals associated with prostate cancer, if you had a family history of prostate cancer. Four of those chemicals were organothiophosphates. So that was very interesting. But not all organothiophosphates were associated.

Now we are looking at it at a genetic level, so we are doing gene/environment interaction, and those same chemicals are showing up as showing a gene environment direction.

Needless to say, I was delighted to see those results, which we hope to get out as soon as possible.

CHAIR HEERINGA: Dr. Bailar?

DR. BAILAR: It is not entirely clear, but I think I know the answer. Do the successive waves of followup bring in new subjects, people who have joined those professions since your initial round?

DR. ALAVANJA: No.

CHAIR HEERINGA: Dr. Lu?

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DR. LU: For those exposures, the number that comes up on the algorithm, I guess they are not chemical-dependent, right? So, for example, the applicator can spray Chemical X, Y, and Z. But when you are, say, for example, the data you present in terms of the algorithm outcome versus 2,4-D in the urine, those exposure outcomes, the algorithm number reflects the true application of 2,4-D or just in general in terms of mixing application and repair?

DR. ALAVANJA: There has been an evolution in time. So, in Phase II and III and a future fourth phase, it will be chemical-specific. In Phase I, the information was category, in the sense of herbicide, insecticide, fungicide. So it was grouped in that way because the information that we had at the time suggests that there was a commonality, not a perfect commonality, but there was a commonality for herbicides being applied in one way, insecticides being

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applied in another way. So, Phase I, which is the information that we have now, is based on that way.

DR. LU: So I just want to kind of clarify. So, as they evolve, the Agricultural Health Study will provide the exposure algorithm number that is tied to a group of pesticides? That's herbicides, insecticides, and fungicides?

DR. ALAVANJA: That is what is being done now in all of our papers to date.

DR. LU: Right.

DR. ALAVANJA: It will be, in fact, even more refined when we start using Phase II data because Phase II and Phase III ask on an individual level.

DR. LU: Okay. Good. Thank you.

CHAIR HEERINGA: Dr. LeBlanc? Then I think we will move on to the next presenter.

DR. LeBLANC: You provided us a few slides of the relationship between the

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exposure categories and urinary metabolite levels for different pesticides, and the trends were all in the right direction. I was wondering if there tends to be significant differences in metabolite levels among the categories. We had no view of error associated with those values.

DR. ALAVANJA: The confidence bars were, in fact, left off. So there is variability, but there is a significant trend in what I have shown. So, in each of those cases that I have put the information on the board, there was, in fact, a significant trend that was associated with it.

And again, we feel that what we can do with all this effort is to put things in the right order most of the time. Now there are some limitations. For the chemicals that we have been using, for example, if we get to fungicides, where an air-blast method of application to peach trees is involved, the algorithm is not as good in those

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circumstances. So there would be a caveat, but there always has been in any paper that we would write about that chemical.

So, for crop farming, for corn, soybean, for a lot of the vegetables and fruits, that is the principal agricultural commodities in Iowa and North Carolina, we feel that the algorithm is good. But when we get to some of the activities such as orchards, then we need improvement in the algorithm. So we would say in any of our etiology papers associated with captan or, you know, other fungicides.

DR. LeBLANC: As this kind of information accumulates in the literature, are there going to be any effects to try to improve on the algorithm?

DR. ALAVANJA: We are actively engaged in trying to improve the algorithm. There is a paper that we are working on that is attempting to change the weights to better fit the algorithm.

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If anybody is familiar with the atomic bomb survivors studies, that there has been going on for 50 years, where they try to make more precise their algorithms. We hope not to sort of emulate it over a 50-year period, but to improve it whenever we can. And when we do, we want to make a big deal about it, so that people will know that we have been using the algorithm for 10 years, we are going to change it slightly, and we are going to use the algorithm now. So people will be clear about what the algorithm is, what the weighting factors are, and we won't do that without making sort of a big deal. So that will be well-known in time.

CHAIR HEERINGA: Well, thank you very much, Dr. Alavanja. Will you be here for the next day or two? I didn't want to put you on the spot, but I guess I did.

Dr. Levine?

DR. LEVINE: Thank you.

I guess the last discussion is a

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good segue to our next speaker, who is Shalu Shelat, who has a degree in industrial hygiene from the Harvard School of Public Health, and in HED, Shalu primarily works on worker exposure assessment. She is a member of our Ag Health Study implementation team and has been working closely with the Executive Committee of the Ag Health Study to acquire data from the Ag Health Study to use in our case studies related to exposure.

MS. SHELAT: Thank you for that introduction, Dr. Levine.

I am just waiting for my slides to pop up.

So, as was mentioned, I am going to provide an overview of Case Study B, which is a comparison of the Office of Pesticide Program and the AHS Exposure Assessment Approaches.

So, to provide you an overview of what the presentation will entail, I would like to start off with the introduction to the

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regulatory processes under which the agency and OPP governs, and, also, touch upon the agency's goals as well as long-term objectives for this particular key study.

Then I will be moving on to the key study itself, first providing background and descriptions of the two approaches, and I am happy to follow Dr. Alavanja. He has provided a great foundation. So I will just be touching upon some of the AHS particulars, and then moving on to the actual three-step case data that we have provided in the document. Then I would like to wrap up with an idea of where we are today and what we would like to achieve in the following months.

So, under the laws of FIFRA, the agency is required to consider exposures and risks to both handlers as well as workers. A handler is defined as an individual who participates in mixing, loading, and/or applying a pesticide. A worker is defined as an individual who enters into a previously-

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treated environment and conducts post-application activities, which could entail weeding or thinning or harvesting.

Also under FIFRA, the label is the law. What that means is that the label establishes the current allowable work practices for that particular pesticide or formulation. The label provides information on application rates, equipment, the types of crops to which those pesticides will be applied, as well as application intervals.

The label also can contain information on the types of personal protective equipment that an individual should don when handling the pesticide, as well as the restricted entry intervals.

So the purpose of this case study will be focusing on the handlers alone, although the workers are another important population to consider, and the allowable work practices that the label establishes are what is used in the risk assessment.

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Now the labels and the risk assessments have an interesting relationship. Though the information from the labels that is provided is used to establish the risk assessment scenarios, if those risk assessments result in risks of concern, according to agency standards, the risk manager in the decisionmaking process can go back to those parameters and make adjustments, and, hopefully, mitigate exposure to the individual.

What that would mean is maybe adding an additional layer of personal protective equipment or reducing application rates and scenarios such as that. That is how the agency uses regulatory means to mitigate exposure to individuals.

So, although a lot of value is placed on the label itself, other aspects of work practices are also considered in the full risk assessment and decisionmaking process. Risk assessments consider the worker

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protection standard as well as certification and training programs, and in addition to incident reporting as well as epidemiology.

So the agency's scenario-based approach considers job tasks, potential formulations, as well as personal protective equipment. As has been previously stated, most of this information is defined by the label. However, extant sources of information are also incorporated. So knowledge of agronomic practices that are particular to that pesticide or crop are taken into consideration.

Within the algorithm, the exposure rates that are commonly also referred to as unit exposures are defined by a publicly-available database called the Pesticide Handlers Exposure Database.

And just to note, a lot of these methods and approaches have been reviewed in the past and, most recently, in 2007 and 2008 by the FIFRA Science Advisory Panel.

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So this is an example of an algorithm used by the agency to assess dermal exposure. The daily exposure is represented in milligrams per day, and the calculation is a multiplicative calculation taking into account the unit exposure, which is the exposure rate normalizes by the amounts handled, the application rate, which is typically produced from information from the label, and the area treated. This represents what an applicator can typically treat within an eight-hour workday, given consideration to the type of application equipment and the crop.

It is important to note that the assessment considers many permutations of these parameters. One label may contain several different application methods. So an algorithm or a calculation will be produced for each of the application methods.

Now that I have provided a bit of a background on the agency's approach, I want

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to move on to the bigger picture relative to this case study. So the agency's overarching goal is to develop a more informed process by which to evaluate and incorporate epidemiology into the agency's risk and exposure assessment approaches.

As part of those overarching goals, one of our long-term objectives is to incorporate chemical-specific data from epi studies into the weight-of-the-evidence analysis that was discussed earlier in the day. For example, there are a number of agricultural health study reviewed and considered chemicals that have also been reviewed by the agency in the last few decades.

By using epidemiology and incorporating it into the risk assessment, the agency can explore associations and risks that have been associated with those chemicals and the degree to which they remain an exposure concern in today's use practices.

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So, before we can really get into the goals and these long-term objectives, the first step is to truly understand the relationship between epidemiology exposure assessment and the agency's approach to exposure.

So, for the purposes of this case study, the Agricultural Health Study was selected because of the high quality and unique prospective study, but it is also based on chemical specificity. Some of the key features that have been discussed earlier today are embedded in the study design of the AHS.

The study population characteristics focus on private and commercial applicators. This is information that, obviously, the Office of Pesticide Programs values and assesses for in our risk assessments.

The AHS also contains information on exposure through both self-reported

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questionnaires as well as substudies that include AHS participants and measurement information.

The AHS also has great consideration for bias and confounding factors. And lastly, because it is such a data-rich longitudinal study, it allows for an investigation of applicability to other applicator populations.

So now I would like to move right into the case study. The case study is divided into three steps. The first step, illustrating method differences, focuses on the algorithm as well as the parameters which go into the algorithm.

Step two focuses on the overall differences between using different exposure metrics, so biomonitoring versus the agency's approach and the Agricultural Health Study approach. And step three is a cohort-wide case evaluation.

Each step is designed to build

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upon the next. So, as the analysis continues, we will refine and develop the analytical methods for the next step.

So, right off the bat, step one, we acknowledge that the purpose of agency risk assessments does differ from that of post-epidemiology research. Even though the approaches differ, there is still a great deal of value in exploring how the high-quality epi study can be used to inform decisionmaking risk assessment, decisionmaking processes in risk assessment.

So, in step one, I will provide a background on the approaches, an overview of the exposure algorithms, and then an example of a comparison exercise.

The agency's handler assessment approach is a scenario-based exposure approach. It includes information on job function, the type of application equipment that is used, application rates, as well as area treated and personal protective

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equipment.

And as has been stated before, the agency hopes to mitigate exposure using regulatory means through the risk assessment in conjunction with what use patterns are provided on the label.

Given that the agency calculation attempts to be protective for workers, the exposure assessments are considered to be high-end. So the main three focused parameters of the calculations are the application method and equipment. For that, the agency uses all reasonable types of application methods that could be corresponding to that pesticide and their related unit exposures.

The application rates used in the algorithm is the maximum application rate allowed on the label, and the area treated, which is an individual's potential area treated, based on the equipment and the crop site, are considered high-end acres based on

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survey information and agronomic practices.

The Agricultural Health Study, for the purpose of this case study, focuses on private and commercial applicators. In contrast to a scenario-based approach, the AHS actually uses an individual's specific exposure approach. The exposure metrics are based on the questionnaire information, as Dr. Alavanja had explained in the previous presentation. This includes information on the types of pesticides that are used, duration and frequency of use, trends in personal protective equipment, as well as additional lifestyle patterns.

This information is then used to accurately ordinarily rank the individuals within the study, and then characterize them into different exposure levels. This could be an "ever or never" situation or a low, medium, and high, as we have seen.

So the three options for characterizing the individuals, first, is an

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"ever/never", whether the individual has ever reported using a specific chemical; the cumulative exposure or lifetime days, as was described, and the intensity-weighted cumulative exposure.

And just for the purposes of the slide, the low, medium, high are hypothetical categorizations. As was explained earlier, they could be broken down into different segments.

This is just to reiterate the algorithm. The intensity level is made up of four parameters, the whether or not an individual mixes, whether or not they repair, the types of application equipment used to apply or whether or not they apply, and the different combinations of personal protective equipment.

A lot of this information is based on the same 2002 paper that Dr. Alavanja has referred to. As the algorithm is updated or exposure weights are updated, that will be

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taken into consideration as part of the case study.

So the equations used by the agency, in contrast to the AHS, look quite different, and there are different parameters that are applied to both. However, for the most part, we can coarsely divide the equations into two concepts. There's the concept of a use pattern and there's a concept of exposure.

The agency's dermal exposure algorithm is chemical-specific, and as we have mentioned before, there are many permutations for the different application equipment or PPE aircraft, and is label-based.

The AHS intensity-weighted algorithm is one algorithm per individual that incorporates all use patterns. This is based on the questionnaire information.

So the two algorithms can be broken down into two concepts: the use pattern concept and the exposure trend

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concept. This is just a simplification of the algorithm.

In terms of the Agricultural Health Study, the exposure determinants comprise the intensity level, which includes the mixing, applying, or carrying, and PPE parameters. The corresponding use patterns within the agency's approach would be the exposure rates or the unit exposures which take these parameters into account.

In terms of the exposure trends, the AHS relies on information on the duration and the frequency provided in the questionnaires. And for the agency, the approach we look at, the application rate, the area treated, and in terms of cancer assessment, we also typically use 30 days and 30 years working lifetime.

As part of the step one, looking at the parameters and how they compare and how they relate to one another, the science has focused for the purposes of this comparison

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just on the use pattern parameters.

Here we have the agency exposure rates. They are commonly referred to as unit exposures and defined within the Pesticide Handlers Exposure Database, and the units are generic, based on specific application method, job function, and personal protective use.

So, for example, if two individuals are applying two different chemicals, but both using the same type of application equipment, both wearing the same levels of personal protective equipment, and both participating in the application activities, their potential exposure rate would be equivalent.

The unit exposures are not based on the physical and chemical properties of that pesticide in particular, but, rather, on the anticipated exposure of that scenario.

Currently, within PHED, there are 37 unique exposure scenarios and corresponding unit exposures. So, for example, a groundboom

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applicator would have a unique unit exposure as compared to an aerial applicator, and so on and so forth.

Within the Agricultural Health Study, the exposure rates are calculating from over 100 published articles as well as the PHED information. They are also generic, based on the specific application method, job function, and personal protective use.

As you recall from the intensity-level algorithm, there are four parameters that make up that score or that number. So each part of that algorithm contains its own exposure weight.

Here the example only focuses on the applied parameter. What this example shows is that if an air-blast application is being conducted, the exposure will result in three times higher an exposure than compared to a groundboom application.

So, the additional example, if an aerial application was being conducted, an

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air-blast application would be nine times higher than an aerial application. Therefore, an aerial application would receive an exposure weight of one.

So, in summary, both the unit exposure and the exposure weights attempt to capture a generic aspect of exposure, potential exposure. The unit exposures are trying to quantify continuous exposure, so they are provided in units of milligrams of a.i. over the amounts of a.i. handled.

The exposure weights, on the other hand, are an ordinal ranking of exposure patterns. So they can range from a zero to nine, based on the current information provided.

So the first step in the preliminary comparison was to understand how these two parameters relate to one another, both within the approaches as well as between the approaches.

So this table just provides a

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simple example of the parameters. The top half of the table represents the agency's exposure approach. Here we have looked at a groundboom application with an enclosed cab and an air-blast application with an enclosed cab, and the two corresponding units of exposures. From the simple comparison, it shows that an air-blast, based on the unit exposure, has a 3.7 times higher exposure rate than a groundboom.

The second half of the table, the bottom half, represents the same example I had given on the previous slide, looking at a boom-on-tractor application and air-blast application. This comparison also shows that air-blast has a three times higher exposure weight than a groundboom.

It is important to note there are many other parameters that are involved in the exposure assessment approach. This comparison is looking very simply at just the unit exposure versus an exposure weight for the

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application.

And as with any comparison, there is some consideration of issues that need to be talked about. The inherent differences of study design between the two approaches, the difficulty in quantifying uncertainty between and within workers, and, also, the issue of looking at a snapshot of exposure versus a longer-term for an exposure practice.

And as I have said, the example that was provided was a very small-scale example. However, in order to fully complete step one, we will have to look at a great deal of the exposure weights as compared to unit exposures, as well as consider characterizing the effects of repair, and also the combination of different PPE and the effects on exposure based on that.

There's also the inherent difference in the use of information. So, as has been said before, the agency's approach is very label-based; whereas, the AHS uses

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questionnaire information. We have to investigate what the implications of that would be.

So now I would like to move on to step two, the consideration of overall differences. So the agency recognizes that step two will follow step one, if step one provides reasonable conclusion that there is a relationship between the two approaches and one that can be characterized.

As part of step two, we have proposed using the Bakke 2008 and Thomas 2009 exposure studies. I will provide our overall goal for this particular analysis.

Step two considers looking at three exposure metric comparisons. One is biomonitoring of urinary metabolite analysis. The second is using the agency's approach, which incorporates PHED as well as activity information. And the third is looking at the Agricultural Health Study approach, using questionnaire data and elements from PHED in

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terms of the exposure weighting.

So the 2008 and 2009 exposure studies measured different chemicals, but both provided information in terms of urinary metabolites. The Bakke study looked at atrazine, and the 2009 Thomas study looked at 2,4-D and chlorpyrifos. They also collected information on dermal and inhalation exposure.

Both studies included information activity, and part of that was looking at personal protective equipment, types of equipment used for application, as well as the amount treated and other such exposure metrics.

And because the participants in both of those studies are from the Agricultural Health Study, there is questionnaire information that may be available on an individual basis, both Phase I and potentially, also, for Phase II.

So the goal of step two is to look at all three of these approaches. Because the

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studies provide adequate information for calculating exposure on three different metrics, we thought it would be interesting to evaluate whether there is a consistency between the trends.

So, as we have discussed before, there are different categorizations when it comes to the epidemiological analysis of the AHS participants. And if there is a way to evaluate whether using the three approaches provides that one individual into the same bin, it would provide some information on how we can characterize the different approaches.

So some things that we have to take into consideration as part of the step two is the inter- and intra-worker variability and uncertainty, methods issues such as the efficacy of sampling media, and, once again, considering the idea of a snapshot of monitoring data versus a longer-term reported use information. Some of these topics and limitations and strengths have been discussed

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as part of the 2007 FIFRA SAP meeting.

So, at this point, I am going to move on to step three. This is the cohort-wide case evaluation. The agency acknowledges that step three will be determined based on the information provided by steps one and two.

They also acknowledge that it will be necessary to do a feasibility assessment before step three can be accomplished or initiated.

And a lot of the information that we are providing right now for step three is just based on the information that we have on the Iowa and North Carolina applicator population and the agronomic characteristics of those two states.

We will also be discussing a bit upon the data request that has been submitted on the potential of initiating step three, and I would like to discuss some ideas about an analytical plan.

So the Agricultural Health Study,

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as we were talking about earlier, comprises of participants from Iowa and North Carolina, and some of the major crops that overlap between the two states include field corn and soybeans. So, based on some of the agronomic practices, the agency has decided to focus on atrazine and alachlor users within those two states.

So we have requested a data request for chemical-specific data and questionnaire information from atrazine and alachlor users. Some of the parameters that we have requested include the frequency and duration of use information, pesticide use factor information such as the types of application used and any sort of personal protective trends that can be provided. If any of the participants have an algorithm intensity score that has already been calculated, we have asked for any information that went into that. And if there are any characterization values, we would like to use

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that as part of our analysis as well.

So, at this point, I just wanted to touch upon where we are today with the case study and how we would like to proceed in the following months.

For our current status, we have established collaboration with the Agricultural Health Study Executive Committee and the interested investigators. We have also submitted a data request for the questionnaire information that was outlined in the previous slide, and we have developed a case study to help initiate the overall goal of the agency to incorporate epidemiology into risk assessment.

Some of our next steps are to complete step one with the assistance from the AHS, as well as attempt to complete step two, also, based on the results that step one provides. And pending a feasibility analysis, we would like to begin developing an analytical plan for the cohort-wide analysis

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as part of step three.

At this point, I would be more than happy to take any clarifying questions.

CHAIR HEERINGA: Thanks, Ms. Shelat.

Any questions for Shalu Shelat from Panel members? Dr. Bailor?

DR. BAILAR: I have three questions.

CHAIR HEERINGA: John, you barely need to, but your microphone.

DR. BAILAR: I have three questions. I hope the answers to all will be fairly brief.

First, I got lost somewhere along the path. You have now these measures for each individual, the two measures. Is that correct?

MS. SHELAT: Are you referring to step two?

DR. BAILAR: Well, I think that is where I am getting lost. But you have two

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ways of assessing exposure that will each be applied at an individual level?

MS. SHELAT: That is correct.

DR. BAILAR: And do you have preliminary results on how those are correlated?

MS. SHELAT: We have not initiated analysis of step one yet because we wanted to establish collaboration with the Agricultural Health Study Committee members.

DR. BAILAR: I was wondering if you had some preliminary data showing how well these match up with each other, or does it make a big difference?

MS. SHELAT: That is part of our case study. Hopefully, in the next few months, we will have some sort of better answer to that.

DR. BAILAR: And that will be available before this exercise is wound up in the fall?

CHAIR HEERINGA: Jeff Dawson?

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Looks like he is reaching for the microphone.

MR. DAWSON: Hi. Jeff Dawson, OPP.

Just to also add to that, I think we anticipate on certain elements there is going to be very good agreement because, for example, on the intensity scores, I mean they were partially derived using the same information that we are using. So those elements of it, we would certainly expect that there would be good agreement as a first cut.

DR. BAILAR: The second question: how much is known about compliance with the regulatory limits on exposure and about compliance with requirements for reporting accidental major exposures?

MR. DAWSON: I can answer it from our perspective. I think Dr. Alavanja may want to answer how some of those situations are treated in Ag Health.

Certainly, as far as looking at the levels of compliance, we are very

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interested in getting to that type of information. When we do our risk assessments per se for regulatory purposes, we assume label compliance, but part of the reason we are involved in this effort is we want to understand in a holistic way.

If there are significant trends toward non-compliance, we are hoping that these kinds of involvement with using epidemiology and incident data, which you will hear about later, will help us identify them. Then we can address them through the regulatory process, but we, basically, do our risk assessments assuming compliance.

In one of the slides that Shalu showed earlier, it was that we not only do the risk assessments, but we try to do certification and training to help with compliance as well.

DR. BAILAR: And the third question: some outcomes of interest have a long lag period, like cancer, and do you have

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ready ways to exclude recent exposures that wouldn't affect that outcome? In other words, you have measures of exposure of through, say, 10 years ago.

MR. DAWSON: I think the answer to your question is yes. As far as what we are doing on our side or how we calculate the exposures, we look at the label as kind of a living entity, and we continually make course corrections for establishing more risk management around certain uses and things to reduce exposures, if we start to identify that there are trends, like incidents or things that we want to address.

So I think, are you going to get the temporal, like how practices change over time? Is that the question?

DR. BAILAR: I am not so much concerned about changing practices over time, but, rather, with excluding recent exposures that would not affect a specific outcome. If you do an analysis of cancer incidents in

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relation to exposure, do you have a way to limit that analysis to exposures up through, say, the year 2000, not use more recent data?

DR. LOWIT: I think maybe I will add a little bit to what Jeff said, and I am hoping maybe, Dr. Alavanja, you can help, too.

I don't know if I am going to answer your question or not, but I think I am hearing what you are asking. One of the inherent challenges that we have in the Pesticides Office in using epidemiology data is really the goal of our risk assessments. Our goal of our risk assessments is to evaluate the extent to which an existing label is safe under those use conditions.

If, in our process, we find that there are risks, our next goal is to evaluate to the extent the changes in that label will mitigate that risk and bring it into a level where there is no longer concern. So the challenge in using epidemiology data, let's say, with the Agricultural Health Study is

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that many, for example, of the things that they may report on a cancer finding are actually exposures that occurred decades ago.

So there is a challenge for us to translate exposures that happened several decades ago, when we know that agricultural practices have changed in some cases very drastically and in some cases not at all, how to apply or to use that information from exposure that happened several decades ago into our process of how we are trying to keep workers safe today and tomorrow. So that is largely a part, really, a part driving all this.

But I think maybe Dr. Alavanja can talk about the Ag Health Study.

DR. ALAVANJA: I would like to start by saying, one, we have not begun this process. So the Ag Health team has agreed to participate in this process because we believe it would be valuable. So we really haven't started.

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But, in answer to some of the questions that I heard, first is that we have data from when we began the study to show that there was certainly some instances of non-label or violating the label. As you are probably aware, pesticide exposure, one of the big areas is the hand and dermal exposure through the hand.

So the label would ask for chemically-resistant gloves. In as many as 20 percent of the population, we would see that it was cloth gloves that were being worn. So this would be a direct violation of the label requirements.

And with regard to specific large exposures, we find that there was 16 percent when we started of the population that had an episode where there was a large, large exposure, but only about 2 percent of those were reported to a healthcare provider, meaning that that information would not get into databases that were based on healthcare

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provider information.

DR. BAILAR: I am really interested in these violations because those much higher exposures are the places where you might be most likely to find effects.

CHAIR HEERINGA: Other questions of clarification? Dr. Portier?

DR. PORTIER: Jeff or Shalu might be able to answer this. In the previous Panel review of the PHED database, one of the issues was kind of the oldness of the data. Has the database been updated significantly since that 2007 review before the Panel?

MR. DAWSON: Jeff Dawson, OPP.

No, you bring up a good point. We may or may not have mentioned this in the paper, and for those of you who are new to this concept of the PHED, we are actually involved in a large process right now to update that. So, I think part of the timeline of this case study would be, as the new information comes online, that where we have

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considered, for example, more rigorous survey design elements to it, and identifying more modern practices for monitoring purposes, we will integrate that in as it becomes available.

DR. PORTIER: Yes, what brought that to mind is looking at your 3.7 versus 3 comparison, and with newer information on expected lower exposures with PHED activities, that could actually bring those more in line.

MR. DAWSON: You are absolutely correct, and we definitely will be looking at that as the new information.

CHAIR HEERINGA: Other questions of clarification? Yes, Dr. Hayton.

DR. HAYTON: Yes, Bill Hayton.

I just want to make sure I understand. I think I understand this correctly, but low-level long-term exposure is not differentiated from the short-term high-level exposure in terms of the metrics? Or they come out the same?

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MR. DAWSON: Jeff Dawson again.

In our risk assessments, we actually look at varying durations of exposure. For example, for doing a cancer calculation, we will try to adjust for values that are more appropriate for lifetime estimates of exposure.

And to follow up with your question and Dr. Portier's question, in the new data that we are getting, and also in exposure data and also efforts to collect better exposure factors information, we are very much interested in having better means for looking at distributions of risk factors that would allow us to be able to better predict that kind of a probabilistic outcome, if you will.

DR. HAYTON: Okay, thank you.

CHAIR HEERINGA: I think that, at this point, we are right on target with timing. I am going to call lunch break. I think one hour, Myrta?

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Let's actually give you an extra 10 minutes because of the turnover on the lunch places. So let's reconvene at 1:10.

I thank everyone for the progress this morning. We will begin the afternoon with a final scientific presentation from the EPA staff, and then turn to the period of public comment.

Just make a note, if you would like to make a short public comment, members of the audience, and have not registered with Myrta Christian, please see her. At this point, you would be limited to the standard public comment of five minutes. But if something has come to mind that you would like to make a public comment, please see Myrta at the break. Otherwise, we will see everybody at 10 after 1:00 to start up again.

Thank you.

(Whereupon, the foregoing matter went off the record for lunch at 11:59 p.m. and went back on the record at 1:11 p.m.)

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A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

1:11 p.m.

CHAIR HEERINGA: Welcome back, everybody, to the first day of our meeting of the FIFRA Science Advisory Panel on the topic of the draft framework and case studies on atrazine, human incidents and the Agricultural Health Study: the incorporation of epidemiology in human incident data into human health risk assessment.

At this point in the proceedings, we have heard four, I believe, of five scheduled presentations from the scientific staff of the Environmental Protection Agency. We are going to start the afternoon with the fifth.

Dr. Levine, if you would like to introduce the speaker?

DR. LEVINE: Yes. I would like to introduce our last speaker, who is speaking on a new topic, and then Anna will sort of sum up.

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Sarah Winfield has a biology degree from Harvard University, and she is leading our current efforts in using human incident data. She will discuss a case study being developed by the incident team on diazinon.

MS. WINFIELD: Thank you, Dr. Levine.

As articulated by Drs. Bradbury, Levine, and Lowit at the beginning of these presentations, and as laid out in the framework, human incident data are one type of human data OPP is looking to work into our risk assessment process.

The diazinon case study is intended to illustrate how we look at human incident data in OPP, and this presentation is an opportunity to both share and eventually get feedback on how we consider, evaluate, and use this data before taking the next step, and integrating the information with other types of human data.

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So, briefly, although I am presenting today, this is most certainly a team effort.

I will first provide an introduction of human incident data in OPP, then discuss our data sources and how we evaluate and use the information in our pesticide licensing program. Finally, I will illustrate the overview by discussing our case studies, which demonstrates how we routinely look at incident data for pesticide risk assessment.

In the early 1990s, under FIFRA, our office began systematically collecting incidents it received from registrants in OPP's Incident Data System, or IDS. The agency defines a pesticide incident as an event in which a pesticide is considered the cause or potential cause of adverse effects to humans, domestic animals, non-target wildlife or plants, or to the environment in general. Although the definition encompasses domestic

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animals and ecological incidents, today we are going to focus on human incidents.

So, generally speaking, human incident data describe acute exposures and outcomes. That is, very few report outcomes based on chronic exposure. They involve a pesticide product rather than a specific pesticide active ingredient, and many incidents may be the result of improper use and not following the label.

So these registrant-reported human incident data, as well as other human incidents directly reported to EPA from the public or other government agencies, are stored in IDS. So, in the past, human incident data have been included in our reviews and our reevaluation pesticide program. And more recently, we have been focusing on even better integrating this type of data into our pesticide reevaluation program.

So one of the ways we have

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improved in respect to the use of incident data over the years is considering additional sources to complement the information already collected in IDS. So listed in this slide are the additional databases we access, and I will go into each of these in a little bit more detail later on in the presentation.

Although this list is not a comprehensive list of all potential pesticide incident data sources, taken collectively, they provide a rich source of feedback to the agency on registered pesticides.

So the agency uses these sources of human incident data in a variety of ways. We use them as part of OPP's performance accountability program to ensure that the risk management actions taken by OPP to protect human health and the environment are, in fact, protective. We use the data as a risk communication tool to really illustrate pesticide risk when we are informing decisionmakers or stakeholders and the public

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about the importance of safe use.

And we use these data as another important source of information to be used to contribute the problem formulation and risk characterization steps in pesticide risk assessment. This particular use is the focus of today's presentation.

Generally, these various databases are important resources, as they systematically collect information, but it is important to note that there are inherent differences across each data source. These differences are noted in the areas of coverage, whether collection occurs at a national or state level; also, in regards to the confidence and certainty we have in the database, which is largely dependent on the degree of followup conducted by health professionals collecting information. Also, the types of fields and parameters collected vary across these databases, and the databases vary in their usability.

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Depending on the issue of interest, it is really the combination and consideration of all these differences that determines to what extent the agency can rely on this data and/or databases for regulatory determination. So, to illustrate this, I will briefly discuss each database, each of the databases listed in that previous slide.

We will start with OPP's own database. IDS is a system that has been in operation from 1992. It is a centralized system that collects direct reports of incidents to the agency from across the U.S.

Another asset is that there are case reports or narratives for each incident with varying levels of details. However, there's no effort at validating or assessing how likely it is that the reported exposure is related to the reported outcome.

Also, currently, the characteristics of each of these narratives are not electronically entered into a

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searchable database, which makes it more difficult to query and pull up the information.

Now, that said, we do have an office-level incident team, established in June 2008, that is focused on developing a strategic plan to improve the agency's management utilization of incident data across the board. Part of the effort is to develop an electronic database for searching, sorting, and managing incident data, with the aim that it will also address the labor-intensive querying that currently takes place with the IDS system.

So, for PCC, the agency has purchased data from 1993 to 2005. We are currently in the process of receiving data from 2006 and 2007. This database is also national in scope, but the incidents are recorded by trained professionals who do designate whether the exposure is likely to be related to the outcome.

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And compared to IDS, PCC is more automated and easier to pull and evaluate data from. That is, it is relatively straightforward to put together a trend-over-time chart or to summarize the severity classifications of the incidents for a particular chemical.

However, there are no narratives with PCC incidents; whereas, the narratives from IDS provide a rich source of information on particular aspects of typical exposure scenarios and sometimes particular health effects.

I guess highlighting this is meant to illustrate that the different database characteristics translate into strengths and weaknesses, depending on what question is being asked or addressed in the risk assessment process.

So NIOSH SENSOR provides another example. We have just discussed that IDS and PPC have extensive coverage. That is, they

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receive many reports of incidents from across the U.S. So these databases are particularly valuable for providing trend-over-time information or determining whether a risk mitigation action has had an effect; whereas, NIOSH SENSOR is limited to 12 states. So it may not be providing a full national picture of what is happening.

Now, that said, NIOSH SENSOR is populated by trained professionals with expertise particularly in pesticide information. So we have more confidence in the information provided for each incident, based on the followup we know that is conducted, as well as the certainty index included in this database.

So, similarly to NIOSH SENSOR, the California Pesticide Illness Surveillance Program, or PISP, is limited to coverage from only one state. But, again, the incident information is input by trained professionals with expertise in pesticides, and there can be

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extensive followup on each of the reported cases. So, again, there is a high level of confidence in the information provided for each of these incidents.

And the last database we will be talking about is NPIC, which is another source of incident information, but it is operated, the Center is operated on a more limited scale than PCC and receives fewer incidents than either PCC or IDS.

Regardless, you know, if a trend or pattern is discerned in PCC or IDS, this is also national scope, and it can be used to see whether we can demonstrate consistency across different sources.

So, while each database has strengths and limitations, taken collectively, they do provide a more holistic picture on pesticide use in the general population.

So we have just discussed the various databases and their strengths and weaknesses, but there are also strengths and

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limitations across all incident data that should be considered. As a whole, incident data provide information on what is happening in the real world. So, unlike laboratory-generated animal toxicity data, there is no need to extrapolate from animal to human.

Human incident data predominantly provide information about acute hazard and exposure. And when patterns of misuse emerge, the agency can target risk mitigation efforts, such as label improvements.

But incident data are not a panacea. One of the main limitations of human incident information is the difficulty associated with establishing a causal determination between exposure and outcome, as indicated kind of by the inclusion of a certainty index field in most of these databases.

Another significant limitation is the lack of context or baseline available to consider incident data. Again, for example,

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does a high frequency of reported incidents for a particular chemical signal a problem or an issue, or does it signal a very large market share?

Additionally, incidents are mainly self-reported and typically neither exposures to a pesticide nor reported symptoms are easily verifiable or reliable. But, as described earlier, different databases have different levels of followup, different certainty associated with them.

And finally, these databases are likely to underestimate the incidence of exposures due to under-reporting.

So, despite these limitations, incident data are important information for the agency to consider in its reevaluation of registered pesticides, which we conduct on a chemical-specific basis.

So human incidents from each database are analyzed first to determine whether they reflect the regulatory history,

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whether risk mitigation actions or new registrations are reflected in the data.

We look to human incidents to see whether they signal a particular hazard potential. Do we see many deaths associated with a pesticide or a higher proportion of more severe incidents? Or is there a pattern of symptoms that we see?

And we evaluate this data to see whether they signal a particular exposure potential. We talked about just a high frequency of incidents or trends over time, or we might see other factors or particular products that kind of pop up repeatedly.

Additionally, narratives of more severe incidents are often evaluated more closely to look for strength of association and temporal association between time of exposure and effects reported.

So, when evaluating this data, after looking for patterns and trends in each database, we look across databases to see if

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any of the patterns or trends identified are reproduced, to see if there is consistency.

And these analyses as a whole are then considered alongside the agency's understanding of the chemical, the chemical's designated purpose, the potential for exposure, you know, what we know about how it interacts in the biological system or in the environment.

As intimated, this incident data evaluation is really anchored on the same weight-of-the-evidence approach described in the framework, where we look for strength of association, temporality of association, consistency and reproducibility, biological plausibility, and coherence. So we use these principles when considering human incident data, and we will again use them when we relate what we have concluded to other data sources and the information included in the risk assessment.

But because of the limitations of

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incidents data, the agency rarely relies on it alone to make determinations on whether there is an issue with a registered pesticide and/or pesticide product.

So we have just gone over incident data and their evaluation in general in our office. Now I will move into our example.

Our case study is an example of what we would provide to a risk assessment team as they begin working on the preliminary risk assessments as part of registration review, which was described earlier as our current pesticide reevaluation program.

So registration review takes a tiered approach to reevaluating each pesticide. There is a problem-formulation phase, which, as mentioned earlier, is often called the scoping or screening phase in the human health side of things. And for incident information, that mainly involves looking at IDS, our own internal system. We look for a high frequency of incidents or a high

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frequency of severe incidents or another pattern or trend that would trigger a Tier II assessment.

And the diazinon case study is an example of a Tier II assessment, which we would routinely conduct for any chemical in registration review that was triggered for further analysis during the problem-formulation or screening-scoping phase.

So, briefly, I will provide some background on diazinon. As part of an agreement between EPA and diazinon registrants, retailers could no longer sell indoor residential products as of December 31st, 2002, and retailers could no longer sell outdoor residential products as of December 31st, 2004. So, as of 2005, it is unlawful to sell diazinon residential products in the U.S.

Additionally, as specified in a 2002 agency decision document, occupational risk mitigation measures were phased in over the subsequent two to five years after that

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document was published.

So that is a little on its regulatory history.

As for hazard, diazinon is an organophosphate, an OP, and in common with other OPs, diazinon's toxic action is achieved by inhibiting acetylcholinesterase, an enzyme essential for normal nerve and pulse transmission. So its hazard is well-understood relative to most other pesticides.

As human incident data are predominantly reports of acute exposure and outcomes, typical symptoms of acute diazinon poisoning include headache, nausea, dizziness, pinpoint pupils, blurred vision, tightness in the chest, difficulty in breathing, a lot of things, weakness or twitching, difficulty in walking, vomiting, abdominal cramps, and diarrhea.

So this particular case study focused on whether the incident data reflect what we understand about diazinon hazard and

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exposures potential, as well as to see whether the cancellation of all residential uses and the agricultural risk mitigation measures are reflected in the data.

So I am going to highlight a couple of the analyses we conducted. One of the analyses which would typically be conducted as part of a Tier II analysis involves looking for patterns of reported symptoms. As discussed previously, we first consider each database on its own.

As depicted here, Poison Control Center data show ocular and gastrointestinal symptoms as the most frequently reported with miscellaneous dermal and neurological following close behind.

As discussed earlier, PCC data provide national coverage, and trained professionals collect the information. But it is important to reiterate that misclassification may occur when symptoms are reported over the telephone and they are not

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confirmed by a physician or laboratory test.

So, moving on to a different database, NIOSH SENSOR, as I said, provides coverage of 12 states, but the database is solely focused on pesticides, and the professionals inputting the information have extensive experience in pesticides.

Here we see neurological and gastrointestinal symptoms as the most frequently-reported symptom, followed by ocular. So there is some overlap and some disagreement across the databases.

So, when we move forward, jump ahead and look across all databases, the picture gets fairly busy. It is certainly difficult to decipher a consistent pattern across databases that may be attributable to exposure.

But, using what we know about diazinon's acute toxicity, the most frequently-reported symptoms across databases include neurological, ocular,

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gastrointestinal, and respiratory symptoms, which we expect based on everything we know about its acute toxicity.

There are a couple of high-frequency points on the top left of this figure. Actually, one of them isn't really showing up that well. So, at that very top left that I just circled, that is California PISP reporting 36 or 37 percent of the symptoms as miscellaneous.

When you look into things like that for California data, we see those symptoms involve excessive salivation and sweating, which, again, is expected based on what we know about diazinon's acute toxicity.

So here's the graph again, but with bars that really highlight the wide ranges of frequencies reported across the different databases, and just, again, kind of highlighting that, using what we know about diazinon, we can kind of make some sense of it.

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So the second analysis I will talk about looks into the exposure, diazinon's exposure potential, as reflected in the data, and determining whether its regulatory history can be reflected in the data.

So, as demonstrated in this figure, this figure is incidents over time in different databases. It shows that variability can occur from year to year within a database and between databases.

There are many possible explanations for this. You know, it could be a particular pest pressure. There could be a marketing campaign happening. There could have been a public outreach effort. It could be there was one incident with many people involved in it.

But when we look grossly at the trend over time, we can clearly see a decrease that tracks well with the risk mitigation decisions and indicates a decrease in exposure potential. So the residential indoor and

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outdoor uses were prohibited from sale and retail establishments at the end of 2002 and 2004, respectively. So we can see that. And just as another reminder, the agricultural risk mitigation measures were phased in over a two-to-five-year period subsequent to 2002.

So, in conclusion, the case study using diazinon demonstrates how human incident data can be considered and organized in order to reflect and provide feedback on the most recent hazard and exposure assessment, and considered in light of its regulatory history.

As described in the case study, diazinon human incident data mainly demonstrates the impact of previous regulatory risk mitigation decisions without meriting a recommendation to reconsider the most recent hazard and/or exposure assessment.

Of course, for another chemical, the conclusions and the analyses we focused on, you know, are likely to be different.

So, in the beginning of the

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presentation, I laid out that our intent for today was to share what we do with incident data, and then, in the next day or so, get feedback on how we consider, evaluate, and use it.

Although we have described the current Tier II assessment in our case study, as indicated in the framework, our aim is really to conduct an integrated analysis that includes additional types of human data, such as medical case reports, biomonitoring information, and epidemiology studies. And we intend to consider these in terms of biological plausibility and human relevance, ultimately, conducting a weight-of-the-evidence assessment as part of the risk assessment process.

So, to do this requires an interdisciplinary effort, drawing on experience from risk assessment teams and the human incident team to integrate the information as each chemical review developed.

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So we really appreciate the SAP's feedback and guidance in this effort. So just thank you for your time and attention. And with that, I will take any clarifying questions.

CHAIR HEERINGA: Thank you very much.

Dr. Bailor and then Dr. Chambers, questions of Sarah Winfield?

DR. BAILAR: I have two questions. First, when you have multiple sources that cover the same population at the same time, how much overlap is there? Do you know? Have you ever tried to match them up?

MS. WINFIELD: We have never tried to match them up, and there can be overlap. But we don't necessarily see overlap all the time. I think, like some of the more severe incidents, we might look into in a particular database in more detail. When we look at another severe incident in another database, we see that they don't match up. Sometimes

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they do, but a lot of times they don't.

DR. BAILAR: I wonder, I need to think about it, but there might be something to be learned from matching to see where they overlap and particularly where they don't.

My second question has to do with whether there is any part of the population where you could expect to find pretty substantially complete reporting. I am thinking about maybe the AHS population, or whatever, and then match one or more of these sources against that to get a sense for what gets reported and what doesn't.

MS. WINFIELD: Yes, there have been some efforts to kind of characterize how much under-reporting there is. I think those ranged to maybe only 5 to 20 percent of acute exposure incidents are captured.

Even in California, where there's a law mandating, you know, if a physician becomes aware of an acute pesticide illness, they have to report, even there, even then,

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under-reporting is assumed.

I don't know if you want to --

DR. MANIBUSAN: Hi. This is Mary Manibusan, the Chief of the Toxic and Epi Branch.

I just wanted to follow up with Sarah's response to two of your questions. The first question, having to target whether or not there was replication in different databases, overall, as we have evaluated each of the databases, the populations are quite different, and the intent of each database is very different.

For example, NIOSH SENSOR focuses primarily on occupational exposure, where PCC focuses on residential exposure. California data is primarily from California.

To the extent that there might be some overlap that could be possible between the IDS database, our own database, compared to NPIC, which is an information database that we, again, support as well, but there is very

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minimal overlap overall.

On the second question of under-reporting, that is a generic issue across all of incident databases. It is really hard to and a real challenge to try to quantify how much under-reporting is actually evident in the database. It is almost so much epi in a way that we consider publication bias. A lot of the negative results are not necessarily published in epi data. Similarly so for incident data.

It is very hard to try to put our arms around the under-reporting. There's different mechanisms that databases try to do to try to tackle that issue in terms of public outreach, getting information available to workers through PCC outreach.

There's a number of activities that are going on, even within our own OPP office through our Field and External Affairs Division, that reaches out to try to address that and try to make people aware that they

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can and should be reporting adverse reports of pesticide exposure.

DR. BAILAR: I know that it is a very, very hard problem, and I appreciate your difficulties, something that could not be tackled on the national level or even a state level.

But I wonder if it might be worth picking a few small geographic regions, counties or maybe even smaller, where you would make special efforts, a research project, to get complete reporting, and then see how that matches up with the relevant databases.

DR. MANIBUSAN: So I think that is a great idea, and I certainly know that that is a focus of two particular projects. One is the ATSDR National Incident Database that they are trying to pull together because of this reason.

The second project is the Environmental Health Tracking System. Again,

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the purpose is to pull together all the public health information that is available, not just incident data, but biomonitoring information, epidemiology information, all of which is public health-centric, and making that all available through pulling together state portals, so that we can get really a good handle on what type of information is really available. So a very, very good idea.

DR. BAILAR: Thank you.

CHAIR HEERINGA: Dr. Chambers?

DR. CHAMBERS: Do you ever have incidents where there are no health effects? Somebody spills something on them and there is really no adverse outcomes?

MS. WINFIELD: Some of the databases do include those. Poison Control Centers, someone might call in for an incident, but the specialist in poison information makes a determination that the exposure and the reported effects were not related. So it will be an incident that is

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classified as no effect.

Is that what you are getting at?

DR. CHAMBERS: Yes, but you would include that in your database then, just no effects?

MS. WINFIELD: Depending on what you are trying to get out of the query or the investigation, if you want to get a handle on potential exposure, you know, how much potential exposure is out there, and the concern people have about particular pesticide products or the feedback that they are giving us, then we would include that field. But if you are looking at effects, you wouldn't include that.

DR. CHAMBERS: And I wanted to confirm what I think I understood. You are getting really only short-term medical effects, not any long-term followups on these folks, right?

MS. WINFIELD: Predominantly. Sometimes there is a report. It is very, very

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rare. And it is particularly hard to establish a relationship between a chronic exposure and the outcome in a system like this that really provides superficial kind of information.

DR. MANIBUSAN: So I just want to add to that response in terms of reported cases, where there is exposure, but not an adverse effect, we certainly do get that information. But one thing to highlight is that, depending on the database, we might not get a whole lot of narrative to support that conclusion.

There are cases, when you utilize that information, a lot of that information comes from Poison Control Centers because it will be moms calling in because their babies were exposed to a particular chemical. They are not really sure what to expect in terms of an adverse outcome, and they will call for information to the Poison Control Center.

But, yes, I just want to reiterate

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that it is really important to us to evaluate each case, and to evaluate that, we need the narrative. We need to have the critical parameters to understand how, then, to use the framework to determine things like temporality, temporal association from time of exposure to the time of the effect, to understand the association between the exposure, and also to determine if there is biological plausibility in what is reported.

I think one of the big messages that Sarah wants to put forward in the presentation is that we are really dependent on the information on symptomology, and that symptomology is coming in self-reported. That is not yet verified, most of the situations, by health professionals. So it is very difficult to interpret a lot of these case reports.

But to the extent that we can with the information that we have, we certainly try to do that in a weight-of-evidence approach,

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bringing in what we know about the chemical, what we understand about the animal toxicity.

In particular, for diazinon, we understand the mode of action. That has been a real rich database to draw upon, and that is why we chose that particular case study to follow up on, but it is really rare that we have all that information.

CHAIR HEERINGA: Dr. Levine?

DR. LEVINE: Can I just do one follow-up thing --

CHAIR HEERINGA: Yes.

DR. LEVINE: -- in terms of followup on a particular incident? Sometimes in IDS, especially if you have a particularly serious incident, you may get a number of reports on the same incident over time. That will eventually clarify what really happened. But that is the exception rather than the rule.

CHAIR HEERINGA: Okay, Dr. Levine.

Dr. Greenwood and then Dr.

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LeBlanc.

DR. GREENWOOD: Because you know the mode of action of diazinon, and it is pretty well understood, and you showed us how you interpreted the data, would you look at the data for a compound whose mode of action isn't understood in a different way? Or do you handle that differently?

MS. WINFIELD: I think we would still look for a pattern of symptoms. But if it looked like diazinon looked, and we had limited information about mode of action and acute tox in humans, it would be hard to make sense of it.

In those cases, I think the focus would probably be more on, what is the proportion of severe incidents? Or if there were particular severe incidents that we had or incidents like medical case reports or incidents with additional information in it, we would focus more on those more robust incidents to gain information from, rather

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than an overview of the database as the whole, to tell us kind of what is happening.

DR. MANIBUSAN: So, just to follow up on Sarah's response, we often don't have mode-of-action information on every pesticide, but we do have the full animal toxicity battery to draw from. For the particular situation where we don't understand mode of action, we do know what the primary endpoints are. We do know what the target organ is. We do have, for example, a six-pack, is what we call it, for acute toxicity on the particular formulation, and that is really the key comparison here because, remember, we are really looking at product exposure, not just active ingredient.

So that has been a challenge for us as well, to really understand what is contributing to the toxicity that we are seeing in the human population. Is it a contribution from inerts or is it from the active ingredient? And to the extent that we

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have information, we draw upon our acute studies on the formulation to compare to what we are seeing in terms of symptomology in the human information.

DR. LeBLANC: In your incident analysis of diazinon, you list nine symptoms, and then you have this catchall of miscellaneous. And I was wondering if the nine symptoms are based upon expected toxicity of diazinon or are they based upon the incident of reports of these symptoms?

MS. WINFIELD: That is a great question. You know, each database has different symptom categories. So you could probably see, you know, there's a muscular category, but not every database designates that as a category. Not every database has a miscellaneous category. So we kind of do our best to fairly look across at them.

And these categories I think are based on, for like Poison Control Center data, let's say, to take an example, for all

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poisonings that are called into the Centers, they try to basically have a dropdown list of all potential symptoms or effects that might be reported. Then they merge those into these broader categories. That is similar to other databases.

DR. LeBLANC: So, in the case that you gave us, the example, there was one dataset that had a high incident of miscellaneous. And you said that, upon looking at the effects, there were things like excess salivation and things you would expect. Is the reason that excess salivation wasn't put in its own category because most databases don't use it? Is that why?

MS. WINFIELD: That they don't use like what?

DR. LeBLANC: Like you couldn't use salivation as one of the symptoms because most databases don't use salivation as a symptom?

MS. WINFIELD: That California

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PISP didn't have a category to put excessive salivation in. Off the top of my head, I can't be sure, actually, if PCC has excessive salivation under miscellaneous or under another category.

You know, IDS, we actually draw those symptoms out of the narratives.

DR. LeBLANC: Right.

MS. WINFIELD: Yes. Okay.

CHAIR HEERINGA: Dr. Reed? And then I would like to move on.

DR. REED: So let me just get a better sense. First of all, so when a 6(a)(2) report comes in, you don't usually go and tease it out? I mean, if there is followup, you are going to get a subsequent 6(a)(2) report, but when you have a 6(a)(2) report, you don't actually investigate into it, right?

MS. WINFIELD: Our team doesn't, and the office does not investigate every single incident. But there are a couple of people who do follow up and investigate

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incidents that trigger concern.

DR. REED: Okay.

MS. WINFIELD: So our team is focused on the risk assessment side of things and how to kind of look at the information as a whole in a way that is useful to inform the risk assessment.

DR. MANIBUSAN: So, under FIFRA 6(a)(2), we require registrants to submit case reports on each adverse reporting incident. To the extent that we need to follow up, we also have that ability to do so under 6(a)(2).

DR. REED: Okay. So, based on that, is it possible that, when you go back to it, that you can get more information about the exposure? Could that be a possibility or not at all?

MS. WINFIELD: It is a possibility. One of the things or one of the items that is supposed to be included in all case reports that get submitted to the agency is a way to follow up on the incident. So

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there have been a couple of times where, you know, you are looking at a chemical as a whole, and you see an incident that is severe or maybe it is part of a lawsuit or something, and there's a phone number. And you can call and try to get additional information on the incident.

DR. MANIBUSAN: So, right, just to clarify, if you do call back and follow up on a case report, it doesn't always mean that you are going to get better information because this is self-reported. So the exposure will be always a bit in question because it is not confirmed.

I think that is where you are getting at with the questioning.

DR. REED: Right. Right. Yes.

DR. MANIBUSAN: Okay.

DR. REED: I was wondering, you know, even within the whole list of incidents database per se, what is the possibility of getting the exposure data? In diazinon case

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study, you see that there is two distinct sort of things that you can glean from it.

One is the sort of hazard ID gives you the comfort, feeling of humans responding similarly to the animals, which for cholinesterase inhibitors is not hard to imagine. So you are not gaining a whole lot out of it.

And the second thing is it traces quite well with your decisions, but in terms of using this type of data for risk assessment, trying to figure out what else can begin, if you have the resources to go back and look at it -- so exposure is kind of hard to get, huh?

DR. MANIBUSAN: Absolutely, and I think that what you described is the challenge that we are presenting to you today with the framework analysis. It is, how do you piece together all this disparate information and tell us story? I think you can. I think the area of exposure assessment can be put

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together by piecing all the information in a holistic manner.

So you are right, I think what you are describing is the difference that we are trying to display with each of the case studies, you know, looking at retrospective ecological studies compared to a prospective, super-duper, platinum study like the AHS, and now bringing it down to incident data, which is in a whole different realm, but it is human data.

But you also need to understand the complexity, the limitations of this database. It is not going to give you causality for sure. It will give you what Sarah has displayed for diazinon, which is a crude way of looking at trends and signals and patterns, but it won't give you that refinement that you are looking for, as in an epidemiology study, for example, where you can get a better handle on the exposure; you can get a better handle on the hazard.

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That is why we are trying to present to you what we are doing to try to collectively look at all the different databases, so that we can look for things like reproducibility and consistency, merely to trigger for additional analysis, and bringing all the information together.

DR. REED: But let me clarify. You mentioned that you are not going to get causality. I think, with diazinon, you know the mode of action, and it is acute kind of effect. Actually, you get pretty good causality, right? I mean at least you think that, in your head, it is reasonable.

But I think, without exposure, you wouldn't be able to get sensitivity of individuals. Is that what you mean by causality?

DR. MANIBUSAN: I think what I am trying to articulate is that incident data alone could not help you arrive at a causal interpretation. What we have with diazinon is

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a rich database that allows us to merge together our understanding of our mode of action, the toxicity outcome, as well as having a pretty good regulatory history to draw upon. So, piecing that all together, you can arrive closer to a causal interpretation, but just incident data alone, it would be very difficult.

CHAIR HEERINGA: At this point in time, I think I would like to move on to the wrapup. Anna Lowit is scheduled to do that.

DR. LOWIT: Yes, I won't say too much, and I didn't make any slides.

I think you have a solid sense of the significant challenge that lays in front of us to make better use of human information from epidemiology and human incident data. These kinds of data can come from very wide-ranging sources of purpose and scope and quality, and it is our job to evaluate those data and put them in combination with what we know from animals, what you can learn from in

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vitro and the new high through-puts, assays, thinking about it in a toxicity pathway sort of way.

We really believe that thinking about organizing information in a source-to-outcome pathway, and using the tool of the mode-of-action framework as an organizing and reviewing tool is really a solid foundation to doing this kind of integration. You take human information from a variety of sources and combine with everything else you know about the chemical to make a weight-of-the-evidence finding.

We are really looking forward to the feedback that you will probably start tomorrow and also to the public comments.

CHAIR HEERINGA: Thank you, Dr. Lowit.

And just for the Panel's sake, we will have a chance to revisit any questions of clarification tomorrow morning before we start the charge questions, and even during the

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charge question period. If there is information that really would be beneficial to bring forward, we will do that, too.

So, at this point in time, I think I would like to bring this period of scientific presentations and overview presentations to a close, and enter into the period of public comment.

We have a fairly large number of public commenters scheduled. I hope to get the majority in this afternoon. I am not sure that we will get everyone in this afternoon. We want to hold people to their prescribed time limits, but I also don't want to rush things as well in this period.

And again, if you have an interest in making a public comment, either this afternoon or first thing tomorrow morning, please contact Dr. Myrta Christian during the break, our Designated Federal Official.

So we will begin our period of public comment, and these are in the order

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that have been provided to me by the Designated Federal Official.

We will begin this afternoon with Dr. Jennifer Sass, who is representing the National Resources Defense Council.

Jennifer, we have allocated you about five minutes.

DR. SASS: Thank you for the opportunity to comment.

My name is Jennifer Sass, and I am a scientist with the Natural Resources Defense Council, which is an environmental, nonprofit. I am in the health program here in Washington.

Actually, my comments I submitted to the docket, and I also have hard copy to hand out. But, to be quite honest with you, I had a lot of trouble with these. Normally, I have been coming in front of you for about nine years now, and I pretty well know exactly what I had wanted you to say all the time, and I usually go through the charge, I read the documents, I go through the charge questions,

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and I sort of provide for you my answers from NRDC's perspective on those. But I had a lot more trouble with this one.

So I think what I want to say to you is that I think what EPA is asking you is to really sort of sit back a little and just talk about how to use these kind of data most effectively in a public health protective way to set out health protective regulations, which is what EPA's mandate is, to protect human health and the environment.

I don't think I have anything to tell you on how to do that. To be quite honest, I don't think there are easy answers to the charge questions.

So, what I have done instead is to make a longer list, and I am going to give you just a few minutes, on the kinds of things that I think about and that I hope that you think about when you are reviewing the data on atrazine specifically.

So atrazine is sold under

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"musclely" names like Bicep Magnum, and the website says that it is how fields get clean and stay clean. So what this means is that it is a non-specific herbicide. It kills most weeds in the fields before the crop is planted, and it also may kill beneficial plants like nutrient-rich plants that are beneficial and beneficial bacteria in the soil.

It has a half-life of several years, longer in colder climates, like the northern U.S. compared to the southern U.S., and can be detected in most streams and rivers in the U.S. I have provided for reference there the USGS report by Bob Billiam that shows that.

Eventually, some of it even gets into the Gulf of Mexico. It continues its herbicidal activity there, and by threatening algae and other beneficial water plants that provide food and oxygen for aquatic life.

In fact, some of the studies that

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EPA reviewed in its earlier atrazine assessments over the last decade showed that when they looked at atrazine acute effects in ponds, they didn't detect any effects. But when the ponds were allowed to ice over for the winter, and then they looked at it the next spring, because the plants, the aquatic life, the plants in the pond had died because of the herbicide, the fish didn't have enough oxygen to winter over once the ice was covering it. So there's some more complicated issues with things like herbicides and also long-term environmental concerns.

On page 1 of my comments, though, the one that I want you to consider is hormone-disrupting effects. So I have outlined some of the data and why I think that is important. It is not, obviously, a full scientific review.

But it does note some studies that aren't included, human studies that aren't included in EPA's packet that they have

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provided, and that they are presenting to you, including the ones by Shanna Swan at Rochester University and Dr. Kerwin with CDC.

And in Kerwin's study, he looked at applicators, and he actually measured atrazine and its metabolites in the urine and showed their exposure. And what he showed was that applicators have a huge amount of exposure compared to what we would expect in the normal population.

Shanna Swan showed exposure, measured, again, by urinary measurements related to sperm quality, poor sperm quality.

So I am not sure why those aren't included in your packet, but, anyway, I think the endocrine disruptor effects are important to consider.

I think short-term exposure effects are also important to consider, and that is because of the endocrine-disrupting activity. So I have a section on page 2, going to page 3, on some of the different

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animal studies, showing that short-term exposures during critical stages of development caused permanent developmental impacts. There are some rodent studies, as well as some amphibian studies, and many of those studies were done by EPA scientists, which I have cited. So I think those short-term studies during critical windows of development should also be considered.

I have a paragraph from U.S. Fish and Wildlife talking about the importance of these short-term spikes on wildlife as well, though I know you are not considering that at this meeting. So I am not going to talk about it.

On page 3, I have talked about synergistic effects. That has come up already in the questions. I think that is really important. Not only is atrazine not confronted by itself, when people are exposed to it, it is with other pesticides and herbicides as well as industrial chemicals,

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but atrazine is in a mixture formulation with many other chemicals as well.

So I have cited a number of studies that show that atrazine has the potential to act synergistically with other chemicals that it is found with. For example, there was an assessment that reported atrazine as more likely to cause non-Hodgkin's lymphoma in men when they are exposed in combination with other pesticides. That is Dr. Darus at CDC.

There's a number of different non-Hodgkin's lymphoma studies actually cited in the IARC, the International Agency for Research on Cancer assessment. I have talked about some of this as well. They have a table in that assessment that provides that data.

I know you are only looking at human data, but there is also a study that was published in Nature last year, I believe, 2008, by Dr. Rohr, Jason Rohr. It showed that atrazine caused different kinds of deformities

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in amphibians, and that when it was in combination with phosphates, which are commonly found in agriculture as fertilizers for corn and sorghum, that it was much more toxic. So these studies are red flags.

The USGS has also found that atrazine is detected in combination with other pesticides in streams and surface water. In fact, the USGS survey found atrazine in water about 90 percent of the time in agricultural streams. All of the time it was with more than one pesticide. About 20 percent of the time, they had more than 10 pesticides they found.

So, failing to consider co-contaminants or even calling co-contaminants confounders and eliminating studies that have those, I think would be a poor reflection on reality with how common it is to find it in co-contaminants.

On page 5, I have a table for you. This is from EPA's data, based on water

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monitoring. What I am trying to show here is we have a report that my organization put out last year, late 2009, I think October, so a couple of months ago. It is available on our website and has a lot more of these data.

But this particular one that I have picked for you is total chlorotriazine metabolites. So it is atrazine and the metabolites. The reason why that is important is EPA considers atrazine and its metabolites to have equal toxicity, and so evaluates all of them, which is appropriate.

What this measured was the total chlorotriazine detections in drinking water. So, again, not surface water, not groundwater, but actually tap water. This is finished drinking water, the stuff that comes out of your tap.

And what they found was that, if you look at this table, you will find some that have an annual average that exceeds the 3 parts per billion, which is the drinking

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water limit. But, most of the time, what you will see is that it doesn't exceed an annual average of 3 parts per billion, but, yet, they have these peaks that can go much higher, spikes. Some of those spikes are in the double digits, and some of them will last for days or weeks.

The top one you see in Illinois here, big corn grain country, it was as high as 43 parts per billion, and it stayed in the double digit for the next 22 days.

So, considering atrazine and its metabolites is important, too, because of their toxicity and because of their detections.

And the last paragraph, on page 6, so my conclusion, I just want to point out to you I guess this isn't for the Scientific Advisory Panel, but consideration for the EPA in registering atrazine or allowing the continued use, registration and use of atrazine. There is supposed to be a

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cost/benefit analysis. In other words, the risks of the chemical are supposed to be measured against the benefits, and the benefits are economic, the economic benefits of the chemical.

There are some analyses that I have cited here that show that, actually, atrazine provides only a modest benefit in terms of crop yield production. It is under 2 percent in a number of them, 2 to 3 percent in a number of the different analyses.

The one I have discussed the most is one by Dr. Frank Ackerman at Tufts University. So, really, the economic benefits are very modest, and that is not even going into whether or not you need such overproduction of corn in this country. That is for EPA to consider.

For you, I think I would just like to point out how important I think those different endpoints are, co-contaminants, metabolites, and some of the exposure studies

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that aren't presented to you by EPA in this package.

Thank you.

CHAIR HEERINGA: Thank you, Dr. Sass.

Comments or questions of clarification for Dr. Sass?

(No response.)

Okay. Thank you very much.

Our next scheduled public presenter is Dr. Gerard Swaen who is with Dow Agrisciences. Dr. Swaen has been allocated 20 minutes in advance agreement with the Designated Federal Official.

Panel members and, also, members of the public and audience, the presentation materials, all of the presentation materials and any materials, of course, submitted to the DFO will be on the docket. Again, there's probably a little bit of a delay to get materials posted. So everything that is being presented and being received by the Panel

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should be publicly accessible.

Dr. Swaen, please.

DR. SWAEN: Thank you very much, Mr. Chairman.

My name is Gerard Swaen. I am an epidemiologist by training, and I work for the Dow Chemical Company, and based in the Netherlands.

I also have an honorary appointment at the University of Maastricht in the Netherlands and am a member of several of the permanent committees of the Dutch Health Council, among which there is one that sets the occupational exposure standards and also makes carcinogen classification.

I have mostly conducted during my career epidemiology cohort studies on worker populations exposed to acrylonitrile, ethylene oxides, dieldrin/aldrin pH, carbon disulfide, and a number of other chemicals.

Of course, being an epidemiologist, I believe human data to be a

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crucial part of the information used for risk assessment. However, there are some quality issues, and it is very important, I think, to compare the value of epidemiology data with the toxicology data, and they both should be taken into account.

My presentation will describe how more evidence-based approaches may contribute to risk assessment, making them more transparent, systematic, consistent, reproducible, and science-based. The presentation basically follows the charge questions on the framework, as given in the memorandum of 12 January 2009, in order to facilitate the discussions by the Science Panel.

So these are the four charge questions that were in the memorandum. I basically will focus on No. 2 and No. 3, but I will go through them one by one.

On the strengths and limitations of epidemiology studies, I would certainly

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recommend the EPA to take into account the essential difference between an exploratory analysis and a hypothesis-driven study.

In 2001, I published a study which I did together with two colleagues of mine at the University, and I analyzed, I compared 150 false-positive epidemiology studies with 150 true-positive epidemiology studies. A false-positive epidemiology study, for example, is a study reporting an association between benzene exposure and lung cancer. That has not really been reproduced that often.

The study showed that those studies with no specific a priori hypothesis had three times more likely risk to generate a false-positive study. Those studies with an a priori hypothesis also have a very small likelihood of being false-positives, but in case of exploratory analysis these type of results were threefold, were three times that prevalent.

Also, I recommend to take into

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account publication bias. I think it is very important to understand that in the scientific literature positive studies are overrepresented compared to negative studies. I don't have any evidence for it. I don't have any empirical basis for that.

Finally, on this charge question, I recommend the Committee to look at the ECETOC Report No. 104, which provides a framework to integrate human data and animal data and come up with a framework for risk assessment. This report is probably going to be the basis for some of the rich guidance that is still now under development.

Use of incident data, charge question 2, I think it can be a very important source, providing it is about acute effects, as we have seen just a few minutes ago, and acute effects being specific for a chemical. And of course, provided that the analyses done are hypothesis-driven and not just of an exploratory nature.

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I don't think that incident data can be very helpful for multifactorial diseases or diseases with an unknown etiology because it will not be possible to take into account the effect of these potential confounding factors.

The mode-of-action framework for human data, I believe that epidemiology studies is not going to contribute that much. I take charge question 1.4 before charge question 1.3 because the rest of my presentation will be about charge question 1.3.

The application of the Bradford Hill criteria, I strongly recommend doing that. I think the Bradford Hill criteria are the best available guidance for causal inference. However, they should be applied in a very systematic manner, and that is something that is not really done very often.

Even if you look at the IARC evaluations, which I am going to use later on,

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it is very uncommon that an evaluation will go through all the nine Bradford Hill criteria.

These are the Bradford Hill criteria. You can have modified criteria, and so on, but, essentially, there is not that much difference.

Now, if you use the Bradford Hill criteria for causal inference, you may come across two weaknesses. First of all, it is not clear how to weigh this criteria against each other. It is not clear if strength of the association contributes more to a causal relationship than consistency or analogy or exploratory or experimental data. This is not clear at all.

A second weakness is that in most cases the evidence available on a chemical is, from my perspective, insufficient to come to a yes/no conclusion. Most of the results are somewhere in between zero percent probability or 100 percent probability of the real causal association. It would be good to have an

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instrument that can help assessing the probability of the causal association.

Now, together with colleagues at the University of Maastricht, we conducted a study and we evaluated a large database with the objective to develop an approach for causal inference that applies to Bradford Hill criteria in a way that is based on empirical evidence that can be reproduced and can be used on other associations also.

We also developed a model that would give us the opportunity to assess the probability of an association being causal, rather than this very unlikely yes/no outcome.

So the research questions were: how can we determine the weights of each of the nine Bradford Hill criteria based on evidence, and can we develop a model that will provide a probability estimate for causality rather than this yes/no association?

In order to do this, you need gold standard data. You need somewhere a database

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that tells you this chemical is a carcinogen, this chemical is not yet a true carcinogen, and you need to have evidence that will support or in a certain magnitude it will support the nine Bradford Hill criteria.

Then, of course, you need to apply the Bradford Hill criteria and let the data determine the optimal weights for each of the nine criteria. The best available gold standard for this is the IARC database. At the time we did this analysis, there were 159 agents evaluated by IARC either as category 1 or 2A, category 1, a proven human carcinogen, category 2A, a probable human carcinogen. So the contrast we have here is between category 1 and 2A.

We evaluated all the evidence that was used by IARC at the time of their evaluation for these 159 agents. So we went through all the literature that you can find in the monographs and we assessed the probability that each of the nine Bradford

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Hill criteria was met. Assessing the probability that a criterion is met requires a number of algorithms which you can find in the publication that came out last year.

The database, the probabilities that we estimated, we analyzed by means of discriminate analysis, and the results show that a model can be made that includes, that contains the weights for each of the nine criteria.

It also showed, to my surprise, that strengths of the association, consistency, and experimental evidence are the three criteria that contributed most. My a priori idea was that dose response would be one of the three that would come out as most important. However, I am now stuck with these three because these are the ones that are empirically-based.

This is the model. As you can see, strengths, consistency, and experimental evidence work well. They explain most of the

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variance, and you can apply this model to any type of association that you would like to assess the causality for.

Here you have an example for cigarette-smoking and cancer, and the algorithm tells you that, if you have relative risks over 10, then the probability that the strengths criterion is met is 95 percent. So these algorithms were used to develop the model, and you, of course, should speak to the algorithms when you try and do another assessment.

2,4-D and non-Hodgkin's lymphoma, a chemical that is produced by us, strength of the association is met with a probability of about 30 percent, which only is a relative risk between one and two, and the algorithm will tell you that you should stick to the probability of 30 percent, and so on.

So you use all the evidence that is available to assess the probability of each of the nine criteria being met. So the

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righthand column is an expert judgment affair. However, the weights are empirically-based.

Another example is the gasoline station attendant. You go to the literature; you can find evidence in support or evidence against a causal association for cancer risk from being a gasoline station attendant.

The strength is designated the probability of 60 percent because there is one study that reported a relative risk of 3.6. I am not going to discuss the study at the moment, but that is just the algorithms that have been used in this analysis.

Overall, the probability that the association between being a gasoline station attendant and a cancer risk afterwards is estimated to be 15.4 percent, when you use this model.

So the results are that we now can apply the Bradford Hill criteria to other scenarios with using these empirically-based weights. They are based on evidence. The

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model appears to work well, although now I am going back to the pitfall and making a circular reasoning. One hundred thirty of the 159 agents would be classified correctly, but I want to depart from classifying these agents. I would rather score or estimate the probability of the association being causal.

So we have two advantages and two issues that I still need to work on. We have now empirically-based weights, and we have an estimate of the probability of an association being causal.

The two issues remaining, of course, are the expert judgment by determining the probability that each of the nine criteria is met. But it is transparent. I can tell you, I can explain how I came or how we came to the 90 percent or to the 95 percent.

You can deviate. You can say, no, I think it is 50 percent, and then you can use those probabilities and assess the probability for the causal association.

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The other issue, of course, is that it is completely based on cancer endpoints. It is not clear whether or not this can be used for neurotoxic endpoints, developmental endpoints, or sensitizers, or whatever.

Now I come to a very different approach, which at the moment I call evidence-based thinking. And for that, I would like to make a parallel, I would like to draw a parallel with clinical epidemiology.

The clinical epidemiologist, the task of the clinical epidemiologist is to help the doctor come to a correct diagnosis and start the correct treatment. Now, for example, the patient presents himself to the doctor with a certain set of symptoms. In that situation, the doctor must establish the diagnosis before starting the treatment.

So he will send in the patient to undergo a certain number of tests that will give him more information on the presence of

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the disease or the absence of the disease. So he needs to make that decision: how probable is the presence of the disease in this patient?

Each test result that the doctor will get back will add to the probability that the patient has the disease, if it is positive, or it will subtract from the probability that the patient has the disease, if the test is negative. Of course, the value of the test that you have conducted depends on the sensitivity, the specificity, and the predictive value of that test.

And here is how the sensitivity and the specificity are obtained. You need data, you need a gold standard. You need to see who really has the disease eventually, who develops the disease eventually, and who is free of the disease.

With this type of data, you can estimate or you can calculate the sensitivities, that is, of course, the

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percentage of patients who test positive on the disease. Specificity is the percentage of patients without the disease that, indeed, test negative.

So Bayesian thinking implies that there is a prior probability that the patient has a certain disease. The patient presents himself with a set of symptoms. If the test is positive, the probability will increase. If the test is negative, the probability will decrease. There are false-positives and there are false-negatives all the time.

Now we apply this way of thinking to health risk. The parallel is, of course, that each type of study is a test with a certain sensitivity, a certain specificity. There are false-positives and there are false-negatives, and there is a predictive value of a positive test.

And with tests, I mean the Ames test, a long-term rat study, a long-term rat study tested at the maximum tolerated dose, a

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long-term rat study not tested at the maximum tolerated dose. These may have different predictive values. A case-control study, a cohort study, instant data, these are all tests.

We should try, or at least that is what I am going to try to do, is determine the test characteristics of each these types of studies. This will require a substantial data collection effort because you must collect data on the large number of chemicals, and, of course, the chemicals, they stand for the patients in parallel. Then we should collect the test results for all these chemicals specific for the type of test that we will apply in risk assessment.

We need to establish a gold standard. That is going to require some discussion. And for each type of outcome, we probably will need a different gold standard. For neurotoxicity, we will have a different gold standard than carcinogenicity. We will

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need different tests with different test characteristics.

So, as an example, we have a data package which consists of a positive Ames test, a positive long-term rat study, a positive case control study, and a negative cohort study.

On the assumption that we have the test characteristics for all these types of information of all these tests, we can now follow this line of reasoning.

The prior probability that a random chemical is a carcinogen is very low. It is about 1 percent. If you take a random chemical, the probability that this chemical is a human carcinogen, that is the gold standard for human carcinogen, is 1 percent.

Now we have a positive Ames test. So the probability is going to increase to 10 percent. We add a positive animal study, and the probability, again, will go up to 40 percent, and so on and so on.

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Of course, the percentage added or subtracted depends on the test characteristics of the test. It depends on the sensitivity and the specificity.

So, an evidence-based approach requires or will be based on the predictive value of each of the tests that we use, standard or non-standard, in risk assessment. The result will be the probability that the association is causal. It sounds very nice, but it is very difficult to obtain because, first, we must determine the gold standard. What is really what we want to do in risk assessment? Do we want to do carcinogen classification? Do we want to do regulation? This is what is going to determine the gold standard. And in addition, it will require a well-established, extensive database on a large number of chemicals.

I have two summary slides. In assessing the quality of epidemiology studies, I would strongly recommend to include the

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distinction, the very important distinction, between exploratory analyses and hypothesis-driven analyses because the first one has a three times higher risk of being a false-positive.

The application of the Bradford Hill criteria I think is very appropriate, but it should be done in an empirically-based manner. I have described just an example. It is certainly going to be possible to improve this type of analysis. Expert judgment meant that we sat down with the three of us and we made this assessment, but expert judgment may be better done by a panel and by consensus. But it is possible to apply the Bradford Hill criteria in an empirically-based manner.

I think the evidence-based approach is promising. However, it will require a huge effort to develop this approach. I am not sure if it ever is going to replace expert judgment because I think the default is still there always needs to be an

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escape. Even if the evidence-based risk assessment tells you a carcinogen or a chemical is not likely to be a carcinogen, there still needs to be an expert who can take the responsibility and say, yes, we are going to designate it to be a carcinogen.

Thank you very much.

CHAIR HEERINGA: Thank you, Dr. Swaen.

Questions from the Panel for clarification on the material Dr. Swaen has presented? Dr. Bailor?

DR. BAILAR: There is a great deal here to respond to. I will limit myself to two points.

One is I am a little bit concerned about the sharp dichotomy between positive and negative studies. Most are not that clean. We have to make decisions which are positive or negative, but conclusions, based on a scientific study, are generally somewhat more nuances. I would be more comfortable if I saw

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that built into any kind of a scheme like this.

The second has to do with not misinterpreting what Bradford Hill was trying to do. He was bringing some clarity and organization to a field of inquiry that was just chaotic, and I think it was a marvelous second step forward.

I think it is interesting that his criteria can be divided into those that deal with individual papers, those that deal with the evidence as a whole, such as in the first case temporality; in the second, consistency. And then there's some that really refer to both of those, and I think these have to be taken in sequence.

I will just add that I called it a second step because Hill was not the first to do this. They are commonly attributed to Bradford Hill, but there is a scheme very much like this that came out a few months earlier in the 1964 Surgeon General's report on

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tobacco and lung cancer. I would like to see our report at least make a point that that Surgeon General's report was really the first to lay this out and should get the credit for leading the way. We can certainly do that.

CHAIR HEERINGA: Other questions of clarification for Dr. Swaen?

(No response.)

Not seeing any, thank you very much.

Oh, we will go over to Dr. Bove.

DR. BOVE: You were puzzled that dose response did not get much weight. In fact, I am not so sure I understand the weights here, but I will leave that aside for a minute.

Why wasn't dose response given weight in this approach, in your opinion?

DR. SWAEN: I didn't expect it. I thought dose response, it had always been my belief that the strength of the association, consistency, and dose response, those would

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turn up -- that was my prior hypothesis -- those would turn up to be the most important ones.

But the facts, not the facts, the empirical approach shows you it is not that important. It doesn't help you distinguish that much the category 1s from the 2As.

DR. BOVE: Right, and oftentimes the distinction between those two has to do with more evidence coming up, and risk assessments change over time, too. So is that all involved in this evidence-based approach?

DR. SWAEN: Well, it is going to be much more complicated. If you look at the 21st century approach, this toxicogenomics, then we start really getting into the area of specificities, sensitivity, and predictive value. I think if you don't have those risk characteristics, it is going to be very difficult to make sense of all these data that are going to come to us in the short future.

The nice thing about -- well,

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there are many nice things, of course. One nice thing about the analysis is that, if you add new information, you will see that, for example, consistency is going to go down because you have the new study contradicts the earlier studies. So you can do the analysis. You can say the probability that the consistency criterion, which is not really criterion, in fact, it goes down from 30 percent to 20 percent. I mean you can do the calculations and you can see the probability doesn't really change that much.

CHAIR HEERINGA: Dr. Reed? Then I think we will move on.

DR. REED: You are talking about dose response, but the three examples that you have given, example No. 2 and 3 says no dose response analyzed. That might sort of explain -- maybe the data itself is harder to come by.

DR. SWAEN: Yes, the algorithm in the paper, which was published last year, will tell you, and it will tell you something about

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how you should classify or how you should evaluate the dose response. Because in many occasions, it is not given. That is, of course, something different than the completely flat dose -- a negative study, because there will not be a dose response there.

CHAIR HEERINGA: Dr. Lu, did you have a question?

DR. LU: Yes, I do.

Say the agency wanted to adopt your evidence-based model. I mean, in your presentation, it seems only a significant factor which is the uncertainty. There are many cases that, say, for example, a pesticide applicator living in Iowa, that he is diagnosed having non-Hodgkin's lymphoma today. When you ask -- and you mentioned that it is just like, you know, if you perform something like in a doctor's office, the testing, whether there is 2,4-D residue in this patient's body, which obviously would not

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happen because the previous exposure occurred 10 or 20 years ago.

So, I mean, we are dealing with this uncertainty here. But in your evidence-based model, how would you address these uncertainties? So you would take into account exposure that occurred earlier, but not be able to detect it at the present time, when the disease outcome occurs?

DR. SWAEN: Well, an epidemiology study is capable of detecting that. That study should have ended up in the IARC database for these 159. So I have taken it into account.

But the case series, I am not aware of case series -- well, perhaps there are some very specific associations for case series, for example, mesothelioma and asbestos, there, of course, but I an not really sure how this speaks into the Bradford Hill, but maybe that is the default, an expert judgment.

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But I ended the presentation by saying that expert judgment is always going to be necessary. I am never going to rely on any model to make the decisions of the Dutch Health Council, for example. I would always like to have the possibility to step out and say, no, now I am going to deviate from the approach that I proposed myself. I am going to say this is a carcinogen or something else.

CHAIR HEERINGA: Thank you, Dr. Swaen. We appreciate your presentation and the exchange to follow. It is very helpful.

Before we turn to our break, we would like to hear from the next public presenter. This is Erik Janus, who is here to represent CropLife America. Erik has been allocated 15 minutes by the DFO.

Erik?

Erik's presentation is available in PowerPoints as part of the distribution after lunch.

MR. JANUS: And while they are

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opening my slides, I will just get started here and say good afternoon to the panel.

I would just like to thank the agency and the Science Advisory Panel for agreeing to tackle such a hot and timely topic right now.

CropLife America for sure appreciates the ability to sit here and comment on behalf of our members.

For those of you who aren't familiar, CropLife America is a trade association that just represents the companies that manufacture and formulate and market virtually all the crop protection products used in the country. We are celebrating our 77th anniversary this year, continuing on in our role, which is to act and speak on behalf of the agricultural chemical industry.

By way of a quick introduction to myself, I have 15 years of experience as an environmental health practitioner and researcher at all levels of government, with

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industry, academia, and the NGO world. So I have seen a little bit of everything in my career. The last 10 years, I have spent, essentially, doing risk assessment science and public policy work.

Now, as such, my role as a trade association, I come to you today with comments that generally fall into one of four broad categories, and generally are the highlights of the concerns of the industry, the issues and the concerns that the industry has.

So, moving on to the first, biological plausibility, exposure, risk assessment, and then a little bit on incident data, is what I will touch in the next 15 minutes.

Now, in terms of biological plausibility, really the basic question that EPA needs to answer here is how well do the epi datasets agree or disagree with the biology and the toxicology datasets that exist in large quantity, particularly for the FIFRA

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registered compounds? The second dataset, that is.

You know, unique endpoints, based on hypotheses generated by epi studies, should not be included in risk assessment at this point, if they have not been replicated or are not biologically-plausible.

Granted, not all substances have this wealth of data, but in the case of the active ingredients registered under FIFRA there is an enormous amount of data on the biology and toxicology.

Continuing on, really, the key question in reviewing epi studies is, were they designed to address known or suspected biological mechanisms? It appears that we have concrete data on hazard identification, which is an early step in the risk analysis process, and concrete data on toxicology, and often enough on mechanism of action, but it appears we might be borrowing hazard data from epi studies, but still using the in vivo, the

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more detailed and informative in vivo, in vitro, and soon in silico studies to actually define the dose response relationship and, thus, characterize the risk.

Ideally, one could design epidemiology studies based on the findings of tox data, not vice versa. However, we are never going to confirm mechanism of action at this point.

And I believe this last point, I feel is consistent with the Tox 21 vision here at EPA, which seeks to flip sort of safety testing on its head over the next 20 years and focus on identifying molecular pathways for adverse outcomes and verifying this in human populations, using epi studies and biomonitoring. It was part of the NRC 2007 report that has been mentioned already once today.

Now, moving on to exposure, the bottom line is that generic exposure assessments lead to generic conclusions. We

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have already heard today these can result in misclassification errors, particularly when we are comparing them against biologic measures, such as biomarkers of exposure.

I also think it is important to point out that no method has yet been developed to assess the accuracy of lifetime self-reports of pesticide use, which is, of course, the backbone of the Ag Health Study right now.

Also, I would like to touch a little bit about daily exposure potential, as measured under the Ag Health Study. This can vary widely, as has been shown in past studies, particularly the Farm Family Exposure Study.

Just to pull a couple of points out here, two key components of cumulative exposure, duration and frequency of use, have been found to not agree. It is not necessarily over time, but don't necessarily agree from one survey to another in the AHS,

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as pointed out by Blair and Zahm early in the process.

Applicators are also not uniformly exposed to herbicides during any single day of application. The extent of the exposure may not be consistent across similar herbicide levels in all pesticides. So these still remain as sort of a generic assessment category.

At which point I ask myself, is a generic approach for exposure prediction possible for all pesticides? The answer is probably not, but I wanted to start by focusing on like categories, like classes of compounds of similar properties, similar formulations, similar application practices.

As we have sort of heard, as somebody alluded to earlier today, assignment of workers into evenly-distributed measures of exposure is not consistent with the findings of monitoring data. Biomonitoring data is almost always a skewed distribution, whereas,

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we were talking earlier today about splitting exposure gradients into tertiles or quartiles evenly distributed.

Another important thing to point out is that there's a general lack of overall biomonitoring data on the Ag Health Study cohort, which I think complicates exposure, the algorithm validation process, if you were. We have heard, I think, what, three different compounds this morning that we've got biomonitoring data on, and I think this probably represents something like less than a half of percent of probably the overall cohort. So this is probably a resource issue in the future that could be addressed, should be addressed.

A couple of things I wanted to point out about the Pesticide Handlers Exposure Database, as it came up earlier today. Exposure prediction is limited here. It is not just exposure assessment that limits you here, but there are multiple chemical and

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physical factors that we need to take into account here.

First of all, physical chemical properties of the molecule which impact dose certainly matters here. It is not necessarily captured in the passive dosimetry data of the PHED database.

In addition, exposure prediction based on formulation is limited. Granular and liquid forms can have different exposure potentials.

Then, earlier this morning, Dr. Alavanja pointed out that application methods can also have an effect here, too, in terms of the intensity algorithm and what comes out of that process.

Now moving on to risk assessment, again, if endpoints identified via epidemiology studies are not consistent with the biology, they should not be part of the risk process. I was encouraged to hear a lot of treatment of this exact aspect of the

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problem. Some of the EPA presenters earlier today, when they discussed some of the things they would tackle during the problem-formulation phase, and that is great because that is consistent with the new NRC report in terms of devoting more attention to that. I think it is a crucial part of this particular process, too.

If these endpoints are, indeed, consistent with the biology, then, sure enough, as EPA quotes, high-quality studies with robust exposure assessment may be used to estimate risk, but we need to emphasize that you have to have robust exposure assessment.

You probably hear a lot about this. The weight-of-evidence approach is clearly crucial to determine how do individual sets of research papers, such as the Ag Health Study, stack up against the rest of the epi literature available on a particular endpoint? How does the overall epi literature stack up against the substantial amount of biological

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and toxicological data that we have got on crop protection products?

I would just point out now that it is crucial to talk about this stuff early and often in the game, but, really, the SAP process is not really addressing the weight of evidence in explicit detail. So, thankfully, we have got the permanent members who will be back in September to pick up this conversation.

Moving on, as was brought up by Dr. Swaen, the gap between causality and association is filled by imposing the classic Bradford Hill criteria. This is not an ala carte option. Really, all should be given initial consideration. Again, during the problem-formulation and hazard-identification phase, we need to look at these individual criterion, define them, and discuss them relative to the available information.

Quantitative use of these criterion and the risk process, of course,

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must be fully transparent. We need to identify all the inherent uncertainties, where possible, and quantify those, where possible, which, of course, is the root of the precautionary principle, as I was taught, you know, in grad school, quantification of uncertainty.

Also, this last point, a little similar to the approach that Dr. Swaen just mentioned on the IARC carcinogens. I would like to offer just a couple of thoughts on incident data before I wrap up.

First is a little note of caution regarding the diazinon case study. It does have all the ideal characteristics for this type of assessment. However, I am afraid you are not going to find that in the world of pesticides very often.

In the case of diazinon, you have a very well-characterized symptom of acute overexposure. You had residential uses. You had agricultural uses, and you had a scheduled

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phaseout. So you could take a careful approach and look at this. I don't know that you are going to find that for a whole lot of other crop protection chemicals. I think that is going to complicate the overall interpretation and application of this.

But that being said, CropLife America, I took a look at their proposed approach, and I think it is pretty good. It does a good job pointing out limitations of the data streams, which is probably the biggest, I think, factor at this point, is how you sift all these individual different data streams together, if you do it.

I do have a few suggestions for improvement in terms of the incident analysis process. Since the residential incidents seem to far exceed the ag incidents in terms of volume, maybe it makes sense to look at these separately. Clearly, there are data quality issues, as you have heard, and will continue to hear with self-reported data, epi and human

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incident data alike.

One rhetorical question I want to throw out there is, how does one do QA and QC on these databases? Does an individual who sets off 10 bug bombs in his small apartment in New York City constitute an incident, when he is clearly not following the label? I don't know the answer to that. I question that.

Clearly, again, we would like to see a transparent and a scientifically-sound process here. I am comforted, again, hearing some of the things I heard this morning with the incident data that appears to be going down the right track.

But we do need to put the total number of incidents in perspective here. I think comparing the overall number of incidents to volume and frequency of sales of certain products is useful, both before and after any risk mitigation measures are taken.

Again, how does one consider an

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off-label incident? How do you treat that data-point?

I just want to wrap up with a few points here. Generic exposure estimates lead to generic conclusions. I can't stress that strongly enough.

Secondly, again, if the endpoints identified via epi studies and incident data, for that matter, are not consistent with the biology, in other words, they are not biologically-plausible, they should not be considered part of the risk process.

And lastly, the weight-of-evidence approach is mandatory here, but just as important are being transparent and using the best available science.

CHAIR HEERINGA: Thank you very much, Mr. Janus.

Questions of clarification on the presentation?

(No response.)

Thank you again.

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I am going to move ahead with the next public commentator or presenter, and that will be Dr. Dominik Alexander, representing Exponent. Dr. Alexander has been allocated 20 minutes by the Designated Federal Official, and then we will move to a break.

For those of you who are scheduled to be public commenters, I am going to try to wrap this up today, so that we get you in there. Our number of people representing the various groups who are here for short comments, rather than hold you overnight, if you had other plans, we will try to get everything in today.

But, for now, Dr. Alexander, please.

DR. ALEXANDER: Okay. My name is Dominik Alexander. I am an epidemiologist with Exponent, and over the course of the next 20 minutes, I will be discussing some of the methodological considerations of our ongoing assessment of pesticides and colorectal

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cancer, a weight of evidence, review of epidemiologic studies.

This work is very much in its preliminary stage. Hopefully, for the September meeting, I will have the opportunity to come back and share the conclusions of this project.

Before I get started, I just want to mention that we do have a multidisciplinary research team. Some of the members are included here who have experience or expertise in epidemiologic methodology, causal applications, weight-of-evidence evaluations, toxicology, risk assessment, and statistics.

Okay. Colorectal cancer, it is the third most common cancer diagnosed among men and women in the U.S. Its etiology is largely unexplained. However, several key dietary, lifestyle, behavioral characteristics have been shown to be associated with both increasing and decreasing the risk of this malignancy.

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One of those happens to be physical activity. We know that farming is an occupation that is physically demanding. Studies have shown that the rate of colorectal cancer is generally lower among farmers compared with the general population, and that result could be due, in part, to the physically demanding nature of the occupation.

We also know that farming encompasses a heterogeneous array of exposures, which vary by type of farming, specific chemicals used, time period of farming, geographic location of the farm.

It has been postulated, based primarily on exploratory studies, that pesticides or specific chemical exposures may be associated with increasing the risk of colorectal cancer.

And to our knowledge to date, there hasn't been a comprehensive or systematic review of pesticides in colorectal cancer in the literature. Therefore, to

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update the state of the science surrounding this topic, we are in the process of conducting a weight-of-evidence evaluation.

I don't have time to go over all the individual facets of our systematic weight-of-evidence approach. However, I will touch upon some key points.

We have just completed the first stage of our comprehensive literature search. In addition, we reviewed the Ag Health Study website, and we identified all studies of pesticides and colorectal cancer.

And I should point out the Ag Health Study cohort is the foundation for which the majority of the chemical-specific studies have emerged. Specifically, there are 25 studies of pesticides in colorectal cancer or specific chemicals in colorectal cancer.

So the focus of the methodological considerations that I will be talking about today should be applied to or will be applied to the Ag Health Study cohort.

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We are focusing on cohort and case control studies at this stage. We are looking at associations between pesticides as a class or as a group, as well as specific chemicals in colorectal cancer. We will be extracting data and information for numerous study characteristics, including the nature of the cohort, exposure assessment, analytical metrics, statistical associations, and so on. We will be synthesizing data within and across studies when we are evaluating the overall epidemiologic evidence.

Our methodological assessment involves or will involve a scientifically-rigorous and systematic evaluation of the epidemiologic literature. Important methodological characteristics, analytical factors will be objectively considered when interpreting the body of epidemiologic data. And we will conduct a critical assessment of internal and external validity.

Now our methodological approach

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will be applied to the literature on pesticides and colorectal cancer. However, the same type of approach can and perhaps should be applied to other cancer endpoints or other disease endpoints.

So, as part of our assessment, we will evaluate how well the hypothesis of interest has been tested in the Ag Health Study cohort. We will look at issues pertaining to the study design being used, the potential impact of confounding, the impact of bias, recall bias, misclassification, selection bias, the direction and magnitude of associations, including the statistical significance power, the precision of associations, and issues involving exposure assessment.

And we will compare the findings that we observe in the Ag Health Study to that of other studies. We will look for methodological and statistical consistency.

Here you can see some of the

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undertones of the Bradford Hill considerations throughout.

Overall, we will look at the consistency of results between and within exposure metrics of the Ag Health Study. We will look at associations for colorectal cancer and separately for color cancer and rectal cancer. The Ag Health Study appropriately reports on these anatomic tumor sites separately.

I, finally, will consider the totality of the available epidemiologic evidence when making our overall interpretation.

So, as we know, the Ag Health Study, it is a prospective design with a relatively large sample size. It does include a semi-quantitative exposure assessment. I will talk about some of the trends in exposure assessment here momentarily.

To date, followup is relatively short, thereby making it somewhat difficult to

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assess rare cancers. For example, the data for colon cancer are much more abundant than they are for rectal cancer, which is reported less frequently.

In addition, we know that exposure is categorized in quartiles, usually tertiles. And if we are starting with a relatively small handful or small number of observed cases, those cases are distributed across the different exposure categories, thereby making single-digit or small numbers in each exposure category.

In a preliminary assessment of many of the Ag Health Studies, it is commonly required that a certain number of observed cases or cases be observed before associations are reported. That may result in a reporting bias. Again, it is a difficulty in really comprehensively evaluating the total body of evidence.

So another potential issue to deal with it involves multiple comparisons. We

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know that upwards of 50 chemicals or compounds are evaluated, 20-plus cancer endpoints, a variety of exposure categories. So, by chance alone, we are going to observe some statistically-significant positive as well as inverse associations. So we need to do a critical assessment of those findings. Are those associations real? We will have to look for consistency within and between the exposure metrics and across studies as well.

Another issue that I didn't include here is collinearity. It is difficult to analytically isolate the independent effects of one chemical on the outcome when the pesticide applicators are exposed to numerous chemicals.

Okay. The exposure metrics, analytical comparisons, these were discussed earlier. The "ever/never" exposed, usually based on internal or external comparisons, are reported in the studies that we have reviewed thus far in the Ag Health cohort.

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The two predominant metrics for data reported are lifetime exposure days, intensity-weighted lifetime exposure days. I am not going to go into all the details of the algorithms or the statistical underpinnings of those metrics.

However, I do want to comment on the trends of associations within and between exposure metrics, and we will be looking closely at associations between the specific chemicals and colorectal cancer within and across those metrics. And I will provide an example of that here momentarily. We will also look at if there is a monotonic relationship, increasing risk with increasing exposure.

And in terms of the referent groups, there's commonly either one or two referent groups that are utilized or at least reported on in the Ag Health Studies. One is no exposure, at least no exposure to the chemical of interest. The other happens to be

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the lowest exposure category. And the selection or determination appears to be commonly based on differences in the baseline characteristics.

So, if we have tertiles of exposure, the baseline characteristics in the third tertile are compared with the lowest exposed category as well as the non-exposed category. And if they are more similar to the lowest exposed category, that may be the referent group that is selected, at least based on many of the studies that we have reviewed thus far.

I feel it should be viewed more as a sensitivity analysis, and selecting one over the other can have a profound impact in these statistical associations observed. And I will show an example of that here shortly.

Okay. So we have lifetime exposure days, intensity-weighted lifetime exposure days. This is just an example of a couple of studies that we have reviewed thus

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far in our preliminary assessment.

Here we have a study of glyphosate and colon cancer. We would presume that, if the self-administered questionnaire for exposure effectively captures the exposure, and the groups are differentiated accordingly, you would expect to see some similar patterns or similar trends of associations, if the exposure is associated with the outcome.

Here we can see, for lifetime exposure, days compared with intensity-weighted lifetime exposure days. We kind of have a mirror image. The association goes up to 1.4, back down to 1.9 in the same study population, the same participants. In the second tertile here, it goes down to 0.8, then back up to 1.4.

The same thing is true for, an example here, for rectal cancer. So, in terms of the analytical considerations, when we are interpreting all the data, these are some of the things that we need to consider and work

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through.

Okay. Now an example of a comparison of the two exposure groups, here we have a paper on colon cancer, where, in fact, they did report associations using both exposure groups, either no exposure as the referent or the low exposure group as a referent.

Again, you can see some pretty striking differences in the observed statistical associations based on the choice of the referent group. You can see the inverse associations here with the not-significant positive association in the fifth quintile. And in the quartile analysis, you can see associations of 1.85 or higher across the groups.

So, again, the choice or selection of the exposure group can have a pretty profound impact on the observed associations. So perhaps it should be viewed as a sensitivity analysis when really interpreting

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the totality of the evidence.

And in this case, the reason is because in the second quintile the association goes down to 0.42, which is considerably lower than the other effect estimate. So, when that group is used as the referent category, it is going to inflate the other estimates, as it does here, in the upward direction.

Okay. Now I would be remiss if I didn't at least have a little comment on recall bias or misclassification of exposure. In reviewing several of the studies thus far, I have noticed text involving non-differential misclassification, and that the observed effect estimates would likely be biased towards the null.

This is not necessarily true. A non-differential misclassification does not guarantee bias toward the null. Empirical evidence has shown that it may produce bias away from the null, particularly if exposure has more than two levels.

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We know that, going back, the exposure metrics that we are concerned with, they do have more than two levels. Here's quintiles and quartiles.

Even compounding this issue is the fact, well, it has been suggested that, even with non-differential misclassification, the highest category of exposure may not be affected. However, that is not necessarily true, either, because if there is misclassification in some of these inner tertiles, this 0.4 maybe be closer to the null, thereby reducing the effect of the highest quartile in this category.

Okay. Just moving on to some other methodological considerations that we will work through in our weight-of-evidence evaluation, in terms of the self-administered questionnaire, chemical formulations may change over time. The reported exposure responses may not account for temporal variability in exposure. The questionnaire

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may not effectively capture exposure for all sites equally; for example, if it weighs dermal exposure more than inhalation.

In terms of the reliability of questionnaire data, that is something that is always under scrutiny, and I guess it always should be under scrutiny. That is how we can improve the accuracy of what we are trying to estimate.

It was alluded to earlier, the Blair 2002 study, where they did show very good agreement or reliability for more of the dichotomous outcomes: have you used this compound or pesticides in the past, yes or no? The agreement did seem to be very good.

However, the agreement is not as good and the reliability is not as good for more detailed exposure metrics, such as duration or intensity of exposure. Those are the ones epidemiologically that we are really concerned with.

In reading several of the studies

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thus far, it is commonly cited that the correlation coefficients or levels of agreement are similar to that observed in nutritional epidemiological studies. However, doing a lot of work in nutritional epidemiology, and being very familiar with the food frequency questionnaire for diet and cancer, those studies should not be viewed as a good measuring stick for reliability. There's several issues there.

What are some methods to validate questionnaire data and to improve the accuracy or to better estimate exposure information? Of course, biomonitoring, which is discussed intensively. The specificity of the biochemical indicator, it may not be specific to a certain chemical exposure or other chemicals may produce the same biochemical indicator. Differences by formulation, and the formulation may change over time. Also, the timing of exposure needs to be considered. If there was a compound or chemical that was

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used 20-plus years in the past, it may obviate the evaluation of using biomonitoring practices to estimate exposure. It may not be feasible as well to sample a very large population, and it may be cost-prohibitive.

Okay. So, finally, the last slide, the generalizability. What we are getting at here is the representativeness of the data, the associations observed in the Ag Health Studies to broader populations.

In the analyses that I have reviewed specific to colorectal cancer, it is apparent many studies are restricted to white males, or white males clearly predominant the study population.

For colorectal cancer, we know that there is a varying distribution of tumors within the colorectum, and they vary by gender and by race. So that limits the generalizability somewhat for colorectal cancer of the data reported in the Ag Health Study.

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And there are 50,000-plus participants, applicators, in the study cohort. Several of the papers focus on, they are chemical-specific evaluations of cancer outcomes. A lot of the detailed chemical-specific information is based on supplementary or more detailed questionnaire information that was only filled out or submitted by a smaller proportion of the eligible study population, sometimes well under 20,000. So, then, the question is whether the sample who fills out the supplementary or chemical-specific questionnaire is representative of the overall study population.

So, finally, at the end of the day, when we are making interpretation, it looks like we will rely upon data largely dominated by one cohort, which is the Ag Health Study. Although it has a prospective design with a large sample size, it still is susceptible to some of the methodological and analytical considerations or limitations that

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other studies are. So we will be applying the same scientific rigor that we do to other epidemiologic investigations to the Ag Health Study cohort.

Again, hopefully, in September, when you folks are meeting about the weight-of-evidence evaluation, I will have the opportunity to come back and share the results, the conclusions of this project.

CHAIR HEERINGA: Thank you, Dr. Alexander. I am particularly pleased to hear your final point. That was my question. I assume this is proprietary work at a point, but whatever could be shared with the Panel, in anticipation of the September meeting --

DR. ALEXANDER: Right, right.

CHAIR HEERINGA: Because it sounds like you are doing a lot of the methodological, statistical type of investigations that are going to have to be replicated.

DR. ALEXANDER: Exactly.

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CHAIR HEERINGA: Any questions of clarification for Dr. Alexander before we move to a break?

(No response.)

Thank you for the presentation.

At this point, what I would like to do is to take a short break, reconvening at 3:30.

We have four additional public commenters that I would like to get in for this afternoon. One of them, the initial one, after our break, from Syngenta, is scheduled for about 45 minutes cumulatively. So I want to make sure that we move directly to that, so we have time for everybody.

So let's, actually, be realistic, 25 of 4:00, let's be back and start again.

(Whereupon, the foregoing matter went off the record at 3:17 p.m. and went back on the record at 3:33 p.m.)

CHAIR HEERINGA: While we are waiting to assemble and get underway, just for

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members of the Panel, there are four documents, two white papers, one dated the 27th, one the 30th, submitted by the team that we are going to hear from, and then the PowerPoint slides. I think there was one other that was submitted right after the lunch hour. So, hopefully, you will find your way through that, particularly the two white papers.

Again, for everyone else, these materials will be available on the docket probably later tomorrow.

Okay. Welcome back, everyone, to the final session for our first day of the FIFRA Science Advisory Panel.

We are in the midst of our period of public comment. My aim is to wrap up the period of public comment today. It will likely take us a little bit past 5:00.

This Syngenta group who will be presenting has 45 minutes. I would like to hold to that today. We will leave the public

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comment period open into tomorrow morning to make sure we wrap up. But to make sure that some of the presenters who have come for shorter presentations can get in on the agenda slot, we will do that.

So, with that, I am going to have to --

DR. BRECKENRIDGE: Thank you, Mr. Chairman and ladies and gentlemen of the SAP. We are very pleased to be back again.

In November, we understood that the agency would be considering approaches for doing weight-of-evidence assessments. Syngenta took the initiative to establish an expert team to help us through a framework, and we are going to discuss that today.

And in the second part of the presentation, we are going to be talking about the application of that framework to the atrazine cases that are being put forward before this.

The presentation on the first

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part, on the framework, will be by the full team. The last part will be Syngenta only.

I would like to identify the members who have participated in this team. Dr. Hans-Olov Adami from Harvard; Sir Colin Berry from Queen Mary University, London; myself and Tim Pastoor, both Syngenta toxicologists; Lewis Smith, who was formerly head of development in Syngenta and now at MRC Toxicology in Leicester; Gerard Swaen, who is also a member of our team; James Swenberg from the University of North Carolina; Dimitrios Trichopoulos, professor from the Department of Epidemiology at Harvard, and Noel Weiss, professor, University of Washington and Fred Hutchinson Cancer Research.

When we started out with this activity in November, we were looking to develop an expert system that would be capable of integrating animal and epidemiologic evidence into a causal inference framework. We were interested in using the best available

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data, developing a transparent process, and using good scientific practices.

With that, then, I would like to turn the podium over to the first speaker, Dr. Noel Weiss.

CHAIR HEERINGA: Thank you very much.

And that is Dr. Charles Breckenridge. I don't think you ever quite introduced yourself.

DR. WEISS: Good morning. I'm Noel Weiss.

When our group met, it was clear that we were going to be wanting to review the results of both epidemiologic and toxicologic studies in trying to decide what would be the groundrules or guidelines or criteria for inferring potential causal relationships between exposure to environmental chemicals and one of a variety of illnesses. I am going to talk about the epidemiology side first before I turn it over to my colleague on my

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left.

The first issue that we had for the epidemiologic studies was to determine what features of these would be of greatest utility in identifying a potential causal relationship. Not every study is as useful as another. We were trying to isolate the features of those that might be particularly useful and, therefore, those studies might be particularly informative in making our judgments.

Broadly speaking, there are three types of epidemiologic studies that we would consider. A fourth type, randomized trials, there's almost never evidence from that source to address this particular issue. So we focused on observational studies, the first of which is what has been termed ecologic studies. This was defined for you earlier today. It is the contrast of disease occurrence across populations or across subpopulations or across periods of time

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within a given population. There is contrast disease occurrence in relation to differences in the presence of exposure of the degree of exposure.

Now these studies, we feel there is at least the potential for them to make an important contribution. They aren't able always to succeed in this, but the potential is there. We felt that if a study could fulfill these three guidelines, then we might pay particular attention to it.

First, there being a large difference in levels of exposure among the population studied or across the time period studied. Second, that there would be accurate and comparable ascertainment, both of exposure levels and disease occurrence. And finally, that there should be little or no difference among the populations with respect to the prevalence of other causes of disease, that is, confounding variables, or if there were confounding variables there, they could be

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measured and adjusted for.

As I say, it is not often, at least in my experience, that all these criteria are met. But when they do occur, we should welcome the studies that meet them.

This is an example, one of the strong biases of our knowledge of the relationship between arsenic exposure in water, arsenic levels in water, and the incident of lung and bladder cancer comes from the unfortunate experience in northern Chile, where there was contamination introduced. Nobody was polluting the water. It was coming out of the rocks in that part of the country, and for a discrete period of time. They could monitor levels of incidence of bladder cancer and lung cancer in relation to the time period in which this contamination was present, and then later was not present. So it can be quite useful.

There are circumstances, to sum things up, where the particular variation that

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we might be wanting to exploit in an epidemiologic study comes not among or within a population, but across populations. If that is true, and if we can have these quality criteria met, then we think these studies can be useful.

Case control studies have been defined for you also, a comparison of the prevalence or history or levels of exposure between ill and well persons. I do case control studies for a living, and I am well sensitive to the issues of selection bias that can be present, the bounding that can be present.

I think with respect to the assessment of environmental chemicals by means of case control studies, the biggest single threat has to do with an impaired ability to accurately measure the relevant exposure, and Michael Alavanja mentioned this earlier. So it is a single biggest problem.

And the fact is that the methods

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we have for ascertaining exposure, be they interviews or records or contemporary, as current levels in cases and controls, in bodily fluids or tissues, all of these can have limitations. The latter you would think ought to be ideal. You are actually measuring the chemical or the residue of the chemical. However, when you are measuring it years perhaps after the illness has been incited, it may simply not be a relevant time period to be measuring that sort of thing.

With that in mind, people have considered doing cohort studies like the Ag Health Study, which can, to a large extent, get around this issue of temporality. You are measuring among healthy people, as far as you know, who is exposed and who is not exposed, or who has different levels of exposure. You can follow these people up for the subsequent occurrence of illness. Usually, you have a more accurate measure of exposure and you get rid of the problem of temporality.

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However, it can happen, depending on the size of the cohort study, depending on the duration of followup, depending on the frequency of the outcome in question, that cohort studies can be hindered by a small number of persons who develop the disease in question, especially among exposure subgroups that you are contrasting.

However, I believe, our group believes that the results of cohort studies can be really important, often because of the ability to study not just residential exposures, but occupational exposures. Many of these chemicals that we are concerned about are present in the occupational environment, and when that is so, cohort studies are facilitated. These cohorts are relatively more easy to identify. They are relatively more easily followed, and they, typically, are exposed to relatively higher levels of the agent.

So, as a consequence, we have

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learned a lot, epidemiologists have learned a lot about chemicals and their relation to disease from occupational cohort studies. Just as an example, if we were concerned about trichloroethylene in residential water supplies, and we wondered if it might be related to cancer, the first place I would look is not at residential studies, which typically involve low levels, and the cohorts are hard to enumerate, but rather to occupational studies, studies of workers who in the course of their employment were exposed to trichloroethylene, and those studies tend to be an important foundation to at least evaluate the proposition that trichloroethylene has some capacity, even at higher doses, to cause one or more forms of illness.

This is Roman numeral II. It says assessment of study quality. Because, in the end, once we have identified the ecologic studies, the cohort studies, the case control

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studies, some decision has to be made about which ones of these are we going to pay particular heed to. We tend to look at the quality. We tend to look at the size, especially the quality, of each type, and decide which ones we are going to really pay attention to.

And who is "they"? Who are we, in terms of making this judgment? Well, I believe it should be groups of experts, people who are really knowledgeable about this, using their own professional qualifications and experience to make such a judgment.

It may be that, on the basis of that judgment -- this scenario I am describing here won't fit every circumstance, but often it is useful to identify studies with minimum limitations and base one analysis simply on those studies. I mean those acceptable studies.

It may be that there is a second category of studies that have moderate

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limitations which can be incorporated into a second analysis, along with the acceptable studies.

Finally, there may well be some studies with limitations that are so severe that they are really deemed unacceptable and not fit to be included in an assessment.

I should mention that I am told that this categorization of acceptable supplemental and unacceptable is something routinely done by the EPA when evaluating mechanistic studies.

Here's my last slide. It is bringing forth these guidelines for causal inference that you have seen now probably too many times. This is kind of an extraction or a condensed version of those proposed, both by the Surgeon General's committee in the mid-sixties, as well as Bradford Hill.

I must point out that only John Bailar and I, I think, are old enough to actually identify the Surgeon General's

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report. I'm sorry.

(Laughter.)

Just briefly, it says, the first one, considering all relevant studies, is there an association? And the important word there is -- with my pointer, which doesn't work -- is the word "studies". We are really looking for the aggregate of information across studies, not the isolated positive finding.

The second point is the issue of temporality. Based on the results of the studies, is there reason to believe that the exposure came first? We are talking about the strong association. The stronger it is, the less plausible it is that a non-causal hypothesis could be responsible.

The fourth one is talking about biological plausibility, which will be discussed very quickly by Dr. Swenberg.

Then, finally, the last one is kind of a combination of the previous two. It

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basically is asking, is the strength of the association in humans, is it greatest when it would be predicted to be so, such as, for example, on the basis of particularly high doses?

Now, when you finally pull all these guidelines together and come up with a judgment, the point has been made earlier today that sometimes it is nice not to be forced into a dichotomy, yes or no.

What Jim Swenberg is going to be doing is talking about two things. One is about incorporating the toxicology data, and, second, what pattern, what framework can we use to sum up these data?

So, Jim?

DR. SWENBERG: Thank you, Noel.

It is a pleasure to be here and address this Committee.

When we started out with this meeting, the EPA framework hadn't come out yet. So these are kind of two interesting,

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independent approaches, and they are going to have a very similar ending, I think.

So, we focused in on following forward with kind of the ICPMS EPA framework for evaluating mode of action, which you heard about today. So I don't need to go through it in any great detail.

This is a program. The meeting started at a meeting, I should say, in Hanover, Germany, in 1998. I forget exactly how many people were there. I think it was about 15 to 18 of us. We had datasets and regulators. The datasets had gone out to regulators around the world, and we had the Netherlands, we had the UK, the U.S., and Australia. They had come to vastly different conclusions in their risk assessments on the same data package.

So this committee was trying to look at this and come forward with a way to bring transparency to the decisionmaking process, not to make the decision for

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somebody, but to have transparency there, so that you could see what decision process they went through.

This is what came out of it. We had actually struggled for a day and a half before we came up with this. Janet Wilsey from the EPA brought the next morning the Bradford Hill criteria and said, "I think we should follow something like this."

So, then, we beat around on how to bring it forward. What I can say is it has been very well-received. It has gone forward from this initial mode of action in animals only to now bringing forward the human relevance.

This is a paper by Bette Meek, one of your panel members, and more later, Alan Boobis have brought this forward on how do we, then, move from just the animal data to how the relevance might be for humans.

So, what this meeting that you are doing here is doing is taking it yet a step

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further, actually, bringing in the epidemiology study and perhaps using a similar framework to that.

I think the broad reception that this has won throughout the world speaks strongly that it may be successful. Hopefully, it will.

So the purpose that we set out to undertake was to establish the key elements of toxicology and epidemiology that would be informative of causal inferences. To do this, we wanted to develop a decision logic that I will go through with you, and then to characterize the degree of confidence that we had in that causal inference conclusion.

So one of the first things you have to do is bucket studies by their type. So, if they are repro studies or cancer studies, we would look at those together. We must evaluate the quality categorization because quality of studies is not equal.

So, as Noel just said, we will

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have some studies that are acceptable and have very minimal limitations. We will have other ones that are still very good studies, but have more limitations. Then, unfortunately, there will be some studies out there that have severe limitations and can't be given the same weight.

Weight is important, where you look at both the positive and the negative studies. So a weight-of-evidence approach is what we believe is the way forward. So you want to examine biological plausibility, epidemiologic evidence, and biological coherence of a dataset to come up with that weight of evidence.

And you have the clear potential of coming up with four different boxes. These could range all the way from having evidence, strong evidence, against a causal inference to having strong evidence for one. Then, most of the data will probably fall in the middle two of these.

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So this is how we pictorially view the process. You will start out, let's say we usually have toxicology data that has already been through much of this process. So it is the easiest place to start. So you collect your data. You evaluate the quality of those data, look at and bin them into the acceptable and supplementary data to put into that weight of evidence.

Then, there, you come down to a decisionmaking step. Is the effect that you are interested in present? Have you identified this in your toxicology studies? This becomes important because, when we are dealing with pesticide exposures, we go from having very high animal exposures in the tox studies to very low population exposures.

So, let's just say that we were looking at decreased pup weight from a reproductive study. Well, is that relevant to the small at gestational age studies that are on the docket for this meeting? Well, you

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would want to look at things like, what is the dose difference?

If you had it in your tox studies, but it was at 10,000 times higher doses and not at 5,000 times, you might not think it is so relevant. If you have it down at lower doses, and you have humans that have high exposures, it might be very relevant.

So you are going to bin these things into different categories. If you deem that it is not very relevant, you come down into this lower quadrant. I will spend some more time on this diagraming of my next and last slide.

On the other hand, if you feel that it may well be relevant, you are going to want to go forward to find out what would the plausibility in humans be by looking at things like dose response and toxicokinetic, pharmacokinetic kinds of examples.

On the epidemiology side, Noel has gone through this very well for us. Again,

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you are going to collect the data, look at the type of study, put it into its acceptable and supplementary bins versus unacceptable, and do your weight of evidence. That is going to tell you what the epidemiologic evidence is that support this observation.

So, ultimately, you come down to a decisionmaking process, and it starts out -- we have tried to diagram. This is not easy. We have already made a few alterations from what was in the framework that we submitted.

So let's just say that you have no data. If you have no data, you end up right in the crosshairs here. You don't have any evidence for or against either the epidemiology or the biological plausibility. So no data doesn't really give you any information.

If you have biological plausibility, let's say, from your toxicology studies, and it is low, anywhere from being low to being high, you can kind of go up and

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down the vertical axis, the Y-axis. As your epidemiology data comes in, it could be for, suggesting that this is seen in humans, it could be actually then studied and not found. So we have a few examples of this.

Obviously, we would love to have primarily No. 1 and No. 4 up here, where we have strong evidence either against something being relevant for causation in humans or something being strongly for causation in humans.

The example I have given here is asbestos and mesothelioma, where we have human data that is very strong. We have fiber counts from lung digests. We have inhalation studies in animals. So there is not any question about that one.

Down in the bottom here, we have d-limonene listed for kidney tumors by the alpha 2U mechanism. This actually was one of the first risk assessment relevance for humans that was done by the agency back in the early

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nineties.

But, most of the time, we are not there. We are somewhere between No. 2 and No. 3. So one I have put up here is phenobarbital, liver tumors in rodents. We know that we can induce these readily. Yet, this started out probably over in the center someplace because we didn't have any epi data. But, then, they looked at the Danish studies where people were being treated for their lifetime for epilepsy with phenobarbital, and there was no evidence for support of liver cancer being induced by phenobarbital at pharmacologic doses.

And finally, we have other cases where we had clear evidence of the epidemiology, but we didn't have a mechanism. That changed with the addition of new data and new understanding.

So I am going to turn this over to Sir Colin Berry to kind of wind things up and expand upon this a bit.

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DR. BERRY: Thank you. Thank you, sir.

Since there seems to be a competition going on about who is the oldest guy, I would just say that I knew Austin Bradford Hill.

(Laughter.)

My first slide is really rendered redundant by the amount of presentations that already have been made, in terms of what we have heard from several people. I think the bullet points that are identified here are those that have been made in one form or another by a number of your correspondents today.

The process has to be transparent, the inclusion of data, and so on. I am going to dwell on this slide since I doubt that there is anything that anybody would want to question or, indeed, would disagree with.

Let me go on to what would be the easiest sort of situation to deal with. That

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is here shows an ideal state where you had a unitary disease entity, diagnostic criteria which is stable, and a single etiology. You can't even do that for leprosy because there are different forms of leprosy. When it gets to tumors, it is virtually impossible.

In general, with practical examples, you have multiple subcategories, certainly, of disease entity. And I want to illustrate this by talking about non-Hodgkin's lymphoma and brain tumors briefly.

Could I just say that nothing changes like non-Hodgkin's lymphoma, which I have been surprised to hear so much discussed today since it is no longer discussed in pathology departments. It doesn't exist anymore. In fact, it never existed. It was an observation by Lukes and Collins in this country, who found that, of the people they irradiated with Hodgkin's disease, a number survived. They were the ones with true Hodgkin's. And the rest died, and they were

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the ones with what they called non-Hodgkin's lymphoma.

Subsequently, there were a number of classifications of this, and they were revised. The last revision before they were abolished, as it were, was in 1995.

The reason that I make that point is that, if you look at studies of non-Hodgkin's lymphoma, you will see that a number of studies that use these kinds of registries use the old classification, now much discarded entirely, and at least 15 years old. Some, in fact, use the 1982 classification, which is simply foolish because many of the tumors included in those groups were, in fact, anaplastic carcinomas, as we know from modern marker studies.

And the proper description I refer to here in the WHO classification describes a great deal more about the tumors than their appearance. The mantle cell lymphoma you see depends on a particular genetic insult, a

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transposition at 1114, with the inserted new fragment close to the Cyclin 1 gene on chromosome 11, affecting cell cycle time, an absolutely specific change which would require an absolutely specific kind of genetic damage; whereas, the mucosal-associated lymphoid tumor, the MALT tumor, is the result of an infection. And if you treat this B cell lymphoma with antibodies, 75 percent of patients recovery. Those that don't are those that have a large lymphoid cell mass, which presumably acquired mutations or has acquired mutations.

I would just emphasize that I think it foolish to look at a category like this in order to look for associations. I mean it is a heterogeneous collection of diseases, and you might as well say we are looking for an association with disease.

In Nature recently, in an article on brain tumors, this point was made: that brain tumors, in particular, are often put

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together as a category, and, of course, they are enormously different. Glioblastoma multiforme will kill patients within three to six months at most. Pilocytic astrocytoma is quite consistent with a comparatively long life. They have quite different genetic characteristics, quite different cell cycle times, and probably quite different etiologies.

But I think catchall diagnoses are the enemy of good epidemiology in this context where you have low exposures over long periods of time.

The difficult part, which we have heard a number of you talk about, is exposure characterization. Here, again, I can emphasize little here. You would like to have a direct measure of exposure. You would like to know where that got to in the target organ, and you would like to know that you have looked at the right time or over the right period. And in practice, the constraints that

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are outlined below are what really apply.

And again, I don't think I need to dilate on this slide. But if I could go on, I can show, I think, if we go back to the slide that Dr. Swenberg described so carefully, I think this is an extremely useful model because it enables to encompass the kind of changes that I have been talking about, both in pathological information, if I might call it that, diagnostic information, and epidemiological change.

If you take something like Kaposi's sarcoma in the HIV-infected patient, the incidence is roughly 400 times the normal population incidence. But it was not immediately apparent why the HIV virus should produce epithelioid angiosarcoma. But then it was discovered by closer inspection of the tumors that they all the bore the hybrid in their nuclei fragments of the human herpes virus 8, and that you find as a nuclear antigen before the tumor develops, and you

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don't find that in other hemangiosarcomas such as those in use by vinyl chloride, and so on.

So here is the slide, as it were, or the framework demonstrating that you can move up in this direction. And here, if you take tumors which I spoke about, if you look at the electromagnetic forces in the production of brain tumors, you may show an association, but break it down into meningiomas, gliomas, gliobastoma, multiforme, the other tumors, and the association disappears. So you have epidemiological evidence, apparently, for, and further studies show, refined show it can disappear.

The interesting example here, we start up here, no ecological evidence for or against, but a higher biological plausibility. It produces tumors in animals. But because we lack the appropriate protein, it doesn't occur in man. Therefore, the arrow goes this way.

And finally, here, melamine, which I think most people would assume that the

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doses that cause renal damage in animals, these wouldn't be likely to occur in man, but, lo and behold, it does and has. Therefore, you move to the right.

So the model allows you to account for changes in information, whether these be etiological and pathogenetic or simply by better, more thorough epidemiology.

I apologize for my voice. I don't normally sound this mature.

CHAIR HEERINGA: Thank you very much, sir.

DR. BRECKENRIDGE: Mr. Chairman, Charles Breckenridge.

We will stop for a minute and take any questions for the core epi team that individuals might like to ask.

CHAIR HEERINGA: Any questions on these three presentations to this point before we move on to Dr. Pastoor's presentation?

DR. REIF: In I think the last slide, you said something regarding all

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epidemiologic studies on a topic. Were you meaning that analysis or full analysis specifically? Or how exactly were you using the word "all"?

DR. WEISS: Maybe the epidemiologists in this room, if you polled us as to the potential utility of pooled analysis or meta-analysis of observational studies, you might get as many opinions as there are epidemiologists.

I did mean by "all", I meant to actually consider all. It may be that the studies are similar enough in their design and broadly similar enough in their results that a pooled analysis actually makes sense. On the other hand, there might be heterogeneity in terms of the methods and heterogeneity in terms of the results, in which case it is probably best to pause and present the results separately, but not to discount them, to consider them all, but not necessarily with a single relative risk.

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CHAIR HEERINGA: Dr. Lu?

DR. LU: I have a philosophical question for the panel here in terms of looking at this graph because this picture, this graph has been shown many times. So, if you just look at melamine, for example, yes, animal data strongly suggests against that. So we kind of set it aside. We let melamine get into our food, our chain, until a significant incident happened in China. Then we take action. We just realized that melamine is not a good thing to be mixed in the food chain.

So the question is, how long should we wait until positive human data surfaces and then we take action on it? Because these things happen over and over again. It is not just melamine.

So, my challenge to this panel is that, if you are willing to sacrifice certainty on the positive data that surfaces that allows EPA to take action? We are

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talking about the public health issue here. It is not just yes or no or epidemiology study design.

DR. SWENBERG: Let me, very briefly, respond to that. I mean I think --

CHAIR HEERINGA: Put your name on the record.

DR. SWENBERG: Pardon?

CHAIR HEERINGA: We need your name on the record.

DR. SWENBERG: Oh, I'm sorry.

CHAIR HEERINGA: Dr. Swenberg.

DR. SWENBERG: James Swenberg.

I was actually on the NTP Board of Scientific Counselors when melamine came through there. The focus, if you go back and read those reports, was on the bladder cancer that was induced. That was not thought to be very relevant to humans because of anatomical differences and major exposure differences.

The real toxicity was clearly there, and it was dose-related, and it went

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down to doses lower than where you got bladder cancer. So I don't think anyone at that point was saying that it was not relevant to humans, but it came home very strongly just in the last two years with the crisis in China. It is not only the melamine by itself. It was also the pet food crisis, where it was combined with cyanuric acid, where it is even more toxic.

So what we put it in here for was just to show how the science evolves. Somebody had a quote this morning about how science doesn't stand still and it evolves. Here is a perfect example that we have all lived with.

DR. BOVE: Well, just on that note, though -- this is Frank Bove -- science does evolve. Sometimes you have a situation where we see it in humans. We don't see it in animals until we get the right animal model.

So, again, maybe you should have some more diagrams showing that kind of

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possibility as well, because we have that with thalidomide, for example.

DR. BERRY: Colin Berry.

I was just going to say that, of course, this is what normally happens in therapy for chronic disease. And a good example of that currently is aspirin, which in the UK I think they are 195 studies in the meta-analysis that resulted in advice being given to the UK population to take 75 milligrams of aspirin a day as a prophylaxis after the age of, I think it was 55.

Many of the criteria we said were ideal are satisfied. A single disease -- and this was usually for atherosclerosis. The event was thrombosis, even if the clinical manifestation of that was different. A mechanism was known, in that aspirin interferes with platelet stickiness. So you had an ideal situation.

But further epidemiological evidence showed that, if you hadn't previously

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had a thrombotic episode, then it is more dangerous to take it. I mean the residual bleeding which occurs in both groups was a greater risk than the benefit conferred by taking it.

Now nothing had changed in the science or the disease. What had happened was a different kind of analysis had been done. That is a constant feature of long-term therapies, that those sort of changes are made.

So I don't think we are ever going to get a solution to your particular philosophical dilemma.

CHAIR HEERINGA: Thank you, sir, and I believe I need a behavior change on that.

(Laughter.)

So I turn to Dr. Bucher and then to Dr. Meek.

DR. BUCHER: I was just going to make the same point that Jim made.

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DR. MEEK: Just a question. I am a little unclear as to where exposure fits into this picture because it seems to build on the mode-of-action human-relevance framework, and it was very clear in that case that exposure wasn't factored in. We were really addressing the hazard.

And in fact, in the example for melamine, we, in fact, concluded that the effect was relevant to humans. So we were trying to separate out the exposure aspect.

So it is a little bit unclear to me where exposure fits in this picture.

DR. SWENBERG: I think exposure is always probably one of the most important things to understand. That is one of the bigger weaknesses of the epidemiology study; whereas, in the toxicology study, we know the exposure in general.

But a place that we need to move forward is to have better toxicokinetic data in animals and humans. So through the

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biomonitoring in the humans and by bringing the ag chem industry into the rest of the world with doing toxicokinetics reviewing, in my opinion.

CHAIR HEERINGA: I think, at this point, I would like -- continue.

DR. MEEK: I am still confused. You are mixing both exposure and hazard into this framework then. You don't explicitly separate out the exposure. The mode-of-action human-relevance framework addressed hazard per se. Exposure was addressed as part of the risk assessment process. When we are weighting epidemiological data, we are purely taking into account exposure. So it is still a little bit unclear.

DR. BRECKENRIDGE: Just briefly, if I could -- Charles Breckenridge -- just refer you back to the general framework. Exposure on the lefthand side is clearly in the animal mode-of-action framework, and under the weight of evidence for epidemiologic, it

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comes in under the context of strength of association and dose response assessment. I mean it does come into it as part of the weight of the evidence.

DR. SWENBERG: Yes, it also came in in the framework. So you are looking at your key events, and do they relate to dose effect? In fact, we saw a beautiful slide from the agency this morning where they showed the increase in pluses coming down, as does went up and as time went out.

DR. MEEK: That was dose response between key events and the end event and not exposure.

CHAIR HEERINGA: At this point, I would like to move on to the next segment of the presentation, again, with the reminder that we will have an opportunity before we turn to the charge questions for a general return not only to the EPA scientific panel, but also to the other public commenters tomorrow morning.

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So, Dr. Pastoor or Breckenridge?

DR. PASTOOR: Thank you, Mr. Chairman. Thank you, members of the Panel, for your patience this afternoon.

Mr. Chairman, I will do my best to try to keep us on time here. My intent here is to go over the six studies that were identified by EPA as case studies involving atrazine.

What you just heard previous was a very distinguished panel of experts that consulted with us over the last six weeks, and that presentation was made by these gentlemen as a representation of that effort.

The current effort, looking at the atrazine-related ecological and retrospective studies, is something that we did ourselves with their advice as well, but it is a Syngenta presentation.

In the process of going through this fairly quickly, I would remind you that we have submitted a document to the docket

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that details all the information that we will be presenting. So the presentation that I have here today is going to be very, very fast, and it will go over the top parts of each one of the particular points that we are trying to make.

What we intend to do here is use the outline of the framework to tell you something about our evaluation. When we read the studies, the six studies that were identified by EPA, we identified two particular outcomes or effects of particular interest. Those break down into birth defects and small for gestational age status, or SGA.

The idea there is that no one epidemiology study or an effect should be taken in and of itself. It would be a collection, as Dr. Weiss, Dr. Swenberg, and Sir Colin Berry have illustrated, that it is a collection of information that gives you the weight of evidence.

So that is why we looked at this,

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first of all, not on an individual epidemiological study basis, but on the basis of an effect or outcome. So, our first question, of course, using the framework, is, what is the biological plausibility and how does that match up with epidemiological evidence?

So, again, this is the scheme that we are using here, which you have seen previously. Working down the lefthand side, of course, is collecting all of the available information that would shed light on whether or not there is biological plausibility for a birth defect or small for gestational age status. Then we will work down the other side on epidemiology as well.

So our first is to collect all the available data and establish quality. So, with regard to atrazine and its four major metabolites, there are acceptable rat and rabbit studies done for teratology or developmental studies. So the atrazine,

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hydroxy-atrazine, deisopropyl-atrazine, deethyl-atrazine, and diaminochloro-triazine have all been tested in developmental studies. We also have an acceptable reproduction, two-generation reproduction study on atrazine as well.

The conclusion from this, with regard to birth defects, is that neither atrazine or its metabolites cause birth defects in the rat or rabbit studies at any dose level, even at dose levels that compromise the maternal health. So, what we conclude there is that the biological plausibility that atrazine could cause birth defects is very low.

The second area of small gestational age status, we looked there again, and at high maternally-toxic doses, where you severely compromise the health of the mother, either the rat or the rabbit, you do get body weight effects in those particular situations. Those are tens of thousands of fold higher

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than the exposures that any human could be exposed to. As a result, we have put that as well into the low category of biological plausibility.

So you can see, down on the righthand corner, the quadrants that we were talking about previously and how biological plausibility for either one of these particular outcomes comes out in the lower end of the scale.

We, then, turned our interest to the studies that were identified by EPA, in the first instance with regard to birth defect studies. There's four here. I will be talking about each one.

What we did is took the Mattix and the Winchester, et al., papers, and we put them together because the structure of these studies is almost identical -- they go over different periods of time -- and collected them for the quality analysis. What we found is that neither of these studies are

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acceptable on the basis of the quality criteria that Dr. Weiss has described.

In this particular study, they are looking at regional raw water from USGS and matching that with the National Birth Defects Incidents Database. That comes from the CDC biostatistics information.

And if I can draw your attention to the graph, the dotted line on that particular graph is the incidence of birth defects that are noted overall. I believe this is a category of 22 particular birth defects collected together. You can see the seasonal uptick in about the late spring/early summer.

What the authors conclude in this particular study is that that correlates with the use season for atrazine. When we looked at this study, we knew that there were lots of other things that this could be correlated with, and that was one of the two ways that we approached the study. And we realized that

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you could correlate the birth defect uptick in the early summer months with a number of different things. I am showing tornadoes and birth defects here, but we used everything from pollen counts to length of day, to temperature, and so forth, rainfall, all of which correlate very nicely with that uptick in the early summer months, late spring.

Now this is a bit of a light touch, I think you would have to admit, but we got more serious with this, too. Because we said to ourselves, well, if, indeed, there is an uptick in birth defects that is seasonal, as you are seeing there, what is it that could be causing that? Of course, we were interested in knowing what potential role atrazine could cause in that as well.

So what we did is we went to the same database that the authors used and we graphed the actual birth defect incidents by states. If I could draw your attention to the middle line, if I could have the pointer,

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please, if you look at the middle blue line, which is all of the United States here, you see that same uptick occurring.

The next question that we asked ourselves is, if you parse that data by states that have high atrazine usage versus those that have low atrazine use, and of course middle, you have the columns that we have up here on the left.

If you look at the states that the states that have 82 percent of the total poundage of atrazine that is used, that is the green line that is here down on the bottom. The lowest use, which is 1 percent of the total atrazine usage, is the upper line here. You can see the same seasonal uptick in birth defects, which is looking at this list that you are seeing down here in the lower lefthand corner.

The conclusion here is less about atrazine and more about the fact that this is something that is seen across states, and an

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interesting result, to say the least. Again, this was taken from the same database, CDC Vital Statistics. And although exposure is not best characterized by total poundage, it gives you some idea of the usage of atrazine in those particular states.

The next study we looked at Ochoa-Acuna and Carbajo. This was a corn study looking at the proximity to living near a cornfield versus a soybean field would have some detrimental effect on birth defects. Very quickly, though, and this is presented in our ancillary documents that we have put in, the critical window here that is shown, identified by the authors, is not congruent with the planting season during which atrazine is actually used. So there's a question about temporality in that particular study.

Furthermore, there was only one reference to atrazine in that particular study, but, overall, it was a study recommended by EPA for case study, and we did

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this analysis. It is an unacceptable study.

The final study in this group, Mohanty and Zhang, is also unacceptable. It is not really an epidemiology study. It is a 23-variable regression model that is looking at 25 outcomes, and there was a selective elimination of data that rendered the study unacceptable.

Turning next to small for gestational age, there were two studies by EPA, one by Villanueva, 2005, and Ochoa-Acuna in 2009. The first study here, by Villanueva, is judged to be unacceptable as well, for a number of different quality criteria issues, not the least of which was that the majority of the samples that were taken were out of raw water, which people don't drink. The exposure, again, was not temporally matched. I believe that this was brought up this morning.

Furthermore, the majority of samples from finished water were actually

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below the level of detection. As a consequence, the authors used half the LOD to produce the values.

The fourth and final point there is that there are, as with other studies, seasonal factors that could account for that marginal effect.

Finally, the Ochoa-Acuna study from 2009 was judged supplemental. The reason is that they had a reasonable design to the study. They tried to match cases with exposure, and there were other factors that render it supplemental.

However, if you take the author's own data and do a simple rank correlation and linear regression, what you find here is, in this particular case, you find no correlation and you also are unable to find a positive correlation. This was the negative correlation.

In this particular example that I am using, it is a simple rank correlation of

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SGA prevalence in those water systems against the median atrazine concentration. Now we did probably a dozen different correlations from the author's data, none of which had R-squareds that were very high, and were typically around the value that you see here, which is .1557.

So those are the studies that we have looked at and evaluated from the standpoint of the framework. Of course, from the standpoint of what we are trying to do here, it is to establish causal imprints. That is what this is all about after all, is, what do studies tell you about the probability of an effect occurring in humans, in this case due to atrazine exposure?

We have already gone through the toxicology side that indicates that it is of low biological significance. We have also gone through the epidemiology study, of which there are more studies out there -- these six studies are not the only ones available -- and

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classified them by quality. None, however, can be used in a weight-of-evidence analysis, which would have otherwise brought us into this category down here to classify it.

Nonetheless, I think what we found here is that the framework that was developed by the panel of experts that we worked with is very helpful in helping us understand something about how you collect the biological or toxicological information, along with the epidemiological information, to make a logical conclusion.

It is useful because it is transparent, it is systematic, and it is data-driven. So that is why we like it. We offered it up as one option that the Panel can consider in bringing epidemiological data into human health risk assessments.

And I will end there and ask for any questions.

CHAIR HEERINGA: Thank you, Dr. Pastoor.

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Questions of clarification for Dr. Pastoor or Dr. Breckenridge? Yes, Dr. Reif?

DR. REIF: Did you apply this model to any of the other studies that you just referred to that are not in the six in the EPA package?

DR. PASTOOR: Yes. In other words, if you were looking at a particular outcome, whether it were birth defects, low gestational age, or otherwise, the idea is to first collect all the available information and go through that quality sieve, first of all.

DR. BRECKENRIDGE: I'm sorry, I think you misinterpreted. The answer is, no, we didn't have time to actually go through the literature to extract all available studies, in fact. So we don't know what --

DR. REIF: Exactly. I meant, did any of the other studies that are not in the six in the case study rise to the level of acceptable --

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DR. PASTOOR: No, in the time that we had, we didn't do that. I'm sorry, I misunderstood your question.

DR. REIF: That's okay.

CHAIR HEERINGA: Dr. Bove?

DR. BOVE: Frank Bove.

The Ochoa-Acuna study is an individual-level analysis. Is this graph here I see an ecologic approach? I mean it looks like you are doing the rank of SGA prevalence is by what?

DR. PASTOOR: This is based on the water systems that were in the paper itself.

DR. BOVE: Okay. So these are the towns?

DR. PASTOOR: That's correct. These are community water systems, individual community water systems.

DR. BOVE: It is an ecologic approach.

DR. PASTOOR: Correct.

DR. BOVE: It is an individual-

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level approach. Now whether there is a dose response relationship in that study, if they have coefficient that is above one for the regression focus, whether you like the analysis or not, and I have faults with the analysis, too, there is a dose response in that. What you have done is make this into an ecologic approach, which is problematic. You say that there isn't. Do you think that that's --

DR. PASTOOR: Well, I think the best thing is to turn to the epidemiologist. But what I understand from this study is that they did a categorical analysis on it. So they had the low-dose group was actually the quartile that was at the lowest end of the exposure as opposed to the next two, which is the middle two-fourths and the upper fourth. That is how they did their dose response. We simply took away those categorizations and made it individual data-points.

DR. BERRY: Colin Berry.

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Just to make the point that birth defects is another catchall diagnosis.

CHAIR HEERINGA: Yes, Dr. Gold?

DR. GOLD: I have a philosophical question that I would like to ask the group, and then, if I had the opportunity, I would like to ask it to the EPA folks maybe tomorrow morning.

CHAIR HEERINGA: Certainly tomorrow morning.

DR. GOLD: Yes.

CHAIR HEERINGA: But do you want to lay it out there now?

DR. GOLD: Well, because people have been using this from biologic plausibility pretty freely in all the presentations. To me, what they are saying when they are saying biologic plausibility is really toxicity, which I wouldn't say is necessarily biologic plausibility.

Given different modes of action, different dosages, different modes of

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administration, routes of exposure, I am not sure that toxicity data from animals is the same as biologic plausibility, but I would like to hear from you all. Because I think, going back to the Surgeon General, I think part of the reason those criteria were developed were because we didn't have really good biologic plausibility.

I mean we didn't have really good data from animals to indicate the path of physiologic mechanism by which smoking caused lung cancer, for example. So I think we are in a similar situation now.

So I would just like to hear philosophically this interchangeable use of -- you are using biologic plausibility, and I think you meant toxicity.

CHAIR HEERINGA: Dr. Swenberg?

DR. SWENBERG: Let me take a crack at this. You raise a very interesting point.

I think that we start out looking at biological plausibility with things like

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when there are massive differences in exposures, could one molecule result in this disease type of thing? But I think this framework mode-of-action analysis that we have worked on now for over a decade has brought us about to think more about plausibility and the mode of action really enhances our knowledge when we go through one of these frameworks on what are the key events, and what is the plausibility of those key events taking place under the circumstances of the exposure?

As one goes to the human relevance part of this that Bette has pioneered, you ask questions about this and go through a decision tree to better define that. So I think biological plausibility that we use in today's context has been influenced by 10 years of working on these framework analyses.

And when we have worked out what looks like a good mode of action, and we have data that follows these criteria, that almost always strengthens the assessment of

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biological plausibility.

CHAIR HEERINGA: Dr. Bailar, and then we will move on.

DR. BAILAR: I think Dr. Gold made a very important and useful point here. I would like to add two footnotes.

The first is that I don't think biologic plausibility is the whole of toxicology. It is a subset. It might be worth defining that subset and then giving it this name.

The second is that biologic plausibility is not entirely limited to toxicology. I think that is where most of it is. But if I find a chemical that is said to be causing 40 different kinds of cancer, I think we are probably looking at bias.

Chemical carcinogens don't work that way. They tend to have much more specific action. This cancer or that cancer, maybe two, three, five, but not across the board. So I would take that as some kind of

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evidence regarding plausibility, but it is not toxicology.

DR. BRECKENRIDGE: Charles Breckenridge. I will just respond briefly to that.

We actually were a little bit concerned about flattening the dimension of plausibility to a single axis when we were involved in this, and we had the element of what we called biological coherence, which was am element of the common understanding of would these processes physically be possible. I suppose the electromagnetic and brain tumor relationship might be an example of a failure to have a relationship that seemed to make sense from a physical point of view, and that would be a concept of plausibility in some sense. It would be physical plausibility though, and maybe that is not toxicology, but it is more, is it in accord with the understanding of science that we have at the moment?

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CHAIR HEERINGA: Dr. Gold, and then I would like to move on, but, please, go ahead.

DR. GOLD: Because EPA ultimately has to make policy in the absence of perfect knowledge, so I just want to make sure that when we are talking about our terms, I think the language is important. That is why I am interested in the philosophy. Because are we saying that they have to have biologic plausibility, which I think we often don't have when we make policy? So I am interested in your philosophic point of view. I mean I will be interested in hearing theirs tomorrow.

CHAIR HEERINGA: Dr. Breckenridge? I think that we will have a little time tomorrow morning in general to continue public comment, and I think we can revisit some of these issues people have thought about them for the evening, too.

At this point in time, I would like to move on to the remaining public

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commenters who have arranged to present.

Before I do, I want to just make sure because some people may be leaving to catch a bus or a subway. Administratively, apparently, there is a little snow anticipated. I say, "a little snow". I'm coming from Michigan.

(Laughter.)

So a little snow is anticipated. I was born in South Dakota. So it is a very little snow.

If the federal government, sort of a three-part strategy, and so if the federal government is delayed, and this is an official decision that the work will be delayed start, say it is delayed to start at 10:30. Our meeting will start at 10:30.

If the government is closed, heaven forbid, the meeting will reconvene on Thursday morning.

If the federal government allows employees unscheduled leave or liberal leave,

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essentially, they have to decide whether they can get through the snow to get here, the rest of us will start at 8:30, as normally scheduled.

So that may be completely confusing, but, again, I understand that the Office of Personnel Management posts this on the website, and the local radio stations, given the density of government employees in the area, and TV stations, I am sure will announce this. And the rest of us can sort of figure it out on the fly.

Okay. At this point in time, I would like to invite up Mr. Tyler Wegmeyer, who is representing the American Farm Bureau Federation. Mr. Wegmeyer as a five-minute comment.

Welcome, Tyler.

MR. WEGMEYER: At least I know you are from Michigan, like I am. So, at least the two of us will be here if it snows.

Since we are losing daylight, I

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would like to amend my prepared comments, if it is okay with you, to say good evening, rather than good afternoon.

My name is Tyler Wegmeyer, and I am Director of Congressional Relations for the American Farm Bureau Federation.

I am also a fourth-generation farmer, growing mostly specialty crops in western Loudoun County, Virginia.

The American Farm Bureau Federation is the country's largest general farm organization. Farm Bureau members grow, produce, and raise the food, fiber, and energy sources that feed, clothe, and field the U.S. and the world.

Our farms and ranches are found in all 50 states as well as Puerto Rico, and we represent producers of every size and scale of operation.

The American Farm Bureau Federation welcomes this opportunity to speak up on behalf of atrazine and what it means to

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the American farmer. Having access to important crop protection products is vital to the success of providing a safe and abundant food supply.

Atrazine is the most important herbicide in soil-saving growing practices, such as no-till and conservation tillage. We use it to control weeds on about two-thirds of the country's corn and sorghum acreage. We know this product and how it affects the land. And after all, a farmer spends his day in the field and spends his night with his family next to that field.

A farmer gets down in the dirt every day, observing how our practices work with the soil, plants, insects, water, and the local environment. And I can tell you that our 51 years of experience with atrazine shows us what a scientific analysis of thousands of studies confirm, that atrazine is gentle, safe, and effective.

The Farm Bureau strongly believes

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having access to important crop protection products such as atrazine is vital to the success of providing a safe and abundant food supply. Ask our corn, sorghum, and sugarcane growers, and they will tell you that we depend on this herbicide to keep a broad spectrum of weeds from robbing nutrients from our crops. They will also tell you that we cannot do it without atrazine.

EPA's own numbers show this to be true, that losing atrazine would cost farmers $28 an acre in lost yields and increased weed cost. EPA also tells us that U.S. corn, sorghum, sugarcane, and other growers would suffer losses of greater than $2 billion if atrazine were not available.

Some activist groups claim that atrazine is easily replaced. It is not. Just two weeks ago, a report from the Minnesota Department of Agriculture quoted University of Minnesota scientists who said there are no direct replacements for atrazine in pre-

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emergence weed control registered in that State.

As you also know, corn is a base commodity for innumerable products. Corn and sorghum are key feedstocks. Undermine these sectors, and you have pretty much dealt a blow to the entire U.S. food industry along with the economic health of the American farm belt.

Of course, no degree of economic dependence would matter if atrazine were a problem. We believe sound science shows it to be safe for use.

The American Farm Bureau Federation has participated in every Scientific Advisory Panel convened to examine atrazine's safety since the first special review in 1994. We were with you through the pain-staking work of the most recent re-registration.

Now that EPA wishes to conduct a fresh investigation, we are here again. I must say, however, that from the perspective

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of Farm Bureau, we are concerned over what appears to be a hastily-convened irregular process.

We hope that this atrazine review process is not being subjected to an unseemingly rush, and we appeal to the scientists who lend so much of your time, expertise, and credibility to continue to ensure that the principles of sound science remain our way forward.

Thank you very much.

CHAIR HEERINGA: Thank you, Mr. Wegmeyer.

Any comments or questions for Mr. Wegmeyer of the Farm Bureau?

(No response.)

Thank you very much.

At this point in time, I would like to invite up our next scheduled public commenter. It is Mr. Scott Slaughter, who represents the Center for Regulatory Effectiveness. Mr. Slaughter's written

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comments were distributed to the Panel.

MR. SLAUGHTER: Hi. I'm Scott Slaughter, and I am commenting on behalf of the Center for Regulatory Effectiveness. I would like to make three comments.

First, an earlier commenter suggested that you ought to focus on endocrine effects in this SAP. I just thought everyone should know, and it is discussed in our comments, that EPA has made a decision to address endocrine effects for pesticides in a separate proceeding called the Endocrine Disruptor Screening Program.

The agency has just sent out multiple test orders, including test orders for atrazine, to assess whether or not any of the pesticides that are registered, including atrazine, might have potential endocrine effects. So I don't think you have to worry about endocrine effects going unassessed. Right now, they are being assessed in a different proceeding.

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Second, I would like to call to your attention a document called "The Atrazine Technical Assessment". It was prepared by the Minnesota Department of Agriculture, the Minnesota Department of Health, and the Minnesota Pollution Control Agency.

This State report, which is now subject to comment, reviews the atrazine studies that are being reviewed in this SAP, except the State is reviewing them in that proceeding, reviews the Ag Health Study with regard to atrazine, and reviews the current EPA regulation of atrazine to determine whether current EPA regulation protects human health in Minnesota. In other words, the State of Minnesota is doing basically what EPA is doing here, and much of what the SAP has been asked to do.

The Minnesota report -- and the report is now out for comment -- concludes that the current EPA regulation protects human health in Minnesota. The Minnesota report

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concludes that the five new atrazine studies, or the six, which are discussed here and discussed by EPA, the Minnesota report concludes that those studies are too flawed and unreliable to be used to assess atrazine human health effects.

The Minnesota report concludes that, and I quote, "The weight of evidence from reviewed studies can be currently summarized as inefficient to establish causal relationships between atrazine exposure and certain adverse effects. For the purpose of this review, animal toxicity studies remain at this time the most reliable and reproducible data on which to base human health assessments for atrazine." Closed quote.

This report was prepared by experts, informed and objective State regulatory authorities, on many of the same issues that are now being addressed by EPA in this SAP.

If you do not read any of the rest

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of CRE's comments, please read the Minnesota report. Its online address is available at page 2 of CRE's written comments. I won't repeat it. I won't even try to repeat it. It is at page 2 of our comments. And if you click on that, you can get the Minnesota report and a lot of background discussion on it.

Third, and last, I want to state for the record that CRE would have filed much more complete and lengthier comments, and perhaps more helpful comments, if EPA had responded to CRE's FOIA request in the manner and in the time required by law.

CRE filed FOIA requests relating to various issues in this SAP. For whatever reasons, EPA has violated its statutory duties by failing to respond to CRE's request at the time required by law. EPA's failure to obey the law has deprived this SAP of EPA documents that we believe would have aided the SAP's performance of its duties.

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Thank you, and I will try to answer any questions.

CHAIR HEERINGA: Thank you very much, Mr. Slaughter.

Any questions of clarification for Dr. Slaughter? Yes, Alex Lu.

DR. LU: Again, this is a philosophical question, but I think that I should ask one of the people who make a public comment about the continued use of atrazine. So the question is that, when you talk to your farmer, saying that that atrazine that you put down in your farm is actually reaching into the aquifer that the rest of the American people drink, how would they feel about it?

MR. SLAUGHTER: Well, you are assuming a lot of things, I think. First, you are assuming that atrazine is present in drinking water at levels which are hazardous to human health. I don't think that is an accurate assumption, and I am sure people back here could address it in far more detail than

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I can.

You ask me that question. You are assuming something which I don't believe is true.

And second, farmers live with this stuff. I mean they have children growing up where they grow their crops and use atrazine and other pesticides. I think, if they really felt that there was a risk, and they are generally very well-informed about these things, they wouldn't use the product, and they do use the product and they want the product.

DR. LU: Well, I think the USGS data suggests that more than 90 percent of the water they sampled had detectable atrazine levels.

MR. SLAUGHTER: Detectable is not the same thing as drinking water, and it is not the same thing --

DR. LU: Right, but --

MR. SLAUGHTER: -- as hazardous

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level.

DR. LU: Right, but the question that I had was not in drinking water --

CHAIR HEERINGA: All right, fellows, I am going to cut off the philosophical discussion. Thanks. That is a scientific question. It can be answered in a quantifiable way.

Dr. Gold? Okay.

MR. SLAUGHTER: I thank you.

CHAIR HEERINGA: Thank you very much, Mr. Slaughter.

At this point in time, I would like to invite up Dr. Jessica Johnson Bennett, who is representing the National Corn Growers Association.

DR. BENNETT: Good afternoon.

I'm Jessica Bennett, Director of Public Policy for the National Corn Growers Association. I appreciate the opportunity to testify before you today.

I am providing comments on behalf

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of the NCGA, which represents more than 36,000 members in 48 states, 47 affiliated state organizations, and more than 300,000 corn farmers who contribute to state CGA programs across the country.

For over 50 years, more than half of all American corn growers have relied on atrazine to protect our crops from a variety of grass and broad-leaf weeds. We especially value its flexibility. Atrazine can be applied to crops before, during, or after planting. It may even be applied after the crop emerges.

By EPA's own estimate, atrazine saves corn farmers as much as $28 an acre in reduced herbicide costs and increased yields. For all these reasons, atrazine is not just a good product, it is a vital product.

Atrazine not only supports corn production, but it also provides environmental benefits. Every farmer is, of necessity, a conservationist. We care deeply about our

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impact on the land and water, and what we will leave behind for our children our grandchildren.

That is why so many corn farmers are proud to rely on atrazine for no-till conservation agriculture on more than 44 million corn acres, a practice that is preventing soil erosion, protecting waterways, and sequestering significant amounts of carbon dioxide across America.

It is with these concerns in mind that our growers have been active participants in supporting the scientific approval of atrazine by the EPA over the last 15 years under three Administrations, both Democrats and Republicans.

We were there when EPA re-registered atrazine three years ago and concluded, as before, that triazine herbicides pose no harm that would result to the general U.S. population, infants, children, or other major identifiable subgroups of consumers.

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We also invest confidence in the fact that the World Health Organization, the National Cancer Institutes, and the British Government have all studied atrazine and found no health concerns.

Yet, now we find ourselves facing an extraordinary, hastily-assembled, and, frankly, unprecedented re-review of atrazine that seems to be inspired by anti-pesticide activists. We are troubled that this process seems rushed and that the scientists on this SAP, who give so much of their time and expertise, are being asked to survey so much new data in so little time.

The good news is that we have seen, time and again, the quality and professionalism of EPA's scientific advisors. We are counting on you for a fair assessment based on sound science, and nothing but sound science.

Thank you for your time.

CHAIR HEERINGA: Thank you very

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much, Dr. Bennett.

Any questions for Dr. Bennett from the National Corn Growers Association?

(No response.)

Okay. Thank you.

And I have one more scheduled public commenter, and that is Dr. Gary Burin with Technology Sciences Group, Inc. And there are written comments that have been submitted, too.

DR. BURIN: Yes, yes.

Good afternoon. Good evening.

My name is Gary Burin. I am a toxicologist with Technology Sciences Group.

I have prepared comments on the EPA framework document and the atrazine epidemiology studies on behalf of the Triazine Network, a coalition of 1,000 local and state agricultural and farmers' organizations.

Jerry White, the Chairman of the Triazine Network, is unable to be here this afternoon due to his Association's Annual

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Meeting, but will be attending the meeting tomorrow.

Now, prior to my becoming a consultant, I worked in the Office of Pesticide Programs and at the World Health Organization, and I have seen that it is difficult to integrate human data into hazard evaluation and risk assessment. But I believe that the EPA framework document can be, for the most part, considered to provide a logical and sound approach to the growing body of information concerning the health effects of pesticides.

The framework document requires that epidemiology studies, such as those of atrazine, not be viewed in isolation of other relevant information. Further, the framework recommends that the contribution to the weight of evidence of epidemiology studies be viewed using the modified Bradford Hill criteria that we have heard about earlier from Dr. Owens and from EPA this morning.

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The framework provides the context for the atrazine case study that is described in Attachment A. My evaluation of these studies can be found in the written comments that have been submitted.

I share some of the concerns that were raised by the previous speakers, including the EPA speaker this morning, regarding the limitations of these studies.

For more details, and I won't go into my comments, given the lateness of the hour on a study-by-study basis, but I hope that you will have the chance to read my written comments.

Thank you.

CHAIR HEERINGA: Thank you very much, Dr. Burin.

Are there any questions for Dr. Burin, questions of clarification?

(No response.)

Thank you very much.

I just want to indicate that there

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are several other communications that the Panel has received, one from Michelle Marcus and another who I think is writing on her own behalf, and then Charles Connor from the National Council of Farm Cooperatives. These will be in the docket, and I believe there may have been some other advance public comments that were already in the docket.

So there is a lot of information that has been submitted by the public and industry representatives that is going to be either on the public docket or will be in it late tomorrow afternoon. I encourage everybody to access that and have a chance to look it all over.

At this point in time, again, just a quick reminder, we are at the end of the day. I am not going to close the period of public comment. I would like to leave it open just briefly, but not for new public comment necessarily or repeats. But if the Panel members require any questions of clarification

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tomorrow morning, I would hold the right to call back up anyone who is here present and would be able to address questions of clarification from the Panel. So, Panel members, any of the public commenters.

Then, also, following that, you will have the opportunity to re-engage with the EPA scientific staff on any questions of clarification on their presentation, and then we will move on to address the actual charge questions.

Just a final reminder, administratively, if a decision is made because of the inclement weather, snow, to delay the start of federal government activity, our meeting will be delayed to start consistent with that official federal decision.

If the government is closed due to substantial snowfall, the meeting will not be held tomorrow, but will reconvene Thursday, consistent with government business, assuming

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it is not closed for two days. I don't know what we would do if it were.

If the federal government has scheduled just informal leave for its employees or gives them flexibility on whether they will come in, we will meet here at 8:30 at the regular time.

So, Dr. Lu?

DR. LU: Where can we get at the information in terms of delay or closure?

MS. CHRISTIAN: WTOP, a radio station, and also in the news. And not only that, if you go to the OPM website, you will --

CHAIR HEERINGA: Office of Personnel Management.

MS. CHRISTIAN: Yes. Yes, tomorrow morning.

CHAIR HEERINGA: Is that correct?

Google federal closure, okay.

MS. CHRISTIAN: Yes, yes, that is correct.

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CHAIR HEERINGA: Probably the best thing to do is just look out the window out there.

(Laughter.)

If there is no snow on the ground, but don't use your Boston standard. Okay?

(Laughter.)

Okay. Very good. We appreciate everybody's contributions today. It has been a very good start. We have gotten a lot of information in, and we look forward to a very productive day and set of discussions tomorrow.

Any last administrative issues?

MS. CHRISTIAN: No, not any new announcement, but please join us tomorrow morning, hopefully, at 8:30, to continue this meeting.

Thank you.

CHAIR HEERINGA: Okay. And, Panel members, if we could just meet briefly for five minutes in the breakout room, just to

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sort of lay out our plan for tomorrow morning?

(Whereupon, at 4:56 p.m., the proceedings in the above-entitled matter were adjourned for the day, to reconvene the following day, Wednesday, February 3, 2009, at 8:30 a.m., weather permitting.)

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