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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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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.

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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On behalf of the Triazine Network

Adjourn

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

2 8:46 a.m.

3 MS. CHRISTIAN: Good morning and
4 welcome.

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

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

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

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

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

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

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

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

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

1 to work with the appropriate agency officials
2 to ensure that all appropriate ethics
3 regulations are satisfied. In that capacity,
4 Panel members are briefed with the provisions
5 of the federal conflict-of-interest laws. In
6 addition, each participant has filed a
7 standard government financial disclosure
8 report.

9 I, along with our Deputy Ethics
10 Officer for the Office of Prevention,
11 Pesticides, and Toxic Substances, and in
12 consultation with the Office of General
13 Counsel, have reviewed these forms to ensure
14 all ethics requirements are met.

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

22 For presenters, Panel members, and

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

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

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

20 (Laughter.)

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

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

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

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

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

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

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

1 is required.

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

8 So thank you, Gerry.

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

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

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

1 flow of the meeting.

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

7 I will turn to the other experts
8 to introduce themselves.

9 Ken?

10 DR. PORTIER: Good morning.

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

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

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

1 toxicologist by training and a member of the
2 permanent panel.

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

9 DR. MEEK: Good morning.

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

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

1 in environmental monitoring.

2 DR. HARRIS: Good morning.

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

8 DR. BOVE: My name is Frank Bove.

9 I am a Senior Epidemiologist at the Agency for
10 Toxic Substances and Disease Registry, which
11 is part of the Centers for Disease Control.
12 My research interests are in drinking water
13 contamination and birth defects and cancers.
14 This is the third SAP meeting on atrazine I
15 have been on.

16 DR. LU: Good morning.

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

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

1 Epidemiology at UC Davis.

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

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

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

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

1 and am a new permanent SAP member.

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

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

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

20 Steve?

21 DR. BRADBURY: Thank you, Dr.
22 Heeringa.

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

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

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

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

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

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

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

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

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

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

22 There's really two themes to what

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

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

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

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

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

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

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

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

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

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

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

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

1 study that EPA has been working in
2 collaboration with NIH.

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

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

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

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

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

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

1 associated with them.

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

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

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

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

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

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

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

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

1 Good morning, Tina.

2 DR. LEVINE: Thank you very much.

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

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

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

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

1 room.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 Thank you.

16 CHAIR HEERINGA: Thank you, Dr.
17 Levine.

18 Dr. Lowit, it is good to see you.

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

22 (Laughter.)

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

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

16 (Laughter.)

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

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

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

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

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

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

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

22 We decided it made a lot more

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

3 So, historically, we have used the
4 NAS 4-step paradigm, where you have hazard
5 assessment, leading to dose response, and
6 exposure assessment to risk characterization.
7 And largely, we still follow this. But the
8 2007 21st Century Tox Testing Report sends
9 that 4-step process in a slightly somewhat
10 important, different direction. I am not
11 going to spend a whole lot of time on this
12 because some of you probably know this better
13 than I do.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

5 This is a graph I took from a
6 recent paper by Boobis, et al. I think it is
7 a very nice picture way of looking at the
8 generics of the key events and mode-of-action
9 analysis. This largely follows, although the
10 words are different, it very much largely
11 follows the source-to-outcome pathway from the
12 2007 NRC, where you begin with here you talk
13 about external dose.

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

1 of interest.

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

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

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

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

4 There are cases occasionally where
5 we have delivered dose studies in humans.

6 Just as an aside, before we use any such
7 study, it is reviewed by the Human Studies
8 Review Board for both ethics and science.

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

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

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

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

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

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

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

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

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

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

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

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

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

13 So the animal component of this
14 has actually been reviewed by the SAB in a
15 joint review that was done with ourselves, the
16 Office of Water, and ORD NCF, back around
17 2005.

18 This color is not looking good.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 (No response.)

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

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

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

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

1 black notebook, obviously.

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

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

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

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

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

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

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

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

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

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

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

4 Then, finally, it is always
5 important to consider how data was collected
6 and how that could potentially bias the
7 results or influence the findings. Then, it
8 is always important to consider the
9 statistical approach used, and what is the
10 approach used and could it potentially
11 influence the results?

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

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

22 I will now go more specifically

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

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

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

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

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

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

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

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

22 So, as discussed in the case

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

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

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

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

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

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

22 A lot of this I mentioned already,

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

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

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

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

1 level exposures.

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

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

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

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

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

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

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

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

22 In contrast, when you have

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

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

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

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

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

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

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

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

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

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

1 larger differences between the different
2 exposure categories.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 And then finally, Study E, which

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

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

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

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

1 in the study. So just limitations to
2 consider.

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

15 Thank you.

16 CHAIR HEERINGA: Thank you,
17 Lieutenant Niman.

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

1 Dr. Bailar?

2 DR. BAILAR: I have two questions.

3 First, has anybody looked at the seasonal
4 patterns in areas where there is little or no
5 exposure to atrazine?

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

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

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

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

22 CHAIR HEERINGA: Thank you very

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

4 Dr. Bove?

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

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

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

22 So, if there are specific studies

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

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

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

14 CHAIR HEERINGA: Dr. Reif?

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

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

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

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

21 CHAIR HEERINGA: Dr. Reed?

22 DR. REED: I was wondering if in

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

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

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

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

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

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

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

17 CHAIR HEERINGA: Okay, we are at
18 10:15, and I apologize, I apparently have a
19 failing battery in my watch. So I can't look
20 at the clocks here because I am totally
21 confused. The man with two watches never
22 knows what time it is.

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

5 Thank you.

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

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

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

21 Dr. Levine, would you like to --

22 DR. LEVINE: I would like to

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

9 So, with that.

10 DR. ALAVANJA: Good morning,
11 everyone.

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

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

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

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

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

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

7 The literature review back in
8 1993, and maybe to the present, would suggest
9 that previous health studies are characterized
10 as having inadequate exposure assessment. We
11 know that exposure or misclassification can
12 result from inadequate exposure assessment.
13 So one of the things, clearly, that we had to
14 do was to improve upon that.

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

22 A lot of the previous studies are

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

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

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

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

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

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

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

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

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

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

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

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

21 We have been generating biologic
22 results to assess biologic plausibility and

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

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

14 We have approximately 52,000
15 private applicators, and private applicators
16 are farmers and nursery operators. We have
17 32,000 spouses of farmers in the study, and
18 that is really important because many of those
19 spouses really represent more of our own
20 experience here; that is, people who are not
21 occupationally-exposed, but get indirect
22 exposures. I am not going to focus on that.

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

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

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

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

22 They are also knowledgeable about

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

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

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

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

1 had the spouse enrollment through a take-home
2 questionnaire.

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

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

18 So, in the EPA field study, we had
19 69 folks who applied 2,4-D using various
20 methods, and we had 17 apply chlorpyrifos.
21 This was basically for both the 2,4-D and the
22 chlorpyrifos on field crops.

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

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

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

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

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

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

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

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

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

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

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

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

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

17 We have over 1 million person-
18 years of followup at the current time. So our
19 ability to look at rarer cancers is increasing
20 with time and rarer exposures. We have buccal
21 cells collected as a source of DNA on over
22 35,000 people, and we are actively analyzing

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

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

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

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

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

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

1 so this is a possibility.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 This is some of the data that

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 For personal protective equipment,

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 studies?

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

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

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

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

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

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

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

1 of those studies will be published this year.

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

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

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

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

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

10 And lastly, I open myself to
11 questions.

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

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

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

1 Dr. Portier?

2 DR. PORTIER: Ken Portier.

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

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

19 CHAIR HEERINGA: Dr. LeBlanc?

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

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

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

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

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

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

9 CHAIR HEERINGA: Dr. Chambers?

10 DR. CHAMBERS: Jan Chambers.

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

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

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

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

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

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

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

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

14 DR. CHAMBERS: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

15 CHAIR HEERINGA: Dr. Bailar?

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

21 DR. ALAVANJA: No.

22 CHAIR HEERINGA: Dr. Lu?

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

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

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

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

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

12 DR. LU: Right.

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

17 DR. LU: Okay. Good. Thank you.

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

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

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

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

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

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

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

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

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

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

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

20 Dr. Levine?

21 DR. LEVINE: Thank you.

22 I guess the last discussion is a

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

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

13 I am just waiting for my slides to
14 pop up.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 Each step is designed to build

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

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

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

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

1 equipment.

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

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

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

1 survey information and agronomic practices.

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

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

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

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

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

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

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

1 taken into consideration as part of the case
2 study.

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

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

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

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

1 concept. This is just a simplification of the
2 algorithm.

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

11 In terms of the exposure trends,
12 the AHS relies on information on the duration
13 and the frequency provided in the
14 questionnaires. And for the agency, the
15 approach we look at, the application rate, the
16 area treated, and in terms of cancer
17 assessment, we also typically use 30 days and
18 30 years working lifetime.

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

1 just on the use pattern parameters.

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

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

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

20 Currently, within PHED, there are
21 37 unique exposure scenarios and corresponding
22 unit exposures. So, for example, a groundboom

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

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

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

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

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

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

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

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

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

22 So this table just provides a

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

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

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

1 application.

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

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

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

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

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

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

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

1 terms of the exposure weighting.

2 So the 2008 and 2009 exposure
3 studies measured different chemicals, but both
4 provided information in terms of urinary
5 metabolites. The Bakke study looked at
6 atrazine, and the 2009 Thomas study looked at
7 2,4-D and chlorpyrifos. They also collected
8 information on dermal and inhalation exposure.

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

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

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

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

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

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

1 as part of the 2007 FIFRA SAP meeting.

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

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

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

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

22 So the Agricultural Health Study,

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

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

1 that as part of our analysis as well.

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

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

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

1 as part of step three.

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

4 CHAIR HEERINGA: Thanks, Ms.
5 Shelat.

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

8 DR. BAILAR: I have three
9 questions.

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

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

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

19 MS. SHELAT: Are you referring to
20 step two?

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

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

3 MS. SHELAT: That is correct.

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

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

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

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

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

22 CHAIR HEERINGA: Jeff Dawson?

1 Looks like he is reaching for the microphone.

2 MR. DAWSON: Hi. Jeff Dawson,
3 OPP.

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

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

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

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

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

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

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

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

1 ready ways to exclude recent exposures that
2 wouldn't affect that outcome? In other words,
3 you have measures of exposure of through, say,
4 10 years ago.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 provider information.

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

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

8 DR. PORTIER: Jeff or Shalu might
9 be able to answer this. In the previous Panel
10 review of the PHED database, one of the issues
11 was kind of the oldness of the data. Has the
12 database been updated significantly since that
13 2007 review before the Panel?

14 MR. DAWSON: Jeff Dawson, OPP.

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

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

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

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

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

16 DR. HAYTON: Yes, Bill Hayton.

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

1 MR. DAWSON: Jeff Dawson again.

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

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

18 DR. HAYTON: Okay, thank you.

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

1 Let's actually give you an extra
2 10 minutes because of the turnover on the
3 lunch places. So let's reconvene at 1:10.

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

9 Just make a note, if you would
10 like to make a short public comment, members
11 of the audience, and have not registered with
12 Myrta Christian, please see her. At this
13 point, you would be limited to the standard
14 public comment of five minutes. But if
15 something has come to mind that you would like
16 to make a public comment, please see Myrta at
17 the break. Otherwise, we will see everybody at
18 10 after 1:00 to start up again.

19 Thank you.

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

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

2 1:11 p.m.

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

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

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

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

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

7 MS. WINFIELD: Thank you, Dr.
8 Levine.

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

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

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

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

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

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

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

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

22 So one of the ways we have

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

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

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

1 about the importance of safe use.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 But because of the limitations of

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

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

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

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

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

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

10 So, briefly, I will provide some
11 background on diazinon. As part of an
12 agreement between EPA and diazinon
13 registrants, retailers could no longer sell
14 indoor residential products as of December
15 31st, 2002, and retailers could no longer sell
16 outdoor residential products as of December
17 31st, 2004. So, as of 2005, it is unlawful to
18 sell diazinon residential products in the U.S.

19 Additionally, as specified in a
20 2002 agency decision document, occupational
21 risk mitigation measures were phased in over
22 the subsequent two to five years after that

1 document was published.

2 So that is a little on its
3 regulatory history.

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

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

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

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

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

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

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

1 confirmed by a physician or laboratory test.

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

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

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

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

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

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

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

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

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

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

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

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

1 outdoor uses were prohibited from sale and
2 retail establishments at the end of 2002 and
3 2004, respectively. So we can see that. And
4 just as another reminder, the agricultural
5 risk mitigation measures were phased in over
6 a two-to-five-year period subsequent to 2002.

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

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

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

22 So, in the beginning of the

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

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

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

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

6 CHAIR HEERINGA: Thank you very
7 much.

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

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

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

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

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

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

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

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

1 under-reporting is assumed.

2 I don't know if you want to --

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

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

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

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

1 minimal overlap overall.

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

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

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

1 can and should be reporting adverse reports of
2 pesticide exposure.

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

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

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

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

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

10 DR. BAILAR: Thank you.

11 CHAIR HEERINGA: Dr. Chambers?

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

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

1 classified as no effect.

2 Is that what you are getting at?

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

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

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

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

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

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

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

22 But, yes, I just want to reiterate

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

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

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

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

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

9 CHAIR HEERINGA: Dr. Levine?

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

12 CHAIR HEERINGA: Yes.

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

21 CHAIR HEERINGA: Okay, Dr. Levine.

22 Dr. Greenwood and then Dr.

1 LeBlanc.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22 MS. WINFIELD: That California

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

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

8 DR. LeBLANC: Right.

9 MS. WINFIELD: Yes. Okay.

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

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

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

1 incidents that trigger concern.

2 DR. REED: Okay.

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

8 DR. MANIBUSAN: So, under FIFRA
9 6(a)(2), we require registrants to submit case
10 reports on each adverse reporting incident.
11 To the extent that we need to follow up, we
12 also have that ability to do so under 6(a)(2).

13 DR. REED: Okay. So, based on
14 that, is it possible that, when you go back to
15 it, that you can get more information about
16 the exposure? Could that be a possibility or
17 not at all?

18 MS. WINFIELD: It is a
19 possibility. One of the things or one of the
20 items that is supposed to be included in all
21 case reports that get submitted to the agency
22 is a way to follow up on the incident. So

1 there have been a couple of times where, you
2 know, you are looking at a chemical as a
3 whole, and you see an incident that is severe
4 or maybe it is part of a lawsuit or something,
5 and there's a phone number. And you can call
6 and try to get additional information on the
7 incident.

8 DR. MANIBUSAN: So, right, just to
9 clarify, if you do call back and follow up on
10 a case report, it doesn't always mean that you
11 are going to get better information because
12 this is self-reported. So the exposure will
13 be always a bit in question because it is not
14 confirmed.

15 I think that is where you are
16 getting at with the questioning.

17 DR. REED: Right. Right. Yes.

18 DR. MANIBUSAN: Okay.

19 DR. REED: I was wondering, you
20 know, even within the whole list of incidents
21 database per se, what is the possibility of
22 getting the exposure data? In diazinon case

1 study, you see that there is two distinct sort
2 of things that you can glean from it.

3 One is the sort of hazard ID gives
4 you the comfort, feeling of humans responding
5 similarly to the animals, which for
6 cholinesterase inhibitors is not hard to
7 imagine. So you are not gaining a whole lot
8 out of it.

9 And the second thing is it traces
10 quite well with your decisions, but in terms
11 of using this type of data for risk
12 assessment, trying to figure out what else can
13 begin, if you have the resources to go back
14 and look at it -- so exposure is kind of hard
15 to get, huh?

16 DR. MANIBUSAN: Absolutely, and I
17 think that what you described is the challenge
18 that we are presenting to you today with the
19 framework analysis. It is, how do you piece
20 together all this disparate information and
21 tell us story? I think you can. I think the
22 area of exposure assessment can be put

1 together by piecing all the information in a
2 holistic manner.

3 So you are right, I think what you
4 are describing is the difference that we are
5 trying to display with each of the case
6 studies, you know, looking at retrospective
7 ecological studies compared to a prospective,
8 super-duper, platinum study like the AHS, and
9 now bringing it down to incident data, which
10 is in a whole different realm, but it is human
11 data.

12 But you also need to understand
13 the complexity, the limitations of this
14 database. It is not going to give you
15 causality for sure. It will give you what
16 Sarah has displayed for diazinon, which is a
17 crude way of looking at trends and signals and
18 patterns, but it won't give you that
19 refinement that you are looking for, as in an
20 epidemiology study, for example, where you can
21 get a better handle on the exposure; you can
22 get a better handle on the hazard.

1 That is why we are trying to
2 present to you what we are doing to try to
3 collectively look at all the different
4 databases, so that we can look for things like
5 reproducibility and consistency, merely to
6 trigger for additional analysis, and bringing
7 all the information together.

8 DR. REED: But let me clarify.
9 You mentioned that you are not going to get
10 causality. I think, with diazinon, you know
11 the mode of action, and it is acute kind of
12 effect. Actually, you get pretty good
13 causality, right? I mean at least you think
14 that, in your head, it is reasonable.

15 But I think, without exposure, you
16 wouldn't be able to get sensitivity of
17 individuals. Is that what you mean by
18 causality?

19 DR. MANIBUSAN: I think what I am
20 trying to articulate is that incident data
21 alone could not help you arrive at a causal
22 interpretation. What we have with diazinon is

1 a rich database that allows us to merge
2 together our understanding of our mode of
3 action, the toxicity outcome, as well as
4 having a pretty good regulatory history to
5 draw upon. So, piecing that all together, you
6 can arrive closer to a causal interpretation,
7 but just incident data alone, it would be very
8 difficult.

9 CHAIR HEERINGA: At this point in
10 time, I think I would like to move on to the
11 wrapup. Anna Lowit is scheduled to do that.

12 DR. LOWIT: Yes, I won't say too
13 much, and I didn't make any slides.

14 I think you have a solid sense of
15 the significant challenge that lays in front
16 of us to make better use of human information
17 from epidemiology and human incident data.
18 These kinds of data can come from very wide-
19 ranging sources of purpose and scope and
20 quality, and it is our job to evaluate those
21 data and put them in combination with what we
22 know from animals, what you can learn from in

1 vitro and the new high through-puts, assays,
2 thinking about it in a toxicity pathway sort
3 of way.

4 We really believe that thinking
5 about organizing information in a source-to-
6 outcome pathway, and using the tool of the
7 mode-of-action framework as an organizing and
8 reviewing tool is really a solid foundation to
9 doing this kind of integration. You take
10 human information from a variety of sources
11 and combine with everything else you know
12 about the chemical to make a weight-of-the-
13 evidence finding.

14 We are really looking forward to
15 the feedback that you will probably start
16 tomorrow and also to the public comments.

17 CHAIR HEERINGA: Thank you, Dr.
18 Lowit.

19 And just for the Panel's sake, we
20 will have a chance to revisit any questions of
21 clarification tomorrow morning before we start
22 the charge questions, and even during the

1 charge question period. If there is
2 information that really would be beneficial to
3 bring forward, we will do that, too.

4 So, at this point in time, I think
5 I would like to bring this period of
6 scientific presentations and overview
7 presentations to a close, and enter into the
8 period of public comment.

9 We have a fairly large number of
10 public commenters scheduled. I hope to get
11 the majority in this afternoon. I am not sure
12 that we will get everyone in this afternoon.
13 We want to hold people to their prescribed
14 time limits, but I also don't want to rush
15 things as well in this period.

16 And again, if you have an interest
17 in making a public comment, either this
18 afternoon or first thing tomorrow morning,
19 please contact Dr. Myrta Christian during the
20 break, our Designated Federal Official.

21 So we will begin our period of
22 public comment, and these are in the order

1 that have been provided to me by the
2 Designated Federal Official.

3 We will begin this afternoon with
4 Dr. Jennifer Sass, who is representing the
5 National Resources Defense Council.

6 Jennifer, we have allocated you
7 about five minutes.

8 DR. SASS: Thank you for the
9 opportunity to comment.

10 My name is Jennifer Sass, and I am
11 a scientist with the Natural Resources Defense
12 Council, which is an environmental, nonprofit.
13 I am in the health program here in Washington.

14 Actually, my comments I submitted
15 to the docket, and I also have hard copy to
16 hand out. But, to be quite honest with you,
17 I had a lot of trouble with these. Normally,
18 I have been coming in front of you for about
19 nine years now, and I pretty well know exactly
20 what I had wanted you to say all the time, and
21 I usually go through the charge, I read the
22 documents, I go through the charge questions,

1 and I sort of provide for you my answers from
2 NRDC's perspective on those. But I had a lot
3 more trouble with this one.

4 So I think what I want to say to
5 you is that I think what EPA is asking you is
6 to really sort of sit back a little and just
7 talk about how to use these kind of data most
8 effectively in a public health protective way
9 to set out health protective regulations,
10 which is what EPA's mandate is, to protect
11 human health and the environment.

12 I don't think I have anything to
13 tell you on how to do that. To be quite
14 honest, I don't think there are easy answers
15 to the charge questions.

16 So, what I have done instead is to
17 make a longer list, and I am going to give you
18 just a few minutes, on the kinds of things
19 that I think about and that I hope that you
20 think about when you are reviewing the data on
21 atrazine specifically.

22 So atrazine is sold under

1 "musclely" names like Bicep Magnum, and the
2 website says that it is how fields get clean
3 and stay clean. So what this means is that it
4 is a non-specific herbicide. It kills most
5 weeds in the fields before the crop is
6 planted, and it also may kill beneficial
7 plants like nutrient-rich plants that are
8 beneficial and beneficial bacteria in the
9 soil.

10 It has a half-life of several
11 years, longer in colder climates, like the
12 northern U.S. compared to the southern U.S.,
13 and can be detected in most streams and rivers
14 in the U.S. I have provided for reference
15 there the USGS report by Bob Billiam that
16 shows that.

17 Eventually, some of it even gets
18 into the Gulf of Mexico. It continues its
19 herbicidal activity there, and by threatening
20 algae and other beneficial water plants that
21 provide food and oxygen for aquatic life.

22 In fact, some of the studies that

1 EPA reviewed in its earlier atrazine
2 assessments over the last decade showed that
3 when they looked at atrazine acute effects in
4 ponds, they didn't detect any effects. But
5 when the ponds were allowed to ice over for
6 the winter, and then they looked at it the
7 next spring, because the plants, the aquatic
8 life, the plants in the pond had died because
9 of the herbicide, the fish didn't have enough
10 oxygen to winter over once the ice was
11 covering it. So there's some more complicated
12 issues with things like herbicides and also
13 long-term environmental concerns.

14 On page 1 of my comments, though,
15 the one that I want you to consider is
16 hormone-disrupting effects. So I have
17 outlined some of the data and why I think that
18 is important. It is not, obviously, a full
19 scientific review.

20 But it does note some studies that
21 aren't included, human studies that aren't
22 included in EPA's packet that they have

1 provided, and that they are presenting to you,
2 including the ones by Shanna Swan at Rochester
3 University and Dr. Kerwin with CDC.

4 And in Kerwin's study, he looked
5 at applicators, and he actually measured
6 atrazine and its metabolites in the urine and
7 showed their exposure. And what he showed was
8 that applicators have a huge amount of
9 exposure compared to what we would expect in
10 the normal population.

11 Shanna Swan showed exposure,
12 measured, again, by urinary measurements
13 related to sperm quality, poor sperm quality.

14 So I am not sure why those aren't
15 included in your packet, but, anyway, I think
16 the endocrine disruptor effects are important
17 to consider.

18 I think short-term exposure
19 effects are also important to consider, and
20 that is because of the endocrine-disrupting
21 activity. So I have a section on page 2,
22 going to page 3, on some of the different

1 animal studies, showing that short-term
2 exposures during critical stages of
3 development caused permanent developmental
4 impacts. There are some rodent studies, as
5 well as some amphibian studies, and many of
6 those studies were done by EPA scientists,
7 which I have cited. So I think those short-
8 term studies during critical windows of
9 development should also be considered.

10 I have a paragraph from U.S. Fish
11 and Wildlife talking about the importance of
12 these short-term spikes on wildlife as well,
13 though I know you are not considering that at
14 this meeting. So I am not going to talk about
15 it.

16 On page 3, I have talked about
17 synergistic effects. That has come up already
18 in the questions. I think that is really
19 important. Not only is atrazine not
20 confronted by itself, when people are exposed
21 to it, it is with other pesticides and
22 herbicides as well as industrial chemicals,

1 but atrazine is in a mixture formulation with
2 many other chemicals as well.

3 So I have cited a number of
4 studies that show that atrazine has the
5 potential to act synergistically with other
6 chemicals that it is found with. For example,
7 there was an assessment that reported atrazine
8 as more likely to cause non-Hodgkin's lymphoma
9 in men when they are exposed in combination
10 with other pesticides. That is Dr. Darus at
11 CDC.

12 There's a number of different non-
13 Hodgkin's lymphoma studies actually cited in
14 the IARC, the International Agency for
15 Research on Cancer assessment. I have talked
16 about some of this as well. They have a table
17 in that assessment that provides that data.

18 I know you are only looking at
19 human data, but there is also a study that was
20 published in Nature last year, I believe,
21 2008, by Dr. Rohr, Jason Rohr. It showed that
22 atrazine caused different kinds of deformities

1 in amphibians, and that when it was in
2 combination with phosphates, which are
3 commonly found in agriculture as fertilizers
4 for corn and sorghum, that it was much more
5 toxic. So these studies are red flags.

6 The USGS has also found that
7 atrazine is detected in combination with other
8 pesticides in streams and surface water. In
9 fact, the USGS survey found atrazine in water
10 about 90 percent of the time in agricultural
11 streams. All of the time it was with more
12 than one pesticide. About 20 percent of the
13 time, they had more than 10 pesticides they
14 found.

15 So, failing to consider co-
16 contaminants or even calling co-contaminants
17 confounders and eliminating studies that have
18 those, I think would be a poor reflection on
19 reality with how common it is to find it in
20 co-contaminants.

21 On page 5, I have a table for you.
22 This is from EPA's data, based on water

1 monitoring. What I am trying to show here is
2 we have a report that my organization put out
3 last year, late 2009, I think October, so a
4 couple of months ago. It is available on our
5 website and has a lot more of these data.

6 But this particular one that I
7 have picked for you is total chlorotriazine
8 metabolites. So it is atrazine and the
9 metabolites. The reason why that is important
10 is EPA considers atrazine and its metabolites
11 to have equal toxicity, and so evaluates all
12 of them, which is appropriate.

13 What this measured was the total
14 chlorotriazine detections in drinking water.
15 So, again, not surface water, not groundwater,
16 but actually tap water. This is finished
17 drinking water, the stuff that comes out of
18 your tap.

19 And what they found was that, if
20 you look at this table, you will find some
21 that have an annual average that exceeds the
22 3 parts per billion, which is the drinking

1 water limit. But, most of the time, what you
2 will see is that it doesn't exceed an annual
3 average of 3 parts per billion, but, yet, they
4 have these peaks that can go much higher,
5 spikes. Some of those spikes are in the
6 double digits, and some of them will last for
7 days or weeks.

8 The top one you see in Illinois
9 here, big corn grain country, it was as high
10 as 43 parts per billion, and it stayed in the
11 double digit for the next 22 days.

12 So, considering atrazine and its
13 metabolites is important, too, because of
14 their toxicity and because of their
15 detections.

16 And the last paragraph, on page 6,
17 so my conclusion, I just want to point out to
18 you I guess this isn't for the Scientific
19 Advisory Panel, but consideration for the EPA
20 in registering atrazine or allowing the
21 continued use, registration and use of
22 atrazine. There is supposed to be a

1 cost/benefit analysis. In other words, the
2 risks of the chemical are supposed to be
3 measured against the benefits, and the
4 benefits are economic, the economic benefits
5 of the chemical.

6 There are some analyses that I
7 have cited here that show that, actually,
8 atrazine provides only a modest benefit in
9 terms of crop yield production. It is under
10 2 percent in a number of them, 2 to 3 percent
11 in a number of the different analyses.

12 The one I have discussed the most
13 is one by Dr. Frank Ackerman at Tufts
14 University. So, really, the economic benefits
15 are very modest, and that is not even going
16 into whether or not you need such
17 overproduction of corn in this country. That
18 is for EPA to consider.

19 For you, I think I would just like
20 to point out how important I think those
21 different endpoints are, co-contaminants,
22 metabolites, and some of the exposure studies

1 that aren't presented to you by EPA in this
2 package.

3 Thank you.

4 CHAIR HEERINGA: Thank you, Dr.
5 Sass.

6 Comments or questions of
7 clarification for Dr. Sass?

8 (No response.)

9 Okay. Thank you very much.

10 Our next scheduled public
11 presenter is Dr. Gerard Swaen who is with Dow
12 Agrisciences. Dr. Swaen has been allocated 20
13 minutes in advance agreement with the
14 Designated Federal Official.

15 Panel members and, also, members
16 of the public and audience, the presentation
17 materials, all of the presentation materials
18 and any materials, of course, submitted to the
19 DFO will be on the docket. Again, there's
20 probably a little bit of a delay to get
21 materials posted. So everything that is being
22 presented and being received by the Panel

1 should be publicly accessible.

2 Dr. Swaen, please.

3 DR. SWAEN: Thank you very much,
4 Mr. Chairman.

5 My name is Gerard Swaen. I am an
6 epidemiologist by training, and I work for the
7 Dow Chemical Company, and based in the
8 Netherlands.

9 I also have an honorary
10 appointment at the University of Maastricht in
11 the Netherlands and am a member of several of
12 the permanent committees of the Dutch Health
13 Council, among which there is one that sets
14 the occupational exposure standards and also
15 makes carcinogen classification.

16 I have mostly conducted during my
17 career epidemiology cohort studies on worker
18 populations exposed to acrylonitrile, ethylene
19 oxides, dieldrin/aldrin pH, carbon disulfide,
20 and a number of other chemicals.

21 Of course, being an
22 epidemiologist, I believe human data to be a

1 crucial part of the information used for risk
2 assessment. However, there are some quality
3 issues, and it is very important, I think, to
4 compare the value of epidemiology data with
5 the toxicology data, and they both should be
6 taken into account.

7 My presentation will describe how
8 more evidence-based approaches may contribute
9 to risk assessment, making them more
10 transparent, systematic, consistent,
11 reproducible, and science-based. The
12 presentation basically follows the charge
13 questions on the framework, as given in the
14 memorandum of 12 January 2009, in order to
15 facilitate the discussions by the Science
16 Panel.

17 So these are the four charge
18 questions that were in the memorandum. I
19 basically will focus on No. 2 and No. 3, but
20 I will go through them one by one.

21 On the strengths and limitations
22 of epidemiology studies, I would certainly

1 recommend the EPA to take into account the
2 essential difference between an exploratory
3 analysis and a hypothesis-driven study.

4 In 2001, I published a study which
5 I did together with two colleagues of mine at
6 the University, and I analyzed, I compared 150
7 false-positive epidemiology studies with 150
8 true-positive epidemiology studies. A false-
9 positive epidemiology study, for example, is
10 a study reporting an association between
11 benzene exposure and lung cancer. That has
12 not really been reproduced that often.

13 The study showed that those
14 studies with no specific a priori hypothesis
15 had three times more likely risk to generate
16 a false-positive study. Those studies with an
17 a priori hypothesis also have a very small
18 likelihood of being false-positives, but in
19 case of exploratory analysis these type of
20 results were threefold, were three times that
21 prevalent.

22 Also, I recommend to take into

1 account publication bias. I think it is very
2 important to understand that in the scientific
3 literature positive studies are
4 overrepresented compared to negative studies.
5 I don't have any evidence for it. I don't
6 have any empirical basis for that.

7 Finally, on this charge question,
8 I recommend the Committee to look at the
9 ECETOC Report No. 104, which provides a
10 framework to integrate human data and animal
11 data and come up with a framework for risk
12 assessment. This report is probably going to
13 be the basis for some of the rich guidance
14 that is still now under development.

15 Use of incident data, charge
16 question 2, I think it can be a very important
17 source, providing it is about acute effects,
18 as we have seen just a few minutes ago, and
19 acute effects being specific for a chemical.
20 And of course, provided that the analyses done
21 are hypothesis-driven and not just of an
22 exploratory nature.

1 I don't think that incident data
2 can be very helpful for multifactorial
3 diseases or diseases with an unknown etiology
4 because it will not be possible to take into
5 account the effect of these potential
6 confounding factors.

7 The mode-of-action framework for
8 human data, I believe that epidemiology
9 studies is not going to contribute that much.
10 I take charge question 1.4 before charge
11 question 1.3 because the rest of my
12 presentation will be about charge question
13 1.3.

14 The application of the Bradford
15 Hill criteria, I strongly recommend doing
16 that. I think the Bradford Hill criteria are
17 the best available guidance for causal
18 inference. However, they should be applied in
19 a very systematic manner, and that is
20 something that is not really done very often.

21 Even if you look at the IARC
22 evaluations, which I am going to use later on,

1 it is very uncommon that an evaluation will go
2 through all the nine Bradford Hill criteria.

3 These are the Bradford Hill
4 criteria. You can have modified criteria, and
5 so on, but, essentially, there is not that
6 much difference.

7 Now, if you use the Bradford Hill
8 criteria for causal inference, you may come
9 across two weaknesses. First of all, it is
10 not clear how to weigh this criteria against
11 each other. It is not clear if strength of
12 the association contributes more to a causal
13 relationship than consistency or analogy or
14 exploratory or experimental data. This is not
15 clear at all.

16 A second weakness is that in most
17 cases the evidence available on a chemical is,
18 from my perspective, insufficient to come to
19 a yes/no conclusion. Most of the results are
20 somewhere in between zero percent probability
21 or 100 percent probability of the real causal
22 association. It would be good to have an

1 instrument that can help assessing the
2 probability of the causal association.

3 Now, together with colleagues at
4 the University of Maastricht, we conducted a
5 study and we evaluated a large database with
6 the objective to develop an approach for
7 causal inference that applies to Bradford Hill
8 criteria in a way that is based on empirical
9 evidence that can be reproduced and can be
10 used on other associations also.

11 We also developed a model that
12 would give us the opportunity to assess the
13 probability of an association being causal,
14 rather than this very unlikely yes/no outcome.

15 So the research questions were:
16 how can we determine the weights of each of
17 the nine Bradford Hill criteria based on
18 evidence, and can we develop a model that will
19 provide a probability estimate for causality
20 rather than this yes/no association?

21 In order to do this, you need gold
22 standard data. You need somewhere a database

1 that tells you this chemical is a carcinogen,
2 this chemical is not yet a true carcinogen,
3 and you need to have evidence that will
4 support or in a certain magnitude it will
5 support the nine Bradford Hill criteria.

6 Then, of course, you need to apply
7 the Bradford Hill criteria and let the data
8 determine the optimal weights for each of the
9 nine criteria. The best available gold
10 standard for this is the IARC database. At
11 the time we did this analysis, there were 159
12 agents evaluated by IARC either as category 1
13 or 2A, category 1, a proven human carcinogen,
14 category 2A, a probable human carcinogen. So
15 the contrast we have here is between category
16 1 and 2A.

17 We evaluated all the evidence that
18 was used by IARC at the time of their
19 evaluation for these 159 agents. So we went
20 through all the literature that you can find
21 in the monographs and we assessed the
22 probability that each of the nine Bradford

1 Hill criteria was met. Assessing the
2 probability that a criterion is met requires
3 a number of algorithms which you can find in
4 the publication that came out last year.

5 The database, the probabilities
6 that we estimated, we analyzed by means of
7 discriminate analysis, and the results show
8 that a model can be made that includes, that
9 contains the weights for each of the nine
10 criteria.

11 It also showed, to my surprise,
12 that strengths of the association,
13 consistency, and experimental evidence are the
14 three criteria that contributed most. My a
15 priori idea was that dose response would be
16 one of the three that would come out as most
17 important. However, I am now stuck with these
18 three because these are the ones that are
19 empirically-based.

20 This is the model. As you can
21 see, strengths, consistency, and experimental
22 evidence work well. They explain most of the

1 variance, and you can apply this model to any
2 type of association that you would like to
3 assess the causality for.

4 Here you have an example for
5 cigarette-smoking and cancer, and the
6 algorithm tells you that, if you have relative
7 risks over 10, then the probability that the
8 strengths criterion is met is 95 percent. So
9 these algorithms were used to develop the
10 model, and you, of course, should speak to the
11 algorithms when you try and do another
12 assessment.

13 2,4-D and non-Hodgkin's lymphoma,
14 a chemical that is produced by us, strength of
15 the association is met with a probability of
16 about 30 percent, which only is a relative
17 risk between one and two, and the algorithm
18 will tell you that you should stick to the
19 probability of 30 percent, and so on.

20 So you use all the evidence that
21 is available to assess the probability of each
22 of the nine criteria being met. So the

1 righthand column is an expert judgment affair.

2 However, the weights are empirically-based.

3 Another example is the gasoline
4 station attendant. You go to the literature;
5 you can find evidence in support or evidence
6 against a causal association for cancer risk
7 from being a gasoline station attendant.

8 The strength is designated the
9 probability of 60 percent because there is one
10 study that reported a relative risk of 3.6.
11 I am not going to discuss the study at the
12 moment, but that is just the algorithms that
13 have been used in this analysis.

14 Overall, the probability that the
15 association between being a gasoline station
16 attendant and a cancer risk afterwards is
17 estimated to be 15.4 percent, when you use
18 this model.

19 So the results are that we now can
20 apply the Bradford Hill criteria to other
21 scenarios with using these empirically-based
22 weights. They are based on evidence. The

1 model appears to work well, although now I am
2 going back to the pitfall and making a
3 circular reasoning. One hundred thirty of the
4 159 agents would be classified correctly, but
5 I want to depart from classifying these
6 agents. I would rather score or estimate the
7 probability of the association being causal.

8 So we have two advantages and two
9 issues that I still need to work on. We have
10 now empirically-based weights, and we have an
11 estimate of the probability of an association
12 being causal.

13 The two issues remaining, of
14 course, are the expert judgment by determining
15 the probability that each of the nine criteria
16 is met. But it is transparent. I can tell
17 you, I can explain how I came or how we came
18 to the 90 percent or to the 95 percent.

19 You can deviate. You can say, no,
20 I think it is 50 percent, and then you can use
21 those probabilities and assess the probability
22 for the causal association.

1 The other issue, of course, is
2 that it is completely based on cancer
3 endpoints. It is not clear whether or not
4 this can be used for neurotoxic endpoints,
5 developmental endpoints, or sensitizers, or
6 whatever.

7 Now I come to a very different
8 approach, which at the moment I call evidence-
9 based thinking. And for that, I would like to
10 make a parallel, I would like to draw a
11 parallel with clinical epidemiology.

12 The clinical epidemiologist, the
13 task of the clinical epidemiologist is to help
14 the doctor come to a correct diagnosis and
15 start the correct treatment. Now, for
16 example, the patient presents himself to the
17 doctor with a certain set of symptoms. In
18 that situation, the doctor must establish the
19 diagnosis before starting the treatment.

20 So he will send in the patient to
21 undergo a certain number of tests that will
22 give him more information on the presence of

1 the disease or the absence of the disease. So
2 he needs to make that decision: how probable
3 is the presence of the disease in this
4 patient?

5 Each test result that the doctor
6 will get back will add to the probability that
7 the patient has the disease, if it is
8 positive, or it will subtract from the
9 probability that the patient has the disease,
10 if the test is negative. Of course, the value
11 of the test that you have conducted depends on
12 the sensitivity, the specificity, and the
13 predictive value of that test.

14 And here is how the sensitivity
15 and the specificity are obtained. You need
16 data, you need a gold standard. You need to
17 see who really has the disease eventually, who
18 develops the disease eventually, and who is
19 free of the disease.

20 With this type of data, you can
21 estimate or you can calculate the
22 sensitivities, that is, of course, the

1 percentage of patients who test positive on
2 the disease. Specificity is the percentage of
3 patients without the disease that, indeed,
4 test negative.

5 So Bayesian thinking implies that
6 there is a prior probability that the patient
7 has a certain disease. The patient presents
8 himself with a set of symptoms. If the test
9 is positive, the probability will increase.
10 If the test is negative, the probability will
11 decrease. There are false-positives and there
12 are false-negatives all the time.

13 Now we apply this way of thinking
14 to health risk. The parallel is, of course,
15 that each type of study is a test with a
16 certain sensitivity, a certain specificity.
17 There are false-positives and there are false-
18 negatives, and there is a predictive value of
19 a positive test.

20 And with tests, I mean the Ames
21 test, a long-term rat study, a long-term rat
22 study tested at the maximum tolerated dose, a

1 long-term rat study not tested at the maximum
2 tolerated dose. These may have different
3 predictive values. A case-control study, a
4 cohort study, instant data, these are all
5 tests.

6 We should try, or at least that is
7 what I am going to try to do, is determine the
8 test characteristics of each these types of
9 studies. This will require a substantial data
10 collection effort because you must collect
11 data on the large number of chemicals, and, of
12 course, the chemicals, they stand for the
13 patients in parallel. Then we should collect
14 the test results for all these chemicals
15 specific for the type of test that we will
16 apply in risk assessment.

17 We need to establish a gold
18 standard. That is going to require some
19 discussion. And for each type of outcome, we
20 probably will need a different gold standard.
21 For neurotoxicity, we will have a different
22 gold standard than carcinogenicity. We will

1 need different tests with different test
2 characteristics.

3 So, as an example, we have a data
4 package which consists of a positive Ames
5 test, a positive long-term rat study, a
6 positive case control study, and a negative
7 cohort study.

8 On the assumption that we have the
9 test characteristics for all these types of
10 information of all these tests, we can now
11 follow this line of reasoning.

12 The prior probability that a
13 random chemical is a carcinogen is very low.
14 It is about 1 percent. If you take a random
15 chemical, the probability that this chemical
16 is a human carcinogen, that is the gold
17 standard for human carcinogen, is 1 percent.

18 Now we have a positive Ames test.
19 So the probability is going to increase to 10
20 percent. We add a positive animal study, and
21 the probability, again, will go up to 40
22 percent, and so on and so on.

1 Of course, the percentage added or
2 subtracted depends on the test characteristics
3 of the test. It depends on the sensitivity
4 and the specificity.

5 So, an evidence-based approach
6 requires or will be based on the predictive
7 value of each of the tests that we use,
8 standard or non-standard, in risk assessment.
9 The result will be the probability that the
10 association is causal. It sounds very nice,
11 but it is very difficult to obtain because,
12 first, we must determine the gold standard.
13 What is really what we want to do in risk
14 assessment? Do we want to do carcinogen
15 classification? Do we want to do regulation?
16 This is what is going to determine the gold
17 standard. And in addition, it will require a
18 well-established, extensive database on a
19 large number of chemicals.

20 I have two summary slides. In
21 assessing the quality of epidemiology studies,
22 I would strongly recommend to include the

1 distinction, the very important distinction,
2 between exploratory analyses and hypothesis-
3 driven analyses because the first one has a
4 three times higher risk of being a false-
5 positive.

6 The application of the Bradford
7 Hill criteria I think is very appropriate, but
8 it should be done in an empirically-based
9 manner. I have described just an example. It
10 is certainly going to be possible to improve
11 this type of analysis. Expert judgment meant
12 that we sat down with the three of us and we
13 made this assessment, but expert judgment may
14 be better done by a panel and by consensus.
15 But it is possible to apply the Bradford Hill
16 criteria in an empirically-based manner.

17 I think the evidence-based
18 approach is promising. However, it will
19 require a huge effort to develop this
20 approach. I am not sure if it ever is going
21 to replace expert judgment because I think the
22 default is still there always needs to be an

1 escape. Even if the evidence-based risk
2 assessment tells you a carcinogen or a
3 chemical is not likely to be a carcinogen,
4 there still needs to be an expert who can take
5 the responsibility and say, yes, we are going
6 to designate it to be a carcinogen.

7 Thank you very much.

8 CHAIR HEERINGA: Thank you, Dr.
9 Swaen.

10 Questions from the Panel for
11 clarification on the material Dr. Swaen has
12 presented? Dr. Bailor?

13 DR. BAILAR: There is a great deal
14 here to respond to. I will limit myself to
15 two points.

16 One is I am a little bit concerned
17 about the sharp dichotomy between positive and
18 negative studies. Most are not that clean.
19 We have to make decisions which are positive
20 or negative, but conclusions, based on a
21 scientific study, are generally somewhat more
22 nuances. I would be more comfortable if I saw

1 that built into any kind of a scheme like
2 this.

3 The second has to do with not
4 misinterpreting what Bradford Hill was trying
5 to do. He was bringing some clarity and
6 organization to a field of inquiry that was
7 just chaotic, and I think it was a marvelous
8 second step forward.

9 I think it is interesting that his
10 criteria can be divided into those that deal
11 with individual papers, those that deal with
12 the evidence as a whole, such as in the first
13 case temporality; in the second, consistency.
14 And then there's some that really refer to
15 both of those, and I think these have to be
16 taken in sequence.

17 I will just add that I called it a
18 second step because Hill was not the first to
19 do this. They are commonly attributed to
20 Bradford Hill, but there is a scheme very much
21 like this that came out a few months earlier
22 in the 1964 Surgeon General's report on

1 tobacco and lung cancer. I would like to see
2 our report at least make a point that that
3 Surgeon General's report was really the first
4 to lay this out and should get the credit for
5 leading the way. We can certainly do that.

6 CHAIR HEERINGA: Other questions
7 of clarification for Dr. Swaen?

8 (No response.)

9 Not seeing any, thank you very
10 much.

11 Oh, we will go over to Dr. Bove.

12 DR. BOVE: You were puzzled that
13 dose response did not get much weight. In
14 fact, I am not so sure I understand the
15 weights here, but I will leave that aside for
16 a minute.

17 Why wasn't dose response given
18 weight in this approach, in your opinion?

19 DR. SWAEN: I didn't expect it. I
20 thought dose response, it had always been my
21 belief that the strength of the association,
22 consistency, and dose response, those would

1 turn up -- that was my prior hypothesis --
2 those would turn up to be the most important
3 ones.

4 But the facts, not the facts, the
5 empirical approach shows you it is not that
6 important. It doesn't help you distinguish
7 that much the category 1s from the 2As.

8 DR. BOVE: Right, and oftentimes
9 the distinction between those two has to do
10 with more evidence coming up, and risk
11 assessments change over time, too. So is that
12 all involved in this evidence-based approach?

13 DR. SWAEN: Well, it is going to
14 be much more complicated. If you look at the
15 21st century approach, this toxicogenomics,
16 then we start really getting into the area of
17 specificities, sensitivity, and predictive
18 value. I think if you don't have those risk
19 characteristics, it is going to be very
20 difficult to make sense of all these data that
21 are going to come to us in the short future.

22 The nice thing about -- well,

1 there are many nice things, of course. One
2 nice thing about the analysis is that, if you
3 add new information, you will see that, for
4 example, consistency is going to go down
5 because you have the new study contradicts the
6 earlier studies. So you can do the analysis.
7 You can say the probability that the
8 consistency criterion, which is not really
9 criterion, in fact, it goes down from 30
10 percent to 20 percent. I mean you can do the
11 calculations and you can see the probability
12 doesn't really change that much.

13 CHAIR HEERINGA: Dr. Reed? Then I
14 think we will move on.

15 DR. REED: You are talking about
16 dose response, but the three examples that you
17 have given, example No. 2 and 3 says no dose
18 response analyzed. That might sort of explain
19 -- maybe the data itself is harder to come by.

20 DR. SWAEN: Yes, the algorithm in
21 the paper, which was published last year, will
22 tell you, and it will tell you something about

1 how you should classify or how you should
2 evaluate the dose response. Because in many
3 occasions, it is not given. That is, of
4 course, something different than the
5 completely flat dose -- a negative study,
6 because there will not be a dose response
7 there.

8 CHAIR HEERINGA: Dr. Lu, did you
9 have a question?

10 DR. LU: Yes, I do.

11 Say the agency wanted to adopt
12 your evidence-based model. I mean, in your
13 presentation, it seems only a significant
14 factor which is the uncertainty. There are
15 many cases that, say, for example, a pesticide
16 applicator living in Iowa, that he is
17 diagnosed having non-Hodgkin's lymphoma today.
18 When you ask -- and you mentioned that it is
19 just like, you know, if you perform something
20 like in a doctor's office, the testing,
21 whether there is 2,4-D residue in this
22 patient's body, which obviously would not

1 happen because the previous exposure occurred
2 10 or 20 years ago.

3 So, I mean, we are dealing with
4 this uncertainty here. But in your evidence-
5 based model, how would you address these
6 uncertainties? So you would take into account
7 exposure that occurred earlier, but not be
8 able to detect it at the present time, when
9 the disease outcome occurs?

10 DR. SWAEN: Well, an epidemiology
11 study is capable of detecting that. That
12 study should have ended up in the IARC
13 database for these 159. So I have taken it
14 into account.

15 But the case series, I am not
16 aware of case series -- well, perhaps there
17 are some very specific associations for case
18 series, for example, mesothelioma and
19 asbestos, there, of course, but I am not
20 really sure how this speaks into the Bradford
21 Hill, but maybe that is the default, an expert
22 judgment.

1 But I ended the presentation by
2 saying that expert judgment is always going to
3 be necessary. I am never going to rely on any
4 model to make the decisions of the Dutch
5 Health Council, for example. I would always
6 like to have the possibility to step out and
7 say, no, now I am going to deviate from the
8 approach that I proposed myself. I am going
9 to say this is a carcinogen or something else.

10 CHAIR HEERINGA: Thank you, Dr.
11 Swaen. We appreciate your presentation and
12 the exchange to follow. It is very helpful.

13 Before we turn to our break, we
14 would like to hear from the next public
15 presenter. This is Erik Janus, who is here to
16 represent CropLife America. Erik has been
17 allocated 15 minutes by the DFO.

18 Erik?

19 Erik's presentation is available
20 in PowerPoints as part of the distribution
21 after lunch.

22 MR. JANUS: And while they are

1 opening my slides, I will just get started
2 here and say good afternoon to the panel.

3 I would just like to thank the
4 agency and the Science Advisory Panel for
5 agreeing to tackle such a hot and timely topic
6 right now.

7 CropLife America for sure
8 appreciates the ability to sit here and
9 comment on behalf of our members.

10 For those of you who aren't
11 familiar, CropLife America is a trade
12 association that just represents the companies
13 that manufacture and formulate and market
14 virtually all the crop protection products
15 used in the country. We are celebrating our
16 77th anniversary this year, continuing on in
17 our role, which is to act and speak on behalf
18 of the agricultural chemical industry.

19 By way of a quick introduction to
20 myself, I have 15 years of experience as an
21 environmental health practitioner and
22 researcher at all levels of government, with

1 industry, academia, and the NGO world. So I
2 have seen a little bit of everything in my
3 career. The last 10 years, I have spent,
4 essentially, doing risk assessment science and
5 public policy work.

6 Now, as such, my role as a trade
7 association, I come to you today with comments
8 that generally fall into one of four broad
9 categories, and generally are the highlights
10 of the concerns of the industry, the issues
11 and the concerns that the industry has.

12 So, moving on to the first,
13 biological plausibility, exposure, risk
14 assessment, and then a little bit on incident
15 data, is what I will touch in the next 15
16 minutes.

17 Now, in terms of biological
18 plausibility, really the basic question that
19 EPA needs to answer here is how well do the
20 epi datasets agree or disagree with the
21 biology and the toxicology datasets that exist
22 in large quantity, particularly for the FIFRA

1 registered compounds? The second dataset,
2 that is.

3 You know, unique endpoints, based
4 on hypotheses generated by epi studies, should
5 not be included in risk assessment at this
6 point, if they have not been replicated or are
7 not biologically-plausible.

8 Granted, not all substances have
9 this wealth of data, but in the case of the
10 active ingredients registered under FIFRA
11 there is an enormous amount of data on the
12 biology and toxicology.

13 Continuing on, really, the key
14 question in reviewing epi studies is, were
15 they designed to address known or suspected
16 biological mechanisms? It appears that we
17 have concrete data on hazard identification,
18 which is an early step in the risk analysis
19 process, and concrete data on toxicology, and
20 often enough on mechanism of action, but it
21 appears we might be borrowing hazard data from
22 epi studies, but still using the in vivo, the

1 more detailed and informative in vivo, in
2 vitro, and soon in silico studies to actually
3 define the dose response relationship and,
4 thus, characterize the risk.

5 Ideally, one could design
6 epidemiology studies based on the findings of
7 tox data, not vice versa. However, we are
8 never going to confirm mechanism of action at
9 this point.

10 And I believe this last point, I
11 feel is consistent with the Tox 21 vision here
12 at EPA, which seeks to flip sort of safety
13 testing on its head over the next 20 years and
14 focus on identifying molecular pathways for
15 adverse outcomes and verifying this in human
16 populations, using epi studies and
17 biomonitoring. It was part of the NRC 2007
18 report that has been mentioned already once
19 today.

20 Now, moving on to exposure, the
21 bottom line is that generic exposure
22 assessments lead to generic conclusions. We

1 have already heard today these can result in
2 misclassification errors, particularly when we
3 are comparing them against biologic measures,
4 such as biomarkers of exposure.

5 I also think it is important to
6 point out that no method has yet been
7 developed to assess the accuracy of lifetime
8 self-reports of pesticide use, which is, of
9 course, the backbone of the Ag Health Study
10 right now.

11 Also, I would like to touch a
12 little bit about daily exposure potential, as
13 measured under the Ag Health Study. This can
14 vary widely, as has been shown in past
15 studies, particularly the Farm Family Exposure
16 Study.

17 Just to pull a couple of points
18 out here, two key components of cumulative
19 exposure, duration and frequency of use, have
20 been found to not agree. It is not
21 necessarily over time, but don't necessarily
22 agree from one survey to another in the AHS,

1 as pointed out by Blair and Zahm early in the
2 process.

3 Applicators are also not uniformly
4 exposed to herbicides during any single day of
5 application. The extent of the exposure may
6 not be consistent across similar herbicide
7 levels in all pesticides. So these still
8 remain as sort of a generic assessment
9 category.

10 At which point I ask myself, is a
11 generic approach for exposure prediction
12 possible for all pesticides? The answer is
13 probably not, but I wanted to start by
14 focusing on like categories, like classes of
15 compounds of similar properties, similar
16 formulations, similar application practices.

17 As we have sort of heard, as
18 somebody alluded to earlier today, assignment
19 of workers into evenly-distributed measures of
20 exposure is not consistent with the findings
21 of monitoring data. Biomonitoring data is
22 almost always a skewed distribution, whereas,

1 we were talking earlier today about splitting
2 exposure gradients into tertiles or quartiles
3 evenly distributed.

4 Another important thing to point
5 out is that there's a general lack of overall
6 biomonitoring data on the Ag Health Study
7 cohort, which I think complicates exposure,
8 the algorithm validation process, if you were.
9 We have heard, I think, what, three different
10 compounds this morning that we've got
11 biomonitoring data on, and I think this
12 probably represents something like less than
13 a half of percent of probably the overall
14 cohort. So this is probably a resource issue
15 in the future that could be addressed, should
16 be addressed.

17 A couple of things I wanted to
18 point out about the Pesticide Handlers
19 Exposure Database, as it came up earlier
20 today. Exposure prediction is limited here.
21 It is not just exposure assessment that limits
22 you here, but there are multiple chemical and

1 physical factors that we need to take into
2 account here.

3 First of all, physical chemical
4 properties of the molecule which impact dose
5 certainly matters here. It is not necessarily
6 captured in the passive dosimetry data of the
7 PHED database.

8 In addition, exposure prediction
9 based on formulation is limited. Granular and
10 liquid forms can have different exposure
11 potentials.

12 Then, earlier this morning, Dr.
13 Alavanja pointed out that application methods
14 can also have an effect here, too, in terms of
15 the intensity algorithm and what comes out of
16 that process.

17 Now moving on to risk assessment,
18 again, if endpoints identified via
19 epidemiology studies are not consistent with
20 the biology, they should not be part of the
21 risk process. I was encouraged to hear a lot
22 of treatment of this exact aspect of the

1 problem. Some of the EPA presenters earlier
2 today, when they discussed some of the things
3 they would tackle during the problem-
4 formulation phase, and that is great because
5 that is consistent with the new NRC report in
6 terms of devoting more attention to that. I
7 think it is a crucial part of this particular
8 process, too.

9 If these endpoints are, indeed,
10 consistent with the biology, then, sure
11 enough, as EPA quotes, high-quality studies
12 with robust exposure assessment may be used to
13 estimate risk, but we need to emphasize that
14 you have to have robust exposure assessment.

15 You probably hear a lot about
16 this. The weight-of-evidence approach is
17 clearly crucial to determine how do individual
18 sets of research papers, such as the Ag Health
19 Study, stack up against the rest of the epi
20 literature available on a particular endpoint?
21 How does the overall epi literature stack up
22 against the substantial amount of biological

1 and toxicological data that we have got on
2 crop protection products?

3 I would just point out now that it
4 is crucial to talk about this stuff early and
5 often in the game, but, really, the SAP
6 process is not really addressing the weight of
7 evidence in explicit detail. So, thankfully,
8 we have got the permanent members who will be
9 back in September to pick up this
10 conversation.

11 Moving on, as was brought up by
12 Dr. Swaen, the gap between causality and
13 association is filled by imposing the classic
14 Bradford Hill criteria. This is not an ala
15 carte option. Really, all should be given
16 initial consideration. Again, during the
17 problem-formulation and hazard-identification
18 phase, we need to look at these individual
19 criterion, define them, and discuss them
20 relative to the available information.

21 Quantitative use of these
22 criterion and the risk process, of course,

1 must be fully transparent. We need to
2 identify all the inherent uncertainties, where
3 possible, and quantify those, where possible,
4 which, of course, is the root of the
5 precautionary principle, as I was taught, you
6 know, in grad school, quantification of
7 uncertainty.

8 Also, this last point, a little
9 similar to the approach that Dr. Swaen just
10 mentioned on the IARC carcinogens. I would
11 like to offer just a couple of thoughts on
12 incident data before I wrap up.

13 First is a little note of caution
14 regarding the diazinon case study. It does
15 have all the ideal characteristics for this
16 type of assessment. However, I am afraid you
17 are not going to find that in the world of
18 pesticides very often.

19 In the case of diazinon, you have
20 a very well-characterized symptom of acute
21 overexposure. You had residential uses. You
22 had agricultural uses, and you had a scheduled

1 phaseout. So you could take a careful
2 approach and look at this. I don't know that
3 you are going to find that for a whole lot of
4 other crop protection chemicals. I think that
5 is going to complicate the overall
6 interpretation and application of this.

7 But that being said, CropLife
8 America, I took a look at their proposed
9 approach, and I think it is pretty good. It
10 does a good job pointing out limitations of
11 the data streams, which is probably the
12 biggest, I think, factor at this point, is how
13 you sift all these individual different data
14 streams together, if you do it.

15 I do have a few suggestions for
16 improvement in terms of the incident analysis
17 process. Since the residential incidents seem
18 to far exceed the ag incidents in terms of
19 volume, maybe it makes sense to look at these
20 separately. Clearly, there are data quality
21 issues, as you have heard, and will continue
22 to hear with self-reported data, epi and human

1 incident data alike.

2 One rhetorical question I want to
3 throw out there is, how does one do QA and QC
4 on these databases? Does an individual who
5 sets off 10 bug bombs in his small apartment
6 in New York City constitute an incident, when
7 he is clearly not following the label? I
8 don't know the answer to that. I question
9 that.

10 Clearly, again, we would like to
11 see a transparent and a scientifically-sound
12 process here. I am comforted, again, hearing
13 some of the things I heard this morning with
14 the incident data that appears to be going
15 down the right track.

16 But we do need to put the total
17 number of incidents in perspective here. I
18 think comparing the overall number of
19 incidents to volume and frequency of sales of
20 certain products is useful, both before and
21 after any risk mitigation measures are taken.

22 Again, how does one consider an

1 off-label incident? How do you treat that
2 data-point?

3 I just want to wrap up with a few
4 points here. Generic exposure estimates lead
5 to generic conclusions. I can't stress that
6 strongly enough.

7 Secondly, again, if the endpoints
8 identified via epi studies and incident data,
9 for that matter, are not consistent with the
10 biology, in other words, they are not
11 biologically-plausible, they should not be
12 considered part of the risk process.

13 And lastly, the weight-of-evidence
14 approach is mandatory here, but just as
15 important are being transparent and using the
16 best available science.

17 CHAIR HEERINGA: Thank you very
18 much, Mr. Janus.

19 Questions of clarification on the
20 presentation?

21 (No response.)

22 Thank you again.

1 I am going to move ahead with the
2 next public commentator or presenter, and that
3 will be Dr. Dominik Alexander, representing
4 Exponent. Dr. Alexander has been allocated 20
5 minutes by the Designated Federal Official,
6 and then we will move to a break.

7 For those of you who are scheduled
8 to be public commenters, I am going to try to
9 wrap this up today, so that we get you in
10 there. Our number of people representing the
11 various groups who are here for short
12 comments, rather than hold you overnight, if
13 you had other plans, we will try to get
14 everything in today.

15 But, for now, Dr. Alexander,
16 please.

17 DR. ALEXANDER: Okay. My name is
18 Dominik Alexander. I am an epidemiologist
19 with Exponent, and over the course of the next
20 20 minutes, I will be discussing some of the
21 methodological considerations of our ongoing
22 assessment of pesticides and colorectal

1 cancer, a weight of evidence, review of
2 epidemiologic studies.

3 This work is very much in its
4 preliminary stage. Hopefully, for the
5 September meeting, I will have the opportunity
6 to come back and share the conclusions of this
7 project.

8 Before I get started, I just want
9 to mention that we do have a multidisciplinary
10 research team. Some of the members are
11 included here who have experience or expertise
12 in epidemiologic methodology, causal
13 applications, weight-of-evidence evaluations,
14 toxicology, risk assessment, and statistics.

15 Okay. Colorectal cancer, it is the
16 third most common cancer diagnosed among men
17 and women in the U.S. Its etiology is largely
18 unexplained. However, several key dietary,
19 lifestyle, behavioral characteristics have
20 been shown to be associated with both
21 increasing and decreasing the risk of this
22 malignancy.

1 One of those happens to be
2 physical activity. We know that farming is an
3 occupation that is physically demanding.
4 Studies have shown that the rate of colorectal
5 cancer is generally lower among farmers
6 compared with the general population, and that
7 result could be due, in part, to the
8 physically demanding nature of the occupation.

9 We also know that farming
10 encompasses a heterogeneous array of
11 exposures, which vary by type of farming,
12 specific chemicals used, time period of
13 farming, geographic location of the farm.

14 It has been postulated, based
15 primarily on exploratory studies, that
16 pesticides or specific chemical exposures may
17 be associated with increasing the risk of
18 colorectal cancer.

19 And to our knowledge to date,
20 there hasn't been a comprehensive or
21 systematic review of pesticides in colorectal
22 cancer in the literature. Therefore, to

1 update the state of the science surrounding
2 this topic, we are in the process of
3 conducting a weight-of-evidence evaluation.

4 I don't have time to go over all
5 the individual facets of our systematic
6 weight-of-evidence approach. However, I will
7 touch upon some key points.

8 We have just completed the first
9 stage of our comprehensive literature search.
10 In addition, we reviewed the Ag Health Study
11 website, and we identified all studies of
12 pesticides and colorectal cancer.

13 And I should point out the Ag
14 Health Study cohort is the foundation for
15 which the majority of the chemical-specific
16 studies have emerged. Specifically, there are
17 25 studies of pesticides in colorectal cancer
18 or specific chemicals in colorectal cancer.

19 So the focus of the methodological
20 considerations that I will be talking about
21 today should be applied to or will be applied
22 to the Ag Health Study cohort.

1 We are focusing on cohort and case
2 control studies at this stage. We are looking
3 at associations between pesticides as a class
4 or as a group, as well as specific chemicals
5 in colorectal cancer. We will be extracting
6 data and information for numerous study
7 characteristics, including the nature of the
8 cohort, exposure assessment, analytical
9 metrics, statistical associations, and so on.
10 We will be synthesizing data within and across
11 studies when we are evaluating the overall
12 epidemiologic evidence.

13 Our methodological assessment
14 involves or will involve a scientifically-
15 rigorous and systematic evaluation of the
16 epidemiologic literature. Important
17 methodological characteristics, analytical
18 factors will be objectively considered when
19 interpreting the body of epidemiologic data.
20 And we will conduct a critical assessment of
21 internal and external validity.

22 Now our methodological approach

1 will be applied to the literature on
2 pesticides and colorectal cancer. However,
3 the same type of approach can and perhaps
4 should be applied to other cancer endpoints or
5 other disease endpoints.

6 So, as part of our assessment, we
7 will evaluate how well the hypothesis of
8 interest has been tested in the Ag Health
9 Study cohort. We will look at issues
10 pertaining to the study design being used, the
11 potential impact of confounding, the impact of
12 bias, recall bias, misclassification,
13 selection bias, the direction and magnitude of
14 associations, including the statistical
15 significance power, the precision of
16 associations, and issues involving exposure
17 assessment.

18 And we will compare the findings
19 that we observe in the Ag Health Study to that
20 of other studies. We will look for
21 methodological and statistical consistency.

22 Here you can see some of the

1 undertones of the Bradford Hill considerations
2 throughout.

3 Overall, we will look at the
4 consistency of results between and within
5 exposure metrics of the Ag Health Study. We
6 will look at associations for colorectal
7 cancer and separately for color cancer and
8 rectal cancer. The Ag Health Study
9 appropriately reports on these anatomic tumor
10 sites separately.

11 I, finally, will consider the
12 totality of the available epidemiologic
13 evidence when making our overall
14 interpretation.

15 So, as we know, the Ag Health
16 Study, it is a prospective design with a
17 relatively large sample size. It does include
18 a semi-quantitative exposure assessment. I
19 will talk about some of the trends in exposure
20 assessment here momentarily.

21 To date, followup is relatively
22 short, thereby making it somewhat difficult to

1 assess rare cancers. For example, the data
2 for colon cancer are much more abundant than
3 they are for rectal cancer, which is reported
4 less frequently.

5 In addition, we know that exposure
6 is categorized in quartiles, usually tertiles.
7 And if we are starting with a relatively small
8 handful or small number of observed cases,
9 those cases are distributed across the
10 different exposure categories, thereby making
11 single-digit or small numbers in each exposure
12 category.

13 In a preliminary assessment of
14 many of the Ag Health Studies, it is commonly
15 required that a certain number of observed
16 cases or cases be observed before associations
17 are reported. That may result in a reporting
18 bias. Again, it is a difficulty in really
19 comprehensively evaluating the total body of
20 evidence.

21 So another potential issue to deal
22 with it involves multiple comparisons. We

1 know that upwards of 50 chemicals or compounds
2 are evaluated, 20-plus cancer endpoints, a
3 variety of exposure categories. So, by chance
4 alone, we are going to observe some
5 statistically-significant positive as well as
6 inverse associations. So we need to do a
7 critical assessment of those findings. Are
8 those associations real? We will have to look
9 for consistency within and between the
10 exposure metrics and across studies as well.

11 Another issue that I didn't
12 include here is collinearity. It is difficult
13 to analytically isolate the independent
14 effects of one chemical on the outcome when
15 the pesticide applicators are exposed to
16 numerous chemicals.

17 Okay. The exposure metrics,
18 analytical comparisons, these were discussed
19 earlier. The "ever/never" exposed, usually
20 based on internal or external comparisons, are
21 reported in the studies that we have reviewed
22 thus far in the Ag Health cohort.

1 The two predominant metrics for
2 data reported are lifetime exposure days,
3 intensity-weighted lifetime exposure days. I
4 am not going to go into all the details of the
5 algorithms or the statistical underpinnings of
6 those metrics.

7 However, I do want to comment on
8 the trends of associations within and between
9 exposure metrics, and we will be looking
10 closely at associations between the specific
11 chemicals and colorectal cancer within and
12 across those metrics. And I will provide an
13 example of that here momentarily. We will
14 also look at if there is a monotonic
15 relationship, increasing risk with increasing
16 exposure.

17 And in terms of the referent
18 groups, there's commonly either one or two
19 referent groups that are utilized or at least
20 reported on in the Ag Health Studies. One is
21 no exposure, at least no exposure to the
22 chemical of interest. The other happens to be

1 the lowest exposure category. And the
2 selection or determination appears to be
3 commonly based on differences in the baseline
4 characteristics.

5 So, if we have tertiles of
6 exposure, the baseline characteristics in the
7 third tertile are compared with the lowest
8 exposed category as well as the non-exposed
9 category. And if they are more similar to the
10 lowest exposed category, that may be the
11 referent group that is selected, at least
12 based on many of the studies that we have
13 reviewed thus far.

14 I feel it should be viewed more as
15 a sensitivity analysis, and selecting one over
16 the other can have a profound impact in these
17 statistical associations observed. And I will
18 show an example of that here shortly.

19 Okay. So we have lifetime
20 exposure days, intensity-weighted lifetime
21 exposure days. This is just an example of a
22 couple of studies that we have reviewed thus

1 far in our preliminary assessment.

2 Here we have a study of glyphosate
3 and colon cancer. We would presume that, if
4 the self-administered questionnaire for
5 exposure effectively captures the exposure,
6 and the groups are differentiated accordingly,
7 you would expect to see some similar patterns
8 or similar trends of associations, if the
9 exposure is associated with the outcome.

10 Here we can see, for lifetime
11 exposure, days compared with intensity-
12 weighted lifetime exposure days. We kind of
13 have a mirror image. The association goes up
14 to 1.4, back down to 1.9 in the same study
15 population, the same participants. In the
16 second tertile here, it goes down to 0.8, then
17 back up to 1.4.

18 The same thing is true for, an
19 example here, for rectal cancer. So, in terms
20 of the analytical considerations, when we are
21 interpreting all the data, these are some of
22 the things that we need to consider and work

1 through.

2 Okay. Now an example of a
3 comparison of the two exposure groups, here we
4 have a paper on colon cancer, where, in fact,
5 they did report associations using both
6 exposure groups, either no exposure as the
7 referent or the low exposure group as a
8 referent.

9 Again, you can see some pretty
10 striking differences in the observed
11 statistical associations based on the choice
12 of the referent group. You can see the
13 inverse associations here with the not-
14 significant positive association in the fifth
15 quintile. And in the quartile analysis, you
16 can see associations of 1.85 or higher across
17 the groups.

18 So, again, the choice or selection
19 of the exposure group can have a pretty
20 profound impact on the observed associations.
21 So perhaps it should be viewed as a
22 sensitivity analysis when really interpreting

1 the totality of the evidence.

2 And in this case, the reason is
3 because in the second quintile the association
4 goes down to 0.42, which is considerably lower
5 than the other effect estimate. So, when that
6 group is used as the referent category, it is
7 going to inflate the other estimates, as it
8 does here, in the upward direction.

9 Okay. Now I would be remiss if I
10 didn't at least have a little comment on
11 recall bias or misclassification of exposure.
12 In reviewing several of the studies thus far,
13 I have noticed text involving non-differential
14 misclassification, and that the observed
15 effect estimates would likely be biased
16 towards the null.

17 This is not necessarily true. A
18 non-differential misclassification does not
19 guarantee bias toward the null. Empirical
20 evidence has shown that it may produce bias
21 away from the null, particularly if exposure
22 has more than two levels.

1 We know that, going back, the
2 exposure metrics that we are concerned with,
3 they do have more than two levels. Here's
4 quintiles and quartiles.

5 Even compounding this issue is the
6 fact, well, it has been suggested that, even
7 with non-differential misclassification, the
8 highest category of exposure may not be
9 affected. However, that is not necessarily
10 true, either, because if there is
11 misclassification in some of these inner
12 tertiles, this 0.4 maybe be closer to the
13 null, thereby reducing the effect of the
14 highest quartile in this category.

15 Okay. Just moving on to some
16 other methodological considerations that we
17 will work through in our weight-of-evidence
18 evaluation, in terms of the self-administered
19 questionnaire, chemical formulations may
20 change over time. The reported exposure
21 responses may not account for temporal
22 variability in exposure. The questionnaire

1 may not effectively capture exposure for all
2 sites equally; for example, if it weighs
3 dermal exposure more than inhalation.

4 In terms of the reliability of
5 questionnaire data, that is something that is
6 always under scrutiny, and I guess it always
7 should be under scrutiny. That is how we can
8 improve the accuracy of what we are trying to
9 estimate.

10 It was alluded to earlier, the
11 Blair 2002 study, where they did show very
12 good agreement or reliability for more of the
13 dichotomous outcomes: have you used this
14 compound or pesticides in the past, yes or no?
15 The agreement did seem to be very good.

16 However, the agreement is not as
17 good and the reliability is not as good for
18 more detailed exposure metrics, such as
19 duration or intensity of exposure. Those are
20 the ones epidemiologically that we are really
21 concerned with.

22 In reading several of the studies

1 thus far, it is commonly cited that the
2 correlation coefficients or levels of
3 agreement are similar to that observed in
4 nutritional epidemiological studies. However,
5 doing a lot of work in nutritional
6 epidemiology, and being very familiar with the
7 food frequency questionnaire for diet and
8 cancer, those studies should not be viewed as
9 a good measuring stick for reliability.
10 There's several issues there.

11 What are some methods to validate
12 questionnaire data and to improve the accuracy
13 or to better estimate exposure information?
14 Of course, biomonitoring, which is discussed
15 intensively. The specificity of the
16 biochemical indicator, it may not be specific
17 to a certain chemical exposure or other
18 chemicals may produce the same biochemical
19 indicator. Differences by formulation, and
20 the formulation may change over time. Also,
21 the timing of exposure needs to be considered.
22 If there was a compound or chemical that was

1 used 20-plus years in the past, it may obviate
2 the evaluation of using biomonitoring
3 practices to estimate exposure. It may not be
4 feasible as well to sample a very large
5 population, and it may be cost-prohibitive.

6 Okay. So, finally, the last
7 slide, the generalizability. What we are
8 getting at here is the representativeness of
9 the data, the associations observed in the Ag
10 Health Studies to broader populations.

11 In the analyses that I have
12 reviewed specific to colorectal cancer, it is
13 apparent many studies are restricted to white
14 males, or white males clearly predominant the
15 study population.

16 For colorectal cancer, we know
17 that there is a varying distribution of tumors
18 within the colorectum, and they vary by gender
19 and by race. So that limits the
20 generalizability somewhat for colorectal
21 cancer of the data reported in the Ag Health
22 Study.

1 And there are 50,000-plus
2 participants, applicators, in the study
3 cohort. Several of the papers focus on, they
4 are chemical-specific evaluations of cancer
5 outcomes. A lot of the detailed chemical-
6 specific information is based on supplementary
7 or more detailed questionnaire information
8 that was only filled out or submitted by a
9 smaller proportion of the eligible study
10 population, sometimes well under 20,000. So,
11 then, the question is whether the sample who
12 fills out the supplementary or chemical-
13 specific questionnaire is representative of
14 the overall study population.

15 So, finally, at the end of the
16 day, when we are making interpretation, it
17 looks like we will rely upon data largely
18 dominated by one cohort, which is the Ag
19 Health Study. Although it has a prospective
20 design with a large sample size, it still is
21 susceptible to some of the methodological and
22 analytical considerations or limitations that

1 other studies are. So we will be applying the
2 same scientific rigor that we do to other
3 epidemiologic investigations to the Ag Health
4 Study cohort.

5 Again, hopefully, in September,
6 when you folks are meeting about the weight-
7 of-evidence evaluation, I will have the
8 opportunity to come back and share the
9 results, the conclusions of this project.

10 CHAIR HEERINGA: Thank you, Dr.
11 Alexander. I am particularly pleased to hear
12 your final point. That was my question. I
13 assume this is proprietary work at a point,
14 but whatever could be shared with the Panel,
15 in anticipation of the September meeting --

16 DR. ALEXANDER: Right, right.

17 CHAIR HEERINGA: Because it sounds
18 like you are doing a lot of the
19 methodological, statistical type of
20 investigations that are going to have to be
21 replicated.

22 DR. ALEXANDER: Exactly.

1 CHAIR HEERINGA: Any questions of
2 clarification for Dr. Alexander before we move
3 to a break?

4 (No response.)

5 Thank you for the presentation.

6 At this point, what I would like
7 to do is to take a short break, reconvening at
8 3:30.

9 We have four additional public
10 commenters that I would like to get in for
11 this afternoon. One of them, the initial one,
12 after our break, from Syngenta, is scheduled
13 for about 45 minutes cumulatively. So I want
14 to make sure that we move directly to that, so
15 we have time for everybody.

16 So let's, actually, be realistic,
17 25 of 4:00, let's be back and start again.

18 (Whereupon, the foregoing matter
19 went off the record at 3:17 p.m. and went back
20 on the record at 3:33 p.m.)

21 CHAIR HEERINGA: While we are
22 waiting to assemble and get underway, just for

1 members of the Panel, there are four
2 documents, two white papers, one dated the
3 27th, one the 30th, submitted by the team that
4 we are going to hear from, and then the
5 PowerPoint slides. I think there was one
6 other that was submitted right after the lunch
7 hour. So, hopefully, you will find your way
8 through that, particularly the two white
9 papers.

10 Again, for everyone else, these
11 materials will be available on the docket
12 probably later tomorrow.

13 Okay. Welcome back, everyone, to
14 the final session for our first day of the
15 FIFRA Science Advisory Panel.

16 We are in the midst of our period
17 of public comment. My aim is to wrap up the
18 period of public comment today. It will
19 likely take us a little bit past 5:00.

20 This Syngenta group who will be
21 presenting has 45 minutes. I would like to
22 hold to that today. We will leave the public

1 comment period open into tomorrow morning to
2 make sure we wrap up. But to make sure that
3 some of the presenters who have come for
4 shorter presentations can get in on the agenda
5 slot, we will do that.

6 So, with that, I am going to have
7 to --

8 DR. BRECKENRIDGE: Thank you, Mr.
9 Chairman and ladies and gentlemen of the SAP.
10 We are very pleased to be back again.

11 In November, we understood that
12 the agency would be considering approaches for
13 doing weight-of-evidence assessments.
14 Syngenta took the initiative to establish an
15 expert team to help us through a framework,
16 and we are going to discuss that today.

17 And in the second part of the
18 presentation, we are going to be talking about
19 the application of that framework to the
20 atrazine cases that are being put forward
21 before this.

22 The presentation on the first

1 part, on the framework, will be by the full
2 team. The last part will be Syngenta only.

3 I would like to identify the
4 members who have participated in this team.
5 Dr. Hans-Olov Adami from Harvard; Sir Colin
6 Berry from Queen Mary University, London;
7 myself and Tim Pastoor, both Syngenta
8 toxicologists; Lewis Smith, who was formerly
9 head of development in Syngenta and now at MRC
10 Toxicology in Leicester; Gerard Swaen, who is
11 also a member of our team; James Swenberg from
12 the University of North Carolina; Dimitrios
13 Trichopoulos, professor from the Department of
14 Epidemiology at Harvard, and Noel Weiss,
15 professor, University of Washington and Fred
16 Hutchinson Cancer Research.

17 When we started out with this
18 activity in November, we were looking to
19 develop an expert system that would be capable
20 of integrating animal and epidemiologic
21 evidence into a causal inference framework.
22 We were interested in using the best available

1 data, developing a transparent process, and
2 using good scientific practices.

3 With that, then, I would like to
4 turn the podium over to the first speaker, Dr.
5 Noel Weiss.

6 CHAIR HEERINGA: Thank you very
7 much.

8 And that is Dr. Charles
9 Breckenridge. I don't think you ever quite
10 introduced yourself.

11 DR. WEISS: Good morning. I'm
12 Noel Weiss.

13 When our group met, it was clear
14 that we were going to be wanting to review the
15 results of both epidemiologic and toxicologic
16 studies in trying to decide what would be the
17 groundrules or guidelines or criteria for
18 inferring potential causal relationships
19 between exposure to environmental chemicals
20 and one of a variety of illnesses. I am going
21 to talk about the epidemiology side first
22 before I turn it over to my colleague on my

1 left.

2 The first issue that we had for
3 the epidemiologic studies was to determine
4 what features of these would be of greatest
5 utility in identifying a potential causal
6 relationship. Not every study is as useful as
7 another. We were trying to isolate the
8 features of those that might be particularly
9 useful and, therefore, those studies might be
10 particularly informative in making our
11 judgments.

12 Broadly speaking, there are three
13 types of epidemiologic studies that we would
14 consider. A fourth type, randomized trials,
15 there's almost never evidence from that source
16 to address this particular issue. So we
17 focused on observational studies, the first of
18 which is what has been termed ecologic
19 studies. This was defined for you earlier
20 today. It is the contrast of disease
21 occurrence across populations or across
22 subpopulations or across periods of time

1 within a given population. There is contrast
2 disease occurrence in relation to differences
3 in the presence of exposure of the degree of
4 exposure.

5 Now these studies, we feel there
6 is at least the potential for them to make an
7 important contribution. They aren't able
8 always to succeed in this, but the potential
9 is there. We felt that if a study could
10 fulfill these three guidelines, then we might
11 pay particular attention to it.

12 First, there being a large
13 difference in levels of exposure among the
14 population studied or across the time period
15 studied. Second, that there would be accurate
16 and comparable ascertainment, both of exposure
17 levels and disease occurrence. And finally,
18 that there should be little or no difference
19 among the populations with respect to the
20 prevalence of other causes of disease, that
21 is, confounding variables, or if there were
22 confounding variables there, they could be

1 measured and adjusted for.

2 As I say, it is not often, at
3 least in my experience, that all these
4 criteria are met. But when they do occur, we
5 should welcome the studies that meet them.

6 This is an example, one of the
7 strong biases of our knowledge of the
8 relationship between arsenic exposure in
9 water, arsenic levels in water, and the
10 incident of lung and bladder cancer comes from
11 the unfortunate experience in northern Chile,
12 where there was contamination introduced.
13 Nobody was polluting the water. It was coming
14 out of the rocks in that part of the country,
15 and for a discrete period of time. They could
16 monitor levels of incidence of bladder cancer
17 and lung cancer in relation to the time period
18 in which this contamination was present, and
19 then later was not present. So it can be
20 quite useful.

21 There are circumstances, to sum
22 things up, where the particular variation that

1 we might be wanting to exploit in an
2 epidemiologic study comes not among or within
3 a population, but across populations. If that
4 is true, and if we can have these quality
5 criteria met, then we think these studies can
6 be useful.

7 Case control studies have been
8 defined for you also, a comparison of the
9 prevalence or history or levels of exposure
10 between ill and well persons. I do case
11 control studies for a living, and I am well
12 sensitive to the issues of selection bias that
13 can be present, the bounding that can be
14 present.

15 I think with respect to the
16 assessment of environmental chemicals by means
17 of case control studies, the biggest single
18 threat has to do with an impaired ability to
19 accurately measure the relevant exposure, and
20 Michael Alavanja mentioned this earlier. So
21 it is a single biggest problem.

22 And the fact is that the methods

1 we have for ascertaining exposure, be they
2 interviews or records or contemporary, as
3 current levels in cases and controls, in
4 bodily fluids or tissues, all of these can
5 have limitations. The latter you would think
6 ought to be ideal. You are actually measuring
7 the chemical or the residue of the chemical.
8 However, when you are measuring it years
9 perhaps after the illness has been incited, it
10 may simply not be a relevant time period to be
11 measuring that sort of thing.

12 With that in mind, people have
13 considered doing cohort studies like the Ag
14 Health Study, which can, to a large extent,
15 get around this issue of temporality. You are
16 measuring among healthy people, as far as you
17 know, who is exposed and who is not exposed,
18 or who has different levels of exposure. You
19 can follow these people up for the subsequent
20 occurrence of illness. Usually, you have a
21 more accurate measure of exposure and you get
22 rid of the problem of temporality.

1 However, it can happen, depending
2 on the size of the cohort study, depending on
3 the duration of followup, depending on the
4 frequency of the outcome in question, that
5 cohort studies can be hindered by a small
6 number of persons who develop the disease in
7 question, especially among exposure subgroups
8 that you are contrasting.

9 However, I believe, our group
10 believes that the results of cohort studies
11 can be really important, often because of the
12 ability to study not just residential
13 exposures, but occupational exposures. Many
14 of these chemicals that we are concerned about
15 are present in the occupational environment,
16 and when that is so, cohort studies are
17 facilitated. These cohorts are relatively
18 more easy to identify. They are relatively
19 more easily followed, and they, typically, are
20 exposed to relatively higher levels of the
21 agent.

22 So, as a consequence, we have

1 learned a lot, epidemiologists have learned a
2 lot about chemicals and their relation to
3 disease from occupational cohort studies.
4 Just as an example, if we were concerned about
5 trichloroethylene in residential water
6 supplies, and we wondered if it might be
7 related to cancer, the first place I would
8 look is not at residential studies, which
9 typically involve low levels, and the cohorts
10 are hard to enumerate, but rather to
11 occupational studies, studies of workers who
12 in the course of their employment were exposed
13 to trichloroethylene, and those studies tend
14 to be an important foundation to at least
15 evaluate the proposition that
16 trichloroethylene has some capacity, even at
17 higher doses, to cause one or more forms of
18 illness.

19 This is Roman numeral II. It says
20 assessment of study quality. Because, in the
21 end, once we have identified the ecologic
22 studies, the cohort studies, the case control

1 studies, some decision has to be made about
2 which ones of these are we going to pay
3 particular heed to. We tend to look at the
4 quality. We tend to look at the size,
5 especially the quality, of each type, and
6 decide which ones we are going to really pay
7 attention to.

8 And who is "they"? Who are we, in
9 terms of making this judgment? Well, I
10 believe it should be groups of experts, people
11 who are really knowledgeable about this, using
12 their own professional qualifications and
13 experience to make such a judgment.

14 It may be that, on the basis of
15 that judgment -- this scenario I am describing
16 here won't fit every circumstance, but often
17 it is useful to identify studies with minimum
18 limitations and base one analysis simply on
19 those studies. I mean those acceptable
20 studies.

21 It may be that there is a second
22 category of studies that have moderate

1 limitations which can be incorporated into a
2 second analysis, along with the acceptable
3 studies.

4 Finally, there may well be some
5 studies with limitations that are so severe
6 that they are really deemed unacceptable and
7 not fit to be included in an assessment.

8 I should mention that I am told
9 that this categorization of acceptable
10 supplemental and unacceptable is something
11 routinely done by the EPA when evaluating
12 mechanistic studies.

13 Here's my last slide. It is
14 bringing forth these guidelines for causal
15 inference that you have seen now probably too
16 many times. This is kind of an extraction or
17 a condensed version of those proposed, both by
18 the Surgeon General's committee in the mid-
19 sixties, as well as Bradford Hill.

20 I must point out that only John
21 Bailar and I, I think, are old enough to
22 actually identify the Surgeon General's

1 report. I'm sorry.

2 (Laughter.)

3 Just briefly, it says, the first
4 one, considering all relevant studies, is
5 there an association? And the important word
6 there is -- with my pointer, which doesn't
7 work -- is the word "studies". We are really
8 looking for the aggregate of information
9 across studies, not the isolated positive
10 finding.

11 The second point is the issue of
12 temporality. Based on the results of the
13 studies, is there reason to believe that the
14 exposure came first? We are talking about the
15 strong association. The stronger it is, the
16 less plausible it is that a non-causal
17 hypothesis could be responsible.

18 The fourth one is talking about
19 biological plausibility, which will be
20 discussed very quickly by Dr. Swenberg.

21 Then, finally, the last one is
22 kind of a combination of the previous two. It

1 basically is asking, is the strength of the
2 association in humans, is it greatest when it
3 would be predicted to be so, such as, for
4 example, on the basis of particularly high
5 doses?

6 Now, when you finally pull all
7 these guidelines together and come up with a
8 judgment, the point has been made earlier
9 today that sometimes it is nice not to be
10 forced into a dichotomy, yes or no.

11 What Jim Swenberg is going to be
12 doing is talking about two things. One is
13 about incorporating the toxicology data, and,
14 second, what pattern, what framework can we
15 use to sum up these data?

16 So, Jim?

17 DR. SWENBERG: Thank you, Noel.

18 It is a pleasure to be here and
19 address this Committee.

20 When we started out with this
21 meeting, the EPA framework hadn't come out
22 yet. So these are kind of two interesting,

1 independent approaches, and they are going to
2 have a very similar ending, I think.

3 So, we focused in on following
4 forward with kind of the ICPMS EPA framework
5 for evaluating mode of action, which you heard
6 about today. So I don't need to go through it
7 in any great detail.

8 This is a program. The meeting
9 started at a meeting, I should say, in
10 Hanover, Germany, in 1998. I forget exactly
11 how many people were there. I think it was
12 about 15 to 18 of us. We had datasets and
13 regulators. The datasets had gone out to
14 regulators around the world, and we had the
15 Netherlands, we had the UK, the U.S., and
16 Australia. They had come to vastly different
17 conclusions in their risk assessments on the
18 same data package.

19 So this committee was trying to
20 look at this and come forward with a way to
21 bring transparency to the decisionmaking
22 process, not to make the decision for

1 somebody, but to have transparency there, so
2 that you could see what decision process they
3 went through.

4 This is what came out of it. We
5 had actually struggled for a day and a half
6 before we came up with this. Janet Wilsey
7 from the EPA brought the next morning the
8 Bradford Hill criteria and said, "I think we
9 should follow something like this."

10 So, then, we beat around on how to
11 bring it forward. What I can say is it has
12 been very well-received. It has gone forward
13 from this initial mode of action in animals
14 only to now bringing forward the human
15 relevance.

16 This is a paper by Bette Meek, one
17 of your panel members, and more later, Alan
18 Boobis have brought this forward on how do we,
19 then, move from just the animal data to how
20 the relevance might be for humans.

21 So, what this meeting that you are
22 doing here is doing is taking it yet a step

1 further, actually, bringing in the
2 epidemiology study and perhaps using a similar
3 framework to that.

4 I think the broad reception that
5 this has won throughout the world speaks
6 strongly that it may be successful.
7 Hopefully, it will.

8 So the purpose that we set out to
9 undertake was to establish the key elements of
10 toxicology and epidemiology that would be
11 informative of causal inferences. To do this,
12 we wanted to develop a decision logic that I
13 will go through with you, and then to
14 characterize the degree of confidence that we
15 had in that causal inference conclusion.

16 So one of the first things you
17 have to do is bucket studies by their type.
18 So, if they are repro studies or cancer
19 studies, we would look at those together. We
20 must evaluate the quality categorization
21 because quality of studies is not equal.

22 So, as Noel just said, we will

1 have some studies that are acceptable and have
2 very minimal limitations. We will have other
3 ones that are still very good studies, but
4 have more limitations. Then, unfortunately,
5 there will be some studies out there that have
6 severe limitations and can't be given the same
7 weight.

8 Weight is important, where you
9 look at both the positive and the negative
10 studies. So a weight-of-evidence approach is
11 what we believe is the way forward. So you
12 want to examine biological plausibility,
13 epidemiologic evidence, and biological
14 coherence of a dataset to come up with that
15 weight of evidence.

16 And you have the clear potential
17 of coming up with four different boxes. These
18 could range all the way from having evidence,
19 strong evidence, against a causal inference to
20 having strong evidence for one. Then, most of
21 the data will probably fall in the middle two
22 of these.

1 So this is how we pictorially view
2 the process. You will start out, let's say we
3 usually have toxicology data that has already
4 been through much of this process. So it is
5 the easiest place to start. So you collect
6 your data. You evaluate the quality of those
7 data, look at and bin them into the acceptable
8 and supplementary data to put into that weight
9 of evidence.

10 Then, there, you come down to a
11 decisionmaking step. Is the effect that you
12 are interested in present? Have you
13 identified this in your toxicology studies?
14 This becomes important because, when we are
15 dealing with pesticide exposures, we go from
16 having very high animal exposures in the tox
17 studies to very low population exposures.

18 So, let's just say that we were
19 looking at decreased pup weight from a
20 reproductive study. Well, is that relevant to
21 the small at gestational age studies that are
22 on the docket for this meeting? Well, you

1 would want to look at things like, what is the
2 dose difference?

3 If you had it in your tox studies,
4 but it was at 10,000 times higher doses and
5 not at 5,000 times, you might not think it is
6 so relevant. If you have it down at lower
7 doses, and you have humans that have high
8 exposures, it might be very relevant.

9 So you are going to bin these
10 things into different categories. If you deem
11 that it is not very relevant, you come down
12 into this lower quadrant. I will spend some
13 more time on this diagraming of my next and
14 last slide.

15 On the other hand, if you feel
16 that it may well be relevant, you are going to
17 want to go forward to find out what would the
18 plausibility in humans be by looking at things
19 like dose response and toxicokinetic,
20 pharmacokinetic kinds of examples.

21 On the epidemiology side, Noel has
22 gone through this very well for us. Again,

1 you are going to collect the data, look at the
2 type of study, put it into its acceptable and
3 supplementary bins versus unacceptable, and do
4 your weight of evidence. That is going to
5 tell you what the epidemiologic evidence is
6 that support this observation.

7 So, ultimately, you come down to a
8 decisionmaking process, and it starts out --
9 we have tried to diagram. This is not easy.
10 We have already made a few alterations from
11 what was in the framework that we submitted.

12 So let's just say that you have no
13 data. If you have no data, you end up right
14 in the crosshairs here. You don't have any
15 evidence for or against either the
16 epidemiology or the biological plausibility.
17 So no data doesn't really give you any
18 information.

19 If you have biological
20 plausibility, let's say, from your toxicology
21 studies, and it is low, anywhere from being
22 low to being high, you can kind of go up and

1 down the vertical axis, the Y-axis. As your
2 epidemiology data comes in, it could be for,
3 suggesting that this is seen in humans, it
4 could be actually then studied and not found.
5 So we have a few examples of this.

6 Obviously, we would love to have
7 primarily No. 1 and No. 4 up here, where we
8 have strong evidence either against something
9 being relevant for causation in humans or
10 something being strongly for causation in
11 humans.

12 The example I have given here is
13 asbestos and mesothelioma, where we have human
14 data that is very strong. We have fiber
15 counts from lung digests. We have inhalation
16 studies in animals. So there is not any
17 question about that one.

18 Down in the bottom here, we have
19 d-limonene listed for kidney tumors by the
20 alpha 2U mechanism. This actually was one of
21 the first risk assessment relevance for humans
22 that was done by the agency back in the early

1 nineties.

2 But, most of the time, we are not
3 there. We are somewhere between No. 2 and No.
4 3. So one I have put up here is
5 phenobarbital, liver tumors in rodents. We
6 know that we can induce these readily. Yet,
7 this started out probably over in the center
8 someplace because we didn't have any epi data.
9 But, then, they looked at the Danish studies
10 where people were being treated for their
11 lifetime for epilepsy with phenobarbital, and
12 there was no evidence for support of liver
13 cancer being induced by phenobarbital at
14 pharmacologic doses.

15 And finally, we have other cases
16 where we had clear evidence of the
17 epidemiology, but we didn't have a mechanism.
18 That changed with the addition of new data and
19 new understanding.

20 So I am going to turn this over to
21 Sir Colin Berry to kind of wind things up and
22 expand upon this a bit.

1 DR. BERRY: Thank you. Thank you,
2 sir.

3 Since there seems to be a
4 competition going on about who is the oldest
5 guy, I would just say that I knew Austin
6 Bradford Hill.

7 (Laughter.)

8 My first slide is really rendered
9 redundant by the amount of presentations that
10 already have been made, in terms of what we
11 have heard from several people. I think the
12 bullet points that are identified here are
13 those that have been made in one form or
14 another by a number of your correspondents
15 today.

16 The process has to be transparent,
17 the inclusion of data, and so on. I am going
18 to dwell on this slide since I doubt that
19 there is anything that anybody would want to
20 question or, indeed, would disagree with.

21 Let me go on to what would be the
22 easiest sort of situation to deal with. That

1 is here shows an ideal state where you had a
2 unitary disease entity, diagnostic criteria
3 which is stable, and a single etiology. You
4 can't even do that for leprosy because there
5 are different forms of leprosy. When it gets
6 to tumors, it is virtually impossible.

7 In general, with practical
8 examples, you have multiple subcategories,
9 certainly, of disease entity. And I want to
10 illustrate this by talking about non-Hodgkin's
11 lymphoma and brain tumors briefly.

12 Could I just say that nothing
13 changes like non-Hodgkin's lymphoma, which I
14 have been surprised to hear so much discussed
15 today since it is no longer discussed in
16 pathology departments. It doesn't exist
17 anymore. In fact, it never existed. It was
18 an observation by Lukes and Collins in this
19 country, who found that, of the people they
20 irradiated with Hodgkin's disease, a number
21 survived. They were the ones with true
22 Hodgkin's. And the rest died, and they were

1 the ones with what they called non-Hodgkin's
2 lymphoma.

3 Subsequently, there were a number
4 of classifications of this, and they were
5 revised. The last revision before they were
6 abolished, as it were, was in 1995.

7 The reason that I make that point
8 is that, if you look at studies of non-
9 Hodgkin's lymphoma, you will see that a number
10 of studies that use these kinds of registries
11 use the old classification, now much discarded
12 entirely, and at least 15 years old. Some, in
13 fact, use the 1982 classification, which is
14 simply foolish because many of the tumors
15 included in those groups were, in fact,
16 anaplastic carcinomas, as we know from modern
17 marker studies.

18 And the proper description I refer
19 to here in the WHO classification describes a
20 great deal more about the tumors than their
21 appearance. The mantle cell lymphoma you see
22 depends on a particular genetic insult, a

1 transposition at 1114, with the inserted new
2 fragment close to the Cyclin 1 gene on
3 chromosome 11, affecting cell cycle time, an
4 absolutely specific change which would require
5 an absolutely specific kind of genetic damage;
6 whereas, the mucosal-associated lymphoid
7 tumor, the MALT tumor, is the result of an
8 infection. And if you treat this B cell
9 lymphoma with antibodies, 75 percent of
10 patients recovery. Those that don't are those
11 that have a large lymphoid cell mass, which
12 presumably acquired mutations or has acquired
13 mutations.

14 I would just emphasize that I
15 think it foolish to look at a category like
16 this in order to look for associations. I
17 mean it is a heterogeneous collection of
18 diseases, and you might as well say we are
19 looking for an association with disease.

20 In Nature recently, in an article
21 on brain tumors, this point was made: that
22 brain tumors, in particular, are often put

1 together as a category, and, of course, they
2 are enormously different. Glioblastoma
3 multiforme will kill patients within three to
4 six months at most. Pilocytic astrocytoma is
5 quite consistent with a comparatively long
6 life. They have quite different genetic
7 characteristics, quite different cell cycle
8 times, and probably quite different
9 etiologies.

10 But I think catchall diagnoses are
11 the enemy of good epidemiology in this context
12 where you have low exposures over long periods
13 of time.

14 The difficult part, which we have
15 heard a number of you talk about, is exposure
16 characterization. Here, again, I can
17 emphasize little here. You would like to have
18 a direct measure of exposure. You would like
19 to know where that got to in the target organ,
20 and you would like to know that you have
21 looked at the right time or over the right
22 period. And in practice, the constraints that

1 are outlined below are what really apply.

2 And again, I don't think I need to
3 dilate on this slide. But if I could go on,
4 I can show, I think, if we go back to the
5 slide that Dr. Swenberg described so
6 carefully, I think this is an extremely useful
7 model because it enables to encompass the kind
8 of changes that I have been talking about,
9 both in pathological information, if I might
10 call it that, diagnostic information, and
11 epidemiological change.

12 If you take something like
13 Kaposi's sarcoma in the HIV-infected patient,
14 the incidence is roughly 400 times the normal
15 population incidence. But it was not
16 immediately apparent why the HIV virus should
17 produce epithelioid angiosarcoma. But then it
18 was discovered by closer inspection of the
19 tumors that they all the bore the hybrid in
20 their nuclei fragments of the human herpes
21 virus 8, and that you find as a nuclear
22 antigen before the tumor develops, and you

1 don't find that in other hemangiosarcomas such
2 as those in use by vinyl chloride, and so on.

3 So here is the slide, as it were,
4 or the framework demonstrating that you can
5 move up in this direction. And here, if you
6 take tumors which I spoke about, if you look
7 at the electromagnetic forces in the
8 production of brain tumors, you may show an
9 association, but break it down into
10 meningiomas, gliomas, glioblastoma, multiforme,
11 the other tumors, and the association
12 disappears. So you have epidemiological
13 evidence, apparently, for, and further
14 studies show, refined show it can disappear.

15 The interesting example here, we
16 start up here, no ecological evidence for or
17 against, but a higher biological plausibility.
18 It produces tumors in animals. But because we
19 lack the appropriate protein, it doesn't occur
20 in man. Therefore, the arrow goes this way.

21 And finally, here, melamine, which
22 I think most people would assume that the

1 doses that cause renal damage in animals,
2 these wouldn't be likely to occur in man, but,
3 lo and behold, it does and has. Therefore,
4 you move to the right.

5 So the model allows you to account
6 for changes in information, whether these be
7 etiological and pathogenetic or simply by
8 better, more thorough epidemiology.

9 I apologize for my voice. I don't
10 normally sound this mature.

11 CHAIR HEERINGA: Thank you very
12 much, sir.

13 DR. BRECKENRIDGE: Mr. Chairman,
14 Charles Breckenridge.

15 We will stop for a minute and take
16 any questions for the core epi team that
17 individuals might like to ask.

18 CHAIR HEERINGA: Any questions on
19 these three presentations to this point before
20 we move on to Dr. Pastoor's presentation?

21 DR. REIF: In I think the last
22 slide, you said something regarding all

1 epidemiologic studies on a topic. Were you
2 meaning that analysis or full analysis
3 specifically? Or how exactly were you using
4 the word "all"?

5 DR. WEISS: Maybe the
6 epidemiologists in this room, if you polled us
7 as to the potential utility of pooled analysis
8 or meta-analysis of observational studies, you
9 might get as many opinions as there are
10 epidemiologists.

11 I did mean by "all", I meant to
12 actually consider all. It may be that the
13 studies are similar enough in their design and
14 broadly similar enough in their results that
15 a pooled analysis actually makes sense. On
16 the other hand, there might be heterogeneity
17 in terms of the methods and heterogeneity in
18 terms of the results, in which case it is
19 probably best to pause and present the results
20 separately, but not to discount them, to
21 consider them all, but not necessarily with a
22 single relative risk.

1 CHAIR HEERINGA: Dr. Lu?

2 DR. LU: I have a philosophical
3 question for the panel here in terms of
4 looking at this graph because this picture,
5 this graph has been shown many times. So, if
6 you just look at melamine, for example, yes,
7 animal data strongly suggests against that.
8 So we kind of set it aside. We let melamine
9 get into our food, our chain, until a
10 significant incident happened in China. Then
11 we take action. We just realized that
12 melamine is not a good thing to be mixed in
13 the food chain.

14 So the question is, how long
15 should we wait until positive human data
16 surfaces and then we take action on it?
17 Because these things happen over and over
18 again. It is not just melamine.

19 So, my challenge to this panel is
20 that, if you are willing to sacrifice
21 certainty on the positive data that surfaces
22 that allows EPA to take action? We are

1 talking about the public health issue here.

2 It is not just yes or no or epidemiology study
3 design.

4 DR. SWENBERG: Let me, very
5 briefly, respond to that. I mean I think --

6 CHAIR HEERINGA: Put your name on
7 the record.

8 DR. SWENBERG: Pardon?

9 CHAIR HEERINGA: We need your name
10 on the record.

11 DR. SWENBERG: Oh, I'm sorry.

12 CHAIR HEERINGA: Dr. Swenberg.

13 DR. SWENBERG: James Swenberg.

14 I was actually on the NTP Board of
15 Scientific Counselors when melamine came
16 through there. The focus, if you go back and
17 read those reports, was on the bladder cancer
18 that was induced. That was not thought to be
19 very relevant to humans because of anatomical
20 differences and major exposure differences.

21 The real toxicity was clearly
22 there, and it was dose-related, and it went

1 down to doses lower than where you got bladder
2 cancer. So I don't think anyone at that point
3 was saying that it was not relevant to humans,
4 but it came home very strongly just in the
5 last two years with the crisis in China. It
6 is not only the melamine by itself. It was
7 also the pet food crisis, where it was
8 combined with cyanuric acid, where it is even
9 more toxic.

10 So what we put it in here for was
11 just to show how the science evolves.

12 Somebody had a quote this morning about how
13 science doesn't stand still and it evolves.
14 Here is a perfect example that we have all
15 lived with.

16 DR. BOVE: Well, just on that
17 note, though -- this is Frank Bove -- science
18 does evolve. Sometimes you have a situation
19 where we see it in humans. We don't see it in
20 animals until we get the right animal model.

21 So, again, maybe you should have
22 some more diagrams showing that kind of

1 possibility as well, because we have that with
2 thalidomide, for example.

3 DR. BERRY: Colin Berry.

4 I was just going to say that, of
5 course, this is what normally happens in
6 therapy for chronic disease. And a good
7 example of that currently is aspirin, which in
8 the UK I think they are 195 studies in the
9 meta-analysis that resulted in advice being
10 given to the UK population to take 75
11 milligrams of aspirin a day as a prophylaxis
12 after the age of, I think it was 55.

13 Many of the criteria we said were
14 ideal are satisfied. A single disease -- and
15 this was usually for atherosclerosis. The
16 event was thrombosis, even if the clinical
17 manifestation of that was different. A
18 mechanism was known, in that aspirin
19 interferes with platelet stickiness. So you
20 had an ideal situation.

21 But further epidemiological
22 evidence showed that, if you hadn't previously

1 had a thrombotic episode, then it is more
2 dangerous to take it. I mean the residual
3 bleeding which occurs in both groups was a
4 greater risk than the benefit conferred by
5 taking it.

6 Now nothing had changed in the
7 science or the disease. What had happened was
8 a different kind of analysis had been done.
9 That is a constant feature of long-term
10 therapies, that those sort of changes are
11 made.

12 So I don't think we are ever going
13 to get a solution to your particular
14 philosophical dilemma.

15 CHAIR HEERINGA: Thank you, sir,
16 and I believe I need a behavior change on
17 that.

18 (Laughter.)

19 So I turn to Dr. Bucher and then
20 to Dr. Meek.

21 DR. BUCHER: I was just going to
22 make the same point that Jim made.

1 DR. MEEK: Just a question. I am
2 a little unclear as to where exposure fits
3 into this picture because it seems to build on
4 the mode-of-action human-relevance framework,
5 and it was very clear in that case that
6 exposure wasn't factored in. We were really
7 addressing the hazard.

8 And in fact, in the example for
9 melamine, we, in fact, concluded that the
10 effect was relevant to humans. So we were
11 trying to separate out the exposure aspect.

12 So it is a little bit unclear to
13 me where exposure fits in this picture.

14 DR. SWENBERG: I think exposure is
15 always probably one of the most important
16 things to understand. That is one of the
17 bigger weaknesses of the epidemiology study;
18 whereas, in the toxicology study, we know the
19 exposure in general.

20 But a place that we need to move
21 forward is to have better toxicokinetic data
22 in animals and humans. So through the

1 biomonitoring in the humans and by bringing
2 the ag chem industry into the rest of the
3 world with doing toxicokinetics reviewing, in
4 my opinion.

5 CHAIR HEERINGA: I think, at this
6 point, I would like -- continue.

7 DR. MEEK: I am still confused.
8 You are mixing both exposure and hazard into
9 this framework then. You don't explicitly
10 separate out the exposure. The mode-of-action
11 human-relevance framework addressed hazard per
12 se. Exposure was addressed as part of the
13 risk assessment process. When we are
14 weighting epidemiological data, we are purely
15 taking into account exposure. So it is still
16 a little bit unclear.

17 DR. BRECKENRIDGE: Just briefly,
18 if I could -- Charles Breckenridge -- just
19 refer you back to the general framework.
20 Exposure on the lefthand side is clearly in
21 the animal mode-of-action framework, and under
22 the weight of evidence for epidemiologic, it

1 comes in under the context of strength of
2 association and dose response assessment. I
3 mean it does come into it as part of the
4 weight of the evidence.

5 DR. SWENBERG: Yes, it also came
6 in in the framework. So you are looking at
7 your key events, and do they relate to dose
8 effect? In fact, we saw a beautiful slide
9 from the agency this morning where they showed
10 the increase in pluses coming down, as does
11 went up and as time went out.

12 DR. MEEK: That was dose response
13 between key events and the end event and not
14 exposure.

15 CHAIR HEERINGA: At this point, I
16 would like to move on to the next segment of
17 the presentation, again, with the reminder
18 that we will have an opportunity before we
19 turn to the charge questions for a general
20 return not only to the EPA scientific panel,
21 but also to the other public commenters
22 tomorrow morning.

1 So, Dr. Pastoor or Breckenridge?

2 DR. PASTOOR: Thank you, Mr.

3 Chairman. Thank you, members of the Panel,
4 for your patience this afternoon.

5 Mr. Chairman, I will do my best to
6 try to keep us on time here. My intent here
7 is to go over the six studies that were
8 identified by EPA as case studies involving
9 atrazine.

10 What you just heard previous was a
11 very distinguished panel of experts that
12 consulted with us over the last six weeks, and
13 that presentation was made by these gentlemen
14 as a representation of that effort.

15 The current effort, looking at the
16 atrazine-related ecological and retrospective
17 studies, is something that we did ourselves
18 with their advice as well, but it is a
19 Syngenta presentation.

20 In the process of going through
21 this fairly quickly, I would remind you that
22 we have submitted a document to the docket

1 that details all the information that we will
2 be presenting. So the presentation that I
3 have here today is going to be very, very
4 fast, and it will go over the top parts of
5 each one of the particular points that we are
6 trying to make.

7 What we intend to do here is use
8 the outline of the framework to tell you
9 something about our evaluation. When we read
10 the studies, the six studies that were
11 identified by EPA, we identified two
12 particular outcomes or effects of particular
13 interest. Those break down into birth defects
14 and small for gestational age status, or SGA.

15 The idea there is that no one
16 epidemiology study or an effect should be
17 taken in and of itself. It would be a
18 collection, as Dr. Weiss, Dr. Swenberg, and
19 Sir Colin Berry have illustrated, that it is
20 a collection of information that gives you the
21 weight of evidence.

22 So that is why we looked at this,

1 first of all, not on an individual
2 epidemiological study basis, but on the basis
3 of an effect or outcome. So, our first
4 question, of course, using the framework, is,
5 what is the biological plausibility and how
6 does that match up with epidemiological
7 evidence?

8 So, again, this is the scheme that
9 we are using here, which you have seen
10 previously. Working down the lefthand side,
11 of course, is collecting all of the available
12 information that would shed light on whether
13 or not there is biological plausibility for
14 a birth defect or small for gestational age
15 status. Then we will work down the other side
16 on epidemiology as well.

17 So our first is to collect all the
18 available data and establish quality. So,
19 with regard to atrazine and its four major
20 metabolites, there are acceptable rat and
21 rabbit studies done for teratology or
22 developmental studies. So the atrazine,

1 hydroxy-atrazine, deisopropyl-atrazine,
2 deethyl-atrazine, and diaminochloro-triazine
3 have all been tested in developmental studies.
4 We also have an acceptable reproduction, two-
5 generation reproduction study on atrazine as
6 well.

7 The conclusion from this, with
8 regard to birth defects, is that neither
9 atrazine or its metabolites cause birth
10 defects in the rat or rabbit studies at any
11 dose level, even at dose levels that
12 compromise the maternal health. So, what we
13 conclude there is that the biological
14 plausibility that atrazine could cause birth
15 defects is very low.

16 The second area of small
17 gestational age status, we looked there again,
18 and at high maternally-toxic doses, where you
19 severely compromise the health of the mother,
20 either the rat or the rabbit, you do get body
21 weight effects in those particular situations.
22 Those are tens of thousands of fold higher

1 than the exposures that any human could be
2 exposed to. As a result, we have put that as
3 well into the low category of biological
4 plausibility.

5 So you can see, down on the
6 righthand corner, the quadrants that we were
7 talking about previously and how biological
8 plausibility for either one of these
9 particular outcomes comes out in the lower end
10 of the scale.

11 We, then, turned our interest to
12 the studies that were identified by EPA, in
13 the first instance with regard to birth defect
14 studies. There's four here. I will be
15 talking about each one.

16 What we did is took the Mattix and
17 the Winchester, et al., papers, and we put
18 them together because the structure of these
19 studies is almost identical -- they go over
20 different periods of time -- and collected
21 them for the quality analysis. What we found
22 is that neither of these studies are

1 acceptable on the basis of the quality
2 criteria that Dr. Weiss has described.

3 In this particular study, they are
4 looking at regional raw water from USGS and
5 matching that with the National Birth Defects
6 Incidents Database. That comes from the CDC
7 biostatistics information.

8 And if I can draw your attention
9 to the graph, the dotted line on that
10 particular graph is the incidence of birth
11 defects that are noted overall. I believe
12 this is a category of 22 particular birth
13 defects collected together. You can see the
14 seasonal uptick in about the late spring/early
15 summer.

16 What the authors conclude in this
17 particular study is that that correlates with
18 the use season for atrazine. When we looked
19 at this study, we knew that there were lots of
20 other things that this could be correlated
21 with, and that was one of the two ways that we
22 approached the study. And we realized that

1 you could correlate the birth defect uptick in
2 the early summer months with a number of
3 different things. I am showing tornadoes and
4 birth defects here, but we used everything
5 from pollen counts to length of day, to
6 temperature, and so forth, rainfall, all of
7 which correlate very nicely with that uptick
8 in the early summer months, late spring.

9 Now this is a bit of a light
10 touch, I think you would have to admit, but we
11 got more serious with this, too. Because we
12 said to ourselves, well, if, indeed, there is
13 an uptick in birth defects that is seasonal,
14 as you are seeing there, what is it that could
15 be causing that? Of course, we were
16 interested in knowing what potential role
17 atrazine could cause in that as well.

18 So what we did is we went to the
19 same database that the authors used and we
20 graphed the actual birth defect incidents by
21 states. If I could draw your attention to the
22 middle line, if I could have the pointer,

1 please, if you look at the middle blue line,
2 which is all of the United States here, you
3 see that same uptick occurring.

4 The next question that we asked
5 ourselves is, if you parse that data by states
6 that have high atrazine usage versus those
7 that have low atrazine use, and of course
8 middle, you have the columns that we have up
9 here on the left.

10 If you look at the states that the
11 states that have 82 percent of the total
12 poundage of atrazine that is used, that is the
13 green line that is here down on the bottom.
14 The lowest use, which is 1 percent of the
15 total atrazine usage, is the upper line here.
16 You can see the same seasonal uptick in birth
17 defects, which is looking at this list that
18 you are seeing down here in the lower lefthand
19 corner.

20 The conclusion here is less about
21 atrazine and more about the fact that this is
22 something that is seen across states, and an

1 interesting result, to say the least. Again,
2 this was taken from the same database, CDC
3 Vital Statistics. And although exposure is
4 not best characterized by total poundage, it
5 gives you some idea of the usage of atrazine
6 in those particular states.

7 The next study we looked at Ochoa-
8 Acuna and Carbajo. This was a corn study
9 looking at the proximity to living near a
10 cornfield versus a soybean field would have
11 some detrimental effect on birth defects.
12 Very quickly, though, and this is presented in
13 our ancillary documents that we have put in,
14 the critical window here that is shown,
15 identified by the authors, is not congruent
16 with the planting season during which atrazine
17 is actually used. So there's a question about
18 temporality in that particular study.

19 Furthermore, there was only one
20 reference to atrazine in that particular
21 study, but, overall, it was a study
22 recommended by EPA for case study, and we did

1 this analysis. It is an unacceptable study.

2 The final study in this group,
3 Mohanty and Zhang, is also unacceptable. It
4 is not really an epidemiology study. It is a
5 23-variable regression model that is looking
6 at 25 outcomes, and there was a selective
7 elimination of data that rendered the study
8 unacceptable.

9 Turning next to small for
10 gestational age, there were two studies by
11 EPA, one by Villanueva, 2005, and Ochoa-Acuna
12 in 2009. The first study here, by Villanueva,
13 is judged to be unacceptable as well, for a
14 number of different quality criteria issues,
15 not the least of which was that the majority
16 of the samples that were taken were out of raw
17 water, which people don't drink. The
18 exposure, again, was not temporally matched.
19 I believe that this was brought up this
20 morning.

21 Furthermore, the majority of
22 samples from finished water were actually

1 below the level of detection. As a
2 consequence, the authors used half the LOD to
3 produce the values.

4 The fourth and final point there
5 is that there are, as with other studies,
6 seasonal factors that could account for that
7 marginal effect.

8 Finally, the Ochoa-Acuna study
9 from 2009 was judged supplemental. The reason
10 is that they had a reasonable design to the
11 study. They tried to match cases with
12 exposure, and there were other factors that
13 render it supplemental.

14 However, if you take the author's
15 own data and do a simple rank correlation and
16 linear regression, what you find here is, in
17 this particular case, you find no correlation
18 and you also are unable to find a positive
19 correlation. This was the negative
20 correlation.

21 In this particular example that I
22 am using, it is a simple rank correlation of

1 SGA prevalence in those water systems against
2 the median atrazine concentration. Now we did
3 probably a dozen different correlations from
4 the author's data, none of which had
5 R-squareds that were very high, and were
6 typically around the value that you see here,
7 which is .1557.

8 So those are the studies that we
9 have looked at and evaluated from the
10 standpoint of the framework. Of course, from
11 the standpoint of what we are trying to do
12 here, it is to establish causal imprints.
13 That is what this is all about after all, is,
14 what do studies tell you about the probability
15 of an effect occurring in humans, in this case
16 due to atrazine exposure?

17 We have already gone through the
18 toxicology side that indicates that it is of
19 low biological significance. We have also
20 gone through the epidemiology study, of which
21 there are more studies out there -- these six
22 studies are not the only ones available -- and

1 classified them by quality. None, however,
2 can be used in a weight-of-evidence analysis,
3 which would have otherwise brought us into
4 this category down here to classify it.

5 Nonetheless, I think what we found
6 here is that the framework that was developed
7 by the panel of experts that we worked with is
8 very helpful in helping us understand
9 something about how you collect the biological
10 or toxicological information, along with the
11 epidemiological information, to make a logical
12 conclusion.

13 It is useful because it is
14 transparent, it is systematic, and it is data-
15 driven. So that is why we like it. We
16 offered it up as one option that the Panel can
17 consider in bringing epidemiological data into
18 human health risk assessments.

19 And I will end there and ask for
20 any questions.

21 CHAIR HEERINGA: Thank you, Dr.
22 Pastoor.

1 Questions of clarification for Dr.
2 Pastoor or Dr. Breckenridge? Yes, Dr. Reif?

3 DR. REIF: Did you apply this
4 model to any of the other studies that you
5 just referred to that are not in the six in
6 the EPA package?

7 DR. PASTOOR: Yes. In other
8 words, if you were looking at a particular
9 outcome, whether it were birth defects, low
10 gestational age, or otherwise, the idea is to
11 first collect all the available information
12 and go through that quality sieve, first of
13 all.

14 DR. BRECKENRIDGE: I'm sorry, I
15 think you misinterpreted. The answer is, no,
16 we didn't have time to actually go through the
17 literature to extract all available studies,
18 in fact. So we don't know what --

19 DR. REIF: Exactly. I meant, did
20 any of the other studies that are not in the
21 six in the case study rise to the level of
22 acceptable --

1 DR. PASTOOR: No, in the time that
2 we had, we didn't do that. I'm sorry, I
3 misunderstood your question.

4 DR. REIF: That's okay.

5 CHAIR HEERINGA: Dr. Bove?

6 DR. BOVE: Frank Bove.

7 The Ochoa-Acuna study is an
8 individual-level analysis. Is this graph here
9 I see an ecologic approach? I mean it looks
10 like you are doing the rank of SGA prevalence
11 is by what?

12 DR. PASTOOR: This is based on the
13 water systems that were in the paper itself.

14 DR. BOVE: Okay. So these are the
15 towns?

16 DR. PASTOOR: That's correct.
17 These are community water systems, individual
18 community water systems.

19 DR. BOVE: It is an ecologic
20 approach.

21 DR. PASTOOR: Correct.

22 DR. BOVE: It is an individual-

1 level approach. Now whether there is a dose
2 response relationship in that study, if they
3 have coefficient that is above one for the
4 regression focus, whether you like the
5 analysis or not, and I have faults with the
6 analysis, too, there is a dose response in
7 that. What you have done is make this into an
8 ecologic approach, which is problematic. You
9 say that there isn't. Do you think that
10 that's --

11 DR. PASTOOR: Well, I think the
12 best thing is to turn to the epidemiologist.
13 But what I understand from this study is that
14 they did a categorical analysis on it. So
15 they had the low-dose group was actually the
16 quartile that was at the lowest end of the
17 exposure as opposed to the next two, which is
18 the middle two-fourths and the upper fourth.
19 That is how they did their dose response. We
20 simply took away those categorizations and
21 made it individual data-points.

22 DR. BERRY: Colin Berry.

1 Just to make the point that birth
2 defects is another catchall diagnosis.

3 CHAIR HEERINGA: Yes, Dr. Gold?

4 DR. GOLD: I have a philosophical
5 question that I would like to ask the group,
6 and then, if I had the opportunity, I would
7 like to ask it to the EPA folks maybe tomorrow
8 morning.

9 CHAIR HEERINGA: Certainly
10 tomorrow morning.

11 DR. GOLD: Yes.

12 CHAIR HEERINGA: But do you want
13 to lay it out there now?

14 DR. GOLD: Well, because people
15 have been using this from biologic
16 plausibility pretty freely in all the
17 presentations. To me, what they are saying
18 when they are saying biologic plausibility is
19 really toxicity, which I wouldn't say is
20 necessarily biologic plausibility.

21 Given different modes of action,
22 different dosages, different modes of

1 administration, routes of exposure, I am not
2 sure that toxicity data from animals is the
3 same as biologic plausibility, but I would
4 like to hear from you all. Because I think,
5 going back to the Surgeon General, I think
6 part of the reason those criteria were
7 developed were because we didn't have really
8 good biologic plausibility.

9 I mean we didn't have really good
10 data from animals to indicate the path of
11 physiologic mechanism by which smoking caused
12 lung cancer, for example. So I think we are
13 in a similar situation now.

14 So I would just like to hear
15 philosophically this interchangeable use of --
16 you are using biologic plausibility, and I
17 think you meant toxicity.

18 CHAIR HEERINGA: Dr. Swenberg?

19 DR. SWENBERG: Let me take a crack
20 at this. You raise a very interesting point.

21 I think that we start out looking
22 at biological plausibility with things like

1 when there are massive differences in
2 exposures, could one molecule result in this
3 disease type of thing? But I think this
4 framework mode-of-action analysis that we have
5 worked on now for over a decade has brought us
6 about to think more about plausibility and the
7 mode of action really enhances our knowledge
8 when we go through one of these frameworks on
9 what are the key events, and what is the
10 plausibility of those key events taking place
11 under the circumstances of the exposure?

12 As one goes to the human relevance
13 part of this that Bette has pioneered, you ask
14 questions about this and go through a decision
15 tree to better define that. So I think
16 biological plausibility that we use in today's
17 context has been influenced by 10 years of
18 working on these framework analyses.

19 And when we have worked out what
20 looks like a good mode of action, and we have
21 data that follows these criteria, that almost
22 always strengthens the assessment of

1 biological plausibility.

2 CHAIR HEERINGA: Dr. Bailar, and
3 then we will move on.

4 DR. BAILAR: I think Dr. Gold made
5 a very important and useful point here. I
6 would like to add two footnotes.

7 The first is that I don't think
8 biologic plausibility is the whole of
9 toxicology. It is a subset. It might be
10 worth defining that subset and then giving it
11 this name.

12 The second is that biologic
13 plausibility is not entirely limited to
14 toxicology. I think that is where most of it
15 is. But if I find a chemical that is said to
16 be causing 40 different kinds of cancer, I
17 think we are probably looking at bias.

18 Chemical carcinogens don't work
19 that way. They tend to have much more
20 specific action. This cancer or that cancer,
21 maybe two, three, five, but not across the
22 board. So I would take that as some kind of

1 evidence regarding plausibility, but it is not
2 toxicology.

3 DR. BRECKENRIDGE: Charles
4 Breckenridge. I will just respond briefly to
5 that.

6 We actually were a little bit
7 concerned about flattening the dimension of
8 plausibility to a single axis when we were
9 involved in this, and we had the element of
10 what we called biological coherence, which was
11 an element of the common understanding of
12 would these processes physically be possible.
13 I suppose the electromagnetic and brain tumor
14 relationship might be an example of a failure
15 to have a relationship that seemed to make
16 sense from a physical point of view, and that
17 would be a concept of plausibility in some
18 sense. It would be physical plausibility
19 though, and maybe that is not toxicology, but
20 it is more, is it in accord with the
21 understanding of science that we have at the
22 moment?

1 CHAIR HEERINGA: Dr. Gold, and
2 then I would like to move on, but, please, go
3 ahead.

4 DR. GOLD: Because EPA ultimately
5 has to make policy in the absence of perfect
6 knowledge, so I just want to make sure that
7 when we are talking about our terms, I think
8 the language is important. That is why I am
9 interested in the philosophy. Because are we
10 saying that they have to have biologic
11 plausibility, which I think we often don't
12 have when we make policy? So I am interested
13 in your philosophic point of view. I mean I
14 will be interested in hearing theirs tomorrow.

15 CHAIR HEERINGA: Dr. Breckenridge?
16 I think that we will have a little time
17 tomorrow morning in general to continue public
18 comment, and I think we can revisit some of
19 these issues people have thought about them
20 for the evening, too.

21 At this point in time, I would
22 like to move on to the remaining public

1 commenters who have arranged to present.

2 Before I do, I want to just make
3 sure because some people may be leaving to
4 catch a bus or a subway. Administratively,
5 apparently, there is a little snow
6 anticipated. I say, "a little snow". I'm
7 coming from Michigan.

8 (Laughter.)

9 So a little snow is anticipated.
10 I was born in South Dakota. So it is a very
11 little snow.

12 If the federal government, sort of
13 a three-part strategy, and so if the federal
14 government is delayed, and this is an official
15 decision that the work will be delayed start,
16 say it is delayed to start at 10:30. Our
17 meeting will start at 10:30.

18 If the government is closed,
19 heaven forbid, the meeting will reconvene on
20 Thursday morning.

21 If the federal government allows
22 employees unscheduled leave or liberal leave,

1 essentially, they have to decide whether they
2 can get through the snow to get here, the rest
3 of us will start at 8:30, as normally
4 scheduled.

5 So that may be completely
6 confusing, but, again, I understand that the
7 Office of Personnel Management posts this on
8 the website, and the local radio stations,
9 given the density of government employees in
10 the area, and TV stations, I am sure will
11 announce this. And the rest of us can sort of
12 figure it out on the fly.

13 Okay. At this point in time, I
14 would like to invite up Mr. Tyler Wegmeyer,
15 who is representing the American Farm Bureau
16 Federation. Mr. Wegmeyer as a five-minute
17 comment.

18 Welcome, Tyler.

19 MR. WEGMEYER: At least I know you
20 are from Michigan, like I am. So, at least
21 the two of us will be here if it snows.

22 Since we are losing daylight, I

1 would like to amend my prepared comments, if
2 it is okay with you, to say good evening,
3 rather than good afternoon.

4 My name is Tyler Wegmeyer, and I
5 am Director of Congressional Relations for the
6 American Farm Bureau Federation.

7 I am also a fourth-generation
8 farmer, growing mostly specialty crops in
9 western Loudoun County, Virginia.

10 The American Farm Bureau
11 Federation is the country's largest general
12 farm organization. Farm Bureau members grow,
13 produce, and raise the food, fiber, and energy
14 sources that feed, clothe, and field the U.S.
15 and the world.

16 Our farms and ranches are found in
17 all 50 states as well as Puerto Rico, and we
18 represent producers of every size and scale of
19 operation.

20 The American Farm Bureau
21 Federation welcomes this opportunity to speak
22 up on behalf of atrazine and what it means to

1 the American farmer. Having access to
2 important crop protection products is vital to
3 the success of providing a safe and abundant
4 food supply.

5 Atrazine is the most important
6 herbicide in soil-saving growing practices,
7 such as no-till and conservation tillage. We
8 use it to control weeds on about two-thirds of
9 the country's corn and sorghum acreage. We
10 know this product and how it affects the land.
11 And after all, a farmer spends his day in the
12 field and spends his night with his family
13 next to that field.

14 A farmer gets down in the dirt
15 every day, observing how our practices work
16 with the soil, plants, insects, water, and the
17 local environment. And I can tell you that
18 our 51 years of experience with atrazine shows
19 us what a scientific analysis of thousands of
20 studies confirm, that atrazine is gentle,
21 safe, and effective.

22 The Farm Bureau strongly believes

1 having access to important crop protection
2 products such as atrazine is vital to the
3 success of providing a safe and abundant food
4 supply. Ask our corn, sorghum, and sugarcane
5 growers, and they will tell you that we depend
6 on this herbicide to keep a broad spectrum of
7 weeds from robbing nutrients from our crops.
8 They will also tell you that we cannot do it
9 without atrazine.

10 EPA's own numbers show this to be
11 true, that losing atrazine would cost farmers
12 \$28 an acre in lost yields and increased weed
13 cost. EPA also tells us that U.S. corn,
14 sorghum, sugarcane, and other growers would
15 suffer losses of greater than \$2 billion if
16 atrazine were not available.

17 Some activist groups claim that
18 atrazine is easily replaced. It is not. Just
19 two weeks ago, a report from the Minnesota
20 Department of Agriculture quoted University of
21 Minnesota scientists who said there are no
22 direct replacements for atrazine in pre-

1 emergence weed control registered in that
2 State.

3 As you also know, corn is a base
4 commodity for innumerable products. Corn and
5 sorghum are key feedstocks. Undermine these
6 sectors, and you have pretty much dealt a blow
7 to the entire U.S. food industry along with
8 the economic health of the American farm belt.

9 Of course, no degree of economic
10 dependence would matter if atrazine were a
11 problem. We believe sound science shows it to
12 be safe for use.

13 The American Farm Bureau
14 Federation has participated in every
15 Scientific Advisory Panel convened to examine
16 atrazine's safety since the first special
17 review in 1994. We were with you through the
18 pain-staking work of the most recent re-
19 registration.

20 Now that EPA wishes to conduct a
21 fresh investigation, we are here again. I
22 must say, however, that from the perspective

1 of Farm Bureau, we are concerned over what
2 appears to be a hastily-convened irregular
3 process.

4 We hope that this atrazine review
5 process is not being subjected to an
6 unseemingly rush, and we appeal to the
7 scientists who lend so much of your time,
8 expertise, and credibility to continue to
9 ensure that the principles of sound science
10 remain our way forward.

11 Thank you very much.

12 CHAIR HEERINGA: Thank you, Mr.
13 Wegmeyer.

14 Any comments or questions for Mr.
15 Wegmeyer of the Farm Bureau?

16 (No response.)

17 Thank you very much.

18 At this point in time, I would
19 like to invite up our next scheduled public
20 commenter. It is Mr. Scott Slaughter, who
21 represents the Center for Regulatory
22 Effectiveness. Mr. Slaughter's written

1 comments were distributed to the Panel.

2 MR. SLAUGHTER: Hi. I'm Scott
3 Slaughter, and I am commenting on behalf of
4 the Center for Regulatory Effectiveness. I
5 would like to make three comments.

6 First, an earlier commenter
7 suggested that you ought to focus on endocrine
8 effects in this SAP. I just thought everyone
9 should know, and it is discussed in our
10 comments, that EPA has made a decision to
11 address endocrine effects for pesticides in a
12 separate proceeding called the Endocrine
13 Disruptor Screening Program.

14 The agency has just sent out
15 multiple test orders, including test orders
16 for atrazine, to assess whether or not any of
17 the pesticides that are registered, including
18 atrazine, might have potential endocrine
19 effects. So I don't think you have to worry
20 about endocrine effects going unassessed.
21 Right now, they are being assessed in a
22 different proceeding.

1 Second, I would like to call to
2 your attention a document called "The Atrazine
3 Technical Assessment". It was prepared by the
4 Minnesota Department of Agriculture, the
5 Minnesota Department of Health, and the
6 Minnesota Pollution Control Agency.

7 This State report, which is now
8 subject to comment, reviews the atrazine
9 studies that are being reviewed in this SAP,
10 except the State is reviewing them in that
11 proceeding, reviews the Ag Health Study with
12 regard to atrazine, and reviews the current
13 EPA regulation of atrazine to determine
14 whether current EPA regulation protects human
15 health in Minnesota. In other words, the
16 State of Minnesota is doing basically what EPA
17 is doing here, and much of what the SAP has
18 been asked to do.

19 The Minnesota report -- and the
20 report is now out for comment -- concludes
21 that the current EPA regulation protects human
22 health in Minnesota. The Minnesota report

1 concludes that the five new atrazine studies,
2 or the six, which are discussed here and
3 discussed by EPA, the Minnesota report
4 concludes that those studies are too flawed
5 and unreliable to be used to assess atrazine
6 human health effects.

7 The Minnesota report concludes
8 that, and I quote, "The weight of evidence
9 from reviewed studies can be currently
10 summarized as inefficient to establish causal
11 relationships between atrazine exposure and
12 certain adverse effects. For the purpose of
13 this review, animal toxicity studies remain at
14 this time the most reliable and reproducible
15 data on which to base human health assessments
16 for atrazine." Closed quote.

17 This report was prepared by
18 experts, informed and objective State
19 regulatory authorities, on many of the same
20 issues that are now being addressed by EPA in
21 this SAP.

22 If you do not read any of the rest

1 of CRE's comments, please read the Minnesota
2 report. Its online address is available at
3 page 2 of CRE's written comments. I won't
4 repeat it. I won't even try to repeat it. It
5 is at page 2 of our comments. And if you
6 click on that, you can get the Minnesota
7 report and a lot of background discussion on
8 it.

9 Third, and last, I want to state
10 for the record that CRE would have filed much
11 more complete and lengthier comments, and
12 perhaps more helpful comments, if EPA had
13 responded to CRE's FOIA request in the manner
14 and in the time required by law.

15 CRE filed FOIA requests relating
16 to various issues in this SAP. For whatever
17 reasons, EPA has violated its statutory duties
18 by failing to respond to CRE's request at the
19 time required by law. EPA's failure to obey
20 the law has deprived this SAP of EPA documents
21 that we believe would have aided the SAP's
22 performance of its duties.

1 Thank you, and I will try to
2 answer any questions.

3 CHAIR HEERINGA: Thank you very
4 much, Mr. Slaughter.

5 Any questions of clarification for
6 Dr. Slaughter? Yes, Alex Lu.

7 DR. LU: Again, this is a
8 philosophical question, but I think that I
9 should ask one of the people who make a public
10 comment about the continued use of atrazine.
11 So the question is that, when you talk to your
12 farmer, saying that that atrazine that you put
13 down in your farm is actually reaching into
14 the aquifer that the rest of the American
15 people drink, how would they feel about it?

16 MR. SLAUGHTER: Well, you are
17 assuming a lot of things, I think. First, you
18 are assuming that atrazine is present in
19 drinking water at levels which are hazardous
20 to human health. I don't think that is an
21 accurate assumption, and I am sure people back
22 here could address it in far more detail than

1 I can.

2 You ask me that question. You are
3 assuming something which I don't believe is
4 true.

5 And second, farmers live with this
6 stuff. I mean they have children growing up
7 where they grow their crops and use atrazine
8 and other pesticides. I think, if they really
9 felt that there was a risk, and they are
10 generally very well-informed about these
11 things, they wouldn't use the product, and
12 they do use the product and they want the
13 product.

14 DR. LU: Well, I think the USGS
15 data suggests that more than 90 percent of the
16 water they sampled had detectable atrazine
17 levels.

18 MR. SLAUGHTER: Detectable is not
19 the same thing as drinking water, and it is
20 not the same thing --

21 DR. LU: Right, but --

22 MR. SLAUGHTER: -- as hazardous

1 level.

2 DR. LU: Right, but the question
3 that I had was not in drinking water --

4 CHAIR HEERINGA: All right,
5 fellows, I am going to cut off the
6 philosophical discussion. Thanks. That is a
7 scientific question. It can be answered in a
8 quantifiable way.

9 Dr. Gold? Okay.

10 MR. SLAUGHTER: I thank you.

11 CHAIR HEERINGA: Thank you very
12 much, Mr. Slaughter.

13 At this point in time, I would
14 like to invite up Dr. Jessica Johnson Bennett,
15 who is representing the National Corn Growers
16 Association.

17 DR. BENNETT: Good afternoon.

18 I'm Jessica Bennett, Director of
19 Public Policy for the National Corn Growers
20 Association. I appreciate the opportunity to
21 testify before you today.

22 I am providing comments on behalf

1 of the NCGA, which represents more than 36,000
2 members in 48 states, 47 affiliated state
3 organizations, and more than 300,000 corn
4 farmers who contribute to state CGA programs
5 across the country.

6 For over 50 years, more than half
7 of all American corn growers have relied on
8 atrazine to protect our crops from a variety
9 of grass and broad-leaf weeds. We especially
10 value its flexibility. Atrazine can be
11 applied to crops before, during, or after
12 planting. It may even be applied after the
13 crop emerges.

14 By EPA's own estimate, atrazine
15 saves corn farmers as much as \$28 an acre in
16 reduced herbicide costs and increased yields.
17 For all these reasons, atrazine is not just a
18 good product, it is a vital product.

19 Atrazine not only supports corn
20 production, but it also provides environmental
21 benefits. Every farmer is, of necessity, a
22 conservationist. We care deeply about our

1 impact on the land and water, and what we will
2 leave behind for our children our
3 grandchildren.

4 That is why so many corn farmers
5 are proud to rely on atrazine for no-till
6 conservation agriculture on more than 44
7 million corn acres, a practice that is
8 preventing soil erosion, protecting waterways,
9 and sequestering significant amounts of carbon
10 dioxide across America.

11 It is with these concerns in mind
12 that our growers have been active participants
13 in supporting the scientific approval of
14 atrazine by the EPA over the last 15 years
15 under three Administrations, both Democrats
16 and Republicans.

17 We were there when EPA re-
18 registered atrazine three years ago and
19 concluded, as before, that triazine herbicides
20 pose no harm that would result to the general
21 U.S. population, infants, children, or other
22 major identifiable subgroups of consumers.

1 We also invest confidence in the
2 fact that the World Health Organization, the
3 National Cancer Institutes, and the British
4 Government have all studied atrazine and found
5 no health concerns.

6 Yet, now we find ourselves facing
7 an extraordinary, hastily-assembled, and,
8 frankly, unprecedented re-review of atrazine
9 that seems to be inspired by anti-pesticide
10 activists. We are troubled that this process
11 seems rushed and that the scientists on this
12 SAP, who give so much of their time and
13 expertise, are being asked to survey so much
14 new data in so little time.

15 The good news is that we have
16 seen, time and again, the quality and
17 professionalism of EPA's scientific advisors.
18 We are counting on you for a fair assessment
19 based on sound science, and nothing but sound
20 science.

21 Thank you for your time.

22 CHAIR HEERINGA: Thank you very

1 much, Dr. Bennett.

2 Any questions for Dr. Bennett from
3 the National Corn Growers Association?

4 (No response.)

5 Okay. Thank you.

6 And I have one more scheduled
7 public commenter, and that is Dr. Gary Burin
8 with Technology Sciences Group, Inc. And
9 there are written comments that have been
10 submitted, too.

11 DR. BURIN: Yes, yes.

12 Good afternoon. Good evening.

13 My name is Gary Burin. I am a
14 toxicologist with Technology Sciences Group.

15 I have prepared comments on the
16 EPA framework document and the atrazine
17 epidemiology studies on behalf of the Triazine
18 Network, a coalition of 1,000 local and state
19 agricultural and farmers' organizations.

20 Jerry White, the Chairman of the
21 Triazine Network, is unable to be here this
22 afternoon due to his Association's Annual

1 Meeting, but will be attending the meeting
2 tomorrow.

3 Now, prior to my becoming a
4 consultant, I worked in the Office of
5 Pesticide Programs and at the World Health
6 Organization, and I have seen that it is
7 difficult to integrate human data into hazard
8 evaluation and risk assessment. But I believe
9 that the EPA framework document can be, for
10 the most part, considered to provide a logical
11 and sound approach to the growing body of
12 information concerning the health effects of
13 pesticides.

14 The framework document requires
15 that epidemiology studies, such as those of
16 atrazine, not be viewed in isolation of other
17 relevant information. Further, the framework
18 recommends that the contribution to the weight
19 of evidence of epidemiology studies be viewed
20 using the modified Bradford Hill criteria that
21 we have heard about earlier from Dr. Owens and
22 from EPA this morning.

1 The framework provides the context
2 for the atrazine case study that is described
3 in Attachment A. My evaluation of these
4 studies can be found in the written comments
5 that have been submitted.

6 I share some of the concerns that
7 were raised by the previous speakers,
8 including the EPA speaker this morning,
9 regarding the limitations of these studies.

10 For more details, and I won't go
11 into my comments, given the lateness of the
12 hour on a study-by-study basis, but I hope
13 that you will have the chance to read my
14 written comments.

15 Thank you.

16 CHAIR HEERINGA: Thank you very
17 much, Dr. Burin.

18 Are there any questions for Dr.
19 Burin, questions of clarification?

20 (No response.)

21 Thank you very much.

22 I just want to indicate that there

1 are several other communications that the
2 Panel has received, one from Michelle Marcus
3 and another who I think is writing on her own
4 behalf, and then Charles Connor from the
5 National Council of Farm Cooperatives. These
6 will be in the docket, and I believe there may
7 have been some other advance public comments
8 that were already in the docket.

9 So there is a lot of information
10 that has been submitted by the public and
11 industry representatives that is going to be
12 either on the public docket or will be in it
13 late tomorrow afternoon. I encourage
14 everybody to access that and have a chance to
15 look it all over.

16 At this point in time, again, just
17 a quick reminder, we are at the end of the
18 day. I am not going to close the period of
19 public comment. I would like to leave it open
20 just briefly, but not for new public comment
21 necessarily or repeats. But if the Panel
22 members require any questions of clarification

1 tomorrow morning, I would hold the right to
2 call back up anyone who is here present and
3 would be able to address questions of
4 clarification from the Panel. So, Panel
5 members, any of the public commenters.

6 Then, also, following that, you
7 will have the opportunity to re-engage with
8 the EPA scientific staff on any questions of
9 clarification on their presentation, and then
10 we will move on to address the actual charge
11 questions.

12 Just a final reminder,
13 administratively, if a decision is made
14 because of the inclement weather, snow, to
15 delay the start of federal government
16 activity, our meeting will be delayed to start
17 consistent with that official federal
18 decision.

19 If the government is closed due to
20 substantial snowfall, the meeting will not be
21 held tomorrow, but will reconvene Thursday,
22 consistent with government business, assuming

1 it is not closed for two days. I don't know
2 what we would do if it were.

3 If the federal government has
4 scheduled just informal leave for its
5 employees or gives them flexibility on whether
6 they will come in, we will meet here at 8:30
7 at the regular time.

8 So, Dr. Lu?

9 DR. LU: Where can we get at the
10 information in terms of delay or closure?

11 MS. CHRISTIAN: WTOP, a radio
12 station, and also in the news. And not only
13 that, if you go to the OPM website, you
14 will --

15 CHAIR HEERINGA: Office of
16 Personnel Management.

17 MS. CHRISTIAN: Yes. Yes,
18 tomorrow morning.

19 CHAIR HEERINGA: Is that correct?
20 Google federal closure, okay.

21 MS. CHRISTIAN: Yes, yes, that is
22 correct.

1 CHAIR HEERINGA: Probably the best
2 thing to do is just look out the window out
3 there.

4 (Laughter.)

5 If there is no snow on the ground,
6 but don't use your Boston standard. Okay?

7 (Laughter.)

8 Okay. Very good. We appreciate
9 everybody's contributions today. It has been
10 a very good start. We have gotten a lot of
11 information in, and we look forward to a very
12 productive day and set of discussions
13 tomorrow.

14 Any last administrative issues?

15 MS. CHRISTIAN: No, not any new
16 announcement, but please join us tomorrow
17 morning, hopefully, at 8:30, to continue this
18 meeting.

19 Thank you.

20 CHAIR HEERINGA: Okay. And, Panel
21 members, if we could just meet briefly for
22 five minutes in the breakout room, just to

1 sort of lay out our plan for tomorrow morning?

2 (Whereupon, at 4:56 p.m., the
3 proceedings in the above-entitled matter were
4 adjourned for the day, to reconvene the
5 following day, Wednesday, February 3, 2009, at
6 8:30 a.m., weather permitting.)

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