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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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REEVALUATION OF THE HUMAN HEALTH EFFECTS OF
ATRAZINE: REVIEW OF EXPERIMENTAL ANIMAL AND IN
VITRO STUDIES AND DRINKING WATER MONITORING
FREQUENCY

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DOCKET NO.: EPA-HQ-OPP-2010-0125

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MONDAY,

APRIL 26, 2010

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The Panel convened at 1:00 p.m. in the
Hamilton Ballroom of the Hamilton Crowne Plaza

Hotel, located at 1001 14th Street, N.W.,
Washington, D.C., Steven G. Heeringa, Ph.D.,
Chair, and Kenneth M. Portier, Ph.D., Session
Chair, presiding.

FIFRA SAP MEMBERS PRESENT:

STEVEN G. HEERINGA, Ph.D., Chair

KENNETH M. PORTIER, Ph.D., Session Chair

JOHN R. BUCHER, Ph.D., DABT

JANICE E. CHAMBERS, Ph.D., DABT, ATS

GERALD A. LeBLANC, Ph.D.

DANIEL SCHLENK, Ph.D.

FQPA SCIENCE REVIEW BOARD MEMBERS PRESENT:

SUSAN F. AKANA, Ph.D.

RICHARD H. COUPE, Ph.D.

KENNETH BARRY DELCLOS, Ph.D.

PENELOPE A. FENNER-CRISP, Ph.D., DABT

ROBERT J. GILLIOM, Ph.D.

RICHARD GREENWOOD, Ph.D.

WILLIAM L. HAYTON, Ph.D.

STEVEN D. HOLLADY, Ph.D.

TERESA H. HORTON, Ph.D.

KANNAN KRISHNAN, Ph.D.

HERBERT K.H. LEE, Ph.D.

KEVIN T. O'BYRNE, Ph.D.

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

JEAN F.L. REGAL, Ph.D.

DANIEL J. SELVAGE, Ph.D.

CARMEN J. WILLIAMS, M.D., Ph.D.

LINDA J. YOUNG, Ph.D.

ALSO PRESENT:

JOSEPH E. BAILEY, Designated Federal Official

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

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

1:09 p.m.

MR. BAILEY: Good afternoon, everyone.

My name is Joe Bailey, and I'm with the FIFRA Scientific Advisory Panel staff. I'll be serving as the Designated Federal Official for this meeting, and I want to welcome everyone, this afternoon.

We have a three and a half day meeting set up here, and I'm very pleased to kick this meeting off this morning -- this afternoon, and get it underway.

As the DFO, I serve as a coordinator between the Panel, the Agency and the public, in putting this meeting together.

The FIFRA Scientific Advisory Panel only provides advice and recommendations to the Agency. All decision making and regulatory decisions are left up to the Agency, and they take the advice and recommendations as they see fit.

We have worked with all of the Panel

1 members, in reviewing ethics requirements. They
2 have all submitted financial disclosure
3 information that we, at the Agency, have reviewed
4 and made sure that we -- that all of the ethics
5 requirements have been met.

6 Part of the requirements, under the
7 Federal Advisory Committee Act, is that this is a
8 public meeting. We do provide an opportunity for
9 public comment, and the -- that is set aside for
10 tomorrow morning.

11 So, if anyone has a desire to present
12 public comments, please, let me know. If you
13 haven't registered ahead of time, I ask that you
14 keep your comments to five minutes or less.

15 There is a public docket that we've
16 set up for the meeting. It should be on the
17 agenda, the docket number. Everything that is
18 presented in this meeting will be in the docket.

19 The presentations that EPA will be
20 putting forward today are current -- they should
21 be available in the docket, as of now, and any
22 public -- any additional public comments or other

1 materials that come of -- become available during
2 the meeting will also be placed in that docket.

3 I'm very pleased to introduce Dr. Ken
4 Portier, sitting to my right, who will be serving
5 as the Chair for this meeting, and without any
6 further adieu, I'll turn the mic over to Dr.
7 Portier.

8 SESSION CHAIR PORTIER: Good afternoon.
9 I want to welcome all of you to this meeting of
10 the FIFRA Scientific Advisory Panel on the
11 Reevaluation of the Human Health Effects of
12 Atrazine Review of Experimental Animal and In
13 Vitro Studies and Drinking Water Monitoring
14 Frequency.

15 I'll give a special thanks to our
16 audience. I think they have ordered a few more
17 chairs. We're going to accommodate everyone.

18 As many of you know, this is kind of
19 the second in a series of three meetings that the
20 Panel is having on atrazine this year.

21 We've put together -- the SAP staff
22 has put together a very good panel of experts, a

1 mixture of experienced panelists, with some new
2 people, some new voices.

3 So, at this point, I'd like to
4 introduce the Panel. I'll start with myself. I
5 am the Director of Statistics with the American
6 Cancer Society National Office in Atlanta. I'm a
7 bio-statistician and a permanent member of the
8 SAP Panel, and I'll move to Dr. Heeringa here, on
9 my right.

10 CHAIR HEERINGA: Good afternoon,
11 everyone. I'm Steve Heeringa of the University
12 of Michigan. I'm presently the Chair of the
13 permanent FIFRA SAP and look forward to this
14 three and a half day session, and I want to thank
15 my colleague, Ken Portier, for agreeing to Chair
16 this.

17 DR. KRISHNAN: Good afternoon. I'm
18 Kannan Krishnan from the University of Montreal.

19 SESSION CHAIR PORTIER: What's your
20 expertise?

21 DR. KRISHNAN: I'm an agriculturist and
22 toxicologist by training. My expertise is in

1 PBPK modeling, risk assessment of drinking water
2 contaminants and chemical mixtures.

3 DR. GREENWOOD: I'm Richard Greenwood
4 from University of Portsmouth in the United
5 Kingdom, and I've got a broad background in
6 pesticide toxicology and also in
7 pharmacokinetics.

8 DR. FENNER-CRISP: I'm Penny Fenner-
9 Crisp. I'm currently a consultant and live in
10 Charlottesville, Virginia, a one-time employee of
11 EPA, including the Office of Pesticide Programs
12 for a few years, and the newest member of
13 Virginia's Pesticide Control Board. So, I'm back
14 in the regulatory milieu.

15 DR. REED: I'm Nu-may Ruby Reed from
16 California Environmental Protection Agency. I do
17 pesticide risk assessment and address pesticide
18 risk assessment issues for our group.

19 DR. LEE: I'm Herbert Lee. I'm a
20 statistician at the University of California,
21 Santa Cruz.

22 DR. YOUNG: I'm Linda Young. I'm

1 Professor and Associate Chair of the Department
2 of Statistics, University of Florida.

3 DR. COUPE: Richard Coupe, I'm with the
4 U.S. Geological Survey. I've worked on fate and
5 transport of pesticides or agricultural
6 chemicals.

7 SESSION CHAIR PORTIER: Dr. Selvage?

8 DR. SELVAGE: Yes, I'm Dan Selvage,
9 Idaho State University, specializing in HPA axis
10 and how gonadal hormones affect it.

11 DR. O'BYRNE: My name is Kevin O'Byrne
12 and I'm from King's College London and my
13 interests are in the effect of stress on
14 fertility.

15 DR. AKANA: I'm Susan Akana. I'm from
16 the University of California, San Francisco. I'm
17 a physiologist and my area is the stress axis and
18 its interaction with energy balance.

19 DR. HORTON: I'm Theresa Horton. I'm
20 from the Department of Neurobiology and
21 Physiology at Northwestern University in
22 Evanston, Illinois. My specialty is reproductive

1 neuroendocrinology and maternal fetal
2 interactions in the developing neuroendocrine
3 system.

4 DR. DELCLOS: I'm Barry, or Kenneth
5 Delclos from the FDA's National Center of
6 Toxicological Research and I'm working on
7 reproductive and chronic toxic effects of
8 endocrine-active agents.

9 DR. WILLIAMS: I'm Carmen Williams.
10 I'm at the National Institute of Environmental
11 Health Sciences in North Carolina, and I'm in a
12 reproductive endocrinology and infertility
13 training position. I do research on reproductive
14 track development.

15 DR. REGAL: Jean Regal, Professor of
16 Pharmacology, University of Minnesota Medical
17 School, Duluth, Immunotoxicology and Allergy.

18 DR. HOLLADAY: I'm Steve Holladay. I'm
19 from the University of Georgia. I'm an
20 immunotoxicologist. Most of what we've done is
21 developmental immunotoxicology.

22 DR. LEBLANC: I'm Gerry LeBlanc and I'm

1 head of the Department of Environmental and
2 Molecular Toxicology at North Carolina State
3 University and my area of interest is in
4 endocrine-toxicology.

5 DR. SCHLENK: Good morning. I'm Dan
6 Schlenk. I'm a Professor of Aquatic Eco-
7 Toxicology in Department of Environmental
8 Sciences, University of California, Riverside.
9 I'm a member of the permanent Panel and my
10 expertise is on fate and effects of pesticides on
11 aquatic organisms.

12 DR. BUCHER: I'm John Bucher. I'm the
13 Associate Director of the National Toxicology
14 Program. I'm a member of the permanent Panel and
15 with a background in general toxicology.

16 DR. CHAMBER: I'm Jan Chambers. I'm a
17 Professor in the College of Veterinary Medicine
18 at Mississippi State University. I'm a pesticide
19 toxicologist with emphasis on neurotoxicology and
20 metabolism, and I'm a member of the permanent
21 Panel.

22 SESSION CHAIR PORTIER: Thank all of

1 you for being here. A couple of, kind of, notes.

2 The agenda has been published, but
3 just note that the times that are published are
4 approximate. We're going to proceed through the
5 agenda as it goes, and my goal today is to get
6 through the EPA presentations before we leave
7 this evening, hopefully, depending on the number
8 of questions the Panel has on the presentations.

9 The second thing is, tomorrow morning,
10 we're going to have a session on public
11 commenters and if anyone wishes to speak before
12 the Panel tomorrow, please, let Joe Bailey know,
13 at this point, so we can schedule you in. If you
14 have any materials for that public presentation
15 that you want to make before the Panel, give it
16 to Joe. It will get onto the docket.

17 All of the public commenters, as well
18 as the EPA presentations are on the meeting
19 docket on the internet.

20 At this point, I'm going to turn it
21 over to Steven Bradbury, the Acting Director,
22 Office of Pesticide Programs, to make his opening

1 remarks. Steve.

2 DR. BRADBURY: Thank you, Ken. I'd
3 like to start off, first, by thanking the Panel,
4 all the members, the standing permanent members
5 of the Panel, as well as all the ad hoc Panel
6 members for this week's peer review.

7 I greatly appreciate the time and
8 effort it takes in preparing for these meetings,
9 the time it takes while you're at the meeting and
10 then, preparing the report, following the
11 deliberations, and the Agency greatly appreciates
12 your investment of your time and efforts and
13 talents in our peer review process.

14 So, ahead of the week, thank you very
15 much and again, I'll be thanking you, as we
16 finish the week.

17 I'd also like to thank Joe Bailey and
18 the staff that -- the Designated Federal Official
19 who helped make these meetings happen. It takes
20 a lot of work to prepare for the meetings and get
21 all the logistics in place and I want to thank
22 Joe Bailey and his colleagues, in all the work

1 that they've been undertaking to get ready for
2 this meeting, as well as the previous meeting
3 that we already had with atrazine.

4 I'd also like to, in advance, thank
5 the public for their participation in the
6 deliberations.

7 As Ken Portier indicated, tomorrow
8 morning is our time for public input into this
9 peer review process and we take the input of the
10 public very seriously and it's a very important
11 part of the overall peer review process that
12 we're going forward with, and I can't stress
13 enough, the importance of the public
14 participation and transparency that an SAP review
15 brings to the decision making process that we do
16 in the Agency.

17 And it's a concept of public
18 participation, transparency and the quality of
19 science in the Agency's decision making
20 processes. There are a couple of the very
21 important principles that Administrator Jackson
22 brings to the Agency.

1 And so, as we go through the Science
2 Advisory Panel process, which our program has
3 done for many, many years, it reinforces these
4 important concepts of the new administration, in
5 terms of ensuring that the science that we do
6 that's a foundation of all the decision making
7 that we make in the pesticide program is based on
8 the best available information and the highest
9 quality science that we can bring to bear, and
10 that includes the very important part of peer
11 review, to ensure that we're getting input from
12 our colleagues in the scientific community, as we
13 look at some very complex issues.

14 The other important aspect of a
15 meeting like this is the openness and the public
16 participation process, so that the public can
17 participate and provide input to the
18 deliberations and that the proceedings of the
19 meetings and the notes from the meetings are all
20 open and transparent, so that as people see us
21 moving forward in our decision making process,
22 the various components that are important to that

1 process aren't mysterious. It's not a black box.

2 In fact, it's quite the opposite, very open
3 process with a lot of lights shining on it, so
4 everyone can see how we're integrating very
5 complex scientific issues with the regulatory
6 decision making that we need to do.

7 And in that context of sound science,
8 high quality science and public participation,
9 chemical safety also reflects one of the areas of
10 emphasis of the administration, in both
11 industrial chemicals, as well as with pesticides.

12 And so, ensuring, as we go forward in
13 our pesticide decision making, that our decisions
14 are those kinds of decisions that ensure safety
15 to human health and the environment, as we go
16 forward with our decision making process.

17 I'd like to spend just a couple of
18 minutes reviewing the processes that we go
19 through, in making our regulatory decisions and
20 then how that connects with the efforts that
21 we're undertaking with atrazine.

22 As we make decisions about new

1 pesticide products and whether or not they should
2 be allowed to go on the market, there's a very
3 extensive amount of scientific information that's
4 required by the registrants, so that companies
5 that own the products, need to bring quite a
6 large amount of information to the Agency,
7 everything from the fate and transport properties
8 of the chemical, human toxicology, ecological
9 effects, a wide variety of information needed to
10 ensure that any decisions we make about the
11 registration of a pesticide will ensure, again,
12 protection of human health and the environment,
13 including worker protection, including
14 protection, if the product is in the food source,
15 including that dietary exposures are safe, as
16 well as any drinking water exposures.

17 The information that is brought to
18 bear in the processes that we use are, in many
19 ways, similar to activities undertaken around the
20 globe. Much of the information and scientific
21 processes that we use have been developed in
22 concert with the European Union, our colleagues

1 to the north in Canada, as well as in Australia.

2 So, the information base and the
3 processes that we use, while unique to our
4 statutes and our approach, as also integrated or
5 collaborative in nature in many ways, with our
6 colleagues around the globe, at the federal
7 level, and as well as with our collaboration with
8 our partners in the state governments, that also
9 undertake risk assessments and regulatory review
10 steps.

11 So, the importance of science starts
12 at the beginning of the life of the chemical, in
13 terms of when we decide whether or not we're
14 going to register a chemical.

15 We also have, through our statutes, a
16 requirement that we periodically reevaluate all
17 pesticides that are on the market, to ensure over
18 time, that as the science change or policies
19 change, in terms of the law or the science, that
20 all the pesticides are current, in terms of the
21 state of the science and the state of scientific
22 approaches and policy.

1 And we have one system that we used in
2 reevaluating pesticides, that ended in the
3 2006/2008 time frame and that reevaluation
4 program, we termed the `re-registration program',
5 and that's when we completed, between 2006 and
6 2008, a reevaluation of all the pesticides that
7 were registered prior to 1984.

8 In 2007, we started our next round of
9 reevaluation, which we call the registration
10 review program, in which we're looking at all
11 currently registered pesticides, to ensure that
12 they're meeting the current scientific standards
13 and policy standards.

14 In the case of atrazine, it completed
15 its re-registration process in 2003, was the last
16 time that atrazine went through its formal step
17 of re-registration.

18 But I want to stress an important
19 concept, in terms of the process that starts the
20 chemical or a pesticide, in determining whether
21 or not it would be registered and in this
22 reevaluation process, which is on a specific time

1 frame, is that the Agency is always looking at
2 all the pesticides, all the time, to ensure that
3 if any new information comes to light, or new
4 perspectives in interpreting the toxicology or
5 the ecological effects of a pesticide, that at
6 any time, the Agency can pause, take a look at
7 the compound and ensure that the current science
8 is such that it meets our continued requirements
9 for safety, in terms of human health and the
10 environment.

11 Now, in the case of atrazine and many
12 other products, as these products went through
13 re-registration, we required additional data or
14 confirmatory data to come in after the re-
15 registration decision, and in the case of
16 atrazine, in particular, we were focused on
17 drinking water and ensuring that we would have a
18 system in place that would allow us to keep track
19 of what was going on in drinking water sources,
20 to ensure the concentrations of atrazine weren't
21 exceeding our level of protection or our
22 benchmark for protection of human health.

1 Just an example of many times
2 activities that are going on with a pesticide on
3 a periodic, sort of regular basis, a dynamic
4 process, in terms of tracking the science and the
5 status of a pesticide.

6 Now, as I mentioned before, atrazine
7 completed its re-registration in 2003, and over
8 the course of the last seven years, there's been
9 quite a bit of research done on atrazine, looking
10 at mode of action, looking at dosimetry.

11 There's also been a lot of information
12 coming into the Agency, as a condition of re-
13 registration, which is in part, a significant
14 amount of drinking water monitoring data required
15 of the registrant.

16 So, the Agency felt that over -- a
17 year or so ago, that the time was right to take a
18 look at the new science that had been emerging
19 with atrazine and the context of the very full
20 monitoring information that we had for drinking
21 water sources, to do a check-in, to ensure that
22 our science is current, that our risk assessment

1 of 2003 is still reasonable, in light of the new
2 information, and to see if whether or not we need
3 to make any adjustments in our current risk
4 assessment for atrazine, in light of the new
5 information that's come out over the last seven
6 or so years.

7 And this Science Advisory Panel
8 meeting is one of several, in which we're
9 systematically taking a look at the scientific
10 information regarding atrazine, as well as some
11 underlying methodology, to ensure that we're
12 current, in terms of the state of the science and
13 our underlying risk assessment.

14 So, back in February, we had our first
15 Science Advisory Panel meeting, which was
16 actually broader than atrazine. It was looking
17 at a number of issues, some of which are very
18 relevant to our work with atrazine, and the
19 February Science Advisory Panel meeting was
20 taking a look at epidemiology data, incidence
21 data, and asking some questions and getting some
22 feedback from the Panel, in terms of a framework,

1 is how do you approach an integration of
2 experimental toxicology data with epidemiology
3 data, as one prepares a risk characterization, as
4 one starts to understand and better express what
5 the uncertainties may be, with the risk
6 assessment.

7 And we brought forward some example
8 atrazine epidemiology studies, as part of that
9 process of understanding, getting some feedback,
10 as to how to approach different kinds of
11 epidemiology studies and to get some initial
12 feedback, as to how to best integrate
13 experimental data with epidemiology data.

14 The Panel's report was made available
15 late last week, and we thank the Panel for their
16 efforts in working on that first peer review that
17 we had and getting the report out, and we're, of
18 course, looking at it over the weekend and
19 appreciate the input that we received thus far.

20 Today's or this week's Science
21 Advisory Panel, as you know, is focusing on
22 primarily experimental toxicology information,

1 both in vivo and in vitro, and taking a look at
2 the non-cancer effects associated with atrazine,
3 everything from mode of action to dosimetry, as
4 well as beginning to get some feedback around
5 that transition from understanding the dosimetry
6 around the toxicology and how do you translate
7 that into monitoring frequencies in drinking
8 water, to understand what's the right time frame,
9 in terms of looking at drinking water exposures
10 in the context of the dosimetry evaluations
11 coming out of the toxicology work, so that our
12 exposure and that our effects information are
13 properly integrated.

14 In today's -- this week's peer review
15 panel will give us some important feedback, as we
16 make a progress towards our September peer
17 review, which will be taking a look, with a
18 little modification that we had to do last week,
19 will be focusing on non-cancer effects and
20 looking at experimental toxicology, as well as
21 epidemiology information in the context of non-
22 cancer effects, and again, taking a look at

1 drinking water, sampling designs and frequency of
2 sampling, to ensure that our interpretation of
3 what's going on in drinking water sources can be
4 properly interpreted, in terms of the risk
5 assessment.

6 We originally had hoped to be able to
7 also take a look at cancer effects, both
8 experimental toxicology and epidemiology data in
9 September and our goal for the September
10 assessment was based on the National Cancer
11 Institute completing some key studies that
12 they've been doing in the agricultural health
13 study, and our hope that it would be at -- those
14 studies would be available during the spring, so
15 that we could have a fall review on those
16 studies.

17 Our colleagues at NCI haven't been
18 able to hit that target, so, we're looking
19 towards 2011, when the NCI studies would be
20 available and then the 2011 time frame, we'll
21 focus on cancer, looking at experimental
22 toxicology information and epidemiology data, and

1 take a look at the cancer issue in 2011.

2 In the coming months, we'll be able to
3 give you all a better handle on the time frame
4 for taking on that specific task.

5 So, one other sort of broad comment,
6 as I wrap up, is that clearly, the information
7 that we're providing you all, and information we
8 get from the public and then the feedback we'll
9 get through the peer review process will be
10 critical for our ongoing evaluation of atrazine
11 and ensuring that our regulatory decisions are
12 based on the most current and sound science.

13 But I want to point out that a lot of
14 the topics that we'll be talking about over the
15 course of the week, also, are very important for
16 our broader program, in terms of how we undertake
17 the emerging fields or issues in toxicology and
18 risk assessment and exposure assessment.

19 And so, taking a look at mode of
20 action and understanding toxicity pathways, how
21 to understand relationships of perturbations
22 across different levels of biological

1 organization, while clearly, very relevant to our
2 discussions on atrazine, those concepts also play
3 out in many of our risk assessments, and as we
4 move forward in the context of the National
5 Academy of Sciences report on toxicology testing
6 in the 21st century and the use of toxicity
7 pathways, to better understand what adverse
8 outcomes may be associated with perturbations in
9 biological systems, the feedback we get on
10 atrazine will also be very helpful, as we think
11 about frameworks and approaches for other kinds
12 of chemicals.

13 As we learn more about how to
14 integrate epidemiological information and
15 experimental toxicology information with
16 atrazine, we're assuming, and I'm confident we
17 will, learn ideas and concepts that will be
18 broadly applicable to the other types of
19 chemicals we deal with and the broad activities
20 that we do in our risk assessment process.

21 Looking at life stage susceptibility,
22 obviously, critical for atrazine, but also

1 critical for many of our risk assessments in the
2 scenarios that we deal with.

3 So, a number of broad range of
4 applicability of the work we're going to be
5 doing, and in the context of drinking water and
6 looking at monitoring frequencies and
7 understanding how to better capture information
8 in source water and drinking water systems and
9 how do you interpret that in the context of a
10 risk assessment, it's not only very important for
11 the pesticide program, but also, very important
12 for our colleagues in the office of water, who
13 implement the Safe Drinking Water Act.

14 And so, as we move forward in ensuring
15 protection of source water and drinking water
16 sources, the lessons that we'll learn today and
17 tomorrow and over the course of the next year or
18 so, are also very important for how we move
19 forward as an Agency, in terms of drinking water
20 protection and moving forward, both in monitoring
21 designs, as well as in the science of doing
22 toxicology and risk assessments.

1 So, not surprisingly, many of the
2 individuals that you'll be hearing from over the
3 course of the week aren't just from the Office of
4 Pesticide Program and our Health Effects Division
5 and our Environmental Fate and Effects Division,
6 but also, you'll be hearing from our colleagues
7 from the Office of Research and Development, who
8 back in 2000, were instrumental in our thinking
9 about atrazine and how to move forward in our
10 understanding of mode of action, back in the
11 early 2000s, but you'll also be hearing from a
12 colleague from the Office of Water, in reflecting
13 the interaction that we had with our colleagues
14 in the Safe Drinking Water Office, in terms of
15 how to advance the science, in terms of
16 monitoring and linking that into risk assessments
17 and toxicological interpretation.

18 So, while it's OPP and we're looking
19 at issues of our statutes and how to ensure that
20 our decisions around atrazine are bringing the
21 best science to the table, again, the principles
22 that we're learning broadly applicable and

1 reflect sort of, a broad Agency perspective, as
2 we move forward with the state of the science.

3 So, with that, unless there's any
4 specific questions, I'd like to turn it over to
5 Dr. Tina Levine, who can introduce the whole team
6 and provide some more detailed introduction into
7 the activities over the next week. Thanks.

8 DR. LEVINE: Thank you, Steve. I'm
9 Tina Levine and I'm the Director of the Health
10 Effects Division in the Office of Pesticide
11 Programs, a job that I will point out, Penny
12 Fenner-Crisp used to have, when she worked in the
13 Office of Pesticide Programs, and I would like to
14 add my welcome and my thanks to everybody that
15 Steve welcomed and thanked, including the SAP
16 Panel, certainly, and the staff of the SAP, Joe
17 Bailey, and the public, who are going to come
18 here -- who are coming here to observe and
19 comment.

20 Particularly to the Panel, we greatly
21 appreciate your time and efforts. Your feedback
22 is an important component of improving the

1 scientific foundation for our regulatory
2 decisions, and we're particularly appreciative of
3 your commitment this year, especially the
4 permanent Panel, as we've been working hard to
5 prepare for multiple SAP meetings on atrazine,
6 and we understand the large amount of material
7 you need to consider and we appreciate your
8 commitment to the high quality science.

9 I want to acknowledge a number of
10 people who have helped work -- are presenting
11 today and have worked -- or have worked behind
12 the scenes, the OPP team, first of all, Dr. Anna
13 Lowit, who is the overall lead for our atrazine
14 efforts, Dr. Elizabeth Mendez, Dr. John Liccione,
15 Dr. Marqueea King and Jessica Kidwell, among many
16 toxicologists in HED who reviewed close to 100
17 new atrazine studies.

18 I also want to thank, from the
19 Environmental Fate and Effects Division, Mary
20 Frankenberry and Nelson Thurman, and from the
21 Office of Water, Michael Messner. I don't know
22 if they're doctors or not, I'm sorry, if I've

1 cited somebody without giving the proper titles.

2 I should have stopped, and I'm just going to give
3 people's names from now on.

4 Nelson Thurman and Mary Frankenberry,
5 and perhaps, Michael Messner too, developed the
6 paper and will be presenting the drinking water
7 aspect of the meeting today.

8 I want, of course, to thank the Office
9 of Research and Development, our ORD team, Ralph
10 Cooper, Susan Laws, Tammy Stoker and Bob Luebke.
11 Both Ralph and Bob will be speaking today. Our
12 colleagues at ORD are vital to this ongoing
13 reevaluation and we truly appreciate their time
14 and talent.

15 As Steve said, the Agency signed the
16 RED for atrazine in 2003. The human health risk
17 assessment that supported the RED was based on
18 the best available science at that time.

19 The science which supports the
20 previous risk assessment, was reviewed by the SAP
21 on at least three occasions and we relied heavily
22 on your input to improve the science in our risk

1 assessments and to inform our decisions.

2 In this current year-long review, we
3 are conducting an objective and thorough review
4 of new science.

5 In this process, we continue to build
6 on our belief, that by understanding how a
7 chemical works in the body, its mode of action,
8 we can better interpret dose response data and
9 better understand life stage susceptibility, and
10 that factors that lead to susceptibility.

11 In this SAP, we will also discuss the
12 connection between atrazine's dosimetry revealed
13 by the toxicological analysis and its -- the
14 connection between this and potential exposure to
15 atrazine, as revealed by drinking water
16 monitoring.

17 We plan to use this information to
18 determine the frequency of water monitoring
19 necessary to ensure the continued protection of
20 public health.

21 As you will hear from the next
22 speakers, the literature review contained in our

1 draft issue paper represents a moment in time
2 with respect to the state of the science.

3 We are aware of important new studies,
4 which further elucidate the mode of action for
5 atrazine, that are not yet available for review.

6 We expect some of these studies to
7 become available, as we move toward preparing
8 materials for the September SAP. We believe
9 these new data will provide information to more
10 confidentially establish the causal links between
11 key events in the pathway to toxicity for the
12 hypothalamic-pituitary-adrenal axis and the dose
13 response of these key events.

14 Dr. Mendez will mention some of these
15 key ongoing studies in her presentation later
16 this afternoon.

17 So, I would like again, to thank you
18 all for your commitment and your efforts, on our
19 behalf. We look forward to your thoughtful
20 deliberations over the next few days, and I would
21 like to introduce our next speaker, Dr. Anna
22 Lowit.

1 DR. LOWIT: The large green button,
2 yes.

3 We're going to spend the next few days
4 talking about a lot of very detailed, very
5 technical, very sophisticated, very exciting
6 science, about some fairly diverse topics, from
7 drinking water statistics, all the way down to
8 hormone regulation, which on the surface, could
9 be -- you would not expect to talk about those
10 same things at the same meeting.

11 But what I wanted to do, before we get
12 into the technical presentations, is just take a
13 few minutes and sort of start from the beginning,
14 start from -- talk about where we need to be, how
15 we're getting there, and really, what the goal
16 is, over the next -- that we're in the middle of,
17 and we'll keep working.

18 The 2009 science and decisions report
19 from the NAS, one of the key messages in that
20 report is that the Agency needs to do a better
21 job at aligning risk assessment and risk
22 management, and specifically, putting more

1 emphasis on problem formulation, at the very
2 beginning of the process, beginning of analysis
3 for the risk assessors and risk managers, to sit
4 down and have very detailed dialogue about the
5 goal of the analysis, what the purpose is, what
6 the scope is, what the data available for
7 analysis is, and what the risk management
8 possibilities are, so that the risk assessors can
9 work with those possibilities in mind, to put
10 together a risk assessment that the risk managers
11 can use, to make them much more -- improve
12 utility.

13 In this example of what we're going to
14 talk about today, and what this atrazine effort
15 is really about, is exactly what the NAS wants us
16 to be doing.

17 It's about taking a risk management
18 need, which is drinking water monitoring, and
19 ensuring safe drinking water and aligning that
20 with a lot of very sophisticated science to get
21 there. That's exactly what we're going to talk
22 about.

1 So, the risk management goal here is
2 really to have safe drinking water, whether it's
3 all over the country or just in the Midwest. So,
4 we're going to talk about two major topics.

5 We're going to talk about hazard
6 assessments and the basic goals of hazard
7 assessment are to think about sensitive
8 populations and life stages, thinking about
9 durations of exposure and dose response
10 relationships.

11 In exposure assessment, we really want
12 to think about the residues in the drinking water
13 and how confident or uncertain we are about those
14 values, because the relative confidence and
15 uncertainty gets at how much monitoring we need
16 to be doing.

17 So, we're on a very long process, you
18 know, it's a very big process, it's accelerated.
19 We started the SAP process in February. Some of
20 you were at that meeting.

21 As Steve said, the report from that
22 meeting just came out a few days ago, and I would

1 say my first read of the report is that the
2 report is very consistent with what we heard of
3 the meeting, that the Panel was overall, very
4 supportive of the approach we're proposing, with
5 some very appropriate versions, I think, in fact,
6 they've already started making.

7 So, to the -- the meeting this week is
8 about thinking about animal toxicology, in vitro
9 toxicology and drinking water monitoring.

10 Originally, we had hoped in September,
11 to do a cancer/non-cancer harmonization, in a
12 weight of the evidence analysis, and to take that
13 and to merge it with drinking water and have a
14 new proposal, but as you heard from Dr. Bradbury,
15 our friends at the National Cancer Institute will
16 not have their studies from the Agricultural
17 Health Study ready in time for that. So, that's
18 been postponed. The cancer component has been
19 postponed to 2011.

20 However, we are maintaining the
21 schedule for September, on the non-cancer effects
22 and largely, as I said at the beginning, this is

1 really the rubber meets the road analysis. At
2 the end of the day, this is about drinking water
3 monitoring and is the drinking water adequate,
4 and largely we believe that that's going to be
5 driven by the non-cancer effects, as they tend to
6 be shorter duration.

7 The longer term cancer outcomes are
8 much longer in duration, which would be less
9 frequent monitoring.

10 Okay, so, a lot of what we're going to
11 talk about over the next few days is about the
12 hazard assessment component.

13 As you will hear from Dr. Mendez, this
14 is -- what we're going to talk about today and
15 what's in the Agency's issue paper is really a
16 snapshot in time.

17 People are doing atrazine work all
18 over the world, all over the country. People
19 that are in labs are continuing atrazine work.
20 It's really a snapshot in time, of where the
21 state of the science was at the end of January.

22 We know that between now and the

1 summer, there are going to be more studies, and
2 in fact, probably some important studies to think
3 about dose response and life stages, and Dr.
4 Mendez will talk to you about those later.

5 But our goal for September is to take
6 our current issue paper with the revisions that
7 we hear from all of you, the suggestions that we
8 get, the comments we get from the public, and to
9 blend in that new analysis with all the new data
10 and to do a formal weight of the evidence
11 analysis, like that we proposed back in February,
12 at the February meeting.

13 Where we will take the animal
14 toxicology data, the in vitro, the modeling, the
15 epidemiology and put it together in a mode of
16 action framework, to think about key events
17 leading to toxicity, dose response and temporal
18 concordance, do explicit evaluation of life
19 stages pre, post and perinatal effects, and we're
20 going to talk about human relevance of those
21 effects, that the qualitative and the
22 quantitative difference between the animals,

1 particularly rodents and humans, and all these
2 effects, and that's largely where the
3 epidemiology will come in.

4 On the exposure side, on the drinking
5 water, you will hear us talk almost exclusively
6 about drinking water, because that is the pathway
7 of concern for this chemical, and as we talk
8 about the rubber hitting the road, on this
9 analysis, it's the thinking about the duration,
10 the temporal aspects of the toxicology, that will
11 drive those frequencies, and there are a variety
12 of ways to think about this, single day peaks, or
13 you can do multiple day averages of any of
14 duration you choose, basically.

15 I believe we'll show some examples of
16 shorter ones, maybe three to seven days. The 90
17 day rolling average, it was done in the last 2003
18 risk assessment.

19 A large component of the drinking
20 water analysis has to do with really
21 understanding the confidence and the data, the
22 data that we have and the data that could be

1 collected if there was a different frequency.

2 It's important to think about it, both
3 temporally and spatially, and you'll hear Nelson
4 Thurman talking about that later.

5 You'll also see this map later.

6 Nelson will talk about it quite a bit in a little
7 while, but I think it's a nice illustration that,
8 as you look at the blue and the dark-blue and the
9 red areas, that the areas in the middle part of
10 the country, particularly those where large row
11 crops are grown, are really the areas where
12 levels of atrazine -- we're concerned about in
13 drinking water.

14 Okay, so, in light of the new science
15 that we'll talk about, particularly on the hazard
16 assessment, in the feedback we hear from you, the
17 feedback we get from the public, we're going to
18 do two things.

19 We're going to decide if a full-blown
20 risk assessment has to be done, and what that
21 means in practice is that right now, the focus is
22 on updating the literature review, deciding of

1 the points of departure, i.e., the line in the
2 sand where the assessment needs to move. The
3 uncertainty factors need to be changed. The
4 duration needs to be changed.

5 If one or all of those need to change,
6 based on the new science, we'll think about that,
7 if a new risk assessment needs to be done, and
8 we'll also decide if the drinking water
9 monitoring requirements for Syngenta need to be
10 changed, and that's all I've got.

11 SESSION CHAIR PORTIER: Before we go on
12 to Dr. Mendez's presentation, are there any
13 questions from the Panel, any clarifying
14 questions?

15 (No audible response.)

16 SESSION CHAIR PORTIER: Okay, we'll
17 move on. Dr. Mendez is going to be talking on
18 the human health effects.

19 DR. MENDEZ: Good afternoon. Before I
20 get started, I want to apologize. I started
21 coming down with a cold over the weekend. So, if
22 my voice breaks in and out, or if I start

1 coughing, I apologize for that.

2 So, the goal of this presentation is
3 really to give you a very brief overview of the
4 review of the mammalian toxicity data that's been
5 conducted, as part of this reevaluation.

6 I'm going to talk a little bit about
7 our peer review history. I'm going to talk a
8 little bit about the 2003 risk assessment, to put
9 this evaluation into context, and then talk a
10 little bit about the current reevaluation.

11 I'm going to defer the really
12 technical talks to our colleagues from the Office
13 of Research and Development, but I just wanted to
14 set the stage, so you know what's coming, over
15 the next few hours.

16 Atrazine is very widely used in the
17 United States. It's approximately 70 million
18 pounds of the active ingredient per year. It's
19 used primarily on corn. It has been registered
20 in the U.S. since the 1950s, and it has been the
21 subject of numerous SAPs over the years, both on
22 topics relating to human health and ecological

1 effects.

2 Today, what we'll be doing is, we'll
3 be concentrating on human health effects. Review
4 evaluation of ecological effects will be coming
5 in the next year.

6 All right, so, a little bit about the
7 peer review history. We had first review of the
8 rat mammary gland tumors. We were seeing tumors
9 in the Sprague Dawley rats and so, we came to the
10 SAP, the first time around, to talk about that.

11 The SAP, at that point, pointed to the
12 Agency, that we should consider the possibility
13 that there was an endocrine component to this,
14 and to try to further evaluate what the mode of
15 action for this might be.

16 Back in 2000, the SAP evaluated the
17 mode of action on mammary gland tumors,
18 reproductive and developmental findings in the
19 rat, and also weighed in on the human relevance.

20 In 2003, we had the evaluation of the
21 prostate cancer and the epi studies and the
22 relationship between atrazine exposure and

1 prostate cancer in workers at an atrazine
2 manufacturing plant, and as Dr. Lowit just
3 mentioned, in 2009, we had a very brief meeting
4 for the permanent members of the Panel, telling
5 you about our plans to re-open or to start the
6 evaluation of the atrazine human health effects
7 evaluation and in February 2010, we had -- we
8 presented to the Panel a draft framework for
9 incorporating epidemiology and human incident
10 data into the risk assessment using a couple of
11 epidemiology studies from atrazine as part of our
12 case studies.

13 So, very briefly, the 2003 human
14 health risk assessment, and the points of
15 departure for the 2003 risk assessment are based
16 primarily on our understanding of the mode of
17 action at the time, the perturbation of the
18 hypothalamic-pituitary-gonadal axis.

19 In 2003, there were a series of key
20 events that were identified, the hypothalamic
21 effects resulting in changes in catecholamine
22 function and regulation of the pulsatile release

1 of GnRH, leading to the attenuation of the LH
2 surge, sensation of ovulation with ensuing
3 persistent release of estrogen, increased
4 prolactin release of the pituitary as a secondary
5 consequence, resulting from the elevated estrogen
6 levels, and the prolactin in estrogen induced
7 proliferative processes in the mammary gland
8 leading to tumorigenesis.

9 So, basically, what the HPG axis
10 perturbation told us is, we had attenuation of
11 the LH surge, which led to our mammary gland
12 tumorigenesis that we were seeing in the rats, as
13 well as the delayed puberty onset.

14 When we came to the SAP back in 2000,
15 what their -- the recommendations of the Panel,
16 or what the input of the Panel was, that these
17 mammary tumors were not relevant for humans, and
18 the reason for that is that the processes that
19 lead to these tumorigenesis in the rats are very
20 different from what would happen in the human.

21 What we are seeing with the LH surge
22 is that we have a constant stimulate, with the

1 attenuation of the LH surge, is that we have a
2 constant stimulation of the mammary gland by the
3 elevated levels of estrogen and prolactin, and
4 that is what leads us to that mammary tumor
5 development.

6 In turn, in the humans, that's -- this
7 entire process of reproductive senescence, which
8 is what's happening in the rat, is not happening
9 in the humans.

10 However, the Panel also recognized
11 that these effects may be relevant to assess
12 potential non-cancer adverse reproductive effects
13 in the humans, and that's how our 2003 risk
14 assessment is based on.

15 So, these are the non-cancer effects.
16 The acute exposure, which for the Agency is one
17 day exposure, is based on delayed ossification in
18 rat fetuses and decreased body weight gain in
19 dams. We do not believe that that is the result
20 of the LH attenuation.

21 It has an NOAEL and an LOAEL of 10 and
22 70 milligrams per kilogram per day. These short

1 exposures are based on the delayed puberty onset
2 in males, with an NOAEL of 6.25 and LOAEL of 12.5
3 milligrams per kilogram, and the intermediate and
4 long-term exposures are based on the attenuation
5 of the luteinizing hormone surge.

6 Okay, so, our current analysis, what
7 are the objectives? And some of these, Dr. Lowit
8 had mentioned.

9 We wanted to conduct an objective and
10 thorough review of the new data, integrate new
11 information with existing data, to evaluate the
12 hazard ID and the dose response relationship,
13 determine the extent to which this new science
14 leads us to believe that we may need to develop a
15 new risk assessment, and reconsider, if
16 appropriate, the frequency of drinking water
17 monitoring conducted by Syngenta, with the
18 atrazine registrar.

19 The scope of the current analysis, we
20 restricted this analysis to mammalian toxicity
21 and in vitro studies. Three databases were
22 searched, EMBASE, PubMed and Medline, and we

1 actually cast a very wide net in an attempt to
2 collect all relevant information generated since
3 the IRED was signed in 2003.

4 A database query yielded close to 300
5 articles. However, some 200 were excluded
6 because either the studies were conducted on non-
7 mammalian species, the articles were commentaries
8 or letters to the editor, they were abstracts
9 that lacked sufficient detail in methods and
10 results, or they were topic reviews that did not
11 present original work, or they were epidemiology
12 studies that we will be looking at, as part of
13 our epidemiology data analyses.

14 In addition to all of that, we also --
15 of the peer reviewed articles, we've also
16 included some studies submitted by the atrazine
17 registrant, and those have been placed in the
18 docket.

19 So, now, to give you sort of an
20 "upcoming attractions". The presentations that
21 you will hear this afternoon, Dr. Ralph Cooper
22 will be speaking about the mode of action

1 analysis. Dr. Bob Luebke will be talking about
2 the immunotoxicity analysis. Dr. John Liccione
3 will be speaking about the neurotoxicity
4 analysis.

5 At the end of their presentations,
6 I'll be coming back to sort of give you a summary
7 of what that -- those analysis lead us.

8 Then, our colleagues from EFED and the
9 Office of Water will be coming in. Dr. Nelson
10 Thurman will be talking about a purchase to
11 evaluating water sampling strategies.

12 Dr. Mary Frankenberry will be talking
13 about evaluating the performance of sampling
14 strategies, and Dr. Michael Messner will be
15 speaking about artificial neural network
16 modeling, and one little bullet that's not
17 included there is, at the end of the day, Dr.
18 Lowit will come back and sort of, wrap mammalian
19 toxicology and the drinking water evaluations
20 together.

21 So, if there are no other questions,
22 I will turn the mic over to Dr. Cooper.

1 SESSION CHAIR PORTIER: Dr. Chambers?

2 DR. CHAMBERS: Let me clarify one thing
3 that you said there. On slide eight, you talk
4 about the NOAEL and the LOAEL for acute. You
5 really mean just one exposure, don't you, and not
6 per day? That wasn't an extended exposure under
7 acute, was it?

8 DR. MENDEZ: No, for acute, we assumed
9 one exposure.

10 DR. CHAMBERS: One, so, it's not per
11 day, just --

12 DR. MENDEZ: But it's from a study that
13 has multiple exposures. It's a developmental
14 toxicity study on the rat, where animals are
15 exposed -- parental animals, maternal animals,
16 are exposed, typically from gestation day six
17 through gestation day 21.

18 It is the Agency's policy that we
19 assume that developmental effects of that nature,
20 because of a rapidly changing environment during
21 development, may be the outcome of a single
22 exposure.

1 SESSION CHAIR PORTIER: Dr. LeBlanc?

2 DR. LeBLANC: In your discussion of the
3 literature review, you mentioned that non-
4 mammalian studies were not included, and I was
5 wondering, were they excluded, with respect to
6 evaluating mode of action?

7 DR. MENDEZ: Well, we looked at them
8 briefly, but they were not -- to the extent that
9 they did inform the data, we considered them.
10 But primarily, we were trying to concentrate on
11 the mammalian toxicity.

12 SESSION CHAIR PORTIER: Okay, let's
13 move on to Dr. Cooper, who will be talking on the
14 MOA of atrazine.

15 DR. COOPER: Thanks, Liz and Anna. My
16 presentation this afternoon is divided into,
17 essentially, three parts, where again, this time,
18 I'm going to do a little historical review of
19 what we considered the mode of action, back in
20 2003, that atrazine alters the hypothalamic-
21 pituitary-gonadal axis, and do a more pictorial
22 than Liz did, but with some added details that I

1 think will help us interpret some of the more
2 recent findings.

3 The second part of this presentation
4 will look at the rationale and studies that we've
5 been looking at over the last several years,
6 indicating that atrazine may have an effect on
7 the hypothalamic-pituitary-adrenal axis, clearly
8 showing an activation of that axis, and trying to
9 fit that into the mode of action and then, the
10 last part is a brief attempt to do some synthesis
11 with the effects that we've observed and that
12 literature has reported of both these different
13 regulatory systems.

14 I put some background slides in here,
15 just to get everyone on the same track. This is
16 the way we look at the estrous cycle in the
17 female rat.

18 Most of the studies, I'll talk about
19 in the adult animal are in the female, and the
20 regulation of the LH surge, of course, was the
21 key event, endocrine event, that was used for
22 interpreting the mode of action, back in the last

1 Science Advisory meeting.

2 The rat has a four-day reproductive
3 cycle, four-to-five-day reproductive cycle that's
4 readily identifiable and measured by just simply
5 following the vaginal smear of the animals and
6 see if distinct changes take place over the
7 course of those four or five days.

8 The key day is, to us -- the
9 endocrinologically key day, anyway, is the day of
10 vaginal proestrus, which is right here, and I've
11 got in cartoon fashion, the indication that what
12 happens on that day is in response to rising
13 levels of estrogen and subsequently, increases in
14 serum progesterone, coming from the ovary and
15 perhaps, the adrenal gland, there is a triggering
16 of a massive outpouring of luteinizing hormone
17 from the pituitary gland that occurs at a very
18 distinct time on the afternoon, approximate --
19 and peaks approximately two hours before dark.

20 That event is what then leads to
21 ovulation and over the evening hours, the animal
22 is sexually receptive. So, the timing of

1 ovulation synchronized with the behavior of the
2 animal.

3 Because the rats are spontaneous
4 ovulators, there's a lot of homology between the
5 neuroendocrine regulation of the rodent
6 reproductive cycle, ovarian cycle, and the human.

7 This is another cartoon of how we see
8 the different parts, and again, to address the
9 mode of action of the HPG, I have the rat brain,
10 the hypothalamic, the hypothalamus, which is the
11 origin of the -- the neuropeptide is secreted
12 from the brain, through the portal system that
13 bathes the interior pituitary gland, GnRH
14 stimulates luteinizing hormone, luteinizing
15 hormone then stimulates the maturing follicle to
16 rupture.

17 Part of this whole system is that you
18 have other hormones, FSH and prolactin. We've
19 shown in the past that prolactin also appears to
20 be a target of atrazine disturbances, and then
21 this whole process involves feedback from the
22 ovary itself, the steroid hormones estrogen and

1 progesterone, feeding back onto the brain, to
2 further regulate -- regulate regulation and
3 reproduction and behavior.

4 This is the kind of data that you see
5 when you measure luteinizing hormone on the
6 vaginal proestrus.

7 This particular slide was taken from
8 a series of studies that we did, looking at the
9 intact female that was dosed with what I guess
10 now, we can -- based on the earlier work,
11 relatively low doses of atrazine, where we sought
12 to find a low LOAEL and NOAEL for this compound
13 in the intact animal, and you can see a dose-
14 dependent decrease in luteinizing hormone
15 occurring on the afternoon of proestrus at 1800
16 hours, which as I mentioned, was approximately --
17 is two hours prior to the time lights are out in
18 these studies, and that was the only time that
19 you see the suppression and importantly, the
20 suppression of the surge isn't a complete
21 blockade of the surge. It's lowered in a dose
22 response fashion. But these animals may, at this

1 time, since they're young adults, still be able
2 to ovulate.

3 Again, by way of background, these are
4 data taken from an earlier study that we did,
5 showing that atrazine did block the LH surge, in
6 two different strains of animals, the Long-Evans
7 and the Sprague Dawley rat.

8 This first slide makes the point that
9 in the Long-Evans rat, if we dose one day with
10 increasing concentrations of atrazine, this is
11 all by gavage, you can see that a single exposure
12 really doesn't do a whole lot to the secretion of
13 LH.

14 What I have here is the dose response
15 on the side. These are animals that received the
16 different doses at 16, 18 and an hour before and
17 an hour after lights out, and even up to 200
18 milligrams per kilogram per day, we're still
19 getting an LH surge in the animals, to 300. You
20 seem to see suppression.

21 If we dose those animals, however, for
22 three days in a row, you see a dramatic decrease

1 in the amount of LH that's secreted, the control
2 animals here, being in the open bars and the
3 different doses you see there.

4 There was the lower dose, an apparent
5 delay in the peak, where it occurred at 2000
6 hours, an hour after lights out, and I should add
7 that other work we've done showed that those
8 higher doses, those animals don't peak, even if
9 you test them or evaluate them later on, in the
10 dark phase of the cycle.

11 If you look at that figure on the
12 right, the three day dosing in the Long-Evans
13 rat, it brings up another interesting thing.

14 First, of course, the main point I
15 wanted to make with this slide, is that as the
16 duration of the dosing increases, the effect that
17 the -- the effective dose decreases.

18 But the other point was that when you
19 compare strains, three days later, there's --
20 we've ran Sprague Dawley rats in the exact same
21 study that you're reviewing here with Long-Evans,
22 and you'll see that when you look at those

1 animals, which I have plotted on the right figure
2 over here, there was still no effect in the
3 Sprague Dawleys, even after three days of dosing.

4 These are ovariectomized, estrogen-
5 primed animals, given the compound for three
6 days, whereas the Long-Evans were affected at
7 three days, the Spragues kept a pretty good size
8 LH surge.

9 However, if we continued dosing both
10 strains for a longer period of time, then
11 eventually, you would see that this compound had
12 an effect on the peak amplitude in all the
13 different doses in both strains, and the way this
14 works is that over here on the right panel, when
15 we dose for 21 days, we only looked at 1800
16 hours. We're pretty convinced that at those
17 doses, we'd see the peak there.

18 So, these are animals that were killed
19 at that time, control animals at 1800 in both
20 strains, and then you dose response down.

21 So, again, the longer the duration of
22 dosing, the more effective the dose would be.

1 Another series of studies that we did
2 back in 2000, were to look at whether or not the
3 disruption of the LH surge was dependent upon
4 changes that were occurring in the brain or the
5 pituitary or the broader axis itself, and in
6 those studies, we took apart the system,
7 essentially.

8 First, ovariectomized the animals,
9 thus removed the ovary. We still saw effects on
10 the LH, so we sort of thought we were ruling out
11 the ovary at that time.

12 Other studies we did is, we took the
13 pituitary out of the animal, that was dosed, and
14 looked at whether or not it could still release
15 luteinizing hormone the same way control animals
16 would do, and what you have here is a perfusion
17 system, where the animal's pituitaries were
18 placed in a bath where the medium was flowed over
19 the tissue for a period of time, went to
20 baseline, and then we dosed with gonadotropin-
21 releasing hormone, which is the peptide that
22 normally stimulates luteinizing hormone.

1 Pulsed it once, saw a response, pulsed
2 it again, pulsed it -- I'm sorry, then we looked
3 at KCL, but the point is, is that there was no
4 difference there, which indicated to us that
5 these pituitaries taken out of animals that were
6 dosed for four days, were perfectly capable of
7 responding to the natural releasing factor.

8 Another study that was done by Dr. Lee
9 Tyrey, who was a visiting professor from Duke
10 OB/GYN, working in our lab, looked at the
11 pulsatile release of GnRH and here, what we have
12 is a 28 day ovariectomized animal who will start
13 to spontaneously surge -- show LH pulses that
14 occur at a frequency of about two per hour, and
15 in the control animals -- and these are mean
16 data, so they're not really as pretty as what we
17 really had, but he puts it together through a
18 program, and can show you the means.

19 But control animals, you'll see these
20 pulses, which reflects the activity of the GnRH
21 neurons in the brain. We can measure the LH and
22 every pulse of LH is reflective of increased

1 activity in GnRH.

2 When we increase -- expose the animals
3 to 50 or 200 milligrams per kilogram -- I can't
4 read that, I hope it's 200 -- 50 and a higher
5 dose, from my eyes, I'm sorry, immediately prior
6 to this time, you can see that the 50 had a
7 little disruptive effect, but with the pulsar
8 analysis that they did, we didn't see any real
9 statistical difference, but that higher dose
10 totally flattened out the pulses.

11 What this meant to us is that
12 atrazine, in some way, was disrupting the brain's
13 control of the release of the hormone itself.

14 The next study, or in another study,
15 later on, in the same series of studies, where we
16 were looking at the intact animal, we measured
17 the amount of GnRH in the basal part of the
18 brain, where the neurons -- or the basal part of
19 the brain, where you have gonadotropin releasing
20 hormone neurons, and we saw that the
21 concentration of GnRH tended to go up in the
22 atrazine-treated animals, which would be

1 consistent, again, changes in the brain occurring
2 and would be consistent with the decreased pulses
3 that we saw when we looked at them in the longer
4 ovariectomized model.

5 And then finally, we did a study where
6 we blocked the LH surge in ovariectomized animals
7 with a very high dose of atrazine and went in and
8 injected IV gonadotropin releasing hormone, and
9 it showed that the pituitary was perfectly
10 capable of responding to the neuropeptide, again.

11 So, these kinds of things told us that
12 it appears as though atrazine was working on the
13 central nervous system to disturb the pulsatile
14 release of GnRH, and I haven't showed it,
15 prolactin release, and in that way, we thought
16 that it was disrupting the ability of the animal
17 to maintain normal ovarian cycles.

18 Another key point, and again, Liz may
19 have touched on it, was, what's actually
20 happening is that as we dose these animals, we
21 were lowering the LH surge and, in a way, that
22 was analogous to what you see during the aging

1 process of the animal.

2 Normally, the female rat, under a
3 four-day cycle, has an abundance of LH secreted
4 between -- just prior to time of lights out. But
5 actually, to get ovulation, you only need a small
6 amount of that.

7 Back with the old reference prep, it
8 was about 2,500 nanograms per mL for a peak, and
9 the people that work showed that you only needed
10 about 200, or less than a tenth of the LH, to
11 actually cause ovulation, which used to lead them
12 to speculate what the rest of that LH is doing.

13 But as the animal ages normally, or if
14 the animal is treated with atrazine, sufficient
15 doses, what happens to the LH secretion is that
16 the peak lowers and actually, the onset of the
17 surge occurs a little bit later, sort of like
18 what we saw with that 50 milligram per kilogram
19 dose.

20 It can still cycle, again, because
21 just like those animals I showed, even though
22 they're statistically bound, they can still

1 function to cause ovulation.

2 As the animal continues to age
3 further, it goes below that threshold. The
4 animal doesn't ovulate anymore, which I show up
5 here in this picture that everyone loves, my
6 symbol for ovulation. Those animal's eggs are
7 retained in the follicles and those follicles are
8 secreting estradiol only into the serum, but not
9 progesterone.

10 Another thing that happens, and again,
11 as Liz mentioned, because of that increased
12 estradiol, you end up with diurnal and a
13 nocturnal peak of prolactin being secreted.

14 So, you have an endocrine milieu,
15 that's totally out of bounds with what it should
16 be, and the hypothesis that we worked with on
17 that MOA was that atrazine, like aging, causes a
18 decrease in this LH surge, which leads to an
19 early reproductive aging in the animals, and when
20 the animals show the persistent or constant
21 estrus then, it will lead to the early appearance
22 of mammary gland tumors.

1 So, again, that's just it, in bullet
2 form. And the summary is that atrazine disrupts
3 hypothalamic control of gonadal function and it
4 contributes to early reproductive senescence,
5 producing that hormonal environment, and again, a
6 key point is, it's well known that reproductive
7 aging in the rat, as I have up there, is driven
8 by brain.

9 We could argue that. I know the work
10 of Tuck Finch and Brower argue that ultimately,
11 it's the amount of estrogen that that brain sees
12 over its lifetime, but really, the events taking
13 place within the central nervous system are
14 what's disrupting the ability of the animal to
15 produce the LH surge and it still has plenty of
16 follicles left in its ovary, so that when the
17 ovary stops cycling, there's lots of estradiol
18 that's put out there into the blood.

19 Reproductive aging in the human is
20 quite different. It's apparently driven by a
21 depletion of the follicles in the ovaries.

22 In turn, you have a situation where

1 with aging, you have a relatively low
2 concentration of estradiol and different
3 endocrine milieu altogether.

4 So, that's where the Agency concluded
5 that the mode of action for mammary gland tumors
6 in the rat was not relevant to, or would be
7 predictive of anything that would happen in
8 humans.

9 But what happened in those studies,
10 when we were doing that work, was, a number of
11 different outcomes showed that there were clear
12 other relevant reproductive effects that were
13 occurring when the animals were dosed with
14 estradiol.

15 Some of those are briefly mentioned
16 here, and we talk about different life stages and
17 that kind of thing. This is part of what was
18 driving some of that.

19 Atrazine will delay puberty in
20 animals. There was a study done by Tammy Stoker
21 and Susan Laws, in the male and female rats,
22 respectively. Those studies were replicated by

1 other laboratories. Those studies were -- or
2 similar studies were conducted with the
3 validation of the pubertal assays in the -- for
4 the endocrine disrupting screening program.

5 So, it was a robust effect that was
6 repeatable, that delayed puberty does occur when
7 you dose animals with atrazine.

8 Other adverse outcomes -- and we know
9 the toxicity pathways for some of these were
10 prostate -- prostatitis, if the dam is dosed
11 during specific developmental periods.

12 We know the disruption of ovarian
13 cycles occur, and I should mention that the
14 registrant did a very nice study, looking at the
15 age-dependent changes in ovarian cycle, or
16 estrous cycles in the rat and again, showed that
17 the reproductive cycle does decrease earlier. It
18 wasn't just a hypothesis, that in fact, these
19 things occur.

20 And more recently, there's been a
21 number of studies looking at testosterone
22 synthesis that I think again, are going to become

1 -- maybe, we can interpret them easier, once we
2 understand what's going on with the adrenal axis,
3 but I think -- in the background paper that you
4 received, I think there was four or five studies
5 that have been published in different strains of
6 animals, saying that atrazine, for an extended
7 period of time, relatively high doses, will
8 impair testosterone synthesis in the developing -
9 - most of the studies, in the developing male
10 rat.

11 So, again, where we were with the 2003
12 SAP, there was general agreement that this
13 pesticide or herbicide was working through a
14 disruption of CNS-mediated decrease in LH and
15 that was the relevant mode of action, and the key
16 event in this whole process was a decrease in
17 luteinizing hormone that contributed to those
18 adverse outcomes, of course, with the exception
19 of the prostatitis studies, which were linked
20 more with changes in prolactin availability.

21 That's what the considered mode of
22 action was, but yet, there were still some

1 nagging questions that existed, at least, in my
2 mind. One of them was that delay.

3 When you dose animals and you disrupt
4 the LH surge, we've worked with a number of
5 different environmental chemicals, and you do
6 this, usually, it's a very -- if it's working
7 through the brain, it's a very rapid, almost --
8 you know, within hours kind of effect that you
9 see, and that business where we saw, it took
10 several days to start to see, there is this
11 trade-off between dose and time that tended to
12 have an effect on the LH surge, always was kind
13 of intriguing to me, and I -- I just couldn't put
14 together what it was that was responsible for
15 that.

16 Secondly, in Dr. Stoker's study, where
17 she looked at everything that she could get her
18 hands on in the pubertal male, she looked at the
19 concentrations of estradiol that were present in
20 those animals, and found a significant increase
21 in the serum estradiol in the males treated for
22 21 days. That's peripubertally. They start the

1 treatment on PMD-21 and kill on PMD-42.

2 Susan Laws -- we asked the question
3 whether or not that was true in adult animals as
4 well, because you really see, at the right dose
5 of atrazine, an increase in estrone and estradiol
6 in these animals, and Susan Laws replicated that
7 study here, with only a four-day exposure.

8 And what she found was an increase in
9 both those estrogens, in both the developing
10 animal and in the adult, and you know, a high
11 dose and -- it was something that we, you know,
12 really didn't know what to make of, at the time.

13 But, at that time, there were a number
14 of other studies reported, either in vitro or in
15 vivo, looking at atrazine and the enzyme
16 aromatase, which was the enzyme that's
17 responsible for the production of estrogens from
18 androgens.

19 So, that led us to look at little more
20 closely at what might be going on, both in vitro
21 and in vivo, with aromatase and estrogen, and
22 whether or not that might be part of some of this

1 -- something that we missed, in terms of the mode
2 of action.

3 So, at that time, because of the in
4 vitro studies, we were looking at -- we were
5 looking at aromatase or one of the cytochrome
6 P450s, which converts the androgens to estrogens.

7 Aromatase is present in a number of
8 different tissues in the body, some there
9 listed, the brain, the gonads, fat and placenta.
10 In the brain, it's responsible or plays a key
11 role in sexual differentiation of the rodent
12 brain.

13 Its regulation is different in the
14 different tissues looked at. You have different
15 promoters and other regulatory factors that are
16 involved, whether you look in the ovaries or the
17 placenta or the breast, and then there is
18 alterations in -- it's been shown that
19 alterations in gene expression that disrupt the
20 estrogen availability are going to eventually
21 impact not only reproductive development, but a
22 lot of other normal functioning of different

1 tissues.

2 So what we want to do over the next
3 few slides is to review the evidence that
4 atrazine does alter aromatase activity, both in
5 vivo and in vitro, and I think set the stage for
6 why a lot of the things that we're looking at, if
7 we stick with this one enzyme, wasn't really
8 necessarily making sense, that we may have to
9 broaden our scope of investigation a little bit
10 bigger, to look at the whole process of
11 steroidogenesis.

12 This is the study, including --
13 actually, the second in a series of studies by
14 Thomas Sanderson, that -- looking at the
15 chlorotriazines, and put everyone onto the idea
16 that atrazine and its metabolites might be
17 affecting the production of estrogens, and what
18 Sanderson did is he used this cell-line up here,
19 the H295R human adrenal carcinoma cell-line,
20 which is kind of a neat and unique cell-line
21 because it possesses all the key enzymes, P450s
22 that are necessary to produce a number of

1 different steroids, right on out to estradiol.

2 So, it does contain aromatase.

3 What Sanderson showed was that at, you
4 know, fairly decent concentrations, around three
5 micromolars -- decent, I'm saying compared to
6 what some of the studies I've seen in the
7 literature show, around three micromolars, you
8 start to see an increase in what he termed the
9 activity of that enzyme.

10 You saw an increase in the production
11 of either tritiated water or the estrone itself,
12 if -- in those cells.

13 But what was also interesting is that
14 he found that only atrazine, the two intermediate
15 metabolites that I call them, that's isopropyl
16 and desethylatrazine, increased aromatase
17 activity.

18 Sanderson also looked at the ability
19 of atrazine to change the message in these cells
20 and reported that there was a modest twofold
21 increase in the message, along with that,
22 indicating that exposure to these compounds, to

1 these three metabolites, anyway, could increase
2 the overall production of estrogens. And
3 importantly, and we'll come back to it in a
4 moment, DACT had no effect on these endpoints,
5 and that's the one there in the square blocks, in
6 red, if you can see it.

7 So that's the -- one of the -- if you
8 look in the blood of the rat, anyway, that's one
9 of the really prominent metabolites, that that
10 had no real effect on aromatase activity in this
11 -- in the H295Rs, and one of his colleagues
12 replicated these studies, looking at the JEG
13 cells.

14 What that did for a time was put a lot
15 of focus on aromatase itself. The light was
16 shining there, and a number of different studies,
17 looking at changes in estrogen production, all
18 came to the conclusion that you could see
19 increased estrogen synthesis, and again, this
20 cell-line was used for the validation of some of
21 the in vitro tests, and I think nine labs
22 replicated the effects of atrazine on aromatase,

1 so -- or, the production of estrogens.

2 But one of the interesting things that
3 we found was that in addition to just estradiol
4 alone or estrone alone in there, you could see
5 increases in other hormones, and recently, a
6 paper published by Higley said that not only does
7 atrazine increase estradiol or estrone, depending
8 on what you're measuring, it also increases
9 testosterone.

10 And in our own lab and others have
11 also shown that some of these other earlier
12 steroids in that pathway are increased when you
13 stimulate with atrazine, or certain of the
14 atrazine metabolites, which suggested to us that
15 it's not just aromatase that is the target here,
16 but in fact, increased steroidogenesis might be
17 really what the whole series of changes that are
18 taking place is.

19 There are some other studies focusing
20 on SF-1, as a target site for this SF-1, as a co-
21 factor involved in the regulation of aromatase.
22 Others have said that that's not necessarily the

1 case. You may see changes in SF-1, but in fact,
2 that's not necessarily the only target, that in
3 fact, you do see a broader increase in a number -
4 - activity of a number of different signaling
5 pathways, and that's what these different studies
6 down here show, and again, these are in the
7 background document.

8 But the point is, is that in addition
9 to aromatase per se, there is this overall effect
10 on steroidogenesis that seems to be the "mode of
11 action" within the cell. We're not sure exactly
12 what all the molecular events are.

13 There is an argument that put forth,
14 actually earlier on, by Sanderson, that atrazine,
15 in some way, increases cyclic AMP activity,
16 perhaps through a decrease in phosphodiesterase.
17 That's something that can be -- has been
18 substantiated by other labs, but the papers
19 aren't published yet.

20 There is a study that I just read,
21 where they block protein kinase activity and that
22 reversed the effects of atrazine on the

1 activation of steroidogenesis in Leydig cells.

2 So, that paper is going to be out
3 shortly, so I guess it's okay if I tip my hat on
4 that one, but the point is again, somewhere
5 upstream, a broader effect on signal transduction
6 seems to be the cellular toxicity pathway and
7 that the aromatase per se is not necessarily the
8 sole target for these chemicals.

9 In vivo, again, as I mentioned, we
10 were interested in whether or not atrazine can
11 affect aromatase in vivo.

12 Walter Modic, who was a student with
13 Dr. Laws' lab, did a series of studies looking at
14 male rats to see if he could identify changes in
15 aromatase activity or the message for aromatase,
16 after being treated with atrazine at relatively
17 high doses for -- in several different ways, and
18 to make a long story short, it's nice to have a
19 lot of slides, but when you get no effects, you
20 end up with a slide like this that says, "Yes,
21 you can induce increases in serum-estrone and
22 estradiol in the male rat."

1 This is a different study that we did,
2 showing that in the ovariectomized female, you
3 can see increases in estrone activity at
4 relatively high doses of atrazine, but nowhere
5 was there -- were they able to identify changes
6 in aromatase, either looking at microsomes taken
7 from testes of animals treated, or, could they
8 see changes in the message, looking in brain
9 testes or adipose tissue.

10 So, it just -- if it's there, it's
11 real difficult to find any specific change in
12 aromatase activity.

13 This summarizes that series of
14 studies, so we still have increases in those
15 hormones. It increases the estrogens. There was
16 little or no evidence to support the idea that it
17 was working specifically through aromatase,
18 either increasing the activity or the message.

19 What we had, and I don't want to get
20 into it, because there's a lot of controversy
21 over whether or not the adrenal hormones can
22 produce -- the rodent adrenals can produce

1 androgens, such as androstenedione, and this
2 literature is -- depends on which side you want
3 to take, but the point is, is that these animals
4 did have increases of estrogen in them, and we
5 were thinking that perhaps one of the sources of
6 this was from the adrenal gland.

7 And that led us to ask the question
8 whether or not atrazine might have some kind of
9 direct effect on adrenal steroidogenesis.

10 Here it is, 2007, and we've been
11 looking at this for all this time and it seemed a
12 little odd that no one else would have reported
13 that.

14 There were dribbles and drabs in the
15 literature and there was a couple of elegant
16 studies by Dr. Pruett's lab, that said in mice,
17 at the time, that atrazine does increase
18 steroidogenesis from the adrenals.

19 So, we decided to look into this axis,
20 arguing about whether or not the adrenal hormone
21 secretion would be altered by atrazine, whether
22 or not that effect would occur because of some

1 kind of central targeting of the compound or
2 whether or not the adrenals may actually be
3 targets themselves, since we know in vitro, there
4 were effects on steroidogenesis.

5 So, Susan Laws published this study,
6 some time late last year, demonstrating that
7 there is really a clear effect of atrazine on
8 both ACTH secretion and corticosteroidal -- or I
9 should say ACTH secretion and a number of
10 different adrenal steroids, and this is from that
11 paper, where she gave doses ranging from five to
12 200 milligrams per kilogram orally, and looked at
13 the production of atrazine -- I'm sorry, the
14 production of ACTH and corticosterone at
15 different doses.

16 And I should just mention here that
17 these animals are all dosed for five days prior
18 to testing. They're dosed with the vehicle
19 carboxymethyl cellulose, that they're all dosed
20 at the same time of day, at the nadir, I think
21 it's nine o'clock in this study, when the
22 concentrations of corticosterone and ACTH are

1 low, and so, when you look at the control animals
2 there, the actual dosing procedure itself seemed
3 to have minimal effects on the secretion of ACTH
4 or corticosterone, which speaks well for the
5 ability of that lab to conduct these studies.

6 But what happens is, as you increase
7 that dose though, there is a clear increase in
8 both ACTH and corticosterone, as well as
9 progesterone and we're -- I'm pretty confident
10 that this is adrenal-derived progesterone.

11 It's in male rats, and if you look at
12 the testosterone that's being secreted, this is
13 probably from -- or more than likely from the
14 test, as you can see a significant increase
15 there, as well. The time course is a little
16 later. The dose required is a little higher.

17 Another important thing that Susan
18 found was that when you dose with DACT, you saw
19 no comparable increase in ACTH or corticosterone,
20 which was sort of like what Sanderson had
21 reported for the H295R cells.

22 Now, for some reason, that particular

1 metabolite of atrazine wasn't active, in terms of
2 increasing the adrenal axis, and I have their
3 DACT and ACT and atrazine on the right side, just
4 so you can compare, there were significant
5 changes, if you, as Liz likes to say, worship at
6 the altar of the star, but I don't think they
7 were really as dramatic as what you see over here
8 with atrazine.

9 And the other thing is that the timing
10 there, I don't think there was a delayed response
11 in that, but again, nothing like what you see
12 with the parent compound itself.

13 Another thing that Melanie Fraites is
14 working on in our lab, did, was a series of
15 studies to further get at whether or not this was
16 a chemically specific activation of the pituitary
17 adrenal axis or it was still some artifact that
18 we were introducing, that we didn't know about,
19 and we thought every -- tried to think of
20 everything that we could to get at that, but up
21 to this point, what we've done so far is, Melanie
22 has shown that if you do things like cut the

1 vagus nerve, it doesn't interfere with it.

2 So, it didn't look like atrazine was
3 getting down into the gut and causing some type
4 of intestinal distress that was going to feed
5 back.

6 There didn't seem to be any change in
7 some of the endocrine components of feedback from
8 the gut to the brain, and I think, to me, anyway,
9 one of the most convincing things that you can
10 get around the -- any signals from the gut being
11 the cause -- the root-cause for this increase in
12 ACTH, is her observation that you can get the
13 same response if you give the chemical IV.

14 So here, you have an animal that's
15 sitting there with an in-dwelling catheter, you
16 dose with atrazine and you see the same immediate
17 15-minute increase in atrazine -- I mean, in ACTH
18 and corticosterone.

19 Another thing that Dr. Laws did was
20 look at not only atrazine in DACT, but the other
21 two intermediate metabolites, not shown here, is
22 DEA, but both atrazine and DIA do cause the same

1 type of adrenal response.

2 In this case, I think it's important
3 to note that the LOEL for that study was 10
4 milligrams per kilograms, which is the equimolar
5 dose to 12 and a half milligrams per kilogram of
6 atrazine, and the other interesting thing in this
7 study was, it wouldn't go away.

8 The increase in corticosterone -- now,
9 she only measured corticosterone in these
10 animals. She didn't measure ACTH here, but in
11 these animals, that response persisted. It was
12 there at the higher dose at four days and even
13 out to 21 days, there was a significant elevation
14 of corticosterone.

15 And this is something that was
16 indicated in the female, in a study by Dr.
17 Fraites, who showed that one dose of atrazine --
18 again, in this case, she used 75 equimolar dose
19 of DIA, caused an increase in both ACTH and in
20 corticosterone, but then, if she dosed for four
21 days, an interesting pattern was present there,
22 that we're still working on, in terms of

1 interpreting it.

2 But if you look at this, this is a
3 single dose, and this is ACTH. The green here,
4 the darker green, is the same animals. This is
5 one dose; this is four doses. These are intact
6 animals that are dosed on the day of vaginal
7 estrus, diestrus one, diestrus two and the
8 morning of proestrus, and they're killed 15
9 minutes after dosing. So, that response, that
10 ACTH response there is markedly attenuated.

11 But if you look at the cort response
12 in these animals, it's almost the same as it was
13 on the first day. That's what you see when you
14 restraint-stress the animals.

15 So, it's a response that's seen, at
16 least in this case, to persist, and the other
17 thing is, in these animals, I wanted to point it
18 out, was that when she dosed with both DIA and
19 atrazine, that lower dose is 12 and a half
20 milligrams per kilogram, or 10 milligrams, the
21 equimolar dose for DIA, and again, there was no
22 real clear effect with this on -- with that. It

1 didn't change the adrenal axis.

2 And in those animals -- or in another
3 population of animals treated the same way, she
4 looked at the LH surge and showed that again, as
5 we showed, I think, on the first slide, that
6 there is a decrease in the LH in the afternoon at
7 the same dose as the 12 and a half milligrams per
8 kilogram for atrazine and the 10 milligrams for
9 DIA.

10 There was a suppression of the surge
11 with DACT. It wasn't significant in this figure;
12 it was significant in others. The point is, is
13 that DACT, I think you can get an effect, but you
14 have to go longer and higher, to see inhibition
15 of the surge, or a suppression.

16 So, in summary, in this series of
17 studies in the male, both ACTH and adrenal
18 steroid hormone production increased within -- as
19 early as 15 minutes following a single injection
20 of atrazine and DIA and DEA.

21 The dose response for the male study,
22 at the moment, with that data that Dr. Laws had,

1 the lowest dose was five. Her next highest was
2 50. So, it was somewhere between 50 and five,
3 but the LOEL that she found for DIA was at 10
4 milligrams per kilogram.

5 Compared to atrazine and DIA, the
6 increases in ACTH and the adrenal steroid
7 hormones is markedly less when you dose with DACT
8 in equimolar doses.

9 That, in the male, corticosterone
10 release was sustained for up to three weeks and
11 in the female, we only went out to four days, we
12 started to see a decline in the amount of ACTH
13 secreted in those animals, suggesting, again,
14 that there may be some direct effect of atrazine
15 on the pituitary gland itself, in addition to
16 that major increase in corticosterone release, in
17 response to ACTH after the first injection.

18 And again in the female, we have a low
19 or no NOEL, of 12 and a half milligrams there,
20 and it's important that I mention this, and we
21 just only have -- I'm already going on too long,
22 but atrazine also induces comparable changes in

1 adrenal progesterone secretion in the female.

2 Take the female's ovary out, you can see --
3 unmask those kinds of effects that are
4 significant, both at one and four days of
5 exposure.

6 Comparing those effects with what you
7 saw, and I'm going back to what we saw with the
8 effects on the LH surge, either in the
9 ovariectomized estrogen-primed animal or in the
10 intact animal, what we found was that in those
11 earlier studies, which is the first three bullets
12 there, with different LOELs, you have a single
13 dose. You needed more than 200.

14 With three doses, we dropped it down
15 to 50 and in an intact animal, we could get it
16 down even lower.

17 It still indicated that you needed a
18 number of days to see an effect on the surge, and
19 we did a lot of studies early on, looking only on
20 the day of vaginal proestrus, trying to either
21 block ovulation or decrease the amplitude or
22 timing of the -- often, the timing of the LH

1 surge, and we couldn't get anything, again, with
2 a single dose up to 200, and if we gave 300, the
3 animals went pseudo-pregnant on us. So they were
4 still ovulating, apparently, or appeared to be
5 ovulating.

6 So, the timing of this and the fact
7 that you see these instantaneous changes in the
8 pituitary adrenal axis, and given the literature,
9 arguing that the adrenal axis is involved in --
10 or could be, if there is hyperactivity in the
11 adrenal axis, could be involved in the disruption
12 of LH, it suggested to us that we see changes
13 that precede and may likely contribute to the
14 disruption of the LH surge.

15 And so, that's what I tried to put
16 together on this figure, where we have our
17 hypothalamic-pituitary-gonadal axis, wherein we
18 know that, time and again, people have published
19 that when you expose in vivo to atrazine, you get
20 a decrease in the amplitude of LH, you end up
21 with, eventually, acyclic animals and the
22 disruption of reproduction.

1 I have over here, the adrenal axis,
2 where we know that -- and we're not clear,
3 exactly whether or not -- obviously, I think,
4 there's got to be a central effect, either
5 hypothalamus or pituitary, given the rapid
6 response that you see with AC -- and the response
7 that you see with ACTH.

8 However, you see that sustained
9 response in the adrenal. Whether that's due to
10 direct effect of atrazine on the adrenal in vivo,
11 we don't know, but I'd bet a dollar that you'd
12 see it in the primary adrenal cells. And, given
13 that effect and the speed with which we saw that
14 and the timing for the pituitary effects, and the
15 rich literature on this stuff, it argues that one
16 of the primary effectors in -- or one of the
17 events responsible for the decrease of the LH
18 surge, may be that feedback of the adrenal
19 steroids onto the brain and pituitary and the
20 ability of it to regulate the LH surge.

21 Another thing that I think this kind
22 of conceptual framework argues is that, if you

1 look at the high dose 21-day exposure of male
2 studies, that seem to be popping up in the
3 literature time and again, that that decrease in
4 testosterone, in the gonads of the males exposed,
5 that that effect may be due to a direct action of
6 corticosterone on the Leydig cells.

7 Again, there is a literature, quite a
8 strong literature, that shows that Leydig cells
9 do have glucocorticoid receptors and when
10 activated, and they're regulated by a -- a
11 process within the Leydig cell itself.

12 But when there's over-stimulation of
13 those glucocorticoid receptors, there is actually
14 a down regulation of the enzymes involved in the
15 production of testosterone, including the key one
16 like STAR and some of the other CYPs, so -- and
17 that's well recognized.

18 So there is another pathway that may
19 explain the data that we see in the male rat, and
20 then, finally, there is the data that shows that
21 there is perhaps, a direct activation -- or I'm
22 sorry, a direct inhibition of the GnRH pulses by

1 CRF in the brain, wherein, stress and other
2 events that increase the activity of that
3 neuropeptide, which acid increases CRF -- or, I'm
4 sorry, increases the activity of CRF and ACTH,
5 that you get a direct innovation -- inhibition on
6 the pulses.

7 So those things make me argue, or
8 feel, that a key part of this whole mode of
9 action on the gonadal axis is this increase, at
10 least early on, increase in the activity of the
11 pituitary adrenal axis, and that's what's
12 summarized here.

13 Again, it has a clear, acute effect on
14 the HPA. We just don't know, haven't well
15 characterized the longer-term effect, increasing
16 both ACTH in the adrenal steroid hormones, that
17 the temporal aspects of atrazine induce changes
18 in the pituitary adrenal axis, and the pituitary
19 gonadal axis, along with the similarities in the
20 dose response -- that's what I was trying to get
21 at there -- for four more days, suggest that the
22 changes in the adrenal axis contribute to the

1 disruption of LH secretion and impairments in
2 reproductive function.

3 And so, the current studies broaden
4 our understanding of this mode of action for
5 atrazine, incorporating those changes that we've
6 already identified and others, in the pituitary
7 adrenal axis, and those that likely contribute to
8 the disruption of LH in the rat. Questions?

9 SESSION CHAIR PORTIER: At this point,
10 do we have any questions from the Panel?
11 Comments? Yes, Dr. Horton?

12 DR. HORTON: Yes, actually, I have a
13 lot, but I'll save some.

14 I'll start with another possible
15 model, besides the reproductive aging and the
16 reduction of the LH surge, and ask, do you have
17 measures or does anyone have measures, on what
18 the LH levels look like on diestrus or metestrus,
19 for the rats?

20 DR. COOPER: Yes.

21 DR. HORTON: And what are they?

22 DR. COOPER: The one thing we've seen

1 consistently, even on the morning of proestrus
2 too, is no change.

3 DR. HORTON: They're not elevated?

4 DR. COOPER: The majority of studies
5 that we've personally done, when we look at it,
6 it appears as though baseline hangs in there.

7 If we really increase the
8 concentrations of atrazine up to 200, I'd even
9 argue 50 and above, it's lower.

10 DR. HORTON: Okay.

11 DR. COOPER: But we haven't seen any
12 indication -- well, I have seen one, we do have
13 one set of data that says we can get an increase,
14 but it's in the afternoon, when we looked at very
15 low doses. So, I don't know whether it's --

16 DR. HORTON: Okay. The reason I'm
17 asking is, I'm wondering if it might fit a PCOS,
18 a polycystic ovarian syndrome model; and also,
19 has anyone looked at the body weights or body
20 compositions in these rats?

21 DR. COOPER: In the earlier --

22 DR. HORTON: In the females, yes.

1 DR. COOPER: When you do the longer-
2 term studies at those high doses, they're down.

3 DR. HORTON: They're down? Okay.

4 DR. COOPER: Significantly, but when
5 you do the -- like, the first slide I showed -- I
6 mean, the early studies that were done were, I
7 think, hitting them with a hammer --

8 DR. HORTON: Yes.

9 DR. COOPER: -- and you do see marked
10 decreases in body weight, but when we look at the
11 shorter-term, lower dose things, we don't see a
12 whole lot of difference.

13 DR. HORTON: Okay.

14 DR. COOPER: I mean, we don't see a
15 difference. It's the same.

16 DR. HORTON: Okay.

17 DR. COOPER: That's not -- I should --
18 I have to qualify that, because sometimes, you
19 say you don't see a lot of difference and they're
20 not eating. But no, that's --

21 DR. HORTON: Okay, okay, but that's in
22 terms of body weight, but no one has actually

1 looked at body composition?

2 DR. COOPER: Not to my knowledge.

3 DR. HORTON: Okay, no one has done a
4 glucose tolerance test?

5 DR. COOPER: We have, yes.

6 DR. HORTON: Yes, from what I --

7 DR. COOPER: I'm sorry, yes, we've
8 measured glucose, and we haven't found any change
9 with blood glucose over the four days that we did
10 the study.

11 DR. HORTON: Okay, thank you.

12 DR. COOPER: So, we didn't do a glucose
13 tolerance test, no.

14 DR. HORTON: Okay, thank you.

15 SESSION CHAIR PORTIER: Dr. LeBlanc?

16 DR. LeBLANC: There's a lot going on
17 here. A couple of questions, for clarification
18 first.

19 In these studies, have you ever looked
20 at the adrenal mass? Do the adrenals enlarge in
21 size?

22 DR. COOPER: Yes, I'm trying to think

1 of the -- again, we got into looking at the
2 adrenals kind of late. So, I'm sort of
3 embarrassed to say, we don't have a real
4 characterization of changes in body weight, nor
5 histopath, and they may have it in some of the
6 longer term studies that were submitted for
7 registration. I haven't had a chance to look at
8 them.

9 But what we see is almost an immediate
10 enlargement in the adrenal gland, dose dependent,
11 and then it settled back down.

12 PARTICIPANT: Did you have one in the -
13 -

14 DR. COOPER: And in the pubertal assay,
15 they were increased, the male pubertal. But,
16 yes.

17 DR. LeBLANC: The 2009 study by Laws,
18 these were done in animals that were not
19 gonadectomized, is that right?

20 DR. COOPER: Right.

21 DR. LeBLANC: Because you said, you
22 thought the testosterone came from the testes.

1 So, obviously, they had testes, and I guess I
2 agree with that presumption.

3 In terms of where the progesterone is
4 coming from, is that because most of the
5 progesterone in the blood comes from the adrenal?
6 You said you thought the progesterone --

7 DR. COOPER: In females, on vaginal
8 proestrus, there is a number of studies. One of
9 my PhD mentors, was his claim to fame, with --
10 showed that the majority of progesterone comes
11 from the adrenal vein --

12 DR. LeBLANC: Okay.

13 DR. COOPER: -- on the day of
14 proestrus.

15 DR. LeBLANC: Okay.

16 DR. COOPER: I wanted to just throw
17 this up. This was a slide -- this is a
18 gonadectomized slide, where the animals were --
19 again, it was a study that Laws did earlier,
20 wherein, she looked at both androstenedione and
21 testosterone, here on the right, in response to
22 50 to 200 milligrams, and the estrogen production

1 over here on the left, and what was -- and this
2 was an intact animal.

3 So, this is your testosterone here,
4 and this is androstenedione -- I'm sorry, this is
5 androstenedione in the intact animal, and in the
6 castrated animal, and this is testosterone in the
7 intact animal and there is nothing there, in the
8 castrated animal.

9 And we've actually looked at the
10 adrenals of these animals, to see if we can find
11 androstenedione using HPLC, and we see it, and
12 you know, you're not suppose to have CYP17 in the
13 adrenals, and there are papers that say under
14 certain circumstances and during development, you
15 can see CYP17, that there is a methylation
16 silencing that's taking place, and I just don't
17 understand it.

18 But the point is, is that those data,
19 to me, argue pretty strongly, A) that it's
20 something coming out of those adrenals, if
21 nothing else, it's androstenedione, and over
22 here, there is a production of estrogens that

1 persisted and if you look at the Y-axis, they're
2 not that different, after castration in the male.

3 So, back to your progesterone
4 question, I'm sorry.

5 DR. LeBLANC: One last point, for
6 clarification.

7 The cartoon you had at the end, the
8 conceptual cartoon, I thought it was very
9 helpful, and in there, you had the inhibition of
10 steroidogenesis by clinical steroids, at the
11 bottom.

12 DR. COOPER: Yes, right there.

13 DR. LeBLANC: Right, so, over and above
14 all of this, are you suggesting that there is
15 something else going on, that's contributing to
16 the increase in testosterone, that -- we're not
17 seeing a great increase, but we are seeing
18 increases.

19 DR. COOPER: Right, okay, good
20 question. Number one, I think those studies,
21 looking at decreased steroidogenesis are really
22 the result of some pretty high doses, 50, 200

1 milligrams per day.

2 I know that there was one that went
3 five, ten, 50, 75 and 100 milligrams per day,
4 from -- in the perinatal, even. But most of them
5 are in the intact animals, peripubertal or going
6 on into adults.

7 So, they're high and I think what's
8 happening there, if you do a single dose with
9 this, you'll always see an increase in
10 testosterone. You'll see an increase in
11 testosterone, and if you take the Leydig cell
12 out, and you stimulate the Leydig cell, you'll
13 see an increase in testosterone, you'll see an
14 increase in progesterone, okay.

15 That's been done at APA, with Gary
16 Klinefelter and there is a publication coming out
17 soon, that that's the case.

18 You put that cell back in the body and
19 can expose it to the glucocorticoids for an
20 extended period of time, increasing
21 glucocorticoid activity by a number of different
22 means, if you want to stress them, and you do

1 that really mean stress, where you put them in
2 the restraint cage, and -- for an hour a day and
3 shine a light on them, and you know, you really
4 keep the cort up, that will overwhelm the
5 protective mechanism within the Leydig cell and
6 you do see this decrease.

7 And there is studies now, even showing
8 that that process, that glucocorticoid
9 activation, stimulation -- hyperstimulation, that
10 receptor is even bad for the developing animal.

11 So, it's a biphasic or bimodal effect.
12 Initially, what you see in vitro and what you see
13 with a single dose is increased T, extended
14 dosing -- and I'm hypothesizing through increased
15 adrenal activity, you're seeing perhaps, a direct
16 effect on the gonads, and then of course, what
17 you're supposed to see is that when you decrease
18 T, the compensatory increase in LH, and the
19 studies that Susan and Walter Modic did, didn't
20 really show a whole lot of decreased baseline LH
21 in those males, and we can go back and look at
22 that.

1 So, that's why I'm leaning a little
2 bit, towards it being a direct gonadal inhibition
3 there.

4 But again, it could be a central
5 mechanism, but I think -- that's central -- you
6 know, I -- there is a paper by Zerkin and Ewing,
7 years ago, that said, "How much LH do I need to
8 keep secreting testosterone," and so, they took
9 the pit out and they put silastic capsules in, or
10 somehow, they fed them LH at real low levels, and
11 it is -- you'd be surprised how low they went,
12 before they would see a decrease in T.

13 SESSION CHAIR PORTIER: Dr. Selvage?

14 DR. SELVAGE: Yes, I just had a
15 question regarding the CORT/ACTH measurements.

16 Do you have any time points that
17 aren't in that -- where you measured these, that
18 aren't in that frame, right after the atrazine
19 administration, in the chronic studies?

20 So, for instance, are you disrupting
21 circadian rhythm or anything like that?

22 DR. COOPER: Yes, Melanie, in the

1 female, what we did -- in other words, if you
2 perturb it in the morning, is this -- the
3 afternoon is going to be altered --

4 DR. SELVAGE: Yes, or the -- yes, or
5 was it -- before, you know, you would normally
6 give it in the morning, and what would be CORT-
7 level?

8 DR. COOPER: The data that we have in
9 the -- it's a four-day exposure. We looked at
10 the dose immediate responses, but then we also
11 looked at the afternoon increase in progesterone,
12 because if you -- we were thinking that maybe
13 progesterone later on in the day was being
14 impaired.

15 And there -- in CORT, and Susan --
16 well, number one, is that there -- I think it was
17 the high dose -- Melanie, was the high dose of --
18 which one knocked down P4 in the afternoon?

19 Yes, the high dose DIA did decrease
20 progesterone in the afternoon, but for the rest
21 of the things that we treated with and doses that
22 we treated, there was nothing there, which was

1 surprising to me.

2 DR. SELVAGE: How many hours was that?

3 DR. COOPER: That would be -- yes,
4 let's see, that would be treat 9:00 a.m. and
5 you're looking at an hour before. So, you're
6 looking from three hours, one hour and one hour
7 after lights out -- three hours before lights
8 out, 1600, 1800 and 2000 hours.

9 DR. SELVAGE: Okay.

10 SESSION CHAIR PORTIER: Dr. Delclos,
11 please, use your mic.

12 DR. SELVAGE: I'm sorry, but you don't
13 have it like, at say, eight? You're dosing them
14 at nine, right?

15 DR. COOPER: When we did the proestrus,
16 we did the -- the day of proestrus, we measured
17 every two hours, up to 2000, from nine to 2000,
18 and most of the dramatic changes we saw were the
19 early --

20 DR. SELVAGE: Right.

21 DR. COOPER: -- ones, because, you
22 know, it's coming up, and one of the things that

1 Susan found in the male was that when you look in
2 the afternoon, if you try to increase cort in the
3 afternoon, that's one of the things she wanted to
4 do, you could get it to go any higher.

5 There's sort of like, a ceiling effect
6 there. She couldn't get it to go up.

7 PARTICIPANT: It was still up then.

8 DR. COOPER: It was still up? Right,
9 yes.

10 SESSION CHAIR PORTIER: Dr. Delclos, I
11 think was next, and then, Dr. Akana.

12 DR. DELCLOS: I just wanted to make
13 sure I understood. Does this mechanism play
14 into the delay of puberty at all? Where you take
15 the DACT having effect on that, but not having
16 effect on the -- it was something that confused
17 me, as I read the document.

18 DR. COOPER: There's two questions
19 there, and the answer is, I don't know, to number
20 one.

21 I mean, boy, you read the pubertal --
22 and you guys are the experts, and you read the

1 pubertal and adrenal literature, especially
2 earlier stuff, I was really -- it's really hard
3 for me to understand it, because you get this --
4 when you do things like adrenalectomy and all
5 this kind of stuff, you seem to see the -- you
6 seem to have an impact on the body weight of the
7 animal, that might confound this a little bit.

8 Conceptually, I could make that
9 argument, and there have been some kind of
10 sophisticated explanations, as to how, if you
11 dose with particular things that either inhibit
12 or activate the glucocorticoid receptor, you
13 could impair -- slow down puberty.

14 But the question about DACT, it's a
15 separate question, because I think DACT -- I'm
16 almost confident that it has to eventually impact
17 regulation of the LH surge, and when I say it has
18 to eventually do it, I mean, by dose, and by
19 duration.

20 If you look at the blood levels in the
21 rat, and we have limited data for this, but when
22 we look at it, DACT is present in such high

1 concentrations, even -- no matter what you give
2 them, and then you give them DACT, this equimolar
3 dosing thing is -- it's nothing like what you
4 really see inside the animal, when you measure
5 it. You have very high concentrations of DACT.

6 And that's even if you -- you know, if
7 you dose them with atrazine, the amount of DACT
8 is way up there.

9 So, why in the pubertal assays, you
10 see that, I don't know whether there's another
11 mechanism kicking in or what, but it is -- it is
12 something over there, that you can't dismiss. It
13 doesn't always fit the picture.

14 I guess, if you were really making the
15 argument that the adrenal was involved, you'd
16 want no effects, with DACT, but that's not what -
17 - the way the system was designed, and it bothers
18 -- or it's something that we can't explain at the
19 moment.

20 SESSION CHAIR PORTIER: Dr. Akana?

21 DR. AKANA: Could you repeat that
22 finding in the hypothalamus, in the Modic study?

1 What I'm thinking about is the
2 possibilities of central action of atrazine, and
3 there are aromatases in the hypothalamus and
4 there are some nice papers showing very site-
5 specific brain localizations, like BNST, and a
6 lot of those sites are also very gonadal-steroid
7 sensitive.

8 So, it seems the framework could be
9 there for some central regulation.

10 DR. COOPER: If I understand your
11 question right, do you mean in the adult or the
12 developing animal, first?

13 DR. AKANA: Adult first.

14 DR. COOPER: Okay, Susan, you looked at
15 -- go ahead, do you want to --

16 SESSION CHAIR PORTIER: Please identify
17 yourself, if you come up.

18 DR. COOPER: This is Dr. Susan Laws,
19 and she's the --

20 DR. LAWS: Hi, I'm Susan Laws, from
21 EPA. The question you were asking, the Modic
22 study, we were looking at the hypothalamus for

1 message, for aromatase CYP19, and those studies
2 indicated that after they were treated in vivo,
3 there were no differences in the message, and we
4 looked at -- after a single dose multiple time
5 points, we looked after three doses, daily doses,
6 and then at -- I think, that had a couple of time
7 points also, and we were not able to see any
8 differences in that.

9 So, it's -- it's challenging to
10 measure, so it's a no-effect study, is what we
11 have.

12 DR. COOPER: But the reason I asked
13 about the developing animal, of course, is then,
14 that's a whole new ball game or a whole different
15 ball game, because of A) the concentration.
16 Susan tells me they're much greater in the
17 neonate, and so, if maybe there is one
18 opportunity where there may be effects that we
19 haven't looked at, that might be important.

20 DR. AKANA: Also wasn't there also some
21 discussion of a critical period, in development
22 for the aromatase?

1 DR. COOPER: Yes, well, early on, I
2 mean, that was one of the driving forces behind
3 her actually measuring the younger animal,
4 because during development, the aromatase was
5 coming down and we figured if we -- what Stoker
6 found was a reflection of the earlier increased
7 importance of the animal.

8 But we didn't look at the peripubertal
9 or anything that would -- we haven't, yet, looked
10 at the peripubertal -- we haven't looked around
11 birth. That's what I'm trying to say, not
12 puberty, perinatal period.

13 SESSION CHAIR PORTIER: Dr. Williams?

14 DR. WILLIAMS: I just want to switch
15 gears a little bit, to get you to clarify the
16 comments you made several hours ago, regarding
17 the mammary gland tumors.

18 You said with aging, the cycles become
19 irregular, the LH surge doesn't happen and this
20 endocrine milieu in the rat promotes a
21 development of mammary tumors, and then in your
22 summary slide, you said that reproductive aging

1 is driven by the brain in the rat and by the
2 ovary in the human, and therefore, the mammary
3 gland tumor development isn't relevant to humans.

4 I don't really see that connection,
5 though. It seems to me that you should be more
6 concerned about the reproductive endocrine
7 milieu, potentially leading to mammary gland
8 development in humans, whether or not
9 reproductive senescence is an issue as a separate
10 story. Can you clarify that for me?

11 DR. COOPER: Let me repeat the
12 question, because that was a long one.

13 DR. WILLIAMS: Okay.

14 DR. COOPER: I want to make sure I get
15 it right. You're asking me, you said that we
16 looked at the aging animal, but you're talking
17 about mammary gland development, or are you
18 talking about mammary gland tumor development?

19 DR. WILLIAMS: So, this is directly
20 from your own slides, the nine and ten.

21 DR. COOPER: Okay.

22 DR. WILLIAMS: So, basically, you said

1 that you don't get the LH surge, so you don't
2 have regular cycling and you end up getting in
3 the -- in the rat, loss of CNS regulation, and
4 that this endocrine milieu causes development of
5 mammary gland tumors, and then in your summary
6 slide, you said, because reproductive aging is
7 different in humans, then the endocrine milieu
8 isn't really relevant to human mammary
9 development -- mammary --

10 DR. COOPER: If I said that, I
11 misspoke. The hormonal environment, I think, is
12 important, in both species, I mean, obviously.

13 I think that what happens with normal
14 aging, and the fact that atrazine appears to
15 accelerate that aging process in the rodent, is
16 different than what you would anticipate in the
17 humans, okay.

18 So, in the humans -- I mean, in the
19 rat, what we're doing is, we're driving a faster
20 pace, disruption of regular cycles and earlier
21 onset, and really, I think once that cyclicity is
22 disturbed, the pattern of constant estrus sets

1 the clock for when you're eventually going to get
2 a tumor.

3 How long you expose estradiol, how
4 long you keep your other hormones out of balance,
5 the more likely you're going to see the tumor
6 over time.

7 When I said it wasn't relevant, from
8 the standpoint of these studies to humans is,
9 that humans don't go constant estrus when they
10 stop cycling. They have not -- they have
11 insufficient number of follicles to -- the reason
12 they stop ovulate -- I'm sorry, the reason they
13 stop cycling their menstrual cycle is because
14 they lose the follicles, critical mass there, and
15 there is a few still left in there, like, 200,000
16 or something.

17 DR. WILLIAMS: Right, but as Dr. Horton
18 brought up earlier, in cases where women don't
19 really ovulate, for example, polycystic ovarian
20 syndrome, they actually do have elevated levels
21 of estradiol that are fairly, you know, prevalent
22 throughout the cycle, rather than the nice peak

1 at pre-ovulatory and then lower during the rest
2 of the cycle.

3 And so, it seems like the hormonal
4 milieu may be fairly similar and --

5 DR. COOPER: Oh, yes, if you want to go
6 -- okay, now, I understand your question better.

7 Yes, especially in light of some of
8 the recent papers in the rodent modeling, trying
9 to develop a model for polycystic ovarian
10 disease, wherein they argue that the induction of
11 constant estrus in the rat is going to produce,
12 not only the endocrine environment, but also,
13 some of the histological changes down within the
14 ovary itself, that are reminiscent of, you know,
15 the persistent follicles that you see.

16 Earlier on, in that literature, people
17 -- and where I did my turnaround was the work
18 that Ojeda has done lately, you may be familiar
19 with -- or not lately, but when he started
20 publishing on it, I began to believe that
21 polycystic ovarian disease may be something that
22 might fit into this picture, with the rodent

1 literature.

2 Now, in that case, I don't -- I would
3 agree, that that's an important consideration.
4 How that plays into the whole atrazine thing, I'm
5 not sure of, because it's different.

6 I mean, those studies would probably -
7 - those studies with the persistent estrous
8 animal are done in a young adult female, and I'm
9 not familiar, if there are any where they started
10 to look at that kind of homology, if you will,
11 between what you see in the aging female rat and
12 what you see in someone with PCOS.

13 But, yes, now I understand your
14 question and I'm in agreement with you.

15 SESSION CHAIR PORTIER: Dr. O'Byrne.

16 DR. O'BYRNE: Point of clarification.
17 You said that you've tried blocking the LH surge
18 with atrazine, in an acute fashion, and failed
19 miserably. With other compounds, it works.

20 DR. COOPER: Right.

21 DR. O'BYRNE: To block the surge.

22 DR. COOPER: Yes, we've done a number

1 of studies using things like dithiocarbamates,
2 which -- or and other fungicides that works to
3 specifically disrupt neuroadrenergic
4 transmission, and usually, we give them,
5 somewhere during the critical period, usually
6 about 15 minutes prior, in our -- between two and
7 four o'clock in the afternoon, and very rapidly,
8 you see the decrease in neuroendocrine and then
9 the decrease in pulses.

10 DR. O'BYRNE: Okay, so, you know the
11 mechanism action is quite clear?

12 DR. COOPER: Yes.

13 DR. O'BYRNE: Just another point, if I
14 may. I'm sure we're desperate for some break and
15 some tea or coffee.

16 Your pulsatile data, I don't know
17 whether it was yours or somebody else's, but
18 averaging pulsatile data and then trying to
19 describe it as pulses, is -- it's very difficult
20 to appreciate.

21 DR. COOPER: Well, yes.

22 DR. O'BYRNE: But you said you had the

1 individual data and you put it through the pulsar
2 program, and the 50 milligrams, which is a
3 whooping great dose, had no effect. Is that --

4 DR. COOPER: In the mean, right.

5 DR. O'BYRNE: No, no, no, in the
6 individuals, and I don't know how many animals
7 were --

8 DR. COOPER: Yes, this model --

9 DR. O'BYRNE: Do you have access to
10 that?

11 DR. COOPER: Do we have access to the
12 data?

13 DR. O'BYRNE: I have not seen those
14 individual profiles. I'm just curious, as to
15 whether there was a suppression of frequency,
16 which you can't read from this average data.

17 DR. COOPER: Right, boy, that was 1997.
18 When we did DMDC, we did the -- these are 28-day
19 females, you put the catheter in, beautiful
20 pulses, okay, and what you see, in the individual
21 animal -- and the question that you're asking is,
22 you inject them with the dithiocarbamate. It's

1 pulse, pulse, boom, okay, like, some data I've
2 seen, other people have pub, and it's immediate,
3 you know.

4 You know, and then they'll hang down
5 there for three or four hours until it clears and
6 then, you can see the pulses resume.

7 For Dr. Tyrey's data, for the 50 -- I
8 know -- I can tell you, what it looked like for
9 the 200, okay, pulse, pulse, flat, all right, and
10 then D-flat, and then you'd see an occasional
11 burst-through with the different -- now, an
12 individual animal, you would see this gigantic
13 pulse, like the GnRH hormones have to dump, that
14 kind of thing.

15 But the 50, I think with the
16 individual animals, you'd see a broader -- the
17 broader pulses. So, it's a slowing frequency,
18 but the amplitude was not down all that much.
19 They're still doing okay, and boy, that was an
20 old memory trace that, to pull back.

21 SESSION CHAIR PORTIER: I think at this
22 point, we are going to take a break. Dr. Young?

1 (Off the record comments.)

2 DR. YOUNG: So, I've been kind of
3 looking at this, you have to understand, I'm a
4 statistician, so, that's going to be my kind of
5 question.

6 So, do you do analysis for each time
7 period or do you synthesize and to one large
8 analysis?

9 DR. COOPER: For which study?

10 DR. YOUNG: Well --

11 DR. COOPER: For the --

12 DR. YOUNG: -- pretty much, all of
13 these? So, for example --

14 DR. COOPER: When we do this --

15 DR. YOUNG: -- the ones on page 20 --
16 on slide 26, the ones on slide 23?

17 DR. COOPER: Twenty-six and 23, boy,
18 Stoker, I hope these are your data.

19 SESSION CHAIR PORTIER: So, you're
20 talking about coming up at the little stars on
21 the top?

22 DR. YOUNG: Yes, how do you get that

1 star?

2 SESSION CHAIR PORTIER: How do you get
3 those stars?

4 DR. YOUNG: Yes, you're right.

5 (Off the record comments.)

6 DR. YOUNG: I saw, on one of your --
7 well, on -- I couldn't find the Tyrey paper, if
8 that's the way you --

9 DR. COOPER: That's an abstract.

10 DR. YOUNG: Okay, I saw the abstract,
11 but where I -- no, I couldn't -- no, I didn't see
12 that.

13 DR. COOPER: We have it in the 2007,
14 but I don't --

15 DR. YOUNG: Okay, I couldn't -- one, I
16 couldn't find the 1997 one.

17 DR. COOPER: Yes, please don't take me
18 to task on the pulsar, because --

19 DR. YOUNG: No, no, I'm just --

20 DR. COOPER: -- we can --

21 DR. YOUNG: I'm just trying to figure
22 this out.

1 DR. COOPER: Right, but here is 25, is
2 that what you want?

3 DR. YOUNG: No, no.

4 DR. COOPER: Oh, the LH surge?

5 DR. YOUNG: Something like that.

6 DR. COOPER: Right, these are -- who
7 did this?

8 DR. YOUNG: So, did you do one at each
9 time point, or did you do one analysis for the
10 whole graph?

11 DR. COOPER: The whole graph.

12 DR. YOUNG: Because sometimes -- in the
13 captions, it talks about by time point. So, my
14 assumption was, analysis was by time point and --
15 but I'm not sure that's right.

16 DR. HOLLADAY: I think that is, for
17 this.

18 DR. YOUNG: This is the time point --

19 DR. COOPER: She did the analysis, let
20 her speak.

21 (Off the record comments.)

22 SESSION CHAIR PORTIER: Can I suggest

1 that we hold this and that you guys talk about it
2 at the break, and then we'll come back with that
3 question?

4 DR. YOUNG: Excellent suggestion.
5 Thank you very much.

6 SESSION CHAIR PORTIER: I know it's a
7 large group of people, and a 15 minute break is
8 very difficult, but my watch says 3:15 p.m. So,
9 we'll be back at 3:30 p.m., on the dot. Thank
10 you.

11 (Whereupon, the above-entitled matter
12 went off the record at 3:15 p.m. and resumed at
13 3:33 p.m.)

14 SESSION CHAIR PORTIER: I was ready to
15 get started, but Dr. Cooper wasn't here, so, I
16 can't.

17 So, we're going to continue on and see
18 if first, EPA can answer Dr. Young's question
19 about analysis, and then, I think Dr. Williams
20 wanted to come back to her question, to see if we
21 can get that clarified.

22 DR. YOUNG: All right, I --

1 SESSION CHAIR PORTIER: I remind the
2 Panel, this is our time to get clarification on
3 the presentations and the material on the white
4 paper.

5 So, it's not quite right on the
6 slides, but you've got something in the white
7 paper you can point to, we can go with that, as
8 well. So, Dr. Young?

9 DR. YOUNG: I think I got clarification
10 in the break. Some of the more recent papers do
11 look at the whole study, some of the older
12 papers, even though an effort has been made to
13 look for proper analysis, do do time-by-time
14 analysis, and some, we don't have the data to
15 even know one way or the other.

16 In addition, I think there was a
17 slight misspeaking, in that, one study in which
18 we talked about a rat, after one dose, in the
19 same rat, four doses later, those were actually
20 different rats. So --

21 DR. COOPER: They had to be different
22 rats. They were killing them.

1 But the one other thing that's
2 important is that these data aren't transformed,
3 and usually, when they do hormone data, they do
4 the transformation and so, it's my estimation
5 that these are really conservative evaluations,
6 and I may be wrong in that approach, that if we
7 didn't do the transformations because of the
8 transformations, the amount of variance that you
9 see, may change. Susan has just re-did a data
10 set, doing that.

11 DR. LAWS: My data was --

12 SESSION CHAIR PORTIER: Identify
13 yourself.

14 DR. LAWS: Susan Laws, U.S. EPA. My
15 data that you see the -- the ACTH and the CORT-
16 data, those that had the different time points,
17 they were first analyzed with analysis of
18 variants in -- for time and time of dose
19 interactions.

20 But however, there is heterogeneity of
21 variance in those data. So, those data, we
22 actually used a non -- rather than transform

1 them, do a live transformation, which is usually
2 done with hormone data, or can be done with
3 hormone data, we used a non-parametric test for
4 those and we did do those by time, each time it
5 was done, in between.

6 And so, it was the analysis of the
7 variants and then, there was a post hoc test for
8 those stars, that you see.

9 Recently, we've transformed some data
10 -- used a live transformation, and actually, it
11 looks like they -- we have lower doses that are
12 significant, not in this data set, but another
13 data set.

14 So, I think the non-parametric test
15 that we used for that report was fairly
16 conservative, when it looked at differences
17 between groups.

18 SESSION CHAIR PORTIER: Dr. Williams?

19 DR. WILLIAMS: Just to try to clarify,
20 the mammary gland tumor development in women
21 versus rats, and the mechanism of action you were
22 talking about, can you clarify, maybe not what's

1 on your slide, but what is in the white paper, in
2 terms of causing -- causative concerns regarding
3 atrazine, LH surge lag, the endocrine milieu and
4 mammary gland tumor developments?

5 DR. COOPER: You mean, the --
6 essentially, the strain difference? You mean,
7 essentially, the strain difference, if you will,
8 in humans versus rats?

9 DR. WILLIAMS: Why is it that you don't
10 believe that the LH and endocrine milieu changes
11 wouldn't be relevant to human mammary development
12 tumor --

13 DR. COOPER: No, no, no, that's -- if
14 I'm giving you that impression --

15 DR. WILLIAMS: That's why I wanted to
16 clarify it.

17 DR. COOPER: That's not true, okay,
18 that's not what we're implying, or I'm implying,
19 is that the -- that environment that you see in
20 the rat, is what's conducive for the growth of
21 tumors, hyperplasia and then eventually, the
22 tumors.

1 The human doesn't get to that
2 condition, is what we're saying that, during
3 aging in the human, what you see is a depletion
4 of the follicles, and therefore, that you don't
5 develop the high levels of estrogen when they go
6 through menopause. Menopause is a period of low
7 estradiol, or estrogen.

8 DR. WILLIAMS: So, then potentially,
9 the mechanism of action would be relevant to a
10 non-menopausal human, though?

11 DR. COOPER: If you can -- yes, that
12 was a question that came up during the break. I
13 would assume that if you could get a constant
14 estrous human, a polyfollicular human maybe, I'm
15 not familiar with one, a model like that, but if
16 it's the case, then I don't know why that
17 wouldn't be the same endocrine environment, yes.

18 So, yes, I apologize if I mislead you.
19 I'm not -- it's -- that hormonal environment is
20 the consequence of differential patterns of
21 aging, rat versus human, and that's why the
22 argument that the relevance that we see for that

1 particular outcome, in the rat, it doesn't appear
2 to apply to humans.

3 And so, there is a -- it's sort of
4 like, you know, I guess we make assumptions and
5 this was our -- that argument was what we tried
6 to make clear, the last meeting, and I -- rushing
7 through that, sometimes, you don't get the -- all
8 the little key events, like that. They don't
9 come out right.

10 But your question is on target from
11 the comment that, if you create this environment,
12 rat or human or even -- you know, no matter what
13 the strain -- I know there's a mouse strain.
14 They say that atrazine doesn't induce mammary
15 gland tumors in mouse, but there is a mouse
16 strain that they used in aging, that was --
17 showed similar patterns of pituitary and mammary
18 gland development in the female, when she grows
19 older.

20 They showed it as a consequence of
21 altered ovarian cycles and perhaps, if that
22 strain is -- you should see the -- if that was

1 what you see, then you brought about the same
2 premature reproductive aging as the experimental
3 -- the studies show in that mouse strain, that
4 you would see the same thing.

5 It's how you get there, or can you get
6 there, in a human.

7 SESSION CHAIR PORTIER: Dr. Fenner-
8 Crisp?

9 DR. FENNER-CRISP: Ralph, back in the
10 stone age, when we were working on the mammary
11 tumor MOA, this -- one could only say that
12 atrazine had some effect, not otherwise defined,
13 with respect to direct or indirect. The work
14 hadn't been done to sort anything out,
15 specifically, yet, adequately.

16 Now, with this new body of data,
17 describing the disturbances in the HPA axis, the
18 inferences, although you haven't stated it
19 explicitly yet, that -- that may have to proceed
20 the disturbance in the HPG axis for the mammary
21 tumors, which would be indirect.

22 What evidence exists for or against

1 the -- a direct pathway being at play, and what
2 could you do or have you done, to separate the
3 two, to show whether or not there's still an
4 opportunity for direct effects?

5 DR. COOPER: For the tumors outcome?

6 There is a study that the registrant did, I
7 think, that might speak to it, is that if the
8 adrenal gland was actually driving the
9 development of the tumors, independent of altered
10 gonadal function, then you would see it, if you
11 removed the gonads and dosed with atrazine for an
12 extended period of time, removed the ovaries, in
13 this case, and didn't they submit that study?

14 (Off the record comments.)

15 DR. COOPER: That would --

16 DR. FENNER-CRISP: Maybe that would --

17 DR. COOPER: That's the statistician --

18 DR. FENNER-CRISP: Maybe then the
19 registrar could speak to my question, tomorrow.

20 DR. COOPER: I thought that that study
21 was done. I guess, I misspoke.

22 DR. FENNER-CRISP: Okay.

1 SESSION CHAIR PORTIER: I think there
2 was a hand in the audience, indicating that
3 tomorrow, probably the registrant will speak to
4 that, if we can --

5 I think at this point, we've kind of
6 picked through this part and we're ready to move
7 on to the discussion of the immunotoxicity. Dr.
8 Luebke?

9 DR. LAWS: Go back to the -- whatever
10 it's called, the hard drive. Go back to the hard
11 drive. Thank you.

12 DR. LUEBKE: Okay, so I'm going to talk
13 about some atrazine immunotox studies and
14 basically, just summarize some of the work that
15 has been done. I will not be going into the
16 level of detail that Ralph did.

17 And because this is the first time
18 through for immunotox, for the SAP Panel, I know
19 that we have a couple of experts here, but for
20 the rest of you, I thought it would be a good
21 idea, just to cover just a couple of very general
22 topics first.

1 So, immunotox is essentially
2 unintended modulation of the immune system, and
3 this can take the form of suppression or
4 enhancement of certain functions that the cells
5 do, and that the body does, and this can result
6 in an increase in allergy, it can increase the
7 risk of hyper-sensitivity, or autoimmune disease,
8 and in very general terms, these mode of actions
9 includes things like an altered supply in the
10 cells, that would be coming in to perform these
11 different duties.

12 There could be altered maturation of
13 the cell types. There could be a difference in
14 how the cells function or in the case of
15 autoimmune disease, which we see up there, this
16 could be a failure just to control auto-
17 reactivity by some fairly sophisticated
18 processes.

19 And the proximal cause of
20 immunotoxicity can either be direct, so there are
21 effects right directly on the immune system cells
22 themselves or on their supporting tissues, or

1 they could be indirect, where there are effects
2 that might perturb some other system and the
3 fall-out from that perturbation would actually
4 change how the immune cell functions.

5 So, host factors, as we have been
6 talking about for the last little while here, can
7 also have a dramatic effect.

8 So, up here at the top, you see that
9 during -- well, that doesn't work, okay. During
10 development and maturation of the immune system,
11 it seems to be one of the more critical times for
12 adverse effects on the immune system.

13 During this maintenance phase, when
14 everyone is young and healthy, we can still get
15 effects, and do, and we see those in adult
16 immunotoxicity studies.

17 Gender and genotype can also have a
18 big effect. Females tend to make a more robust
19 response than males do, immunologically, and
20 genotype controls a wide array of things.

21 So, the wide array of what constitutes
22 normal function in an individual, normal function

1 across a broad scale of the population, and it
2 also, as we've heard for effects on endocrine
3 disruption, with Ralph, it can also control how
4 an animal responds to exposure to an
5 immunotoxicant.

6 So, mice exposed to very small amounts
7 of dioxin get immunosuppression and doses many,
8 many times, 30 times that high, don't have much
9 of an effect on rats.

10 So, why would we do immunotox hazard
11 IV studies? Sometimes, there is some clues from
12 general tox studies, and these can be things like
13 a change in organ weight, input organ weights
14 with the cellularity. These tend to be sort of
15 observational snapshots captured at one in time
16 and it tells you sort of like, what the immune
17 system was like, right then.

18 There may be a known or suspected mode
19 of action. So, if -- we know that the compound
20 alters protein-synthesis or cell division or
21 alters neuroendocrine effects, that may be a clue
22 that we need to look for immunotoxicity.

1 In some cases, testing is actually
2 mandated for certain types of compounds, and they
3 may be planned, like the NTP would look for
4 effects, and these are generally functional
5 effects that people are going to be looking for.

6 So, in those assays, you'll have some
7 of those -- these observational snapshots, but
8 what you might not have are these functional
9 assays and what you will not have in the general
10 tox studies.

11 So, in these functional studies, we
12 ask the immune system to do something. So, it's
13 generally challenged with an antigen, and then we
14 measure the response to that.

15 So, the critical mode of action for
16 evaluation of the immunotoxicity of atrazine was
17 obviously, endocrine function.

18 We know that there are a variety of
19 industrial compounds and pesticides and other
20 compounds that are endocrine-active compounds,
21 and they also have an effect on the immune
22 system.

1 So, this first study that I'm going to
2 talk about was done in my laboratory, at EPA in
3 Research Triangle Park, and it was done by a
4 postdoctoral student, Andrew Rooney, when he came
5 through my lab.

6 He came out of Lou Gillette's lab at
7 University of Florida, where he had studied the
8 Lake Apopka alligators. So, he was very
9 interested in endocrine disfunction and he had
10 measured some endpoints in the immune system, as
11 well, and this seemed like a perfect project for
12 him.

13 So, he picked a dose of atrazine that
14 would be just above what Susan Laws had reported
15 for changes in the onset of puberty in female
16 pups, and for a reduction in the NOEL of
17 prolactin, in Tammy Stoker's studies.

18 Rather than including a dose response
19 here, we included a couple of pharmacological
20 agents, because we wanted to see if we could
21 produce the same effects by altering prolactin
22 production and we chose our dose there, to be the

1 LOEL for prostritis, and we also included PTU,
2 propylthiouracil, to see if there was -- if we
3 could do this by altering thyroid hormone
4 production.

5 So, after the moms gave birth, we took
6 the pups away. We segregated them out by gender
7 and dose and then we re-distributed five males
8 and five females to all the -- all the dams. We
9 didn't make any attempt to return animals to
10 their biological mom or to not return them, and
11 we also got weights on the animals, at that day.

12 Then on day 14, we took one pup from
13 each gender and we got thyroid hormone -- we got
14 thyroid hormone levels on those animals and we
15 also took a spleen and a thymus weight at that
16 day, to see if anything had happened to those
17 immune systems organs.

18 Then, once the animals became
19 immunologically mature, we asked their immune
20 system to do something by immunizing them to have
21 them make antibodies or to make a cell mediated
22 immune response.

1 We also looked at the ability of cells
2 to produce phagocytosis, which can be the first
3 step in resistance to certain sorts of
4 infections, and we also evaluated natural killer
5 cell activity, which is something done by
6 specialized lymphocytes that kills tumor cells.

7 And we did these -- the assays -- the
8 functional assays at a couple of time points, to
9 see if the effects were persistent, and if you
10 look at these data here, you can see that there
11 was a real increase in the percent mortality.

12 So, two-thirds of the atrazine litters
13 actually lost pups, and the numbers of litters
14 that actually lost pups was also increased for
15 bromocryptine. This didn't happen for PTU.

16 As Ralph mentioned earlier, we know
17 that changes in prolactin levels will alter
18 maternal behavior and we think, but don't know
19 for a fact, that the reason that we had this
20 increased mortality in the atrazine pups was for
21 the same reason we did in the bromocryptine pups,
22 because maternal behavior had been altered, and

1 they just weren't as good a mom.

2 We looked at the pup weights, to see
3 how well they did during development, just as
4 sort of a general measurement of pup health, and
5 as you can see, we didn't really have any effects
6 at all of atrazine in these animals at PND2.

7 We did pick up what was a
8 statistically significant effect in the males, on
9 PND7, but if you also look at the n value there,
10 you can see that we had a lot of pups who -- this
11 was a very large study and because of this, the
12 one gram difference between the controls and the
13 atrazine pups showed up as being statistically
14 significant.

15 So, the bromocryptine and PTU had some
16 effects as well, particularly on PND7.

17 Now, this one, I know is sort of busy.
18 I'm going to try and show you here. These are
19 body weights, going across here at the top, and
20 you can see, there was no effect on PND14, in the
21 body weights of the offspring, in the atrazine
22 group, although the bromocryptine and the PTU

1 animals were still suppressed.

2 We also looked at the spleen to body
3 weight ratio, sort of a somatic index, and spleen
4 weights were not affected, nor were thymus
5 weights affected in the atrazine-exposed animals.

6 They were, in the thymus -- I mean, in
7 the PTU and the bromocryptine groups as well, but
8 those were transient effects and PND62, they had
9 all recovered.

10 So, this was a functional assay, where
11 we immunized a large group of mice and then, we
12 bleed them and we measured antibody titers, and
13 what we found was there was actually a
14 suppression in the male mice, but not in the
15 female mice that were exposed to atrazine, and
16 these effects were not re-capitulated by
17 bromocryptine or PTU, and then a sub-group of
18 those animals was given another dose a week --
19 two weeks later, of the same antigen, and we
20 measured the IgG response and in this case, there
21 was no effect on males or females.

22 We did a cell mediated immune assay,

1 where we had the animals respond to the swelling
2 response to an antigen and what we found again
3 here, was this sexually dimorphic effect, where
4 there was suppression in the males, but not in
5 the females.

6 This occurred at nine weeks, and I
7 should mention here, on the antibody response, we
8 looked again at six months and the effects that
9 we saw on the primary antibody response were no
10 longer apparent at six months, just at the -- at
11 eight weeks of age.

12 So, here, we see that there was
13 suppression of cell mediated immune responses at
14 nine and 12 weeks. This did not persist out to
15 six months.

16 So, in both of these cases, where IgM
17 was suppressed and cell mediated immune function
18 was suppressed, although it recovered, there was
19 a time period there where the suppression could
20 have rendered the animals more susceptible to
21 certain sorts of infections, and these include
22 viral infections and certain types of bacterial

1 infections.

2 There were also a number of negative
3 effects that we had here. There was no effect on
4 maternal weight gain, so, these effects, we don't
5 think, were due to any sort of overt toxicity on
6 mom.

7 There was on effect on phagocytic
8 activity of these phagocytes at all. These
9 phagocytes also do other things, like
10 participating in antibody responses. So, we
11 don't know whether they were responsible at all
12 for suppressed antibody responses, but their
13 phagocytic activity was not affected.

14 Natural killer cell activity was not
15 affected and at least, you think these things
16 might be refractory to any sort of developmental
17 effects. Diethylstilbestrol given to neonatal
18 female mice will suppress natural killer cell
19 activity almost for life, in these animals. So,
20 it is possible for an endocrine disrupting
21 compound to change that.

22 We didn't see any effect on the

1 relative or absolute spleen and thymus weights,
2 which suggests that there wasn't any sort of
3 effect on the supply of cells that these animals
4 had to work with, but clearly, somehow, their
5 function had been altered, and we didn't seem to
6 reproduce effects whatsoever, by using these
7 pharmacological inhibitors.

8 So, this made us think that low levels
9 of prolactin and low levels of thyroid hormone
10 were not really to blame for the effects that we
11 saw in the immune response, and so, since Andy
12 had a background in endocrine disruption, he came
13 up with the idea, before he talked to Ralph
14 Cooper, that the GnRH may have something to do
15 with this.

16 We know from a variety of different
17 subjects, different studies, that this is
18 sexually dimorphic, GnRH expression and the
19 protein and the receptor expression are set early
20 in development. They're sexually dimorphic.

21 Antagonists that are given to primates
22 actually do suppress cell mediated and humoral

1 immunity in the males, but not in the females.

2 The agonists, ironically, up-regulate effects on
3 cell populations, not on function, but on cell
4 populations in the female offspring, and we know
5 that once this receptor is bound by its agonist
6 on the lymphocytes, this leads to increased
7 antibody production and it leads to increased
8 cytokine production.

9 So, now, for the caveat, we did all --
10 we did those studies that I just described twice.
11 Each time we did them, the data came out pretty
12 much the same. Then, we moved about half a mile
13 down the road, to a new facility, and because we
14 didn't have a dose response, we went back to
15 generated dose response, which we were unable to
16 do.

17 We did the study three or four times.
18 The same people were involved, that did the
19 studies both times. We had used different lots
20 of atrazine in the first study, and it didn't
21 have any effect. So, I don't think that could
22 have any -- you know, out -- bearing on the

1 outcome.

2 We did monitoring for parasites, the
3 normal sentinel animal stuff in both facilities.
4 There was no difference in infections.

5 I have a whole lot of confidence in
6 both data sets, because of the things that I've
7 just told you about. What I don't know is what
8 this unknown environmental factor is, that in one
9 case, the animals were suppressed, but in another
10 case, at the same dose, they were not.

11 It could be something, just sort of an
12 additive thing, with cage movement or something
13 like that, some change in the way they were cared
14 for, but we have not been able to figure out what
15 that was.

16 So, there was another developmental
17 immunotox study done. This time, it was done in
18 mice and these mice were done for again, going
19 back to these host factors that we talked about
20 earlier, to see if there were differences in
21 genotype.

22 The exposure here was quite a bit

1 different because they used a little implant that
2 constantly delivered a trickling dose of
3 atrazine, the same amount within a 24 hour
4 period, and so, when they started dosing, they
5 were at about our same level. They chose these
6 doses, based on the studies that we had done.

7 But this had gone down to about 23
8 milligrams per kilogram per day, at the time that
9 the animals were born, and then, they weaned the
10 animals a little bit later than we did, at 28
11 days and then they assayed them, once they were
12 mature.

13 They also found sexually dimorphic
14 effects here, but what they found was that
15 humoral immunity, the antibody response, was
16 actually increased in the mice, where we had seen
17 suppression, and it didn't matter how you -- how
18 they expressed the data, whether they
19 standardized it to the number of cells in the
20 spleen or the number of cells in the spleen that
21 were precursors to the antibody-forming cells.

22 They also found that there was an

1 effect on cell mediated immunity. They used
2 different assays than what we did. The one on
3 the left actually has -- causes cells to
4 proliferate in response to foreign antigens. The
5 one on the right, specifically armed cytotoxic T-
6 cells kill target cells.

7 But just as was the case with the
8 humoral immunity, what they found was increased
9 reactivity in the mice.

10 And so, we talked about suppression in
11 our animals, leading to a greater risk of
12 infection. There are a lot of animal models out
13 there that are shown. Compounds that cause this
14 unwanted increase in immune reactivity can also
15 make auto-immune disease worse or can lead to
16 hyper-sensitivity and allergic effects in
17 susceptible individuals.

18 They found the same sort of negative
19 effects that we did. So, mom wasn't really
20 affected in her weight gain, pregnancy rate,
21 litter rate, things like that, were not really
22 affected. There was no effect on offspring

1 weight gain, when they looked at it, at a single
2 time period, so, the pups weren't particularly
3 sick or anything like that, and because they
4 didn't find any effects on the spleen weight, or
5 they looked at the distribution of lymphocytes
6 from within the spleen, for various types of
7 cells. They didn't see any effects there, which
8 would suggest that the supply of cells was not
9 altered, but once again, the function of the
10 cells was clearly altered because of what the
11 outcome was.

12 So, what might have caused all of
13 this? Well, we heard a great deal, a few minutes
14 ago, about how much of a dose and for how long a
15 dose, and what effects that might have on the
16 outcome.

17 Rowe et al. put their doses sub-Q, and
18 so, that means that not the same proportion of
19 parent and metabolite is going to be produced in
20 those animals.

21 But also, from the work that was done
22 by Ralph Cooper and Tammy Stoker, it looks like

1 we might be looking at some sort of a qualitative
2 -- I mean, quantitative effect there, by the
3 amount of atrazine that was given, metabolite
4 that actually reached the brain, but not a
5 qualitative one.

6 So, that doesn't seem to explain the
7 difference. The functional assessment end points
8 were well recognized, and I think that they were
9 really measuring the same thing that we were.

10 So, it comes down to species,
11 differences in mouse strains, and we've already
12 talked about how we can have very different
13 effects, depending on what's the species of
14 exposure.

15 The mice that they used were sort of
16 prone to make antibody and allergic responses,
17 but that might explain some of the effects that
18 they saw, but not all of them, because both cell
19 mediated and humoral immunity were up-regulated
20 in those.

21 So, then the question is, are those
22 results really in conflict? What are these

1 results telling us?

2 Well, we know that the effects on --
3 of gender were constant and the supply of cells
4 seems to be pretty constant. It's genotype
5 that's sort of, out of phase, and we can't really
6 explain this.

7 However, we've realized, in the
8 immunotox community, in the last maybe five to 10
9 years, that the thing that we really need to
10 think about is immunomodulation and not really
11 worry about whether we've suppressed the response
12 or whether we've enhanced the response or whether
13 it's allergy or what have you, we've caused
14 something to happen that we didn't intend to
15 happen, and so, immunomodulation is the thing
16 that we tend to focus on.

17 So, those were sort of full gestation
18 studies. There was one study that looked at just
19 the late part of development. This was a study
20 that was done in C57 black 6 mice, and you can
21 see the doses that were used there.

22 They exposed these mice, starting at

1 four weeks of age, and these animals become
2 immunologically mature around seven or eight
3 weeks of age. So, what they did was expose the
4 animals, just for this last period of the immune
5 system development.

6 But rather than spend a lot of time on
7 the details of the study, we can summarize it by
8 saying that most of the effects that they saw,
9 particularly at the lower doses, say, 25 and
10 five, were sort of ephemeral and they were gone
11 by a day.

12 Even at the higher doses, most of the
13 effects had resolved by seven days, and all of
14 the data that they used -- unfortunately, all of
15 the data that they collected here were
16 observational endpoints, and that can give you
17 some really important information, if you know
18 that there is a defect, and it will help you
19 maybe choose what path to go down, to figure out
20 what the defect is.

21 But all we know right now is that
22 something happened in these animals and they

1 recovered fairly quickly.

2 There have been a number of adult
3 exposure studies here, and probably the most
4 complete one that has been done to date was one
5 that was contracted by the National Toxicology
6 Program, and was carried out by a contractor up
7 at Medical College of Virginia, and they looked
8 at a whole bunch of these different functional
9 endpoints and observational endpoints, and they
10 found very few effects in these animals at the
11 lower dose group.

12 The one thing that is sort of
13 interesting is that second bullet point there,
14 where they found a 35 percent increase in
15 antibody production, at 25 milligrams per
16 kilogram, but it was perfectly flat across the
17 rest of the spectrum, and so, I'm not really sure
18 what that might mean.

19 They challenged the animals with tumor
20 cells. They found that at the top two doses that
21 -- the resistance to this tumor cell challenge
22 was decreased in these animals, but when you go

1 back -- they also went back and looked at the
2 primary effector cells in these animals, and
3 those cells weren't really suppressed.

4 And so, I'm not exactly sure how to
5 interpret those data either, but they were --
6 they occurred at some pretty large doses.

7 And they also had a lot, as I
8 mentioned, these observational endpoints -- and
9 none of those things really pointed to any sort
10 of a clear picture of immunotoxicity.

11 They did look for antibody -- changes
12 in antibody production, using the same assay that
13 we did, and didn't find anything. They
14 challenged the animals with bacteria that would -
15 - that live inside cells and take a response of
16 their adaptive immune response T-cells to get
17 over it. They didn't really see anything there.

18 And so, we don't really have any clear
19 picture in the NTP study, even at doses up to 500
20 milligrams per kilogram.

21 There was another study that was done
22 in C57 black 6 mice and here, they based their

1 doses on percentages of the LD50, and you can see
2 that the -- on the second line, the next to the
3 highest dose, that should be 433, not 4,300. I
4 think those animals would have been dead, without
5 any questions, if you could have gotten that much
6 into them.

7 So, there was really no effect on body
8 weights in these animals. They had sort of a
9 mixed bag, and I don't mean to be insulting, when
10 I say a mixed bag of changes, but that's
11 essentially what it was. There was no clear
12 arrow pointing and even suggesting even one
13 direction.

14 They didn't seem to have any effects
15 whatsoever on the supply of cells, because they
16 did the same sort of thing where they looked at
17 spleen cellularity and the distribution of these
18 cells, and there was no effect on the phagocytic
19 activity of the animals.

20 They also took spleen cells out of
21 these guys at different time points, and they
22 immunized these spleens in vitro and then they

1 looked at the number of antibody producing cells
2 that resulted from that, and it was sort of
3 interesting there, at their lowest dose, at 25
4 milligrams per kilogram, they were initially
5 suppressed and then, as they were allowed to
6 recover out over time, over a period of about
7 three weeks, that lowest dose came back to about
8 control levels.

9 But at other doses, you didn't see
10 that picture at all. The very highest dose
11 jumped right back up to control levels at 14 days
12 and then sort of dove back down to being
13 suppressed and then went back up to being
14 enhanced by 21 days, and the doses that came in
15 between there were also somewhat mixed, like
16 that, and again, I'm not really sure what to make
17 of these studies, other than, most of the effects
18 that they saw tended to be at the higher doses,
19 with these effects on the antibody response, that
20 I just don't understand.

21 Then, there were a number of really
22 excellent studies that were done by Steve Pruett

1 and his co-workers, and they chose large doses of
2 atrazine and large doses of ethanol, and large
3 doses of some other compounds that they knew
4 would induce a stress response, that they knew
5 would really increase corticosteroid production,
6 and their goal here was not really to do a hazard
7 ID study for whether or not atrazine is toxic to
8 the immune system or not, but rather, to see
9 whether they could use this rate of production of
10 corticosterone over time, as a predictor for how
11 they would affect a variety of endpoints,
12 including antibody production and things like
13 that.

14 I happen to see that Steve Pruett is
15 here at the meeting and I -- he may be talking
16 about some of this tomorrow. He may not be, I'm
17 not really sure. But these studies -- we know
18 that at these levels, that corticosterone levels
19 will definitely be up.

20 The interesting thing about one of
21 Steve's studies was that he never did habituate
22 the cort response after 28 days, the restraint

1 stress habituated alcohol habituated, but this
2 didn't. This was sort of in keeping with what
3 Ralph was talking about a few minutes ago, where
4 you continue to see, when you expose the system
5 to atrazine, that there's an increase in cort
6 production.

7 So, if I was to try and sum everything
8 up here in just one sentence, it would be that,
9 we have pretty clear evidence that it's the
10 developing immune system that seems to be the one
11 that's more sensitive than the adult immune
12 system, and it seems to be working through what
13 might be similar mechanisms.

14 We never got a chance to pursue the
15 GnRH thing, because we applied for funding, for
16 Andy to continue his postdoctoral fellowship and
17 that did not work out.

18 So, the other thing that I can say is
19 that we really don't have any evidence to suggest
20 that the developing immune system is any more
21 sensitive than the neuroendocrine system, at
22 least from the studies that we've done.

1 Then, just to sum it up, there's one
2 more type of study that's been done, which is an
3 in vitro study, and this is where they put
4 different amounts of atrazine or the same amount
5 of atrazine on the spleen cells, over time. They
6 harvested those spleen cells and then they sent
7 them onto one of these natural killer cell
8 assays, and as you can see in the graph on the
9 left, that the more atrazine that was given, the
10 more suppression of the natural killer cell
11 activity went on in vitro.

12 In the graph on the right, the dark
13 black bars there -- I know that they're sort of
14 hard to see, and I apologize. I copied and
15 pasted out of a PDF, and it did not really work
16 out well.

17 But the dark black bar is the atrazine
18 on the right and as you can see there, the longer
19 you put those cells in culture with 10 micromolar
20 atrazine, the more suppression of the natural
21 killer cell activity there is.

22 But if you look at the graph at the

1 bottom, these are the natural killer cell. This
2 is natural killer cell activity from the mice in
3 the NTP study, and what you can see there at the
4 bottom is -- if I can make this arrow appear,
5 right here is this one little blip, and this is
6 at 250 milligrams per kilogram per day, and it is
7 at the very lowest effector to target cell ratio.

8 So, in this assay, what you do is, you
9 mix more natural killer cells in there with the
10 numbers of target cells that you have in there,
11 and so, at the very lowest level of natural
12 killer cell activity, at this medium dose, they
13 found this one in vivo effect on natural killer
14 cell activity, which sort of makes me dismiss the
15 other ones as it was -- they were interesting
16 studies, there's no doubt about it.

17 Rowe found, in these studies, that he
18 did, that there was a specific defect in the
19 natural killer cells, that prevented them from
20 delivering a lethal hit to the target cells.

21 But these two studies don't tell us a
22 whole lot more about the effects, potential

1 effects from natural -- of atrazine on natural
2 killer cells, because all of the animal studies
3 have tended to point to no effects on natural
4 killer cells, particularly at rational doses, and
5 that's all.

6 SESSION CHAIR PORTIER: Why don't we
7 open it up to any questions? Dr. Regal?

8 DR. REGAL: Yes, do you know in the
9 Rowe study, with the mice, was there any
10 mortality in the litters?

11 DR. LUEBKE: No, according to their
12 paper, they didn't see -- they didn't even see
13 any effects on pup numbers or weight gain or
14 anything, in those.

15 SESSION CHAIR PORTIER: Any other
16 questions? Yes, Dr. Holladay?

17 DR. HOLLADAY: Yes, Steve Holladay,
18 good overview. I think we've all been there
19 before, where something works well and then for
20 some reason, something changes and it doesn't
21 quite come back, but you know you did it well the
22 first time, and not much more Balb/c mouse work

1 has been done. The B6C3F1's and the C57's are
2 more T-helper 1 strains on the Balb/c, T-helper
3 2.

4 You commented in rats that a much
5 higher dose of dioxin could be used before you
6 see the immune changes in mice, and it made me
7 think of Ralph Smialowicz in that. What do you
8 use, like one-tenth of a microgram per kilogram,
9 and suppress the DTH?

10 DR. LUEBKE: That was a developmental
11 study. Now, in that study, the developmental
12 exposure to rats caused life long suppression of
13 DTH in the offspring, and the male were a little
14 bit more sensitive than the female, and that was
15 in rats, and the same sort of thing happens in
16 mice.

17 I was talking about an adult study.
18 So, the ID50 for suppression of the antibody
19 response in a C57 black 6 mouse is .7 micrograms
20 per kilogram of TCDD, and doses in rats with
21 STARS and F344's, up to 25 or 30 micrograms per
22 kilogram, don't do anything, and once you get

1 above 30, you get some enhancement of the immune
2 response.

3 DR. HOLLADAY: I guess we've got
4 automatic shutoff switch here.

5 Some of the differences, I think, are
6 undoubtedly strain related. The rat is not a
7 mouse. You have the Balb/c as a T-helper 2
8 skewed strain, or that's likely the case.

9 It makes me think too, that we're
10 seeing more and more with different compounds,
11 when we realize where we need to look.

12 I can remember when we said DES
13 produced transient effects on the immune system
14 of mouse and then we realized, if we looked in
15 different places, that these were actually
16 permanent changes.

17 Then the same became true with dioxin.
18 We described them as transient in the early 90's,
19 and then they became permanent shifts, and with
20 your different mouse models, are different models
21 of rodents.

22 In one case, you're describing immune

1 suppression and in the other case, immune
2 enhancement is being described, and I'm wondering
3 if we look in the right places, in the same or
4 different models, if we're going to see that
5 actually both occur and they co-exist, which is
6 kind of a strange phenomenon, but we're finding
7 out that in fact, it's true, when you treat an
8 animal with dioxin, they are both immune
9 suppressed and skewed toward immune enhancement.
10 It just depends on which area you're looking,
11 what part of the immune system you're evaluating.

12 So, I don't know, I wonder if some of
13 this is going on with atrazine and that's part of
14 why we're seeing these differences and -- between
15 the models. What do you think?

16 DR. LUEBKE: Okay, so, that was a
17 question. So, yes, I think that it's strain
18 related and that was the first thing I thought,
19 when I saw Rowe's antibody data.

20 The problem is, it would be
21 interesting to go back and challenge these
22 animals with a dust mite allergen and see what

1 happens, because that's the sort of model that
2 you're talking about there, and it's not just
3 endocrine disruptors that do that. We know that
4 heavy metals and a variety of things do that.

5 So, you're right, you have to use the
6 right assay, to see what's suppressed.

7 Hexachlorobenzene is a perfect example, where you
8 have some effects going this way and that way and
9 the other way, and they're auto-immune and it's a
10 real mess.

11 So, we may not have done enough assays
12 on these animals, and you know, if -- in terms of
13 immunotox hazard ID, I think the best way to look
14 at this is that we had unintended modulation at
15 the same dose in two different strains of rodent,
16 that behave immunologically different, somewhat,
17 but that's still unintended, and I think that's
18 probably the crux of the matter here.

19 DR. HOLLADAY: Something else too, that
20 I was curious about. In your mice, the thymic
21 weight didn't go down, but T-cell function was
22 changed. Do you think it's corticosteroid

1 independent, based on that, or is it too early to
2 say that?

3 DR. LUEBKE: Well, we didn't measure
4 cort levels in these animals. From all the work
5 that's been done by our colleagues over in the
6 reproductive tox group, I would have to say that
7 cort is involved here, some place. It just --

8 I mean, even if it's going to be
9 alteration of GnRH, you know, that seems to trace
10 back to an initial effect on -- you know, on the
11 HPA axis.

12 But I don't think that this is the
13 sort of sledge-hammer effects that you see, when
14 people start talking about, "Well, that's not
15 immunotoxicity. It's generalized toxicity,"
16 because you have huge levels of cort.

17 I almost wish now, that we had gone
18 back and measured cort levels on these, because
19 it would give us some idea early on in those
20 pups' lives, what their cort levels were like,
21 how long it took for them to smooth out, how long
22 before they came back to normal and whether that

1 -- you know, there are a number of studies that
2 have shown that if you do restraint stress on an
3 animal and then you come back and challenge that
4 animal later, if you -- I'm sorry, if you stress
5 mom, and you look at her offspring later, that
6 they make a much more pronounced stress response,
7 and that can have real consequences, just in
8 resistance to infectious disease, when you
9 challenge those animals with bacteria and
10 viruses.

11 But I wish that I could connect that,
12 I wish that I could tell you what prolactin
13 levels were like. I wish I could have, you know,
14 but I can't.

15 SESSION CHAIR PORTIER: Dr. LeBlanc?

16 DR. LeBLANC: What happened to thyroid
17 hormone levels in the Rooney study?

18 DR. LUEBKE: I can show you the -- no,
19 I can't. Yes, I have that on my laptop. They
20 were suppressed. They were non-detectable in the
21 day 14 PTU animals.

22 DR. LeBLANC: Okay.

1 DR. LUEBKE: Surprisingly enough, there
2 were some papers that showed that if you
3 compromise thyroid function, in -- particularly
4 in adults, you also compromise immune function.

5 That certainly did not happen here,
6 and I was, frankly, surprised, when -- you know,
7 when we did the repeat study, we got exactly the
8 same thing, that there were -- you could tell
9 that those PTU treated animals just weren't quite
10 right, as they say, but their immune function was
11 fine.

12 SESSION CHAIR PORTIER: Yes, Dr. Akana?

13 DR. AKANA: Just a small comment on the
14 troublesome sets of data that didn't repeat.

15 We lost a whole year of research and
16 it was because our university decided to do
17 construction, unplanned, all around us, and it
18 had an amazing effect, but we did publish a paper
19 afterwards called "Beware Construction."

20 So, unplanned, unpredictable
21 vibration, which they like to do at the night, so
22 they don't bother the investigators or the

1 patients, is just -- it was deathly for us, and
2 my other personal observation is, when we repeat
3 an experiment and we shift to the new barrier
4 facility, with the filtered air flow, that had a
5 decided effect on HPA.

6 So, small things, environmental, that
7 are not atrazine conducting.

8 SESSION CHAIR PORTIER: Okay, I don't
9 see any additional questions. We're going to
10 move on to Dr. Liccione and discussions of
11 neurological effects of atrazine.

12 DR. LICCIONE: Good afternoon,
13 everyone. In this presentation, I will be
14 discussing new studies that have been published
15 since 2003 on the broader effects of -- the
16 broader neurological effects of atrazine, and I
17 will be presenting our assessment of these
18 studies.

19 Okay, four new studies since 2003 have
20 been identified and were reviewed. The first two
21 pertain to monoamine systems in the brain and the
22 third one was reported on potential effects on

1 the brain somatostatinergic system, and the last
2 one was on neurobehavioral development.

3 I will just go briefly through these
4 studies. The Rodriguez study examined, in part,
5 the broad effects of atrazine on various
6 monoamines that included dopamine, serotonin and
7 norepinephrine in the hypothalamus and various
8 extrahypothalamic areas of the brain.

9 However, the focus primarily in the
10 study was still on the nigrostriatal dopaminergic
11 system.

12 This was a six month dietary study to
13 several doses of atrazine. Monoamine levels were
14 measured only at the end of the study. Locomotor
15 activity following and acute D-amphetamine
16 administration was monitored at one time, and
17 then spontaneous locomotor activity was monitored
18 at several points in the study.

19 The number of dopaminergic and non-
20 dopaminergic neurons in the substantia nigra and
21 the ventral tegmental area were measured and
22 micro-dialysis was included to examine dopamine

1 release from the striatum.

2 Coban and Filipov focused specifically
3 on the dopaminergic system, and in particular,
4 the nigrostriatal dopaminergic system and the
5 ventral tegmental area.

6 This was a 14 day oral gavage study,
7 and included various doses. Dopamine and its
8 metabolites, as well as the number of
9 dopaminergic neurons were measured in this study.

10 The third study, Giusi, reported
11 effects of atrazine on the mouse
12 somatostatinergic system in the hypothalamus in
13 various extrahypothalamic areas.

14 Dams were given atrazine in corn oil
15 solution and the rats were actually trained to
16 self-administer the solution from drinking it
17 from a syringe, and that was administered on
18 gestation day 14, through postnatal day 21.

19 The authors were trying to simulate
20 what they refer to as environmentally relevant
21 concentrations of atrazine as has -- that had
22 been detected in the drinking water.

1 The dams were removed, the F1-
2 offspring were continued with treatment. Then
3 they were sacrificed at postnatal day 60 to 65,
4 and the measurements in this study included the
5 various somatostatinergetic receptor sub-types.
6 There are five receptor sub-types, and neuronal
7 degeneration.

8 Belloni, who was actually a co-author
9 to Giusi study, investigated the potential
10 neurobehavioral development in the mouse, and
11 dams were given atrazine as was done in the Giusi
12 study, on post-day -- on gestation day 14 to
13 postnatal day 21.

14 Various neurobehavioral parameters
15 were measured. This included writing reflex,
16 cliff aversion, four-paw grasp, auditory startle.
17 They also look at pup ultrasound vocalization.
18 Auxiliary temperature and body weight were also
19 measured.

20 This slide summarizes our overall
21 assessment of the monoamine studies. The brain
22 monoaminergic studies indicated potential broad

1 effects of atrazine on dopamine, norepinephrine
2 and serotonin, as well as a decrease in the
3 numbers of dopaminergic and non-dopaminergic
4 neurons in the substantia nigra and the ventral
5 tegmental area.

6 Only one study, that's the Rodriguez
7 study, actually provided some evidence of altered
8 behavioral responses. The overall findings from
9 these studies, however, are inconclusive because
10 of the number of limitations that I will discuss
11 briefly in the next slide.

12 Okay, limitations of the study include
13 the very small sample size that were used for the
14 stereology, the reverse transcriptase polymerase
15 chain reaction and the immunohistochemistry
16 experiments, to illustrate the impact of this.

17 In the Rodriguez studies, the results
18 of the stereology were based on a very small
19 sample size, and there was high individual
20 variability in the count data, when you looked
21 across all of the groups, and the decrease count
22 that was reported at the high dose, reflects a

1 decrease in the counts in a few individuals when
2 you're considering the variability range.

3 They only presented median values.
4 Other statistical data, such as the mean and
5 standard deviation, coefficient variation,
6 interquartile range were not available, that
7 would help interpret the statistical dispersion
8 that you can see in the data.

9 The high variability raises some
10 questions in the precision of the stereological
11 estimates.

12 There was limited information on the
13 sampling procedure that they used and there was
14 no statistical data that would give you a clue on
15 the biological variation and the coefficient
16 variation, because these estimates, along with
17 the coefficient of error would give a better
18 assessment of the precision of the study, which
19 is very important in stereological examinations,
20 and insight that will give you an idea of the
21 biological variation between individuals and the
22 variance of the estimates at the level of the

1 respective individual brain regions.

2 There was also a lack of a dose
3 response in these studies and there was also
4 overall, minimal alterations in the monoamine
5 levels.

6 The minimal changes in the dopamine
7 was also noted in the Rodriguez's micro-dialysis
8 experiment, which they commented on, when they
9 tried to interpret the lack of the change of
10 dopamine metabolites, DOPAC and HPA.

11 And the lack of dose response was also
12 evident in the count data for the dopaminergic
13 neurons, that was reported in the Coban and the
14 Filipov study.

15 There's also a lack of supporting
16 evidence. For example, in all of these studies,
17 there were either no photomicrographs on the
18 reverse transcriptase polymerase chain reaction
19 and immunochemistry results or only a few that
20 were of very poor quality.

21 Both studies also relied on positive
22 tyrosine hydroxylase immunoreactivity in those --

1 as well as the stereology, to assess the actual
2 changes in the number of neurons, and Coban and
3 Filipov expressed this very well, the limitations
4 of this, where he acknowledges that it is unknown
5 if the decrease in the positive tyrosine
6 hydroxylase immunoreactivity is actually due to
7 neuron mortality or the loss of the positive
8 tyrosine hydroxylase phenotype.

9 Other quantitative approaches, for
10 example, morphological methods, would have been
11 useful to support their conclusions, given the
12 limitations, such as the small sample size, the
13 variability, the minimal changes in dopamine, the
14 lack of a dose response and limited or no
15 behavioral measures.

16 Now, to discuss a little bit about
17 behavior, I want to just elaborate, just a little
18 more.

19 In the Rodriguez study, it was not
20 possible to fully correlate the reported
21 increased locomotor activity with the levels of
22 dopamine levels, which were measured only at the

1 end of the study.

2 A rationale for D-amphetamine
3 selection was not given and only one dose was
4 examined.

5 The persistent locomotor activity that
6 was reported as puzzling and is uncertain, as to
7 what -- how to interpret this.

8 There was no inclusion of any direct
9 dopamine receptor agonist and antagonist, as well
10 as any kind of receptor binding assays in the
11 study design.

12 All of these limitations are important
13 to consider because the authors concluded that
14 the altered behavioral response to D-amphetamine
15 may be due to an up-regulation of the striatal
16 dopamine receptors by atrazine, yet, they
17 provided no support for this critical hypothesis.

18 Their alternate hypothesis, that the
19 response may be due to dopamine release produced
20 by atrazine is actually not supported by their
21 own data, and that of Coban and Filipov, and in
22 Rodriguez's micro-dialysis study, it actually

1 shows that atrazine actually attenuated the basal
2 and high potassium stimulated release of striatal
3 dopamine.

4 Coban and Filipov did not include any
5 behavioral measurements at all, to assess any of
6 the relevancy of the reported changes in the
7 dopamine and the metabolites in the dopaminergic
8 neuron counts.

9 This is important because in the Coban
10 and Filipov study, the reported loss of dopamine
11 neurons did not correlate well with the dopamine
12 and metabolite changes at the various time points
13 that were measured. In addition, there was no
14 inclusion of dopamine receptor agonist and
15 antagonist, or any receptor binding assays that
16 would clarify the observations.

17 And another problem with the Coban and
18 Filipov study is although they studied the total
19 neuronal population that would include some of
20 the non-dopaminergic neurons, at various time
21 points, they did not actually present this data
22 with very good stereological estimates and that

1 is another limitation of the study.

2 Okay, finally, another important point
3 that I want to address is that the authors, in
4 particular, Coban and Filipov, suggest a link
5 between atrazine exposure and human neurological
6 disorders, in particular, Parkinson's disease.
7 But the data did not support this for several
8 reasons.

9 Although it is limited, the Rodriguez
10 study suggests potential non-specificity of
11 atrazine effects on monoamine levels in neuronal
12 populations other than dopaminergic neurons,
13 which contrasts with the clinical picture of
14 Parkinson's disease and what was known with
15 animal models of Parkinson's disease, which
16 reflected clearly a selective degeneration of
17 nigrostriatal dopaminergic pathway.

18 More over, the results of the
19 Rodriguez study suggest potential effects on
20 hypothalamic serotonin, as possibly more
21 sensitive than dopamine, and -- but no additional
22 investigation of this was actually performed.

1 This is important because the authors,
2 in turn then, concluded that the effects on the
3 hypothalamic serotonin are consistent with
4 atrazine's neuroendocrine alterations, which we
5 know to date, are the most sensitive effects of
6 atrazine.

7 They did not explore this further, but
8 simply focused on the nigrostriatal dopaminergic
9 system.

10 In addition, the Coban and Filipov
11 study suggests that there is a maximal limit in
12 the loss of dopaminergic neurons, which again, in
13 contrast what is known with the clinical picture
14 of Parkinson's disease, which involves a
15 progressive loss of neurons, which can culminate
16 in greater than 50 percent of the neuronal loss.

17 There is also a lack of histological
18 behavioral correlates that you see with
19 Parkinson's disease. Neither in vivo study
20 demonstrated any significant increase in dopamine
21 turnover rates, which would be typical of the
22 clinical picture in Parkinson's disease and what

1 you see in -- with animal models of Parkinson's
2 disease.

3 None of them included any clear
4 positive controls for Parkinson's disease, like
5 6-hydroxydopamine or MPTP, that would help to
6 support or -- their claims.

7 The limitations of the studies,
8 besides the limitations that I mentioned, another
9 limitation that would impact any conclusion on
10 Parkinson's disease relates to the lack of the
11 examination of neuronal loss in the striatum, per
12 se. The focus was only on the substantia nigra
13 pars compacta and the ventral tegmental.

14 Now, since Rodriguez' study indicates
15 non-selectivity of neuronal loss, this would be
16 important and had they looked at this, this might
17 clarify some of the potential effects that
18 they're seeing, and also, it would be a good
19 comparison with what is known with Parkinson's
20 disease.

21 Finally, the epidemiological evidence
22 itself, to date, does not support a link between

1 atrazine exposure and Parkinson's disease or any
2 other neurological disorders.

3 Okay, moving onto the brain
4 somatostatinergic system, the Giusi study
5 reported altered expression of specific
6 somatostatin receptor sub-types in the
7 hypothalamus and various extra hypothalamic
8 regions of the brain in the males and female
9 mice.

10 However, the findings are inconclusive
11 because of serious limitations that limited its
12 use in risk assessment.

13 Limitations of the study include the
14 small sample size that they used for the staining
15 to assess neuronal degeneration, the reverse
16 transcriptase polymerase chain reaction and the
17 in situ hybridization experiments.

18 There was a lack of supporting
19 evidence. For example, somatostatin, per se, was
20 not measured, that would have supported the
21 neuronal degeneration and possibly provide some
22 insight into the up-regulation and the down-

1 regulation that they were reporting in the
2 various receptor sub-types.

3 No in situ hybridization photo-
4 micrographs were provided for support. There was
5 no functional assessment of the reported changes,
6 for example, behavioral tests, growth hormone
7 measurements, which was one of the rationales for
8 looking at the study, or any other hormonal
9 measurements.

10 There was no -- the study design also
11 did not include any specific somatostatin
12 receptor antagonist, that would help to explain
13 all of this up-regulation and down-regulation
14 that is very confusing to understand.

15 There were some discrepancies between
16 statements made in the text, that were not
17 supported by the reference citations. There was
18 a lack of details on the age and body weights of
19 the mice used in the source and purity of
20 atrazine.

21 The study also did not include any
22 measurements of systemic toxicity that might be

1 confounding factors, and the photo-micrographs of
2 the amino cupric silver staining were of poor
3 quality. This is important because this is the
4 evidence that they used to support the neuronal
5 degeneration.

6 Finally, there was actually no
7 quantification of the neuronal degeneration,
8 especially in supporting an important conclusion
9 by the authors who state, in the dentagyros, the
10 neurons showed a rather significant overall
11 reduction in the total number of neuronal cells.

12 But yet, no quantitative data were
13 provided with appropriate statistical analysis to
14 support a very critical conclusion and no photo-
15 micrographs of the dentagyros were actually
16 provided.

17 And all of these limitations would
18 help to help in assessing the -- what is going
19 on, because it was very difficult to correlate
20 the neuronal degeneration with -- consistently
21 with the changes in neuronal expression of the
22 somatostatin receptors, as an example, in the

1 high dose female, you will see some hippocampal
2 degeneration, but no change in the neuronal
3 expression.

4 Okay, now, for the neurobehavioral
5 development study, the Belloni study reported
6 alterations in writing and grasping reflex and
7 also, ultrasound vocalization in mouse pups.
8 They also reported decreased auxiliary
9 temperature.

10 The findings, we think, are
11 inconclusive because of the serious limitations
12 of the study.

13 Limitations include inappropriate
14 statistical analysis. The authors relied
15 primarily on the pup as the statistical unit.
16 The failure to count for the litter effects can
17 result in an increase in Type-1 errors and
18 overestimate any of the effects, thus, reducing
19 the validity of the findings.

20 In addition, there was no convincing
21 statistical evaluation of the potential
22 interactions, for example, sex, age and

1 treatment, which the authors claim.

2 There were two -- there were a number
3 of discrepancies in the reported number of pups
4 that were evaluated in the tables, which raises
5 questions about the accuracy of the results that
6 were reported.

7 There was no clear dose response
8 relationship for the reported effect on the
9 number of ultrasound vocalization and auxiliary
10 temperature. These effects were noted only in
11 the low dose mice, but not in the high dose mice,
12 and the authors did not provide any support for
13 their hypotheses that were put forth, to explain
14 the lack of the dose response.

15 They hypothesized effects on aromatase
16 modulation and hormone levels, but no
17 measurements -- such measurements were actually
18 made to support in -- at their conclusion.

19 In addition, Belloni acknowledged that
20 they cannot exclude the possibility that the
21 hormonal alterations in the dams may have
22 resulted in altered maternal care and

1 consequently, in altered pup behavior, and as I
2 mentioned, those -- the study did not examine
3 hormonal levels, which would clarify this as a
4 possible confounding factor.

5 And another important point is that
6 the spectrographic analysis of the ultrasound
7 vocalization were very limited. It's not clear
8 to me, why considerably less number of pups that
9 were evaluated for the number of ultrasound
10 vocalization were subsequently examined for
11 spectrographic analysis, and this was an
12 important measurement to assess the various
13 specific parameters of the ultrasound
14 vocalization, especially since the authors
15 conclude that lower atrazine exposure was more
16 effective than the higher dose in modifying
17 behavioral response.

18 There was also a lack of objective and
19 validated behavioral methods. The authors relied
20 on methods published in 1965 and the final point
21 was that there was no neuropathology that would
22 help to clarify some of the results.

1 In conclusion, the recent
2 neurotoxicity studies of atrazine on the brain
3 monoaminergic and somatostatinergetic system and
4 neurobehavioral development, because of the many
5 numerous limitations, are -- did not provide any
6 definitive conclusions, and the effects on
7 neuroendocrine function, we think, are still the
8 most sensitive effects of atrazine.

9 SESSION CHAIR PORTIER: Okay, any
10 questions? Dr. Chambers?

11 DR. CHAMBERS: John, I was trying to
12 assess the dose levels of these things, and I was
13 confused when I read the Rodriguez paper.

14 Since that was a dietary study, how
15 did they go about assessing that those were the
16 dose levels?

17 Not the rationale, it's just, I didn't
18 get a sense of how they assumed it was five
19 milligrams per kilogram per day, when it was a
20 dietary study. They didn't describe that very
21 well, did they?

22 DR. LICCIONE: No, they did not

1 describe it. They reported the results at five
2 milligrams and 10 milligrams per day, but they
3 don't provide any information to verify how that
4 was derived.

5 A lot of these studies don't give any
6 information on quantification of the samples, any
7 analytical measurements, food consumption. I
8 think that would have helped to support their
9 conclusion.

10 So, I agree with you, that that's
11 another limitation that one could actually add to
12 the study.

13 SESSION CHAIR PORTIER: Dr. LeBlanc?

14 DR. LeBLANC: Do you have any idea if
15 the Giusi and the Belloni studies represent the
16 same experiment, with different analyses
17 performed?

18 DR. LICCIONE: Well, the study design
19 is the same, but there are -- there were some
20 differences in a sense, that the Giusi study --
21 they removed the dams -- then the Fls were
22 treated for a longer time, but as far as I can

1 tell, they were not part of the same experiment,
2 but one wonders, if they were two overlapping
3 studies, if that's what you're asking.

4 DR. LeBLANC: So, in the Belloni study,
5 the pups weren't treated?

6 DR. LICCIONE: Right, that's true.
7 They were trying to look at lactational and it --
8 in gestational lactational exposure to the pups
9 only. In fact, they actually state that they
10 prevented the pups from drinking from the
11 syringe.

12 So, there are differences in the
13 study.

14 SESSION CHAIR PORTIER: Yes, Dr. Reed?

15 DR. REED: I think what the Rodriguez
16 study -- I think -- I thought they restricted the
17 diet, so that they can do the calculation. They
18 didn't just let the animal eat as much as they
19 want. So, that was how they calculate the dose.
20 I think there was --

21 DR. LICCIONE: It wasn't clear to me,
22 from --

1 DR. REED: But I have a separate
2 question. I agree, then when I was looking at
3 these studies, they're not -- you know, they have
4 holes and gaps.

5 When I see your conclusion, saying
6 that the other, you know, endpoints were still
7 more sensitive, so, my question to you is, would
8 you be thinking of -- because some of the
9 deficiencies are reporting deficiencies and so
10 forth, that you might be able to go back to the
11 authors and say, "You know, if you have
12 something, some information, some protocol and
13 study design," you cannot.

14 DR. LICCIONE: Right.

15 DR. REED: The litter effects and how
16 they called the litters, and stuff like that.

17 DR. LICCIONE: That's an interesting
18 question, because give this some thought. If you
19 look at the Rodriguez study, which is a very
20 interesting -- is that the very first initial
21 results that they report are on brain
22 norepinephrine, dopamine and serotonin,

1 indicating a non-specificity of effect.

2 Then they jump in to the nigrostriatal
3 dopaminegic pathway, without any good rationale.
4 The only thing I can think of is maybe the lab is
5 comfortable with that, they're specialized in
6 that. Same thing with Filipov.

7 However, given that you're seeing
8 hypothalamic serotonin -- and Rodriguez actually
9 acknowledges that, this may be related to the
10 neuroendocrine effects, it seems like, to me, the
11 more proving experiment would have been to study
12 that, rather than focusing so much on dopamine
13 and Parkinson's -- and trying to -- you know,
14 with Filipov's study, I thought I was reading a
15 new model of Parkinson's disease.

16 So, I think the right experiment would
17 be to look at this, especially since the
18 serotonin was reported, it looks like it may be
19 more potential, but the results are limited,
20 because they only did a preliminary assessment of
21 these monoamines.

22 It seems like to me, that the

1 neuroendocrine in serotonin thing might be more
2 fished out, rather than relying on dopamine.

3 DR. REED: And that was actually one of
4 the questions that I was curious about, in that
5 given all the gaps and deficiencies these studies
6 have, my question was since -- you know, your
7 conclusion is that they're still not the most
8 sensitive endpoints, but apparently, you have
9 some idea of how the study could be conducted, as
10 you were just describing.

11 Would you be interested in designing
12 something, just to see, you know, what the
13 endpoint is going to fall out to be, because for
14 example, I think most of them were very high dose
15 studies --

16 DR. LICCIONE: Right.

17 DR. REED: -- but the Rodriguez study
18 was, you know, five --

19 DR. LICCIONE: Five milligrams, the
20 lowest dose.

21 DR. REED: And they were seeing some
22 effects. So, my question to you, so, it's

1 getting close to the endpoint issue, in terms of
2 what is most sensitive. Are you thinking of
3 designing something that could get the answer
4 that you were looking for?

5 DR. LICCIONE: I haven't given --

6 DR. LOWIT: John, if we could answer
7 that. Liz, do you want to jump in?

8 SESSION CHAIR PORTIER: That's Anna
9 Lowit.

10 DR. LOWIT: Yes, sorry, and I've been
11 moving around chairs. That's a good question. I
12 think the short answer would be, we're not sure
13 of the value of what those studies would be, and
14 if there is an argument that those studies would
15 be valuable, with respect to keeping in mind,
16 that at the end of the day, we're asking risk
17 assessment questions, and if you could design an
18 experiment that will lead you to something of a
19 lower endpoint, of a shorter duration, that's in
20 a separate direction from where the HPA,
21 particularly new data, is leading us, which we
22 think was going to really drive many of those

1 regulatory decisions.

2 So, you're a regulator, you know how
3 it goes. If it's something that's going to --
4 that you believe would change the direction of
5 the assessment, I think those would be valuable.
6 But that's the question, how valuable would those
7 experiments be?

8 SESSION CHAIR PORTIER: Dr. Horton?

9 DR. HORTON: I have more of a comment
10 than a question here, because I think, in
11 response to your question, in terms of the
12 development of the neuroendocrine system, with
13 respect to both the hypothalamic-pituitary-
14 gonadal axis and the hypothalamic-pituitary-
15 adrenal axis, both of those are in play, at this
16 point.

17 Anything that's going to influence the
18 development, and since things seem to be pointing
19 back to the developing axes, we do know that in
20 the development of those, both the BNST and the
21 brain regions that we're talking about right now
22 play important roles.

1 Also, the hippocampus plays important
2 role in the regulation of those areas, and that
3 if there's anything that's going to have a toxic
4 effect, or not even a toxic effect, but alter the
5 developmental pathways of those in a plastic way,
6 we need to be aware of it.

7 And so, if there's anything in this
8 data that suggests that that might be there, then
9 it's probably worth going back and evaluating
10 those under-properly controlled and properly
11 designed studies.

12 DR. LOWIT: Just one follow up and we
13 can probably close this.

14 To the extent that, you know, that
15 there is science to support those things, we
16 would encourage it to appear in your report, or
17 in your deliberations over the next few days.

18 I just want to be weary, that -- and
19 in the days of limited resources and moving
20 towards less animals and not more, that we design
21 those experiments in a way that we get the most
22 out of them.

1 SESSION CHAIR PORTIER: I think we will
2 go on. I would like to say, I'd like to see one
3 of these studies done with adequate sample sizes,
4 though.

5 We've seen a lot of neurotox studies
6 and they're always under-powered, for the kind of
7 results they're looking for, and it's very
8 frustrating, because I think we all kind of
9 agree, that this should be important, but why
10 aren't we putting the effort into those studies?

11 Dr. Mendez, you have a summary.

12 DR. LOWIT: And we're doing a computer
13 pass, as we speak. Well, maybe Liz can start
14 talking, since we're running really late.

15 SESSION CHAIR PORTIER: How many mics
16 can we drop? He's got it untangled. Now, watch
17 the water jug.

18 DR. MENDEZ: I sure require a lot of
19 assistance, don't I? Just give me one second.
20 Okay, I don't think this is mine.

21 All right, I promise, I'm going to try
22 and move quickly, and pick up the pace here.

1 So, what I wanted to sort of do is
2 bring us back, wrap things up, as to where we are
3 and where we hope to go, between now and
4 September.

5 The status of the reevaluation, we
6 have reviewed approximately 100 studies that have
7 a wide range of topics, from mode of action,
8 reproductive and developmental effects,
9 immunotox, neurotoxicity and carcinogenesis.

10 You'll notice that we did not talk
11 about the carcinogenesis when we were putting
12 this paper together. We were hoping that we
13 would be able to address cancer issues in
14 September.

15 As that is not the case, we've chosen
16 to defer that conversation so that we can look at
17 both the animal and the epi data together.

18 We still believe that the effects of
19 neuroendocrine function are the most sensitive
20 effects, based on the data that we have in front
21 of us today.

22 We continue to evaluate additional

1 studies that have become available since
2 February, and studies that will become available,
3 hopefully, in the spring and summer.

4 Having said that, where are we right
5 now? Mode of action, our understanding of the
6 mode of action is expanded.

7 In 2003, it all hinged about the
8 perturbation of the HPG axis and that is still
9 applicable. The activation of the HPA axis,
10 however, has come into play over the past seven
11 years, and we think that it may precede the
12 effects on HPG axis, and Dr. Fenner-Crisp
13 actually alluded to that a little earlier, in one
14 of her questions.

15 We see changes in ACTH, corticosterone
16 and progesterone, within minutes of exposure.
17 However, the toxicological significance of these
18 adrenal hormone changes per say is still unclear
19 to us. Were those 15 minute blips sufficient to
20 cause an adverse health outcome?

21 From the data that Dr. Cooper
22 discussed earlier today, we believe that there is

1 a general stimulatory effect in steroidogenesis,
2 not necessarily a direct effect on aromatase.

3 We see the delays in puberty onset in
4 both genders. Prostatitis is related to decrease
5 in prolactin and atrazine exposed dams during
6 lactation, and we didn't talk a lot about that
7 today, but it's described in the paper in some
8 detail, and the mammary gland tumor development,
9 based on the findings in the -- and the
10 conclusions of the 2000 SAP and what we have in
11 front of us today, still do not appear to be
12 relevant to humans, in terms of the mode of
13 action that we're addressing today.

14 Oh, this is a little skewed, but this
15 is a schematic that appears in the paper, about
16 the mode of action. Can I have the pointer,
17 please?

18 And what -- I'm not going to go
19 through each one of these steps. I think that
20 what's important to keep in mind is that we had
21 some of these steps back in 2003. We had the
22 GnRH pulses going down. We had the decreases in

1 LH and prolactin, and we had the gonadal changes
2 that led us to the altered reproductive function.

3 As important as the understanding of
4 the additional steps are, as they pertain to the
5 HPA axis, one of the things that I find very
6 important about this, one of the reasons why I
7 like this particular schematic is, to my mind's
8 eye, this almost looks like a house, and the idea
9 that in 2003, we had this mode of action data,
10 and the foundation of that house is still solid,
11 seven years later. It still stands, and that's
12 important, that's an important message to take
13 home, in my mind.

14 Immunotoxicity, I'm going to really
15 fly over this. Immunotoxicity exposure during
16 development may lead to altered immune function
17 of the offspring. However, that does not appear
18 to be more sensitive than the atrazine induced
19 effects on neuroendocrine function, and as Dr.
20 Luebke alluded to, during his talk, it may be
21 related to some of that GnRH changes, that we're
22 seeing.

1 Immunotoxicity, we've just had a
2 discussion about that. Based on the data that we
3 have in front of us, it does not appear to be
4 more sensitive than the atrazine induced changes
5 in neuroendocrine function, and it does not
6 appear to be related to Parkinson's disease.

7 So, where does that leave us? Well,
8 that leaves us with the understanding that the
9 toxic effects are due to multi-level interactions
10 of a variety of systems, neuroendocrine,
11 reproductive, nervous, immune.

12 At the activation of the HPA axis is
13 followed by the disruption to the HPG axis, which
14 then leads us to the most sensitive effects
15 attributed to atrazine exposure, but what is
16 still not clear is the extent of HPA activation,
17 both in terms of duration or dose level, that
18 meet -- that are needed to elicit the decrease in
19 GnRH, and subsequent LH surge attenuation.

20 All right, so, I just told you where
21 we are, as of today, and we sort of give you the
22 coming attractions.

1 The next steps in preparation for
2 September, as we want to apply the mode of action
3 framework to analyze the data that we have in
4 front of us. We want to further characterize the
5 HPA/HPG axis interactions, describing the
6 temporal relationship between HPA axis activation
7 and adverse health outcome.

8 We want to better describe the dose
9 response relationship between atrazine exposure,
10 HPA axis activation and adverse health outcomes.
11 We have some data that we hope will be coming in,
12 in the spring and the summer, that will help us
13 address these two issues.

14 Once we have that data, we intend to
15 conduct benchmark dose analysis, to better
16 characterize the dose response curve for the
17 effects on HPA and HPG.

18 Dr. Cooper alluded that some studies
19 we had in NOAEL-5 and in LOAEL-50, we'd like to
20 be able to define that a little bit better.

21 We have additional review of data that
22 is coming in, in the spring and summer. Again,

1 data available between February 2010 and July
2 2010, in the mammary gland development, which is
3 a separate issue from the tumorigenesis.

4 We have decided to postpone that
5 conversation because we are aware that there are
6 data that will be hopefully published very, very
7 shortly, that will really help us have a fuller
8 picture and a fuller understanding of that issue,
9 and we felt that it was best that rather than
10 roll it out piecemeal, to bring it all together.

11 We need to start thinking the duration
12 of exposure. How long must somebody be exposed,
13 before an adverse outcome occurs?

14 Life stages, we all know that response
15 to chemical exposure may vary through life
16 stages. How do we do that, in terms of atrazine?

17 We've seen that we have a variety of
18 effects, whether we have animals expose pre-
19 natal, perinatal or postnatal. So, we need to
20 start thinking about that, as we think about the
21 risk assessment.

22 What is the life stage that we really

1 need to be protecting and therefore, will protect
2 all other life stages?

3 We are going to review the available
4 non-cancer epi data. We're going to start
5 working on a weight of evidence analysis
6 integrating the experimental tox data and the epi
7 data.

8 If warranted, we intend to propose new
9 points of departure. We will reevaluate the FQPA
10 safety factor and we will reconsider the drinking
11 water sampling strategy, in relationship to the
12 toxicological duration of concern, because we all
13 understand that the shorter duration of
14 toxicological concern may lead us to more
15 frequent sampling.

16 So, as I said, we're going to apply
17 the moral framework. Let me tell you where we
18 are, within that process.

19 Postulating the MOA, can the MOA be
20 established in animals? Well, we already had the
21 HPG axis that's been going through review, so, we
22 have the MOA in the animals.

1 We're going to describe the key
2 events. We've been starting to do that, as we
3 talked about the changes in ACTH, the changes in
4 cort, changes in progesterone. That's where we
5 are at this point.

6 We're going to start working on
7 establishing the dose response concordance and
8 establish the temporal concordance.

9 Once we've narrowed that down a little
10 bit further, then we'll proceed with the
11 analysis, talking about the strength and
12 consistency of the finding, the biological
13 possibility, whether other MOA's can be ruled
14 out, and the statement of confidence analysis and
15 implications.

16 So, additional data that we expect in
17 the spring and summer, sort of wet your appetites
18 for what's coming.

19 We have studies coming on in effect of
20 four day atrazine exposure on ACTH, cort,
21 progesterone and LH. Effect of atrazine on
22 steroidogenesis in rat granulosa cells, and that

1 study has actually been submitted for
2 publication.

3 Effect of atrazine exposure on GnRH
4 and kisspeptin neuron regulation. Effect of
5 gestational exposure to atrazine, an oral gavage
6 immunotoxin and hormone evaluation study for the
7 effect of atrazine in male rats, and male
8 prostate inflammation on low dose metabolite
9 exposure, and that manuscript is in preparation.

10 Other data that we expect is oral
11 study of effects of atrazine on estrous cyclicity
12 and the estrogen induced hormone surge in female
13 rats, comparison of effects of atrazine on
14 pulsatile LH release and the LH surge in non-
15 adrenal-ectomized compared to adrenal-ectomized
16 female Wistar rats, and I believe that somebody
17 in the Panel asked about that. We know that the
18 study is underway, we just don't have the data
19 yet.

20 Use of a PBPK model, to characterize
21 atrazine by transformation to inactive moieties,
22 in relationship to dynamic changes in hormone

1 levels, and potential adverse outcomes, and a
2 dose response modeling and determination of
3 points of departure for risk assessment and the
4 validation methods for that.

5 So, what we hope to do with the dose
6 response concordance is establish the extent of
7 corticosterone changes needed to result in
8 adverse health outcome, incorporate this data in
9 the point of departure and determinations as
10 needed, and with regards to temporal concordance,
11 situation of changes in GnRH, ACTH,
12 corticosterone and progesterone needed for an
13 adverse health outcome, changes seen within
14 minutes, sustain changes need to elicit the
15 adverse outcome, one day, four days, one week.

16 We do know that atrazine and its
17 metabolites are quickly absorbed and distributed
18 in the body, so, we need to take that into
19 consideration, as we move forward in our
20 analysis.

21 And just a little bit about the
22 mammary glands development. These are some of

1 the data that are currently available and it's
2 the adverse effects. You can see -- you can read
3 them as well as I can.

4 A number of studies are currently
5 available in the literature, about potential
6 adverse effects on mammary gland development and
7 a few more are coming.

8 Atrazine dose dependent effects on
9 mammary gland development in Sprague Dawley's and
10 Long-Evans rats, the effects of atrazine induced
11 mammary gland effects in Sprague Dawley and Long-
12 Evans rats and carcinogen induced tumor incident,
13 and an oral development study of atrazine in the
14 rat, including cross-fostering and pair feeding.

15 The Agency already has that last
16 study, but because it speaks to the mammary gland
17 development, we have deferred the discussion to
18 it for a later date.

19 And then the 2011 SAP on
20 carcinogenesis, AHS epidemiology study on
21 atrazine in human cancer publication, we hope
22 that that will happen some time by the end of

1 this year. We integrate experimental
2 carcinogenesis data and the epi data, AHS and
3 other cancer epidemiology studies, and we will be
4 seeing you then, in 2011.

5 So, if there are no questions --

6 SESSION CHAIR PORTIER: Any questions?
7 Dr. Krishnan?

8 DR. KRISHNAN: A minor one, related to
9 the -- your house pictorial, number five slide.

10 Actually, I was -- since it's more of
11 a statement of the mode of action, I was looking
12 for some level of statement about the dose
13 metrics involved or the consideration of
14 alternative dose metrics.

15 So, I know if it's a split-level or
16 cottage, I could see that, but I don't see the
17 final connects of this. So, if you just want to
18 clarify what level of thinking has gone into that
19 or is it only the pharmaco-dynamic, if you will,
20 without potential toxic being captured in here?
21 What was intended?

22 DR. MENDEZ: At this point in time, my

1 intent with the little house was to sort of
2 illustrate the key events.

3 We are thinking about the PK aspects
4 of it, but that's not at this point, in there,
5 just yet.

6 SESSION CHAIR PORTIER: Dr. Fenner-
7 Crisp?

8 DR. FENNER-CRISP: I guess my question
9 earlier, goes to whether or not your roof is
10 leaking. The point being whether or not the
11 whole left side of the roof exists. That was --
12 I interpreted that step one as being the old
13 direct effect.

14 DR. MENDEZ: So, your question was
15 about step seven?

16 DR. FENNER-CRISP: No, one, one.

17 DR. MENDEZ: Okay.

18 DR. FENNER-CRISP: The roof. Does the
19 whole roof exist? That was the essence of my
20 question earlier. Is there evidence to support a
21 direct effect of atrazine in this whole thing, or
22 is it all going to be shown to be indirect

1 through initial disruption in HPA to get to the
2 disruption in the HPG?

3 DR. MENDEZ: Ralph, you want to attempt
4 it?

5 DR. COOPER: Yes, I think I understand
6 the question. I think that right now, the -- I
7 just told Dr. Levine, this looks more like -- it
8 needs an arm out there, to be a children's swing
9 set, and --

10 But one and seven, seven are the -- if
11 we put it this way, I think based again, on the
12 temporal aspects, at least for the CNS ACTH
13 response, I'd argue that one is centrally up
14 there. If it's not at the brain, it's so rapid,
15 it would have to be brain impaired. So, that one
16 still exists.

17 Whether GnRH is still the target, I
18 think it's -- those shingles are still there, but
19 seven, there's an increasing number of shingles
20 on that roof, that says that seven is growing
21 credence, if nothing else.

22 So, but so, that means then -- and you

1 know, we always think linearly, or we always
2 think sequentially, and they say tox pathways
3 paint us in these boxes that are lines, and this
4 is more -- we understand, given the assumption,
5 anyway, right now, that we're dealing with a very
6 basic cellular mechanism, disruption of maybe
7 cyclic AMP signaling, and we're going to have a
8 lot of pits in the whole neuroendocrine axis.

9 So, I'm not going to place my bets on
10 whether that roof is going to hold up under a lot
11 of scrutiny, but seven seems to be winning out,
12 right at the moment.

13 SESSION CHAIR PORTIER: Okay, is most
14 of this team going to be available tomorrow
15 morning, because I doubt if we're going to get
16 through all of the EPA presentation today, at
17 this point, since we're running about 45 minutes
18 behind.

19 I'm just wondering if the Panel has
20 questions in the morning, and we have kind of an
21 open -- Anna, will any, or most of these people
22 be available?

1 DR. AKANA: We're all here, all the
2 meeting.

3 SESSION CHAIR PORTIER: Okay, good.

4 DR. AKANA: Including our colleagues
5 from North Carolina.

6 SESSION CHAIR PORTIER: Okay, good.

7 Okay, I think we need probably a few minutes, for
8 you to change over to the hydrology groups and
9 so, we can stand, but don't leave the room,
10 unless you really have to.

11 (Whereupon, the above-entitled matter
12 went off the record at 5:13 p.m. and resumed at
13 5:16 p.m.)

14 SESSION CHAIR PORTIER: Let's begin
15 again. Just for the Panel's -- just so you know
16 my thinking, I think we probably will try to get
17 through six o'clock, but depending on the -- I
18 guess, we'll ask the -- Mr. Thurman, when he
19 wants to make the break, but I'm certain that
20 we're going -- we probably won't get the summary
21 and conclusion until tomorrow morning, and maybe
22 -- you know, the water sampling summary, until

1 tomorrow morning and maybe the artificial neural
2 network might be a good topic for tomorrow
3 morning.

4 Okay, Mr. Thurman is going to be
5 starting the discussion on evaluating the water
6 sampling strategies.

7 MR. THURMAN: Okay, I thought I'd start
8 out, because it seems odd to have water sampling
9 in the middle of a toxicity SAP. So, I'm going
10 to kind of remind you why we're here.

11 You know, in light of new science, we
12 may end up looking at a different endpoint than
13 we looked at for the 2003 -- based on 2003 RED,
14 and if that's the case, the question is going to
15 become, we had registrants do monitoring study in
16 community water systems in vulnerable areas with
17 a sampling frequency sufficient to characterize
18 in 90 day exposure period.

19 They sampled weekly during that --
20 during the use and run-off season and biweekly in
21 other parts of the year. If we end up with a
22 shorter duration, the questions that are going to

1 be coming to us are, well, how well does that
2 existing monitoring design characterize the
3 shorter durations of exposure, if they don't, do
4 you need to sample more frequently, in order to
5 do that?

6 We want to be able to answer those
7 questions when they come, instead of having to
8 say, well, wait, we've got to go separately.

9 One thing I'm going to point out, this
10 is a question that doesn't just apply to
11 atrazine. It's the type of question we wrestle
12 with, with other pesticides as well.

13 Atrazine is a little unique, and we're
14 going to be focusing on atrazine because it's
15 probably got more monitoring data than you're
16 going to see in all of the other pesticides
17 combined, and that may be a hyperbole, but the
18 point is, atrazine may be one of the few
19 pesticides where we're able to do drinking water
20 exposure almost entirely on monitoring, rather
21 than supplementing monitoring and modeling
22 together.

1 So, that does make it unique, but we
2 are interested in what may apply beyond this.

3 Very quickly, I'm going to provide you
4 with some considerations, you need to take into
5 account, both in designing a monitoring study and
6 evaluating existing monitoring studies. Then,
7 I'm going to provide an overview of some of the
8 approaches we've been looking at, for analyzing
9 monitoring data of varying sampling frequencies
10 and in terms of applying through various
11 durations of exposures.

12 Then, we will either get to one or
13 both of these example approaches that are in the
14 background paper we gave you, today, or split it
15 between today and tomorrow, and then I'll come
16 back and provide you with a summary.

17 The next few slides are going to
18 illustrate the -- how -- the complex spatial and
19 temporal patterns we find in pesticides in water.
20 Some of the other -- these factors all -- from
21 the temporal and spatial patterns, to the
22 temporal autocorrelation, which means the

1 pesticide concentrations you measure on one day
2 are related to exposures that you would find the
3 day before, and the day after.

4 We also tend to find, when we talk
5 about sensor data, we're talking about pesticide
6 concentrations that are below a level of
7 detection, and we often see infrequent sampling.

8 All of this provides us with
9 challenges, both in terms of looking at a
10 monitoring study design, as well as interpreting
11 that, and so, I want to make sure we have that
12 background, as we go forward.

13 You saw this map in Anna's
14 presentation. I'm not going to spend too, too
15 long on this, I hope. When you're looking at
16 spatial -- and we know atrazine has widespread
17 use, but at the same time, there's enough
18 information on atrazine that we know that we can
19 zoom into certain parts of the country, and
20 that's where we expect to find community water
21 systems with higher concentrations than in other
22 parts.

1 When you're trying to address spatial
2 variability, there's a number of ways of doing
3 that. On one extreme, you could sample every
4 community water system in the country. That's
5 several thousand of them, and you're probably not
6 going to get that with any level of intensity.

7 On the other end of it, you may look
8 it -- and this is what we did for an ecological
9 monitoring study that we brought to the SAP in
10 the past. So, you've heard that, this one is
11 focusing on drinking water.

12 We started out by using a model
13 developed by U.S. geological survey, a watershed
14 regression on pesticide, which was developed
15 using atrazine monitoring data, to identify the
16 watersheds that would be most vulnerable to
17 atrazine exposure, based on that model, and
18 that's what you see in the dark blue.

19 What we did in that case is, we
20 basically had a study set up, that sampled
21 watersheds that represent those most vulnerable
22 areas and we looked at how far we could apply

1 that.

2 The drinking water is a little
3 different than that, in that, what we did for
4 this is, as a result of the 2003 IRED, atrazine
5 is already being monitored quarterly at each of
6 the community water systems, as part of the Safe
7 Drinking Water Act.

8 We were looking at a 90 day exposure
9 period, so, we said, you know, quarterly sampling
10 probably isn't frequent enough to characterize a
11 90 day exposure period.

12 So, what we did is, we looked at
13 community water systems that had annual average
14 concentrations above a certain threshold of
15 concentration, and those were put into more
16 intensive sampling.

17 The interesting thing that I want to
18 show here is that almost -- the vast majority of
19 those community water systems fell into this area
20 as identified as the most vulnerable watersheds
21 using the WARP modeling.

22 So, that helps us know that -- we've

1 already a good bit, and we're working with what
2 we've learned, but it tells us that we know we
3 can zoom in on certain areas. Even within those
4 areas, we're seeing that there are some water --
5 community water systems that tend to have higher
6 concentrations of atrazine more frequently than
7 others.

8 So, there is localized variability
9 that further drives that. Some of this, we're
10 learning and it is a result of ecological
11 monitoring and some of the feedback we've gotten
12 from the SAP on that, that we hope to pass on.

13 But because of the nature of the fact
14 that we're looking at individual community water
15 systems that get thrown into this because of the
16 monitoring data, spatial patterns aren't as much
17 of a challenge for us in this regard as the
18 temporal patterns, and because we were looking at
19 these individual community systems, each of which
20 serves its own population, and each person --
21 each population potentially drinks the same
22 concentration of atrazine, as their neighbors do.

1 So, I'm going to go into the temporal
2 patterns. One of the things, when you're trying
3 to show temporal patterns and try to show daily
4 variations, you quickly find that there's not a
5 whole lot of monitoring data out there, that
6 samples daily or almost daily.

7 What I'm showing you here are some
8 monitoring that was done with the ecological --
9 atrazine ecological exposure monitoring program.
10 They tend to be a little farther upstream than
11 what you would see for most of the community
12 water systems, although there are a few community
13 water systems that are in those same type of
14 stream networks.

15 These were flowing water systems and
16 what you would expect for flowing water body is,
17 you expect to see a short, higher pulse moving
18 through than you would for a reservoir, which
19 would tend to dampen it out and spread it out.

20 But what I wanted to do is illustrate,
21 this is -- when we're talking about seasonal
22 variations, this is -- typically, what you'll see

1 is one or two short pulses, where you get
2 elevated concentrations that decline fairly
3 rapidly and a lot of times, either low in
4 negligible detections.

5 This is in one year. The previous
6 year at that site, the same site, we got a little
7 different pattern, and a different pattern can
8 result from different application periods,
9 different rain fall events, different ways it's
10 used.

11 There's a couple of things I wanted to
12 show you. When we're talking about the auto-
13 correlation, you can really see it here, where
14 you see how the concentrations are related to the
15 neighbors. You also tend to see a tail coming
16 out, where you could -- a rapid, initial peak and
17 then a tail, tailing out. This is common in a
18 lot of our -- particularly, flowing water, but it
19 is a common thing that we see, and just to throw
20 in another one, when Mary Frankenberry starts
21 talking about short exposures, longer exposure
22 chemographs, shapes of the chemographs, this is

1 an illustration of one where you do -- what you
2 actually have is multiple peaks running together,
3 so that you get a longer duration of exposure.

4 This is interesting because it does
5 make a difference on how frequently you have to
6 sample. We're not always able to predict those
7 shapes of those chemographs A-priority, but to
8 the point that we can, it helps us interpreting
9 the results of the monitoring data.

10 It's not enough just to worry about
11 how much -- how -- variability you have in a
12 season, but you do have year-to-year variability.

13 The first slide I showed you happens
14 to be this year, and the second one was -- this
15 was the double-peaks. What you tend to see from
16 the year-to-year, and this is a six year period,
17 is not only do you see differences in the
18 magnitude of your exposures, but you also see
19 different shapes in the chemographs.

20 And just to drive home the spatial
21 variability again, this site is 50 miles south,
22 same years, and you can see the difference in

1 your exposures from year to year, so that it does
2 thrown in the fact that it's -- that a lot of
3 these differences are also localized and it does
4 present some challenges to us.

5 So, now, all we have to do is figure
6 out how to take that into account, when you're
7 looking at designing a monitoring study.

8 When we're looking at monitoring study
9 proposal, a protocol that would be submitted to
10 us, we need -- the questions we have is, how is
11 it going to account for spatial and temporal
12 patterns in exposure, and a lot of that is by
13 targeting areas where the pesticide is used and
14 when it's used.

15 So, you have a limited number of
16 samples. Instead of spreading them out
17 throughout the year, you would concentrate them
18 in the times when you expect to find it. There
19 are a lot of variabilities, additional
20 variabilities, based on the nature of the
21 pesticide itself, how it's applied, the weather
22 patterns, it's mentioned some of the water body

1 types.

2 It's also important, as you've -- as
3 we've heard referred to throughout the day, the
4 exposure duration of concern is also very
5 important, in terms of how frequently you have to
6 sample, and it makes sense that you're going to
7 have to have more intensive sampling, if you're
8 looking at shorter duration exposure, than a
9 longer term duration.

10 If we were to come out with an
11 exposure period that's 90 -- similar to what we
12 have now, 90 days or longer, we're probably okay
13 with it, but we are okay with the monitoring data
14 we have. But if it's a much shorter duration
15 exposure, that's where we have some questions.

16 On top of that, we're also looking at
17 the consequences of rather -- of failing to
18 detect high exposure, exposures above our level
19 of concern, when they do occur, or on the other
20 hand, estimating an exposure that's above the
21 level of concern when, in fact, it turns out not
22 to be.

1 Because FTPA requires us to come to a
2 conclusion of reasonable certainty of no harm, we
3 tend to err on the side of false negatives, more
4 so than false positives, but at the same time, we
5 want to try to be as reasonable with our exposure
6 estimates as possible. We don't want to end up
7 with an outrageously high exposure estimate that
8 really doesn't do anybody any good in that
9 regard.

10 Finally, the reality is, we can't
11 overlook the cost. It's prohibitively expensive
12 to sample daily, at enough sites, in enough
13 years, to give a full characterization of any
14 potential exposure you're looking at.

15 So, we end up with less frequent
16 sampling and less -- and fewer monitoring sites.
17 In a lot of cases, we rely on modeling to fill in
18 the holes, and sort of help us focus on more
19 vulnerable areas.

20 What we're coming to you today isn't
21 inventing a new wheel. It's building on things
22 that have already been done in the past.

1 Shortly after FTPA was passed and we
2 had to look -- and we started looking at drinking
3 water exposures routinely, International Life
4 Science Institute convened a pattern that -- a
5 panel that provided some recommendations on how
6 frequently you'd have to sample for -- for
7 instance, in estimating peak exposures.

8 We brought some information to an SAP
9 on what kind of monitoring study design you would
10 need to estimate chronic exposures. So, we've
11 built from that.

12 Charlie Crawford provided some --
13 evaluated some varying sampling strategies and
14 you'll see in our paper, that we refer to a lot
15 of a Crawford's work and tried to take advantage
16 of what he found, to build on that.

17 And both of these particular authors
18 noted that the number and frequency of sampling
19 will depend on the time frame of concern. So,
20 that's, once again, bringing it back to that,
21 linking it together.

22 What I'm going to do is, spend a

1 little bit of time now, talking about how we
2 analyze and interpret existing monitoring data,
3 because most of the time, we're not designing new
4 studies, but we're looking at existing monitoring
5 data that's already out there.

6 In the case of atrazine, we're looking
7 at several years of monitoring community water
8 systems, and once again, we're going to be asked
9 that question very soon, is that adequate for a
10 new exposure duration?

11 So, we want to be able to get at that.
12 I'm going to begin with some of the basic
13 approaches and then walk through to more complex
14 approaches, as we go along.

15 Let's go back to that chemograph we
16 had, that I showed you earlier, that has two
17 exposure peaks, one that occurs in late April and
18 another one, about a month later, and let's say,
19 for this particular thing, we know -- this is an
20 actual -- the true chemograph that you would see,
21 and let's say, we had monitoring that was done on
22 a weekly basis, beginning April 1st.

1 So, those red dots you see are the
2 actual samples, and what you see is, well, we did
3 -- the timing of sampling happened to hit this
4 first peak pretty well.

5 For the second peak, we're on the
6 down-slope side of that, and what we ended up
7 with is roughly about half of what the actual
8 maximum concentration was, in that regard.

9 So, we already know that if we're
10 looking at an acute exposure, that we're going to
11 end up with an under-estimate.

12 We're still at the point is, if we're
13 looking at an average concentration over another
14 duration, exposure duration of concern, to get to
15 that, we've got to figure out, how best do you
16 fill in the holes in between? We've got these
17 seven day snapshots. How do we fill in the
18 holes?

19 Well, one way to fill them is to
20 assume the same concentration on subsequent days,
21 until you get your next monitoring, kind of a
22 stair step approach, and you end up with a blocky

1 chemograph, which, if you blur it, a little bit,
2 it's not too bad, but it's still kind of blocky.

3 Another one that's done, probably more
4 commonly, is kind of doing a linear interpolation
5 between the sampling points, it's like connecting
6 the dots.

7 If you're looking at a short term
8 exposure of concern, and particularly, if you're
9 looking at duration of exposure that is less than
10 your sampling, then there's a good chance, in
11 most cases, you're going to miss your highest
12 exposures.

13 If you're looking at longer term
14 durations, that may not be as much a problem,
15 because of the -- it will average out over time.
16 In fact, if you look at some of the things that
17 Mary will talk about later, that we do find that
18 for the longer your exposure duration of concern,
19 the less error we see in the estimates, but
20 shorter duration, the more error we see.

21 Now, even weekly sampling is still
22 kind of a Cadillac in a lot of monitoring

1 studies. Typically, we will see studies that may
2 be sampled biweekly or monthly or quarterly. So,
3 we're going to go back to our original site and
4 instead of sampling monthly -- I mean, weekly,
5 we're going to sample every other week.

6 And so, you see, we still hit that
7 first peak, but suddenly, we're way down on the
8 tail of the second peak. So, any type of -- no
9 matter what interpolation you do, you see -- you
10 have missed where the highest exposure is.

11 What we'd like to do is, try to figure
12 out -- you know, at some point, the sampling is
13 going to be so infrequent, that your exposure
14 estimate is probably not going to reflect a whole
15 lot of what we see out there.

16 Some of the questions we've been
17 wrestling with over the years is, how do you know
18 if you've missed this? Are the ways that can
19 help us know when we may have missed the exposure
20 point of long term concern?

21 We're still wrestling with that. Some
22 of the modeling methods that we mentioned at the

1 end of our chapter are ways that we think might
2 help us start to get at that, but it's still a
3 challenge we have.

4 And so, the basic interpolation
5 approach, as I just showed you, like I said,
6 these are the ones that are commonly used.
7 They're quick and they're simple and if you have
8 a long enough exposure duration, and in
9 particular, your sampling frequency is more
10 frequent than your exposure duration, that may be
11 fine, within incertain error bounds.

12 The disadvantages are, they assume no
13 concentration is greater than the maximum that
14 they measured. They're likely to under-estimate
15 your peak or your short term exposures, and how
16 well they characterize actual concentration
17 profile depends on the timing of sampling
18 frequency. The farther apart it is, the more
19 likely those methods are to fall apart.

20 So, what if we, instead of trying to
21 draw boxes or connecting dots, we want to try to
22 fit that monitoring data with more some type of a

1 curvilinear pattern or something that may better
2 reflect what you're actually seeing there, or we
3 want to provide some type of confidence interval
4 around our exposure estimates.

5 You're going to see some of this
6 illustrated in Mike Messner's talk. He's going
7 to talk about one way, one approach, using
8 artificial neural networks, to try to fit that
9 pattern, the pattern of the monitoring data, and
10 some of the things that can be done, in terms of
11 providing some kind of confidence intervals and -
12 - and also, in terms of looking at how frequently
13 you did monitor, or where do you have to set your
14 threshold of exposure to kind of provide either
15 balance between the false positives and false
16 negatives?

17 Mary Frankenberry is going to present
18 an approach where we think we can start getting
19 us at providing some types of confidence
20 intervals.

21 The next couple of slides I'm going to
22 show you are ones that we did not provide an

1 example for you yet, and I put it in there
2 because it is definitely something that we are
3 considering and we've done a little bit of
4 testing with.

5 If you've heard of kriging or nearest
6 neighbor approach, you've probably heard it used
7 in geo-spatial analysis. It's been a way to take
8 a look at monitoring points over an area, in
9 other words, monitoring points in space, and fill
10 in, in between those sample points.

11 It's a way, essentially, the way you
12 do it, is you have the points, you analyze them,
13 you look for any correlation between the sampling
14 points, which is what this variogram is one way
15 that it's done, and then, you fill in, by waiting
16 -- the waiting, based on the correlation between
17 the points with the nearest neighbor type
18 approach.

19 And so, most of the time, it's been
20 used for spatial analysis. We've looked at this
21 because I think, that same concept seems like it
22 would also work for temporal analysis, and I have

1 seen -- I have been to some national meetings,
2 where I have seen this approach tried out.

3 We had a couple of people, Jim Hetrick
4 and Jim Wolf in our office, who looked at it and
5 did give it a try, and so, what I want to show
6 you is, very quickly, what they did is, some of
7 their preliminary analysis, they looked at
8 atrazine and they looked at a couple of other
9 pesticides.

10 The basic approach is first doing a
11 visual inspection of the data, and you noted from
12 the atrazine chemographs I showed earlier, that
13 you could see the temporal correlation -- auto-
14 correlation in there. It was evident.

15 They did some variogram analysis and
16 it did -- to quantify the temporal dependence,
17 and what they found is that you did get
18 correlation between measurements that ranged from
19 10 to 60 days apart.

20 The other thing they found is, it
21 wasn't constant from year to year. So, it's not
22 something you can apply to one year -- that you

1 can analyze in one year, and apply year to year.

2 So, it isn't constant from year to
3 year, but it does find a way of pin-pointing that
4 auto-correlation and they've done some cross-
5 validation and what they have -- some of the
6 preliminary analysis is they can do a conditional
7 simulation with -- that can give you an imaging
8 of the time series over years. They can use --
9 come up with a probabilistic generation of
10 exposures, and do some stochastic simulations, so
11 that we can get some confidence bounds on that.

12 So, in addition to what you're going
13 to hear from Mary and Mike, this is another
14 approach that we're going to be taking a look at.

15 The statistical approaches that I've
16 mentioned, their disadvantages are complex. They
17 take a lot more effort. It's not a quick
18 analysis of your data.

19 But where we need to provide
20 probabilistic distributions or where we need
21 confidence bounds around existing monitoring
22 data, that may be -- we see that as an approach

1 to take.

2 One of the other advantages, they
3 don't necessarily assume that the greatest -- the
4 highest exposure has already been detected, and
5 that's one of the reasons for the confidence
6 intervals on that, and they provide us with some
7 non-subjective way of estimating missing values
8 and the ways to account for temporal correlation.

9 They're more complex. The other issue
10 is, they don't necessarily capture the underlying
11 explanatory variables, or explaining what caused
12 that spike to occur when it did, but they may
13 have a utility in certain instances, particularly
14 when we're looking at needing a confidence bound
15 on our exposure estimates.

16 I've mentioned a little bit about
17 modeling methods and we are getting -- you know,
18 getting into a lot more detailed, involved
19 procedures. WARP, I showed you how we've been
20 using WARP and a lot is, in terms of identifying
21 -- raking watersheds, based on vulnerability and
22 then targeting areas of -- where more monitoring

1 would be needed.

2 But WARP has provided an estimate of
3 selected percentiles, as well as an annual mean,
4 an annual maximum -- and it's provided some
5 moving average concentrations.

6 We look at it as a potential for use.
7 A lot of it, as the authors and developers of
8 WARP have said, it helps us screen areas where we
9 need to have more targeted monitoring.

10 They have -- they do provide some
11 estimates of these various exposure percentiles,
12 with some confidence bounds on there, so, it's
13 something that we may be looking at, as we go
14 forward with this.

15 In a lot of cases, we've used
16 deterministic models to provide ground water -- I
17 mean, surface water exposure estimates. We've
18 used pesticide route zone model, which simulates
19 pesticide run-off from the field and we use exams
20 with exposure analysis modeling system, which
21 simulates the receiving body.

22 And we've used that to provide

1 multiple years of daily concentrations, varying
2 with weather patterns, and so, again, it gives us
3 a way of assessing the effect of different
4 weather patterns, and we've used that in various
5 tiers of our drinking water exposures, exposure
6 estimates.

7 In the 2007 SAP, that we had on
8 atrazine's ecological exposure monitoring
9 programs, Syngenta investigated a potential for
10 using PRZM, to fill in concentrations between
11 measured data from the chemographs.

12 We've looked at that. It probably was
13 a little bit more intense involved and complex
14 than we were planning to go into, but it's
15 something we were considering and have taken a
16 look at.

17 I put this in, we really didn't
18 include this in the paper, but we have seen some
19 attempts to try to use stream-flow as a way to
20 adjust pesticide concentrations in between
21 monitoring events.

22 I've seen as many chemographs where it

1 didn't work, as where it did. There are -- it's
2 not -- what we quickly learn is, it's not just
3 the flow, but it is also the flow in relating to
4 the timing of the planting, the timing of the
5 rain fall events, all those together.

6 Some folks at the USDA's ARS research
7 center and -- in Missouri, Columbia, Missouri,
8 have looking at an index of trying to couple flow
9 adjustments with the timing of planning of rain
10 fall events, and we're keeping an eye on that,
11 because that offers some promise, that we might
12 be able to use that.

13 At this point, I'm finishing my
14 presentation, and I'll open it for questions,
15 then, we will move on to the next one or two of
16 the next two examples. I'll let you folks figure
17 that.

18 SESSION CHAIR PORTIER: Likely, one.
19 Questions? Yes, Dr. Krishnan?

20 DR. KRISHNAN: I have two clarifying
21 questions. First one is, in the graphs you
22 showed, it was atrazine, but was that like, a

1 total, in terms of including also the other
2 duration products, or do such figures exist for
3 other duration products?

4 MR. THRUMAN: In that particular --
5 this particular illustrations, it was atrazine
6 only.

7 One thing I just want to clarify,
8 we're not -- at this point, we're not really
9 doing -- presenting a drinking water exposure
10 assessment. We're using whatever available data
11 we have, to try to come up with approaches that
12 we'd use to analyze, that we would then apply to
13 the drinking water exposure assessment.

14 The monitoring data that we got from
15 Syngenta on community water systems is total
16 chlorotriazines. So, that would be what we would
17 be focusing on, in that regard.

18 DR. KRISHNAN: Okay, my second one, in
19 your initial slide, you refer to the 90 day
20 rolling average, probably you or someone else can
21 answer, as well, and you refer to the time frame
22 of concern being the major reason for the choice

1 of 90 days.

2 I have seen some justification along
3 those lines, as well. I'm wondering if we could
4 get some further clarification on the choice of
5 the 90 days, as to what went into that thinking?
6 Is it based on the tox studies, during which --

7 DR. AKANA: I guess, I'll answer a
8 question, and I'm not asking, just to make sure
9 that we're on the same page.

10 The 90 day rolling average was what
11 was used in the 2003 risk assessment. So, one of
12 the major points on the table for
13 reconsideration, as part of this analysis, is in
14 a pretty straight forward question, is the 90 day
15 still the right time frame, and that, hopefully,
16 will get a lot of conversation over the next few
17 days.

18 So, it's absolutely on the table, to
19 move that 90 days shorter or longer, for that
20 matter, depending on, you know, where the data
21 move.

22 At that time, the 90 day rolling

1 average was selected by a match to the toxicology
2 data, specifically, the LH data, specifically, a
3 six month rat study. I don't know the exact
4 author, if you really want to see it, but that's
5 my --

6 DR. KRISHNAN: No, I think we're on the
7 same page. At least, I understand, that's what I
8 wanted to make sure, because 90 days, typically,
9 in rodent studies, represents about a tenth of
10 the life time, which is not what corresponds to
11 what's typically the sub-chronic.

12 On the equivalent human, typically,
13 it's a tenth of a duration -- a life time is
14 considered to be about seven years. That's what
15 people normally use. That's why I tried to see,
16 but this clarification helps -- would help in
17 other discussions.

18 DR. AKANA: It was done as an equal
19 matching of the days, on an effect, the 90 days
20 or short than the six months. So, that was a
21 quite conservative choice on the Agency's part.

22 SESSION CHAIR PORTIER: Dr. Lee?

1 DR. LEE: I have a question and a
2 comment. First, the question, do we know about
3 the measurement error uncertainty, in taking
4 these samples, from the water streams, and
5 they're sort of presented up here, as stated
6 points without any error.

7 Presumably, if you sent several people
8 to the same stream and had them all take a sample
9 and then go analyze them in separate labs, you'd
10 get different answers.

11 MR. THURMAN: First of all, we probably
12 can get a little bit of that information. They
13 have -- they did do some fill-blanks and such.

14 I think the question you ask is
15 complex in all kinds of different ways, because
16 it does -- what you saw were daily chemographs,
17 but they were basically sampling, for the most
18 part, taken in one day, one time -- one incident
19 a day, dipping graph sampling.

20 Now, a few of those actually were
21 auto-samplers that sift at intervals, and then
22 what you have for a daily is a 24-hour average

1 over that.

2 You still have sampling taking one
3 point, across the stream. So, you will get some
4 variation in that. We don't really have that
5 characterized in this particular study.

6 DR. LEE: That could be a useful thing
7 to know a little bit more about, if you're trying
8 to make any sort of confidence interval. That's
9 going to be critical for your intervals.

10 MR. THURMAN: Yes, that's true. Now,
11 what I will say is that for the community water
12 systems, it comes from the -- they have --
13 they've sample both source water and the treated
14 water. We're focusing on the source water. It
15 comes from the intake.

16 So, what you see is what is integrated
17 at that intake, which takes some of that
18 variability out. You still have a temporal
19 variability that you're going to get in that.

20 In fact, sometimes, what we'll see is
21 monitoring data is, where they've paired the
22 source water with the treated water is, that

1 sometimes, you'll see treated water with higher
2 concentrations than source water because it's
3 differences in time, and so, it's part of the
4 variability that's --

5 DR. LEE: That's natural variability.

6 MR. THURMAN: Yes.

7 DR. LEE: You can't get rid of it. The
8 question is just can we quantify it a little
9 better, and it's not that you need to sample it
10 everywhere, but if you had some sort of global
11 idea of what it might be like, that would be
12 really helpful.

13 MR. THURMAN: I know we have a couple
14 of USGS folks on the Panel, who hopefully, can
15 provide some words of wisdom to help us figure
16 that out.

17 That's one we've wrestled with,
18 because we do know that --

19 DR. LEE: I figured it's something you
20 must have looked at before, but I didn't see
21 anything about it in the white paper.

22 The other comment I want to make is,

1 I think that the kriging Gaussian process type
2 approach has a lot of potential here. I'm glad
3 to see you folks are looking at it.

4 I did want to comment, that you talked
5 about some variogram analysis, and they've
6 noticed that it varies a lot from year to year.
7 It's actually a very noisy process to try and
8 analyze a variogram, and I'd expect that even if
9 you sort of just took repeated samples, you'd get
10 very different variograms within the same year.

11 And so, there is a lot more possibly
12 going on there, and it may be that it actually
13 doesn't change that much year to year, and you're
14 just looking at variability, sampling
15 variability.

16 MR. THURMAN: Well, I will say that
17 their initial analysis was with a limited data
18 set. We were going -- we're going to be looking
19 at a lot -- hopefully, a lot more data -- sets of
20 data.

21 So, hopefully, some of that will start
22 shining in, but I appreciate that.

1 SESSION CHAIR PORTIER: I had a
2 question, it was just a clarification. The
3 hydrographs we're seeing here are for the raw
4 water is raw water at the intake, or is this from
5 the ecological studies that we --

6 MR. THURMAN: The ones I showed you
7 were illustration of ecology studies, and the
8 reason I showed you that is because -- and you
9 see in the paper, we showed some of the
10 chemographs with the drinking water, but those
11 are weekly samples.

12 So, what I wanted to do, to try to --
13 particularly, when I started illustrating, you
14 know, let's take seven day samples, I realized,
15 that's not going to work for those -- you know,
16 for those chemographs we generated before.

17 So, that's why I went to the
18 ecological exposure monitoring, because it did
19 have daily variations.

20 SESSION CHAIR PORTIER: I was thinking
21 about intake water coming from -- well, we have a
22 dendritic system, right, and you're up here, at

1 the ecological studies were high up here, level
2 one, level two streams, and rarely do community
3 water systems draw from that level. They're
4 drawing three, four and five, right?

5 MR. THURMAN: Yes, that's true,
6 although, as we've looked at this, I have found -
7 - I have come across looking at maps and
8 analyzing particularly, some of the monitoring
9 sites and where it goes, I've found community
10 water system intakes up in those same areas, and
11 some of --

12 So, it can happen. We know that those
13 are typically higher up in the watershed than
14 what you're going to see farther down. I
15 selected those because while they're farther up
16 stream, they do show the shape of the chemographs
17 that you're likely to see, even farther down
18 stream.

19 SESSION CHAIR PORTIER: That's the
20 confirmation. Dr. Young?

21 DR. YOUNG: I just have a basic
22 question. I don't -- I think I'm missing some big

1 idea, because you talk about false positives and
2 false negatives. So, then that -- I'm not
3 clearly, exactly what you're trying to estimate,
4 because if you get a value, it could have
5 measurement error, but it may -- what if it's
6 right on, but you take another value and it's
7 right -- no measurement error, but you get
8 different values?

9 Are you trying to estimate the mean
10 for the area, a quartile? You see, I don't see
11 what the foundation is for false positive and
12 false negative.

13 MR. THURMAN: I think that's one where
14 I think Mike Messner will be able to illustrate
15 it a little bit better in his presentation, than
16 what --

17 What we're looking at is, and just to
18 try to give you -- which I don't know if it will
19 help you or not, we get exposures -- monitoring
20 sample -- data samples, say, weekly, and we've
21 got to come up with an estimate of a duration --
22 of an exposure for a duration that's say, one

1 month.

2 And so, if we take those weekly
3 samples, there's various approaches that you can
4 take. I mean, if you assume that the same
5 concentration for the next -- for a seven day
6 period until your next sampling and average --
7 and use that to average those together, to come
8 up with a one month sample, there are times when
9 you may have hit, where if the one sampling point
10 happened to hit your peak, and you carry that out
11 seven days, when in fact, it drops pretty
12 rapidly, you're going to end up with an over-
13 estimate of that monthly average.

14 There are other times when you may be
15 an under -- under-estimating, because you don't
16 hit that peak. So, that's what I'm --

17 DR. YOUNG: I think, let me see if I
18 have it. So, what you're trying to estimate is
19 the average for the temporal scale of interest?

20 MR. THURMAN: That's correct.

21 DR. YOUNG: Okay.

22 MR. THURMAN: That's correct.

1 SESSION CHAIR PORTIER: Dr. Hayton,
2 from the Ohio State University joined us. He
3 wasn't here when we started, and he's got a
4 question, and --

5 DR. HAYTON: Well, a couple of
6 questions. One is, what -- you're talking --
7 these chemographs, what happens to that in the
8 pipe? I mean, when I open my faucet, am I -- you
9 know, if I took a sample out of my kitchen sink,
10 once a week, would it look like what you're
11 showing us, or does that get modulated in the
12 distribution?

13 MR. THURMAN: It gets modulated. There
14 are a number of factors that go into that. It
15 goes through a treatment system. Depending on
16 the type of treatment that the community water
17 system has, you may have some non or all of the
18 atrazine removed, depending on the treatment
19 system.

20 Because you're going into collecting
21 and holding tags of processing tags and moving
22 through, it does get -- tend to get modulated as

1 you go through what's exposed.

2 However, I will point out that EPA's
3 goal is to protect the source water. So, we're
4 focusing on how do we protect the source water?

5 We need to generate exposure estimates
6 that are going to reflect drinking water for
7 human health, at the same time. If you look at
8 the reasonable certainty of no harm, if we can
9 get the source water concentration lower than our
10 levels of concern, we can be certain that the
11 treated water is going to --

12 DR. HAYTON: So, there's a margin of
13 safety there, and then finally, what -- it wasn't
14 clear to me, exactly how do you use those
15 concentrations? I mean, obviously, protecting
16 public health, but how -- does a bell go off
17 somewhere, when the atrazine concentration spikes
18 and the whole water system shuts down, or what
19 happens?

20 MR. THURMAN: What we do is, we have a
21 dietary exposure assessment and Dr. Lowit will
22 probably be able to answer a little better than I

1 do, but you basically, you take your drinking
2 water exposure estimate, with the average for
3 whatever duration of concern it is, couple that
4 with your dietary exposure and in cases where you
5 do have residential exposure, you couple those
6 together.

7 Atrazine, the dominant route of
8 exposure, and maybe the only real route of
9 exposure for atrazine is from the drinking water.
10 So, we don't really have exposure in food that we
11 would expect, and while there may be some long
12 use in some areas, for the most part, we don't
13 have residential exposure, that we look.

14 So, essentially, we are looking, in
15 this case, at concentration in drinking water,
16 but for other pesticides, it's coupled with the
17 dietary exposure.

18 DR. HAYTON: But if you think it's too
19 high, do you -- you know, what's the next step?

20 SESSION CHAIR PORTIER: I think Dr.
21 Bradbury can answer that.

22 DR. BRADBURY: So, just let me touch on

1 your question and reaffirm that the conditions of
2 the re-registration in 2003 are designed to
3 protect the source water.

4 So, the monitoring analysis that
5 you're going to hear about from the team,
6 combined with whatever you decided the
7 appropriate exposure window is, if we need to
8 change it, the whole construct of the regulatory
9 decision is that people are drinking the raw
10 water, not the finished water, and their goal is
11 to ensure protection of the source water, because
12 5th RED, we can protect the source water.

13 Safe Drinking Water Act, we use
14 technology, if necessary, to get the
15 concentration down to a safe level. Our approach
16 is, we should be protecting the source water
17 through a regulatory decisions.

18 Now, the conditions of re-registration
19 in 2003 have this monitoring program in place in
20 the community water systems, and if we get a
21 level above our level of concern, we're aware of
22 it quickly and I believe in our condition of re-

1 registration, if in two -- let me back up.

2 The community water system is
3 monitored for five years. So, if it goes into
4 the program, it's monitored for five years. If
5 during the course of the five years, it never
6 exceeds the level of concern, then it can get out
7 of the monitoring program, but it could always
8 come back in again, if it's safe drinking water
9 sampling regime, which is once every quarter,
10 starts to approach the three part per billion MCL
11 and then it goes back into the sampling program.

12 So, it's an ongoing monitoring
13 program. But five years in a row, you don't
14 exceed a rolling 90 day average, then you -- it
15 comes out of the monitoring program.

16 If it hasn't exceeded in two years,
17 so, one year, it exceeds, it exceeds the next
18 year, then atrazine is off-labeled in that
19 drinking water schedule and it can't be used in
20 that watershed.

21 So, we do have a bell that goes off
22 and the bell that goes off is, you can't use

1 atrazine in that drinking watershed, if you
2 exceed the level of concern.

3 Some of the dialog we'll have on the
4 science is, is that 90 day rolling average
5 changing, as we look at the toxicology? Do you
6 have a monitoring program in place, if exposure
7 window is variable? How should your frequency of
8 sampling vary?

9 SESSION CHAIR PORTIER: Well, a bell
10 has gone off. It's 6:02 p.m. by my ruling and we
11 have about an hour's worth of presentation by
12 EPA, that we're going to put off, I'm sorry,
13 Mary, until tomorrow morning.

14 Well, I'll looked at your slides, and
15 the statisticians over here could probably stand
16 it, I'm sure this whole Panel would -- would fall
17 off.

18 We're going to pick up in the morning.
19 This will impact the public presenters, in the
20 sense that they're going to be moved back another
21 hour. If there are presenters for which this is
22 going to cause a problem, please, let myself or

1 Joe Bailey know. We'll try to schedule you a
2 little earlier. I know some people don't stay
3 for all of this discussion.

4 We start again tomorrow morning at
5 8:30 a.m., on time, with EPA's continued
6 presentation on the water.

7 (Whereupon, the above-entitled matter
8 concluded at approximately 6:05 p.m.)
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