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FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

REEVALUATION OF THE HUMAN HEALTH EFFECTS

OF ATRAZINE:

REVIEW OF NON-CANCER EFFECTS AND

DRINKING WATER MONITORING FREQUENCY

DOCKET NUMBER: EPA-HQ-OPP-2010-0481

UNITED STATES

ENVIRONMENTALPROTECTION AGENCY

CONFERENCE CENTER LOBBY LEVEL

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ARLINGTON, VIRGINIA 22202

SEPTEMBER 15, 2010

8:30 A.M.

1 FIFRA SCIENTIFIC ADVISORY PANEL
2 MEETING
3 SEPTEMBER 15, 2010
4 **DR. STEVEN HEERINGA:** Good morning
5 everyone and welcome to the second day of the four-day
6 proceeding of the FIFRA Science Advisory Panel, a
7 meeting on the topic of the Re-Evaluation of the Human
8 Health Effects of Atrazine: A Review of Non-Cancer
9 Effects and Drinking Water Monitoring Frequency.
10 I'm Steve Heeringa of the University of
11 Michigan. I'm the Chair for this Panel and will be
12 serving in that role for the next three days.
13 I'd like to go around the table today
14 and have the Panel members briefly introduce themselves
15 and state their affiliation and specific expertise in
16 relation to this particular Panel with you, and I'll
17 begin with Dr. Portier on my left.
18 **DR. KENNETH PORTIER:** Thank you.
19 Good morning, I'm Ken Portier, Director
20 of Statistics at the American Cancer Society National
21 Office in Atlanta. I'm an applied biostatistician and
22 a member of the permanent Panel.
23 **DR. JANICE CHAMBERS:** I'm Jan Chambers,
24 I'm Professor in the College of Veterinary Medicine at
25 Mississippi State University. I'm a pesticide

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1 toxicologist with an emphasis on neurotoxicology, and
2 I'm a member of the permanent Panel.
3 **DR. CAREY POPE:** Good morning. My name
4 is Carey Pope. I'm a Professor and Head of the
5 Division of the Department of Physiological Sciences at
6 the Center for Veterinary Health Sciences at Oklahoma
7 State University. I am a toxicologist, and neurotox is
8 my interest and expertise.
9 **DR. JOHN BUCHER:** I'm John Bucher. I'm
10 the Associate Director of the National Toxicology
11 Program at the NIEHS, and I'm a member of the permanent
12 Panel.
13 **DR. DANIEL SCHLENK:** Good morning, my
14 name is Dan Schlenk. I'm a Professor of Environmental
15 Toxicology in the Department of Environmental Sciences
16 at University of California Riverside. My expertise is
17 in fate and effects of pesticides in aquatic organisms,
18 and I'm a member of the permanent Panel.
19 **DR. RICHARD GREENWOOD:** I'm Richard
20 Greenwood from University of Portsmouth. I'm Professor
21 of Environmental Science, and my expertise is in the
22 area of general toxicology and pharmacokinetics.
23 **DR. KANNAN KRISHNAN:** I'm Kannan
24 Krishnan, Professor of Occupational and Environmental
25 Health at the University of Montreal, Canada. I'm a

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1 toxicologist.
2 **DR. NELSON HORSEMAN:** Good morning,
3 Nelson Horseman from the University of Cincinnati. I'm
4 a physiologist with particular expertise in mammary
5 gland biology.
6 **DR. JAMES MCMANAMAN:** Good morning, I'm
7 Jim McManaman from the University of Colorado
8 Department of Obstetrics and Gynecology, and I have
9 expertise in the mammary gland.
10 **DR. KATHERINE ROBY:** Good morning, Kathy
11 Roby from University of Kansas Medical Center,
12 Department of Anatomy and Cell Biology, and my
13 expertise is in female reproduction.
14 **DR. BARRY DELCLOS:** Barry Delclos from
15 the FDA's National Center for Toxicological Research. I
16 do research on toxicology and carcinogenesis.
17 **DR. SANDRA LEGAN:** Good morning. My
18 name is Sandy Legan. I'm Professor of Physiology at
19 the University of Kentucky, and my expertise is in
20 female reproductive neuroendocrinology.
21 **DR. WESLEY STONE:** Good morning, Wes
22 Stone with United States Geological Survey; area is
23 chemical transport.
24 **DR. RICHARD COUPE:** Richard Coupe with
25 the U.S. Geological Survey at the Water Science Center,

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1 and I'm a hydrologist.

2 **DR. HERBERT LEE:** Herbert Lee of

3 University of California Santa Cruz, Professor of

4 Statistics and Associate Dean of Graduate Studies and

5 Research in the Baskin School of Engineering, and I'm

6 an applied statistician.

7 **DR. BETTE MEEK:** And I'm Bette Meek from

8 the University of Ottawa on interchange with Health

9 Canada with a background in toxicology and regulatory

10 risk assessment.

11 **DR. SUSAN AKANA:** Susan Akana, a

12 research physiologist from the University of California

13 San Francisco. I study the hypothalamic-pituitary-

14 adrenal axis and its interaction with energy balance.

15 **DR. PENELOPE FENNER-CRISP:** Penny

16 Fenner-Crisp, I'm a private consultant from

17 Charlottesville, Virginia. My area of expertise is

18 toxicology and risk assessment.

19 **DR. ELLEN GOLD:** I'm Ellen Gold. I'm a

20 Professor of Epidemiology and Chair of the Department

21 of Public Health Sciences at the University of

22 California Davis, and my expertise is the epidemiology

23 of adverse reproductive health effects on women.

24 **DR. SHELLEY HARRIS:** Hi, I'm Shelley

25 Harris; I'm Associate Professor at University of

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1 Toronto and a scientist at Cancer Care Ontario, and I'm
2 an epidemiologist with expertise in pesticide exposure
3 assessment.
4 **DR. JOHN BAILAR:** John Bailar, retired
5 from the University of Chicago, now Scholar in
6 Residence at the National Academies here in Washington.
7 I am a physician and statistician.
8 **DR. GERALD LEBLANC:** Gerry LeBlanc, I'm
9 Professor and Head of the Department of Environmental
10 and Molecular Toxicology at North Carolina State
11 University. My area of expertise is in endocrine
12 toxicology, and I'm a member of the permanent Panel.
13 **DR. STEVEN HEERINGA:** Thank you, Panel
14 members, and we'll give Dr. Mumtaz a moment to get
15 seated to introduce himself.
16 **DR. MOIZ MUMTAZ:** I'm Moiz Mumtaz at
17 ATSDR, interested in clinical research risk assessment.
18 **DR. STEVEN HEERINGA:** At this point, I
19 want to turn it over briefly to the Designated Federal
20 Official for this FIFRA meeting, and that's Mr. Joe
21 Bailey.
22 **MR. JOSEPH BAILEY:** Good morning,
23 everyone; as Dr. Heeringa said, my name is Joe Bailey,
24 the Designated Federal Official for the meeting.
25 I want to welcome everyone back this

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1 morning, and the public and Panel as well. If you
2 weren't here yesterday, EPA made its presentation, and
3 all of the slides for that presentation are now
4 available in the Public Docket, along with all the
5 other background materials for the meeting.
6 And with the public comment session
7 today, we'll probably have quite a bit of handouts to
8 give to the Panel. They will be placed in the Docket
9 as well and will be available for the public as soon as
10 we can get them up.
11 Once again, welcome, everyone, back to
12 day two, and I'll turn the mic back to Dr. Heeringa.
13 **DR. STEVEN HEERINGA:** Thank you very
14 much, Joe.
15 And again, just to review where we're at
16 in the proceedings, we have heard presentations from
17 the Scientific Staff of the Environmental Protection
18 Agency that have been working on the Issue Paper and
19 the background work.
20 We have another presentation scheduled
21 this morning with Dr. Suzanne Fenton, and following
22 that presentation and the Panel's questions and
23 clarification, we'll move on to the period of public
24 comment.
25 The period of public comment will be

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1 substantial today, with a number of people contributing
2 various links. Times have been agreed upon with the
3 FIFRA SAP Office, and so I'm going to hold all of the
4 presenters in the public comment period to the allotted
5 timing so use the time wisely; we want to make sure
6 that we have an open exchange and that the Panel has
7 the opportunity to hear everything that you need to
8 present, but I also need to keep the meeting on track.
9 We have a busy three days ahead of us, and so I'll try
10 to enforce times pretty rigidly today.
11 At this point in time, I'd like to turn
12 to Dr. Steven Bradbury, who is the Acting Director of
13 the Office of Pesticide Programs at the EPA, and just
14 to see if there are any opening comments or any follow-
15 ups from yesterday's proceedings.
16 **DR. STEVEN BRADBURY:** Thank you, Dr.
17 Heeringa.
18 I want to thank the Panel for
19 yesterday's interaction. I thought it was a very good
20 first opening day, a lot of time to get your clarifying
21 questions, and appreciate the opportunity to go over
22 the Charge Questions at the end of the day. I think
23 that will help us as we move forward.
24 We don't have anything additional to
25 offer after yesterday's discussion at this time. Thank

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1 you again, and we're prepared to move towards Dr.
2 Fenton's presentation. I think that's it for the
3 Panel.
4 **DR. STEVEN HEERINGA:** Okay. I think
5 just briefly to the Panel members, any
6 Oh, Dr. Levine?
7 **DR. TINA LEVINE:** We're just checking
8 with you to see if there are any follow-up questions
9 that you have.
10 **DR. STEVEN HEERINGA:** Right. Panel
11 members, anything from yesterday that's a question or
12 clarification that you'd like to have answered before
13 we move on to Dr. Fenton's presentation?
14 Yes, Dr. Greenwood.
15 **DR. RICHARD GREENWOOD:** I'd just like to
16 clear up one point. Yesterday in Slide 61 where you
17 showed the trapezoidal rule and you showed and
18 indicated that it was first-order elimination, and
19 you've got three points, is that correct? You could
20 only use the last three points, the last --
21 **MALE:** Yes, that is correct. Yeah, we
22 only have three data points for each of those groups.
23 **DR. RICHARD GREENWOOD:** It just seems
24 that you are missing something, because there's a very
25 rapid fall before those three points that you use.

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1 And then I guess you fit in a two-
2 parameter model with three points, because for a first-
3 order PK, you have two parameters to estimate them.
4 You've got three points, so there could be a little bit
5 of doubt about the values of those rate constants.
6 **DR. CHESTER RODRIGUEZ:** So the only
7 thing that we estimated from that plot was slope of
8 line
9 **DR. RICHARD GREENWOOD:** Yeah.
10 **DR. CHESTER RODRIGUEZ:** Okay. So you
11 plot pretty much the natural log, the plasma
12 concentration versus time, and you take the slope of
13 that line as your initial rate constant.
14 **DR. RICHARD GREENWOOD:** Right.
15 **DR. CHESTER RODRIGUEZ:** So it's really
16 one parameter of estimating.
17 **DR. RICHARD GREENWOOD:** The function
18 does have two parameters, because it's a measure of
19 location as well. But in those curves, there is this
20 big speed drop before the first point that you start to
21 use. Did you have any idea of what that's about?
22 **DR. CHESTER RODRIGUEZ:** No, actually, we
23 did not.
24 **DR. RICHARD GREENWOOD:** Okay.
25 **DR. CHESTER RODRIGUEZ:** Those points are

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1 the only representation of the elimination phase.
2 **DR. RICHARD GREENWOOD:** Because if it
3 were biphasic, what you've done is estimate the second
4 phase; it may be a good explanation to give. And
5 there's no way you can get at the first points.
6 Also, to some extent I guess the scaling
7 is set by the time points, because there's a big gap
8 between the time points. If I understood correctly,
9 there was three hours between the last dose and the
10 first point that you could use, that's correct?
11 **DR. CHESTER RODRIGUEZ:** Yes, that is
12 correct.
13 **DR. RICHARD GREENWOOD:** Okay, thanks
14 very much.
15 **DR. CHESTER RODRIGUEZ:** Yeah, but is it
16 okay if I make one more point?
17 **DR. RICHARD GREENWOOD:** Yes.
18 **DR. CHESTER RODRIGUEZ:** So that's why we
19 decided to use a non-compartmental approach for the
20 analysis. That means that we're not selecting a
21 substitute model.
22 **DR. RICHARD GREENWOOD:** Yeah. No, no,
23 I understand that.
24 I think the other point which I'm a
25 little unclear about I guess was in that work, the

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1 blood samples are always taken virtually having this 21
2 hours after the dose; is that correct?
3 **DR. CHESTER RODRIGUEZ:** It's actually 24
4 hours.
5 **DR. RICHARD GREENWOOD:** 24 hours, okay.
6 So it's before the next dose?
7 **MALE:** Yup.
8 **DR. RICHARD GREENWOOD:** So the top of
9 that factor isn't really the average, because it will
10 be at its lowest point before you get the next dose
11 every time you take a sample.
12 **DR. CHESTER RODRIGUEZ:** That is correct,
13 and that's why we're describing that as pseudo-steady
14 state and not a steady state per se.
15 **DR. RICHARD GREENWOOD:** Yeah, but with
16 the way that it's being done will probably
17 underestimate the area under the curve. You should
18 always take it to the lowest point, not the mean point
19 or average.
20 **DR. CHESTER RODRIGUEZ:** Yeah, but that's
21 the only information we have.
22 **DR. RICHARD GREENWOOD:** No, I understand
23 that. I just want to be clear.
24 Thank you.
25 **DR. STEVEN HEERINGA:** Thank you, Dr.

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1 Greenwood; Dr. Rodriguez, too.
2 Dr. Akana.
3 **DR. SUSAN AKANA:** I'd like clarification
4 on one detail. It's on Figure 5.8, which is the very
5 flat tall figure on 71 of the Issue page. This is the
6 one that has multiple studies plotted with the X axis
7 of the atrazine dose. The question is, the Y axis is
8 LH surge attenuation, percent control. Is that peak LH
9 at 1800 of LH area under the curve?
10 **DR. CHESTER RODRIGUEZ:** That represents
11 the peak of the surge at 1800 hours.
12 **DR. SUSAN AKANA:** Thank you.
13 **DR. STEVEN HEERINGA:** Good, Dr. Akana.
14 Any other questions or clarification at
15 this point? We'll have another opportunity before we
16 move to the public comment period; but Dr. Greenwood,
17 Dr. Akana, thank you for bringing those up.
18 At this point in time, I think we're
19 ready to view the presentation by Dr. Suzanne Fenton of
20 the Cellular and Molecular Pathology Branch of the
21 National Institute of Environmental Health Sciences.
22 Good morning, Dr. Fenton.
23 **DR. SUZANNE FENTON:** Good morning. I
24 hope that everyone has gotten my handouts. I estimate
25 you have. Sorry to not be here yesterday, but my

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1 schedule did not permit it.
2 Today I'm going to talk about The Fetal
3 Mammary Gland and Prostate as Sensitive Developmental
4 Targets for Atrazine. I understand that you will also
5 have access to one of the papers I am going to talk
6 about today that is actually available online in ECOG.
7 There are many potentially mistakes and misconceptions
8 in the Summaries of some of our work, and I want to
9 make sure I hit the highlights of our work today so you
10 understand what our findings are, how we came to those
11 conclusions.
12 The reason we do the work that we do is
13 because breast cancer is a global problem. In 2010,
14 about 1.5 million people will be diagnosed with breast
15 cancer. It's the most common cancer of women in the
16 world. One of every ten women in the world will have
17 breast cancer in their lifetime. It is a primary cause
18 of death, and in the U.S. one in eight women are
19 diagnosed with breast cancer each year.
20 Men are also affected by this disease,
21 and the most recent SEER data in 2006 reports 400 men
22 died of breast cancer; it does not just affect women.
23 Also precocious breast development in
24 girls, especially in the U.S. and Scandinavian
25 countries, is at an epidemic rate. Pediatricians have

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1 rewritten the book on precocious puberty, and several
2 studies have been reviewed by the NCEA, the USEPA's
3 NCEA, a couple of years ago when our Panel decided that
4 or came to the conclusion that body fat and endocrine
5 disruptors were regarded as critical modifiers of
6 breast developmental timing.
7 Also a recent study by Dr. Biro at
8 University of Cincinnati with over 1500 girls with
9 puberty at the age of 9, almost 23% of white girls had
10 breast development at age 9, and over 50% of black
11 girls had breast development at the age of 9. Body fat
12 and Tanner scores were not very well correlated and
13 only explained 30% of the variance in this outcome. So
14 the effect of endocrine disruptors on breast
15 development, breast cancer, is something that is very
16 near and dear to my heart, and that's why I do the work
17 that I do.
18 There is a technique that you may have
19 read about in the Summary, mammary gland whole mounts,
20 that I'm going to go through very quickly today; but
21 it's very important that you understand how we do this
22 and why we do it.
23 This is a mouse and a rat. Hopefully,
24 I'm going to point to the front. In the rat there are
25 six glands, not five as shown here. The sixth one

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1 would be down here near the tail. We removed the
2 entire fourth and fifth gland as a unit, with the
3 inborn lymph node being in between those two.
4 The whole mount procedure is very quick
5 and is not very expensive. In fact, I had a high-
6 school junior in my lab this summer who was able to
7 learn this technique in less than a day. After a week
8 she was able to teach it to others, and after two weeks
9 she was evaluating the slides in a manner that was
10 consistent with my own.
11 On the day of necropsy, we place the
12 slides in a Carnoy's fixative. It's glacial acetic
13 acid, ethanol and chloroform. This takes us about
14 15 minutes.
15 The next day we rinse these slides and
16 put them in Carmine Alum stain; takes about 25 minutes.
17 The day after that, or maybe one after,
18 we may, depending on the thickness of the tissue, rinse
19 these slides in increasing graded alcohol to 100%;
20 transfer to xylene. This clears the fat pad so that
21 you can see through the gland on the slide, takes about
22 30 minutes; and then these are allowed to sit in xylene
23 entirely until they're clear.
24 We permanently mount the slides and dry
25 them on bench coat. We fill the air pockets as needed.

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1 It takes us about an hour-and-a-half for 100 slides.
2 We recommend three time points of
3 collection for potentially estrogenic or anti-
4 androgenic compounds so that developmental pace and
5 permanence of the effect can be determined. We
6 evaluate these on a macroscope, which is a dissecting
7 scope, or computer-generated scans. It may take
8 between two and four hours on the macroscope.
9 We evaluate the slides in a way that is
10 consistent with pathology assessment of sliced sections
11 and H&E stain sections. This is something that's been
12 going on for 40 or 50 years in pathology. This is not
13 a new technique.
14 We assess all controls within an age group first, and
15 we determine what it's for: what is our best-looking,
16 most well-developed slides; what do they look like;
17 what is our best situation. We then assess all high-
18 dose slides within that same age group and define that
19 as 1, what is our worst-case scenario, essentially the
20 same as a pathologist would do.
21 We then mix the slides, evaluate the slides
22 as an entire set. We don't know the identification of
23 the slide when we are evaluating it. We stack the
24 slides into scores; so 4 is the best, 1 is the poorest.
25 They don't always fit into a single category, so there

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1 may be a stack in between a 4 and a 3.
2 We then pick up each stack, re-evaluate them
3 again to make sure that a 2 at the beginning of the
4 study, at the beginning of a 2- or 4-hour microscope
5 session, is the same as a 2 at the end.
6 We then record the ID off that slide and the
7 score that we gave it and any other notes that we used
8 to decide the score.
9 We then repeat the entire process with
10 another score, mixing the slides, starting from
11 scratch. They have to know what a 4 and a 1 is also,
12 so they start from scratch.
13 We evaluate the two sets of scores and
14 reconsider any scores for which there was a variance of
15 more than 1. We want the scorers to be thinking in a
16 consistent manner, and usually we have about 13% to 16%
17 error. So we average the scores and report them. The
18 pictures that we show you in pictures that you'll see
19 today represent the mean score of that group.
20 When we score these glands, when we evaluate them, we
21 have six criteria that we're really most interested in:
22 the terminal end number and the stage of development;
23 that they are a terminal duct, a terminal end bud, an
24 alveolar bud. We look at longitudinal duct growth;
25 lateral duct growth; number of primary ducts; density

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1 at ductal branching; and the amount of budding on the
2 ducts.
3 So you can see here a picture of what we
4 normally look for. You can see the lateral branching
5 would be from side to side. One of the longitudinal
6 growths would be from the nipple area down here not
7 shown to the end of the glands. The terminal end buds
8 are a specific size. They should measure about 120 to
9 150 microns. We do look at the size of these; we don't
10 just count any end as a terminal end bud, even though
11 it just looks like one.
12 We also look at the budding off the ducts
13 that's shown here. And here is an example of the
14 operating procedure that we had signed off on at the
15 EPA; it is actually an operating procedure that we use.
16 So essentially you can see that 1 would have few or
17 none; that we use words like "few", "none",
18 "undersized" and "one or few".
19 When increased to a 2, you'll see minimal,
20 few branches, few buds.
21 Increase to a 3, you are going to see
22 moderate growth, moderate branching, moderate budding.
23 I mean, we do use a scale to determine this for each of
24 these end points.
25 The visual mammary gland evaluations or the subjective

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1 scoring is not a new concept. Historically, this has
2 been used by mammary gland biologists evaluating early
3 life environmental exposures. Some very well-known
4 mammary gland biologists used this method back in the
5 '70s and '80s and still today: Cliff Welch has used it
6 on a 1:6 scale for caffeine exposure following prenatal
7 development -- and you'll notice one of the themes
8 here is prenatal or early life exposure -- Leena
9 Hilakivi-Clarke, Marc Lippman, who was at one time the
10 Head of the Lombardi Cancer Center at Georgetown, and
11 they work within the NCI or use developmental
12 polyunsaturated fat exposures and genistein exposures
13 using a 4-point scale. They found a 0.7 to 0.9
14 correlation coefficient between morphometric analysis
15 and visual evaluation. This work was published in
16 PNAS.
17 Again this same group with Nick Kenney, who has worked
18 with Dick de Augustine and Ken Croik at the NIEHS, used
19 neonatal estrogen, TGF-alpha and ICI estrogen
20 inhibitor. Again, they used both methods, and you'll
21 see here a statement from that paper that characterizes
22 the density of the whole thing. The relative density
23 of the following characteristics were evaluated using a
24 double-blind 4-point scale, and you can read that:
25 "This scale was used instead of counting the actual

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1 number of different structures on total mammary gland
2 or randomly selected areas, which we found not to give
3 an accurate description of the mammary tree." So
4 others also use this method.
5 But in my own work, early work on TCDD, we
6 felt the same as the early researchers and others that
7 measuring one component of the system or one or a
8 couple of components doesn't give you a very good
9 estimation of what the actual gland looks like.
10 At the bottom, you can see control and TCDD-
11 treated mammary glands from postnatal day 4, which is
12 what we are going to really focus on. You see here
13 this large structure here -- these are on the same
14 scale -- this smaller structure with much less
15 branching.
16 What we did in the study is we measured the
17 number -- sorry this is off; it was not yesterday --
18 but we measured the number of primary branches; we
19 looked at the percent extension to the gland, which it
20 looks at longitudinal growth. We also looked at the
21 number of terminal structures, giving us an idea of how
22 many branch points there were, because each branch will
23 form an end. And what we found is that the sum of the
24 parts really equals the whole; that each one of these
25 things didn't really give us an accurate picture of

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1 what we were looking at. And we then confirmed this
2 with immunohistochemical stains, or with re-sectioning
3 the tissue, so these are contralateral glands. Here
4 you can see much epithelium staining dark purple in
5 this fat pad and much less shown here, and these are
6 longitudinal sections.
7 So one of the important things that we do is
8 we assess pace of development. So the fourth and fifth
9 mammary gland are separate and then grow up together
10 within that fat pad. Once they grow together, they
11 have contact inhibition. The ends differentiate. They
12 are no longer proliferating actively; they are more in
13 a static state, varying just slightly based on the
14 stage of the estro cycle that they're in. Normally
15 after puberty, we see this contact inhibition and
16 differentiated ends. We see fewer terminal end buds,
17 increased number of lobules and budding and a decreased
18 proliferative index measured by BrdU Incorporation or
19 however else you'd like to measure it.
20 If you see a delay at puberty, one of the
21 things that we always see with a delay is an increase
22 in the number of terminal end buds in the gland, a
23 decreased number of lobules and buds compared to
24 control and an increased proliferative index. This
25 increase in terminal end buds has been shown by

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1 multiple groups, and Jose Russo and his wife Irma are
2 the most thorough example, where the terminal end buds
3 are correlated with the number of tumors that may be
4 formed if exposed to a carcinogen. So having these
5 terminal end buds around for an extended period of time
6 could lead to an increased susceptibility to another
7 carcinogen or another EDC. Impaired lactation is also
8 possible if they're mated when terminal end buds are
9 still present and the gland is not fully formed.
10 So one of the other things that we like to do -- and we
11 don't always do this, but it is very useful in aged
12 animals studies and highly recommended -- is that we
13 look at horizontal or longitudinal sections of the
14 mammary gland. These are cut in the same plane as what
15 we're looking at on the whole-mount evaluation. Here
16 you can see all of the mammary gland in a cross-
17 section: you can see duct development; you can see
18 stroma; you can see if there was a problem with the
19 lymph node such as lymphoma; and you can see entire
20 ductal structures this way. Using a cross-section or
21 transverse section, which has been far overused in
22 pathology, you see very little of the gland and only
23 really a very small snippet of what's going on.
24 There are three major critical periods of
25 development in the mammary gland. They are that in

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1 early life, either just early gestation or in just
2 postnatal, pubertal development and pregnancy. These
3 are times when the gland is undergoing rapid
4 proliferation, metallic index is elevated, and the
5 effect of environmental chemicals has been noted by
6 labs across the country -- not just mine, a lot of labs
7 have participated in this effort. Changes in
8 development during these times can lead to adverse
9 outcomes, including lactational impairment, breast
10 cancer, altered susceptibility to other compounds.
11 In our studies of atrazine, we have three
12 main aims. The aim was to define the atrazine dose and
13 exposure parameters that are the minimum requirements
14 to induce female offspring mammary gland effects
15 without changes in body weight. Changes in body
16 weight, significant changes in body weight, will affect
17 mammary gland development. You will have a smaller
18 mammary gland if you have a smaller animal, and
19 therefore body weight is very important in the analyses
20 that we do.
21 We always plot body weight, and we always
22 compare to it in our analyses. We also want to
23 determine if an environmentally relevant mixture of
24 atrazine and chlorotriazine metabolites affect the
25 mammary gland and prostrate during developmental

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1 exposures, and are there adverse mammary gland effects
2 of fetal and early neonatal atrazine exposures.
3 For all of these studies, we have used the
4 Long-Evans hooded rat as a model. We always get them
5 from Charles River. Normal cyclicity patterns,
6 reproduction, good reproductive patterns and the fact
7 that they are not really prone to spontaneous mammary
8 tumor formations or other abnormalities in mammary
9 development were the reasons that we chose this strain.
10 Also because some of the early work in Ralph Cooper's
11 lab had used the LE rat. They have large litters, and
12 they're good mothers if you leave them alone.
13 You cannot stress these rats, and this is
14 really important for us in the conversations that are
15 coming up next. You should not manipulate these pups
16 at birth. Food restriction, metal-bottom cages, twice-
17 a-day inspection of the newborns, which is typical in
18 19 GLV studies and removal of pups from their dam will
19 stress these animals to the point of cannibalism, and
20 it will increase pup loss and weight loss in the
21 animals. We were trained in how to use these animals
22 by Earl Gray and Linda Birnbaum's group, who had used
23 them extensively before us. And we typically equalize
24 our litters on PND4. We took special care, and then
25 the next study that I'm going to describe, to make sure

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1 that we did not stress these animals.
2 So in our cross-foster study, which is the
3 Rayner 2004 study, which is in the section on aromatase
4 for reasons that I don't understand; but we carried out
5 a cross-foster study in which half-litters were crossed
6 on PND1. We removed the five pups from a dam, tattooed
7 these pups and returned them immediately. We changed
8 gloves in between every cage, and we were intensely
9 quiet in the room while doing this; we didn't speak.
10 We had a plan.
11 So we took the rest of the pups out of the
12 cage, and five of those animals were removed and went
13 to another cage, making four cross-foster groups. So
14 there were controls where half the litter was cross-
15 fostered to another control, there were controls where
16 half the litter was cross-fostered with atrazine, and
17 there were atrazine-exposed animals that were given
18 control pups and atrazine-atrazine groups; but in every
19 case, half a litter was crossed. Always, the dams' own
20 pups were tattooed.
21 So one of the major findings from this study
22 is the effect on mammary gland development. It was the
23 first study that we'd done demonstrating this effect.
24 We saw the effects in the animals that were not only in
25 utero-exposed but also lactationally exposed. The

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1 effect was worse when they were in utero- and
2 lactationally exposed, and you can see here at
3 postnatal day 33 it's a little easier to see that
4 there's a delay in growth of these glands together.
5 Also in these animals we looked at vaginal
6 opening, which was delayed in the animals lactationally
7 exposed to atrazine and atrazine-atrazine-exposed. But
8 interestingly, we saw changes in both aromatase and EGF
9 receptor gene expression that were prepared from
10 contralateral glands from the same animals, as shown
11 here. We saw significant decreases in aromatase with
12 gene expression, which would suggest slowed and less
13 rapid development, and also EGF receptor. EGF receptor
14 is one of the important growth factors in mammary gland
15 development, and aromatase in the mammary gland
16 produces endogenous estrogen for the gland itself,
17 which helps in the branching morphogenesis.
18 We also did look at BrdU Incorporation in the
19 study. It's noted in your Charge that we did not, and
20 we did look at this. We did not see significant
21 effects; but there was an increase, a general increase
22 in the atrazine-treated animals in BrdU Incorporation
23 at this time point, suggesting that they're more
24 rapidly dividing than the controls, trying to catch up
25 in development.

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1 We also looked at males in this study. This
2 is reported in Rayner 2007 paper. In this study, we
3 looked at 120 days and 220 days at the offspring, male
4 offspring. We saw an increase in lateral prostate
5 weight at 120 days in the atrazine-atrazine group, and
6 actually in all the treated groups; but we always base
7 these on body weight, and one body weight was
8 considered. This group was a little larger, so this
9 became insignificant. So there was an increase in
10 lateral prostate weight there, also.
11 This is just an example of an unaffected and
12 an affected gland. I don't want you to associate this
13 with any dose in particular, but this is just an
14 example of what we were seeing in the prostate. These
15 sections were read by EPL pathologist Angela Wolf, who
16 is an EPL employee and a pathologist by training,
17 veterinary pathologist by training.
18 We saw an increase at necropsy of prostate
19 abnormalities. These were like focal areas on the
20 outside of the prostate that were noted. There was
21 also a change in preputial separation timing or
22 pubertal timing in these males in only the atrazine-
23 atrazine group, and this is reported in that study.
24 At 120 days, the pathology results were
25 significant changes in this lactationally exposed group

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1 in distribution of the inflammation, and we also saw
2 significant effects in severity. In the affected
3 animals, we saw an increase of severity due to atrazine
4 treatment. Also in the atrazine-atrazine group there
5 was only one noted, and there was a significant effect
6 on the severity there as scored as a 5.
7 In the next paper I want to bring up, this is Critical
8 Windows of Mammary Sensitivity to Atrazine found in the
9 Regrown Tissue section of the Issues Paper. Here,
10 really, the main goal of the study was to assess not
11 only the F1 offspring as we had done in the previous
12 study but also to assess the F2 offspring. These
13 animals were treated for shorter windows of time, again
14 with 100 mg/kg of atrazine. We needed to make sure
15 that we had a positive control, a negative control, and
16 then we broke down this 7-day period into 3-day
17 stretches: 13 to 15, 15 to 17 and 17 to 19.
18 In this study we dosed and we evaluated the
19 offspring at several time points, also assessing
20 vaginal opening; early cyclicity. And then at 67 days,
21 the animals were bred over a 3-day period. And at this
22 time we saw changes in the mammary gland development
23 study, with rat data. We assessed their offspring 4
24 days later and 11 days later after birth.
25 In this study there were two blocks of eight

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1 dams per treatment group that were dosed. There were
2 no block effects.
3 And by the way, this paper received Best
4 Paper in Tox Sci as voted by all of their reproductive
5 and developmental tox papers that year by the
6 Reproductive and Developmental Tox Specialty Section as
7 a team.
8 The major thing that we found in the study
9 was that the 3-day exposure during late gestation did
10 also cause this persistent mammary gland developmental
11 delay. On the top, you can see postnatal day 22.
12 These are just examples of what we saw. Here's the
13 control, here's the delayed development of the 3-day
14 exposure and the 7-day exposure.
15 Shown here at day 67, these are mature
16 animals. We saw very few terminal end buds remaining
17 in this tissue at 67 days in the control. We saw
18 numerous terminal end buds in the 3-day exposed and
19 even more in the 7-day exposed animals. There was no
20 change in VO in these 3-day exposed animals, and there
21 was also no change in body weight in these animals at
22 any point and, if anything, there was a slight increase
23 in body weight. There was delayed vaginal opening down
24 in the 7-day exposed animals.
25 When we bred the siblings to the animals I

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1 just showed you, because obviously we can't breed them
2 if we've taken a mammary gland out, we looked at the
3 weight of the offspring. We also did a lactational
4 challenge on postnatal day 11, in which we didn't find
5 anything; essentially, there was no change in maternal
6 behavior that could be measured, and there was no
7 change in weight gain of the pups after nursing its
8 period of 20 minutes that was significant.
9 What is shown here is in green the control.
10 Yellow is 13 to 15, orange is 15 to 17, blue is 17 to
11 19, and red is 13 to 19. You can see here that a 3-day
12 period and a 7-day period ended up with significantly
13 decreased weight gain in both female and male pups on
14 PND4, ranging from about 12% to 15% and what most would
15 consider adverse, and on postnatal day 11 these weight-
16 gain deficits were even worse. They were between 13%
17 and 25% in the varying groups. This is an indication
18 that this very brief period -- so these are the
19 granddaughters and grandsons. This very brief period
20 caused persistent changes in the mammary gland that,
21 when present and bred, led to lactational deficits. We
22 did not test them at a period past this time. We
23 tested them when we saw the effect.
24 In the third study that I want to talk about
25 today, we looked at an atrazine metabolite mixture.

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1 This mixture is similar to what was presented in some
2 USGS and state-level biomonitoring data from Illinois
3 and North Carolina. We developed this mixture in a way
4 that was similar to what was found in the groundwater
5 in a ratio of how it was found in the groundwater, with
6 25% being atrazine, 20% being hydroxyatrazine, 5% DIA,
7 15% DEA and the majority of it being DACT final
8 metabolite. The percentages were on a massed basis.
9 The estimated maximum cumulative level from the
10 literature that we found was 25 parts per million, so
11 the estimated maximum cumulative level sorry, I just
12 said "million"; I meant billion. So in our study, the
13 minimum level that we gave them was 25 parts per
14 billion.
15 In the study there is some more that I just showed you.
16 We dosed with again the negative control, positive
17 control: 0.09 mg/kg, or 2.5 parts per million; 0.87
18 mg/kg, or 25 parts per million; 9 mg/kg, or 250 parts
19 per million. And the way that we developed this is
20 detailed in this Enoch paper. So there is a chart
21 there that can give you much more information than I am
22 going to go over here.
23 This study was done in two blocks with
24 greater than six dams per treatment group that were
25 dosed. There were between 10 and 18 dams in every

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1 treatment group for the final analyses.
2 In this paper, we state that we evaluated
3 this data using the dam as the unit; that is true.
4 There is confusion in this paper, and I'm glad we did
5 this because it brought it to my attention and I didn't
6 realize this was here.
7 In the paper, we say that the dam was the
8 unit of measure; that is true. The significant results
9 that are reported are correct. This paper states pup
10 numbers, though; so in several of the figure legends,
11 you'll see "and greater than 10 pups". That's true,
12 but they were not the unit used for the analyses. So
13 that is a misconception, and I'm sorry for the
14 confusion; but what's in the paper is correct. So
15 these numbers, the dam number is at least as great as
16 10 for all of these data.
17 One of the major things that we found in this
18 paper is again this delay in mammary gland development.
19 At the low doses, we did not see it consistently in all
20 the time points and in all of the doses. It was not as
21 consistent in the early stages. We saw this decreased
22 branching pattern again; so here is the control, the
23 branching pattern was decreased in all the doses, and
24 over time you can see these changes. In this postnatal
25 33 group, for whatever reason -- and this happens

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1 sometimes, it's happening in most studies of ours using
2 different compounds before also -- sometimes we get a
3 control that is not normally developed; but as an
4 average, the average mean for that group is not what we
5 typically expect. We typically expect somewhere
6 between 3.2 and 3.5; this PND 33 group was at 2.5. We
7 have no reason for it. There was no weight differences
8 to account for it. But it did cause us to lose
9 significance in this one group; however, at all the
10 time points after 33, which there were two, we did see
11 significant effects of atrazine in all the groups. And
12 you can see here in these groups that the branching
13 morphogenesis just is not what it is in the control.
14 Oh, no, this is really messed up and I'm
15 sorry. I don't know how this happened. It was good
16 this morning.
17 So let me just explain. These are the males
18 from this same study, and these are not discussed in
19 your Issue Paper because there was a snafu with the
20 Journal. The embargo was not released on time, and so
21 this was not in press by the July, although it was
22 accepted and we were told that was in press; but it was
23 not publicly available in mid-July. But it is publicly
24 available now in Reproductive Toxicology. So let me
25 just explain, and you are going to have to watch the

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1 front screen to see if you can follow with me.
2 So we're going to look at controls 0.9, 0.87,
3 8.73. In incidence of information in the controls, we
4 saw 48% of the animals, and there was 25 animals in
5 this group; 48% had inflammation in the lateral and
6 ventral prostate; 67% in the 0.9 group had
7 inflammation; 76 in the 0.87 group; and 80% in the 8.73
8 group, similar to what we saw in atrazine, which was
9 81%. So you can see there was between 21 and 25
10 animals in these groups. These were significantly
11 increased inflammation.
12 We also saw an increase in severity of the
13 affected animals. And this was again the severity
14 scoring that pathologists typically use; this is
15 typical, done by one of the NIEHS pathologists and EPL
16 and a pathology team at the NIEHS. So there was an
17 increase in severity of inflammation for all three of
18 these; but it wasn't quite significant for atrazine,
19 the inflammation severity.
20 And then we also looked at whether or not
21 preputial separation was delayed in these animals, and
22 for 0.9 the answer was no because there was a little
23 bit of higher variability in that group; but for 0.87,
24 8.73 and atrazine, we saw delayed preputial separation.
25 And again, you can probably access that paper.

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1 The male prostate effects were also noted at
2 necropsy. This necropsy was not done by my laboratory;
3 it was done by a pathology team, a necropsy team from
4 EPL with a Board-certified pathologist onsite
5 overseeing the necropsy. We saw an increase in the
6 observation of epididymal fat necrosis which looked
7 like lipomas and also prosthetic foci, as I explained
8 we saw in the Rayner paper in the cross-foster study.
9 Shown here again is a control on the top
10 panels, and the bottom panels are examples of what we
11 saw in inflammation, and an example on the bottom of
12 what we saw in the fat.
13 So one thing that I did not talk a lot
14 about today is body weight. In our studies, 100
15 mg/kg of atrazine does cause a significant decrease in
16 body weight gain in the dams in all of these studies.
17 This information is reported on our papers. However,
18 when we used the atrazine metabolite mixtures, not only
19 did we not see a decrease in body weight gain, we saw
20 small increases in body weight gain. This low-dose
21 atrazine metabolite mixture did not affect weight gain
22 in the dams.
23 Not only did it not affect weight gain in the
24 dams, it did not affect weight gain in the pups. In
25 two of our studies, both the Rayner paper and the Enoch

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1 paper, we specifically go over the effects on body
2 weight in the fetuses. So separate studies were done
3 in which we exposed the animals to either a dose-
4 response of atrazine, 25, 50 or 100 mg/kg of
5 atrazine, during the normal dosing period that we have
6 used for all of our other studies; but we also did this
7 for the high dose and the mixture, for the 8.73 AMM
8 mixture. In all these cases, we either saw slight
9 increases in fetal body weight at gestation day 20 or
10 no change at all, as shown here and in the papers. So
11 body weight is not the issue here.
12 So some final thoughts, and so I kind of
13 bring all of these back together. What we've found in
14 all of our work is that atrazine has little, if any,
15 effect on body weight of the F1 pups. We saw a 5% and
16 6% decrease in the PND4 pups in the cross-foster study
17 that were transient; that weight deficit disappeared,
18 and that was only found in the atrazine- atrazine
19 exposure group, again 5% and 6% decreases.
20 We also saw that a high dose of atrazine
21 affects vaginal opening.
22 Preputial separation seems to be more
23 sensitive to the effects of atrazine, and the lowest
24 dose that we saw with an effect was .87 mg/kg.
25 There is little effect on serum hormones.

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1 And I didn't talk about it at all today, because they
2 were either inconsistent or showed no pattern and they
3 were also transient; so if we saw it one time, we
4 didn't see them at the next time period that we
5 evaluated them.
6 We strongly thought that prolactin may be
7 involved in branching morphogenesis issues that we have
8 in these glands. That did not turn out to be the case.
9 There is also little effect on female
10 reproductive tissues, which I didn't show you besides
11 the mammary gland. There is some consistency in
12 increased anterior pituitary weight gain in 100 mg/kg
13 across all of our studies, and that has been shown in
14 other studies by Tammy Stoker and Susan Laws.
15 There is no effect of this exposure on early
16 cyclicity, none at all. We evaluated it in two
17 different studies, there was no effect.
18 Prostatitis is apparent on postnatal day 120
19 in two different studies that we've done; but it does
20 not seem to worsen in the rat. We've used two time
21 periods to evaluate this, and in both studies the
22 latter time period was not worse than the earlier one.
23 We have not gone past 220 days to evaluate this effect;
24 but the inflammation is present in both lateral and
25 ventral prostate, with the ventral having a higher

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1 background of inflammation than the lateral.
2 And finally, the mammary gland development
3 changes are visible to the eye. I hope I've shown you
4 that today. You can look at the gland, and you can see
5 the effects. We show you the mean score; we don't show
6 you the worst scenario in these situations.
7 We've also shown that there is gene
8 expression changes that are concomitant with these
9 morphological changes, changes in genes that are known
10 to be involved in early growth and development. We've
11 also shown adverse effects on F2 pup body weight gain
12 if bred when the developmental delays are apparent in
13 the mammary gland siblings.
14 There is an extended window of terminal end
15 bud development in mammary gland. This may also be
16 present in young girls who are taking longer to develop
17 their breasts, so they may start development early and
18 take a longer period of time to reach full development
19 of the breasts. Numerous pediatric epidemiological
20 studies are now discussing this non-progression in
21 girls; it does happen. Unfortunately, I just had a
22 daughter that had it happen; I never believed it until
23 I saw it myself, but it is happening. The NIEHS funds
24 a study called the Breast Cancer and Environment
25 Research Centers. Within that Center there is three --

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1 Mount Sinai, University of Cincinnati and Kaiser
2 Permanente in San Francisco -- that are evaluating
3 girls early in their life looking at the environmental
4 exposures, and they are reporting non-progression.
5 So this issue of extended windows of terminal end bud
6 development is not just important in the rat; it is
7 important in girls also. This leaves them susceptible
8 to increased susceptibility to another hit: a
9 carcinogen, another endocrine destructor. I can't
10 define what another hit would be; but in an animal
11 study, chemical carcinogens are known to increase
12 tumors if there are more terminal end buds present.
13 Also, the mammary gland does seem to be more
14 sensitive than other reproductive endpoints in our
15 studies, in the female at least. And that is not just
16 true in this study -- and I'm sorry it's a little hard
17 to read, and I hope you can read it on your handouts --
18 but in a paper that has been submitted to EHP, four
19 scientists have gone through all the mammary gland
20 literature that they could find where the mammary gland
21 and any other reproductive endpoint were evaluated in
22 the same study -- and that's part of the problem with
23 mammary gland development is that not everyone looks at
24 multiple reproductive outcomes, so it's hard to assess
25 if mammary gland is more sensitive in these studies.

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1 But in the studies shown here, mammary gland was found
2 to be more sensitive or to need a shorter exposure
3 parameter than other reproductive endpoints to have
4 significant outcome.
5 So two of our papers, both the Enoch paper
6 and the 2005 Rayner paper, were noted. Several papers
7 on this interlay, DDT, genistein and one by one of your
8 SAP Panel members, Barry Delclos. And I just want to
9 let you know that it's not just these studies in which
10 it happens, but other studies are showing the mammary
11 gland is a very sensitive endpoint.
12 And finally, I just want to make it clear
13 that we do not know the mechanism of action for these
14 effects. We are studying that in my lab now, but some
15 of the data that is presented in the Summaries document
16 -- maybe you want to bring this to everyone's attention
17 -- and that is that I don't think we know a whole lot
18 about atrazine and oxytocin. Many of you are probably
19 much more well-versed on oxytocin than I am. But it is
20 critical in stimulation of milk ejection reflex, it
21 stimulates uterine smooth muscle contractions at birth,
22 and it establishes maternal behavior.
23 As you can see here, this is one of the many
24 studies that were done back in the '80s showing that
25 just injection of oxytocin will bring on rapid onset of

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1 maternal behavior. It's critical, and one of the
2 important things about oxytocin is that it is a stress
3 hormone; it's released from the hypothalamus. Acute
4 stress, such as food restriction, wire-bottom cages,
5 pup handling, removal just after birth, will inhibit
6 oxytocin release. If that happens, you and actually,
7 I have some examples here of things that you can see.
8 I mean, atrazine could interfere with oxytocin release
9 at the level of the hypothalamus, and this could lead
10 to decreased oxytocin, which could then cause decreased
11 milk production just after birth, which may be why we
12 saw transient declines in PND4 body weights here and
13 there and potentially in F2 study.
14 We know that it causes delayed parturition,
15 atrazine causes delayed parturition. If we dose all
16 the way up to gestation day 21, we will cause delayed
17 parturition in these animals; they will lose their
18 litters. They may or may not have undergone normal
19 birth. And this is reported by Mike Narotsky eight to
20 ten years ago in the Fischer rat. And they also put
21 this show for maternal behavior, and this can be even
22 worse if they are stressed.
23 And so I just want to leave you with the
24 thought of where we're going with our mechanistic
25 studies. The prostate and the mammary gland do seem to

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1 be sensitive tissues affected by atrazine. There are a
2 lot of similarities, actually, between the prostate and
3 the mammary gland. They both develop late in the
4 fetus, they are developing in the last third of the
5 gestational period. Budding of the epithelium happens
6 just prior to birth in both tissues. And there is an
7 important role in androgens, actually, in both tissues;
8 so androgens make male mammary glands either not have a
9 port to the nipple area, not develop a nipple, or in
10 the mouse they don't have branching of epithelium at
11 all. There is also branching morphogenesis that occurs
12 primarily just before and after birth, and there is
13 also differentiation of the epithelium.
14 But the one good thing about the similarities
15 between these two is that there is a whole lot more
16 known about prostate and its branching morphogenesis
17 than there is about the mammary gland. So we're using
18 some of the information known from the prostate to look
19 for candidate genes that may be involved in regulation
20 of the effects of androgen in the mammary gland, and I
21 understand the fetal mammary gland development is going
22 to be critical to that.
23 With that, thank you.
24 **DR. STEVEN HEERINGA:** Thank you, Dr.
25 Fenton.

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1 At this point, if you will, I'd like to
2 open it up to the Panel for some questions or
3 clarification on your presentation or material that is
4 presented in the Issue Paper.
5 Dr. Akana.
6 **DR. SUSAN AKANA:** Thank you.
7 In your studies when you order pregnant
8 rats to come into the lab, I assume that this is all
9 their first-time pregnancy, primiparas?
10 **DR. SUZANNE FENTON:** Yes.
11 **DR. SUSAN AKANA:** And when did they
12 generally arrange for them to be shipped to your lab?
13 What gestational date are they in when they come to
14 your lab?
15 **DR. SUZANNE FENTON:** There were fixed
16 days that deliveries took place. We usually had them
17 in the room for gestation in 10 for an acclimation
18 period.
19 **DR. SUSAN AKANA:** The other question I
20 had is between your studies, did you have a difference
21 in the gavage, like once daily or twice daily, in the
22 different studies?
23 **DR. SUZANNE FENTON:** In the first study,
24 the Rayner 2004 paper, there was a once-a-day gavage.
25 Information that was gathered after that time caused us

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1 to change our scheduled dosing to half-doses twice
2 daily. So the total for the day was the same as we had
3 given previously; but we split the dose based on the
4 morning body weight of the animals, and then we studied
5 after that.
6 **DR. SUSAN AKANA:** Are you willing to
7 comment on the rationale for changing to twice?
8 **DR. SUZANNE FENTON:** Sure, sure. We had
9 better information on the half-life of atrazine, and
10 that's really what caused us to shift this. So the
11 half-life is short, anywhere from estimations at that
12 time were from 11 to 17 hours half-life. So we thought
13 that it would be more accurate and less episodic if we
14 gave half-doses twice daily.
15 **DR. SUSAN AKANA:** That's true; but then,
16 of course, you have to handle the moms twice.
17 My next question is, there is some
18 literature that when you cross-foster pups mom still
19 knows her own pups, and there is more licking and
20 grooming of her own pups. So that could be a concern -
21 - well, there is the control there -- but in the
22 atrazine-atrazine litter, that litter. And did you
23 actually test within litter the cross-fostered groups -
24 -
25 **DR. SUZANNE FENTON:** Yes. So the beauty

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1 of having her own pups tattooed and keeping some for
2 her own pups in the litter was for exactly the reason
3 you mentioned; so thank you for that comment, because
4 that's exactly why we did it. We knew exactly which
5 animals had a tattoo on their paw. Those animals and
6 the other animals within the litter were compared to
7 see if there was an effect, and we did not see any. So
8 we tested for block effect; any sort of differences
9 that could be there, we always tested for those.
10 **DR. SUSAN AKANA:** That's great. And
11 then I have a couple more questions but a comment. I'm
12 interested in a lot of the results that hit on
13 postnatal day 4 and 11 because, as you know, those are
14 the ends of the critical period for the hyporesponsive
15 period in the adrenal-pituitary axis, and I'm wondering
16 if you had thought about how that might impact the
17 reproductive results.
18 In other words, in a standard rat
19 litter, roughly the ages postnatal day 4 to 10, 11, 12,
20 there is a period where the pup is secreting very low
21 corticosterone, and it's thought to be a protective
22 mechanism for the development of feedback mechanisms in
23 the brain. But of course if you're not secreting as
24 much corticosterone because of this feedback
25 inhibition, that could mean that hypothalamic circuits

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1 are also vulnerable in other areas of the hypothalamus.
2 **DR. SUZANNE FENTON:** That's a really
3 good question, and actually not one that we considered.
4 I mean, in going forward in our mechanistic studies,
5 that is something that we should consider, and thank
6 you for your comment.
7 What we focused more on was the
8 potential for fetal programming. So it's still kind of
9 our thoughts that we may be affecting something in the
10 fetal mammary gland and the fetal prostate that's
11 changing our receptor population for the lifetime of
12 the animal or changing the responsivity to the normal
13 hormonal milieu. That's the hypothesis we were working
14 off of, but what you just suggested is interesting
15 also. So our thoughts were somewhat a little
16 different; but definitely, it's something to think
17 about. Thank you.
18 **DR. SUSAN AKANA:** I have three more
19 questions. I respect the subjective scoring of the
20 mammary gland development and its long validated
21 history; but have you tried a head-to-head comparison
22 of the classic method versus the imaging programs that
23 you can get on software nowadays, and how did they
24 compare if you
25 **DR. SUZANNE FENTON:** Yes. So now that

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1 I'm at the NIEHS in the National Toxicology Program,
2 I've been challenged to do that on a very specific
3 level. So that is something that we are doing now. We
4 are using the Holland Sprague-Dawley rat, and we're
5 looking at from gestation to day 15 out to day 70, and
6 that is exactly what we're doing: we're doing a head-
7 to-head comparison.
8 But again, in other studies that I have
9 performed, not talked about today because they had
10 nothing to do with atrazine, we have done that in the
11 mouse, and again single measurements do not seem to get
12 us a very good portrayal of what you actually see in
13 the scope. And we're working with a pathologist within
14 the NIEHS, Mark Cesta, and a pathologist at the NCTR,
15 John Otondras, to further evaluate what endpoints need
16 to be measured so that it does look like what you see
17 underneath the scope. So there are three of us, and
18 we're all kind of working together toward that end.
19 **DR. SUSAN AKANA:** I was thinking perhaps
20 of analysis with four compartments or more for each of
21 your hallmark so a combination in the genotype, say
22 four times on four different elements.
23 **DR. SUZANNE FENTON:** Uh-huh.
24 **DR. SUSAN AKANA:** Okay. My next
25 question is, I'm very interested in the lactational

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1 challenge. If I understand correctly, the mom and pup
2 3 separated for a stretch of time, reunited. You
3 measured the time before mom was allowed to latch on,
4 and 20 minutes after that you reweighed the litter and
5 there was no difference in the weight gain in different
6 litters across different treatment groups; is that
7 correct?
8 **DR. SUZANNE FENTON:** That is correct,
9 and that was in the F2 pups.
10 **DR. SUSAN AKANA:** Okay. My question
11 here, if I recall correctly in the F2 pups, they were
12 lighter in weight.
13 **DR. SUZANNE FENTON:** Uh-huh.
14 **DR. SUSAN AKANA:** So if the litter as a
15 whole gained the same amount of weight, the little pups
16 must have drank more milk.
17 **DR. SUZANNE FENTON:** Or more often.
18 **DR. SUSAN AKANA:** Or more often.
19 **DR. SUZANNE FENTON:** And when we found
20 the results, it was already too late to have assessed
21 that. We have not had an opportunity to repeat the
22 study to see if that's the case. It is possible that
23 they nursed a lot more often than did the pups in the
24 control group. We were not able to assess that.
25 **DR. SUSAN AKANA:** But is this correct:

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1 the likelihood is that they had more milk in their
2 stomach at the end of 20 minutes?
3 **DR. SUZANNE FENTON:** I don't know. I
4 think what we could I can't directly answer that; but
5 what I can address is the fact that they gained a
6 similar amount of weight, which tells me that their
7 thriftiness was similar to control animals. They
8 didn't have a problem suckling.
9 **DR. SUSAN AKANA:** Uh-huh.
10 **DR. SUZANNE FENTON:** So why did they
11 gain less weight? I don't know.
12 **DR. SUSAN AKANA:** One last comment is in
13 the rat there is on day about 10 an incredible spike in
14 leptin developmentally, and it's thought to have
15 important, important roles in programming feeding
16 circuits in the brain. So there would be an incredible
17 opportunity to measure leptin in those animals that
18 they
19 **DR. SUZANNE FENTON:** Uh-huh. Actually,
20 John Rogers at EPA is doing some studies on fetal basis
21 of adult disease, and he used atrazine as a model
22 compound because at high enough doses you can cause
23 small decrements like 10% weight decrements in
24 offspring. So he's using like 150 or 200 mg/kg -- I
25 can't remember which one -- to cause those weight

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1 decrements. And in his study, he actually saw an
2 increase in weight gain over time in those animals. So
3 in late adulthood and in late life, he saw an increased
4 weight gain in the animals.
5 So, I mean, there may be some issues
6 going on there, and we have an interest in leptin
7 because of the mammary gland. And it also impacts the
8 mammary fat pad development, and so we also have an
9 interest in that. So we will be looking at that in the
10 future.
11 **DR. STEVEN HEERINGA:** Thank you, Dr.
12 Fenton, and we'll make sure that the observations that
13 were made are recorded in the final report, too; so Dr.
14 Fenner may not be here for Charge Questions.
15 Dr. LeBlanc.
16 **DR. GERALD LEBLANC:** Gerry LeBlanc.
17 A couple of quick questions of
18 clarification. In the histological examination of your
19 slides I think you mentioned it, but I missed it. How
20 are discordant results between the two examiners dealt
21 with?
22 **DR. SUZANNE FENTON:** We sit down
23 together, and we evaluate them together. We talk about
24 why one might have scored one higher or lower so that
25 we can understand the perspective that each is coming

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1 from. Typically, we're not more than one apart; I
2 mean, it doesn't happen very often. So there have been
3 a few instances where one of us needs to have more
4 consistency with how to score the rest of them.
5 **DR. GERALD LEBLANC:** So if the scores
6 vary by one or less, you use the average?
7 **DR. SUZANNE FENTON:** Yes.
8 **DR. GERALD LEBLANC:** And if the scores
9 vary by greater than one --
10 **DR. SUZANNE FENTON:** Actually, if it's
11 less than one.
12 **DR. GERALD LEBLANC:** Okay.
13 **DR. SUZANNE FENTON:** If it's one or
14 greater, we sit down and talk about it.
15 **DR. GERALD LEBLANC:** And then you decide
16 on it.
17 **DR. SUZANNE FENTON:** Yeah.
18 **DR. GERALD LEBLANC:** And with regards to
19 the scoring, it's a qualitative measure; but I was
20 wondering within the derivation of a score, are there
21 any quantitative measures? In other words, do you
22 count limb buds or terminal buds, or do you measure
23 branch lengths or anything of that nature?
24 **DR. SUZANNE FENTON:** Yeah. One of the
25 things that we like to do is to get an assessment of

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1 how many terminal ends there are and then what
2 percentage of those are terminal end buds, especially
3 at weaning if this is easy to do, and a lot of times we
4 will do that. We don't necessarily report it; it
5 doesn't add anything, as it's usually consistent with
6 our score. We haven't had instances where it wasn't.
7 **DR. GERALD LEBLANC:** Thank you.
8 **DR. STEVEN HEERINGA:** Dr. Bailar.
9 **DR. JOHN BAILAR:** Could you say a little
10 more about the relevance of these dose levels to
11 ordinary human exposures?
12 **DR. SUZANNE FENTON:** Sure. The mixture
13 that we used, like I said -- and I probably didn't do a
14 great job of explaining this, because it is complicated
15 -- but we used data that was produced in Illinois and
16 North Carolina on what is actually present in ground-
17 and surface water. So essentially any wildlife species
18 could be exposed to this water as is, and the maximum
19 contaminant limit there was 25 parts per
20 billion. So when you added all the different
21 chlorotriazine metabolites together with atrazine that
22 was measured, it was 25 parts per billion. So that
23 essentially is what any wildlife species could be
24 exposed to.
25 We went 100, 1,000 and 10,000 higher than that, so

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1 that's the actual translation: it's 100, 1,000,
2 10,000. So our high dose of atrazine metabolite
3 mixture was 10,000 times higher than what's found in
4 ground- and surface water. The lowest dose, 0.09, is
5 only 100 times higher.
6 **DR. JOHN BAILAR:** Thank you.
7 **DR. STEVEN HEERINGA:** Dr. Horseman.
8 **DR. NELSON HORSEMAN:** I wonder if you
9 could go back to your Slides 7 and 8 on the scoring
10 system
11 **DR. SUZANNE FENTON:** Uh-huh.
12 **DR. NELSON HORSEMAN:** and clarify
13 for us; it seems to be saying two different things.
14 **DR. SUZANNE FENTON:** Okay.
15 **DR. NELSON HORSEMAN:** In 7 it seemed
16 like a post hoc scaling within your experiment, whereas
17 in 8 it sounds like an a priori scaling based upon some
18 absolute scoring criteria. So if you could, help us
19 with that because that scoring system runs through the
20 experiments.
21 **DR. SUZANNE FENTON:** Sure. So once we
22 have all of our mammary gland hallmarks prepared and
23 cleaned and ready to go, we go through all the
24 controls. Someone goes through and makes a pile of
25 controls. We go through all of them. We want to know

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1 what the best developed glands look like. Then someone
2 has made a pile of the high dose, of the positive
3 control usually in our studies.
4 **DR. NELSON HORSEMAN:** So this is within
5 a particular experiment.
6 **DR. SUZANNE FENTON:** Within each
7 experiment, right. And so something that I didn't
8 mention and that is listed on here is that a lot of
9 times what we'll do is we'll take slides from a
10 previous study and put them back in with our group to
11 make sure that whatever we scored them in the previous
12 study is still what they're being scored that day. We
13 use the same strain of rat from the same distributor
14 each time so we should be able to do that, and so we
15 use that for consistency's sake. So what looks like a
16 4 in one study should look like a 4 in another.
17 But every study, we do this fresh each
18 study. Controls are defined, high doses defined so we
19 can have a 1 and a 4. Again we mix the slides, and we
20 go through the entire set, making these stacks of
21 scores, and we usually have a tray with 1 through 4 on
22 it and we just lay them out on there. Once we're done,
23 pick up each stack, every stack, and go through it,
24 make sure every 4 looks like each other, every 3 looks
25 like a 3, every 2 looks like a 2 so that when we're

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1 done, we're fairly certain that we were consistent
2 throughout, however much length of time it took us to
3 do that.
4 Then our second score within, you know,
5 we take the slides, put them all back. Someone comes
6 in and starts all over again.
7 So I don't know what the post hoc part
8 of that was, sorry.
9 **DR. NELSON HORSEMAN:** So within the
10 experiment, what seemed to guarantee that there'd be a
11 difference between your high dose and your control
12 group, which is different?
13 So in Slide 8, if we go to back, these
14 are not experiment-particular definitions of these
15 rats. In other words, you could have conceivably in
16 this with these criteria on their own, you could have
17 an experiment where every sample is a 4
18 **DR. SUZANNE FENTON:** Oh, we don't see
19 that.
20 **DR. NELSON HORSEMAN:** or every --
21 well, I'm just trying to conceivably --
22 **DR. SUZANNE FENTON:** Right.
23 **DR. NELSON HORSEMAN:** I mean, that is
24 just outside of --
25 **DR. SUZANNE FENTON:** Conceivably, yeah.

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1 Right.
2 **DR. NELSON HORSEMAN:** So there's no bias
3 per experiment in the system where the morphological
4 definitions are a priori as opposed to post hoc
5 **DR. SUZANNE FENTON:** Yeah. Well, we --
6 **DR. NELSON HORSEMAN:** kind of
7 system, that's my question.
8 **DR. SUZANNE FENTON:** Right. We set
9 these criteria actually, these criteria have been set
10 since we did our first experiment with dioxin. We felt
11 we had to have criteria to base this on. We do see 1s
12 in control groups. Not every control is a 4. But we
13 do try to stay on the same scale for everything that we
14 do so that we have a basis and an unbiased way to make
15 this assessment.
16 **DR. STEVEN HEERINGA:** I think we'll take
17 a few more questions. I just want to mention we want
18 to keep these compact here, because I will close it off
19 at 10:00; I just have to keep things moving today.
20 So Dr. Chambers, Dr. Pope.
21 **DR. JANICE CHAMBERS:** Two questions for
22 clarification. One is with respect to the Enoch paper.
23 It had low mammary gland scores on day 33 in the
24 controls. How did you handle that? Did you have your
25 three groups compare to that low control, then?

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1 **DR. SUZANNE FENTON:** There were 4s in
2 that group, in that control group; there just weren't
3 very many of them, all right? And honestly, we have no
4 idea why that one group was so low. We have had that
5 happen here and there in other studies -- not atrazine
6 studies, but it's happened in our mouse studies; it
7 does happen every once in a while. We just used all
8 the data that we had.
9 **DR. JANICE CHAMBERS:** Okay. And the
10 other question I had, with respect to your prostate
11 data that you presented on the slides here, you had 48%
12 inflammation in the controls. Is that typical?
13 **DR. SUZANNE FENTON:** Most of that is
14 coming in the ventral prostate. In the Rayner paper,
15 the 2007 Rayner paper, we actually noticed this high
16 background inflammation in the ventral prostate, and
17 our pathologists were very, very thorough in this
18 evaluation. So most of the background is coming from
19 the ventral; very little in the lateral prostate. You
20 can't tell that from the percentages, but percentage of
21 animals with inflammation goes up pretty dramatically
22 in the atrazine-treated groups.
23 **DR. JANICE CHAMBERS:** Well, I saw that;
24 but I'm just wondering, is your typical control that
25 high in the amount of inflammation?

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1 **DR. SUZANNE FENTON:** Yeah, in two
2 different studies we saw the same thing in the ventral.
3 **DR. STEVEN HEERINGA:** Dr. Pope.
4 **DR. CAREY POPE:** Yes, I'd like to kind
5 of repeat the earlier thought about the confusion over
6 this ranked scoring. It makes perfectly good sense if
7 you use a scale like this that's a number of the
8 animals as you see them; but to me, I'm still confused
9 about the pile as controls and now calling them a 4 and
10 calling another group as a high dose and calling them
11 1.
12 **DR. SUZANNE FENTON:** I think you
13 misunderstood that, I'm sorry.
14 **DR. CAREY POPE:** Yeah.
15 **DR. SUZANNE FENTON:** We looked through
16 all the controls to see what a 4 looks like; we don't
17 put them into a pile as 4s.
18 **DR. CAREY POPE:** I'm asking you about --
19 **DR. SUZANNE FENTON:** That's not their
20 assessment. Right.
21 **DR. CAREY POPE:** Yeah.
22 **DR. SUZANNE FENTON:** So we just need to
23 know in each study what does a 4 look like, what does
24 the best developed gland look like for reference. We
25 then look at all the high-dose, assuming that those

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1 will be our worst-case scenario. To date, that has
2 been the case. We look at what does a 1 look like.
3 Then those slides are not scored at that point. We
4 just need to know what our reference points are.
5 Those slides are then taken and mixed in
6 with everything else, scattered, we don't know what
7 they are; we go through them all one by one, and then
8 we make the stacks. And we may have treated animals at
9 the 4 group, which certainly does happen sometimes,
10 especially at the lowest doses.
11 But the stacks are made for
12 consistency's sake in the scoring; they are not made at
13 the initial look-see to see what a 4 and a 1 look like.
14 They're not done then.
15 **DR. CAREY POPE:** Okay. I think the
16 white paper makes a point about the hydroxyatrazine as
17 not a measurement-making metabolite; but you were
18 basing this mixture of concentration on water
19 concentrations?
20 **DR. SUZANNE FENTON:** Yes, sir. So
21 that's a very important point, and I'm glad you brought
22 it up. We didn't make this mixture based on what the
23 animal produces in its body; we made it based on what's
24 going to be in the water that you drink, or any mammal
25 might drink.

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1 **DR. CAREY POPE:** Okay.
2 **DR. SUZANNE FENTON:** So that's why we
3 added hydroxyatrazine to this mixture: because we
4 could all drink it.
5 **DR. CAREY POPE:** Yeah, and
6 hydroxyatrazine is approximately the same concentration
7 as atrazine, roughly?
8 **DR. SUZANNE FENTON:** Yeah, 20, 20% --
9 **DR. CAREY POPE:** And 25%?
10 **DR. SUZANNE FENTON:** -- and 25%, right,
11 uh-huh.
12 **DR. CAREY POPE:** Yeah, okay. The last
13 thing is regarding again this ranked data and how it
14 was analyzed. It was unclear from Enoch's paper the
15 statistical approach to evaluate that kind of data.
16 **DR. SUZANNE FENTON:** Actually, I thought
17 it was clear in the paper. It's not clear from the
18 review of our paper or the Summary that you have in
19 your Issues document.
20 We used the dam as a unit of measure in
21 all of those studies. She, the dam, was the identifier
22 for those pups throughout the entire study, even at the
23 older time points. We did have some confusion in the
24 way we reported the end in the paper, but this data
25 analysis was done with the dam as the unit of --

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1 **DR. CAREY POPE:** Yeah, I'm not referring
2 of the number of the pups or dams used, but how was the
3 data actually analyzed.
4 **DR. SUZANNE FENTON:** Using ANOVAs and
5 ANCOVAs with dams; so when we do our analyses we always
6 look for block effect, and once we're clear that
7 there's no block effect, we use the entire database and
8 run ANOVAs, which usually has done its comparison so
9 that each of them are compared back to control, and
10 this squares reporting. So in addition to the dam as
11 the unit of measure, we always consider body weight as
12 a random variable or covariant in our analyses.
13 **DR. CAREY POPE:** So there's no kind of
14 normalization or derivatization the day before that
15 kind of analysis?
16 **DR. SUZANNE FENTON:** No, sir.
17 **DR. STEVEN HEERINGA:** Dr. Krishnan.
18 **DR. KANNAN KRISHNAN:** Regarding the
19 mixture study, I just wanted to know whether there's
20 been any interpretation of these data, particularly the
21 ones at much lower doses such as 0.9 or 0.09 mg/kg
22 based on individual competence, simply meaning in dose-
23 response that are any thoughts of interpretation along
24 those lines since that 2007 publication?
25 **DR. SUZANNE FENTON:** No, sir; just our

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1 recent publication on the prostate effects that confirm
2 the low-dose effect in the prostate. We've tried.
3 Nothing there.
4 **DR KRISHNAN:** Then so it would be fair
5 to say that there is not a dose-response even just for
6 atrazine using this experimental design. I know
7 there's one dose that's used here under fetal weight,
8 so, dose-response.
9 **DR. SUZANNE FENTON:** No. So there is a
10 dose-response for the fetal weight, and we have
11 performed and submitted papers on dose-response for
12 mammary gland development with using atrazine only.
13 Didn't present that here today, because we've only just
14 submitted the work. Beyond that, no, we have not.
15 When we developed the atrazine mixture
16 slide, we didn't do this for cumulative risk
17 assessment; we wanted to know if environmentally based
18 exposures would affect the mammary gland. And, yes, I
19 think it's important to understand each of the
20 individual components; that isn't why we did the study.
21 We just wanted to know if those relevant mixtures would
22 cause an effect.
23 **DR. KRISHNAN:** Okay. The objective was
24 clear, right?
25 The later study material, just referring

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1 to the effects on mammary gland, what were the doses of
2 atrazine used?
3 **DR. SUZANNE FENTON:** We used 25, 50 and
4 100.
5 **DR. STEVEN HEERINGA:** Dr. Legan,
6 question?
7 **DR. SANDRA LEGAN:** Thank you.
8 Dr. Fenton, it's clear from what you've
9 said you understand very well about not stressing the
10 animals, and with regard to that I wondered in looking
11 at one report of your serum for prolactin models, you
12 say -- I think it's in the 2005 paper -- and this was
13 taken from samples obtained I guess at necropsy,
14 because you did all the hormone levels and you need a
15 lot of sample to do that. And you have a really large
16 range in some of your hormone levels, and prolactin was
17 I thought a very high range; and prolactin is a stress
18 hormone, and I'm wondering
19 **DR. SUZANNE FENTON:** Uh-huh.
20 **DR. SANDRA LEGAN:** and it also varies
21 with time of day and for the period of dependence. So
22 did you do necropsy on a given postnatal day at the
23 same time of day, or how did you do it --
24 **DR. SUZANNE FENTON:** Good question, good
25 question. So this is what we did for all the studies

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1 that I talked about today. In the EPA Building, we
2 have a very nice animal facility that has a holding
3 room just across the hall that's a quiet room, closed
4 door, that the animals are being moved there the day
5 ahead of necropsy. We would walk across the hall with
6 a plastic decapping cone, place the animals in there,
7 and they were decapitated within 20 to 30 seconds based
8 on the technical person that's doing a count. I hope
9 that's a fair estimate, 20 to 40 seconds, something
10 like that. And so we made every effort to keep the
11 noise down, to keep the stress down, to very quickly
12 euthanize the animals. So we took every precaution
13 that we could to minimize that stress, any stress.
14 **DR. SANDRA LEGAN:** So do you think --
15 **DR. SUZANNE FENTON:** Also -- oh, sorry.
16 You had a second part of that question.
17 **DR. SANDRA LEGAN:** All right.
18 **DR. SUZANNE FENTON:** So the time of day
19 was similar for all the studies. We typically started
20 between 8:00 and 9:00 in the morning, typically ended
21 around 2:00 or 3:00 in the afternoon. We tried to kill
22 the animals in rotating order so that you're not
23 killing all your controls first or something like that.
24 We do controls, treated, controls, treated all through
25 the day.

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1 **DR. SANDRA LEGAN:** Okay. So do you have
2 any idea why you had such a large range in prolactin?
3 Is it always that much?
4 **DR. SUZANNE FENTON:** No. I think we had
5 prolactin measures in more than just that one study,
6 and so taking it one study at a time, I'm not sure I
7 can answer that; but generally, we found prolactin
8 levels that were typical prolactin levels, that were
9 comparable to looking normal that we find, I think.
10 Did you feel like they were out of range of normal?
11 **DR. SANDRA LEGAN:** Well, the range, I
12 don't measure prolactin and I don't remember the
13 normal; but you mentioned in the paper that there were
14 wide ranges, and I looked and it was from 20 to 144,
15 and that seems like a really large range to me. And
16 I'm not familiar, as I said --
17 **DR. SUZANNE FENTON:** And without having
18 that in front of me, I can't answer it specifically.
19 **DR. SANDRA LEGAN:** Okay. Just wondered.
20 **DR. SUZANNE FENTON:** But we have
21 measured it in other studies. You know, we try to take
22 care to interpret that data and say whether or not it
23 was within normal range.
24 **DR. SANDRA LEGAN:** Yeah, well, other
25 studies also have shown, some of them show increases in

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1 prolactin, some of them show decreases in prolactin; so
2 there's something I don't understand about prolactin.
3 **DR. SUZANNE FENTON:** Yeah, more than
4 likely it's a necropsy data-specific event.
5 **DR. SANDRA LEGAN:** That's why I asked.
6 **DR. SUZANNE FENTON:** Yeah, right.
7 **DR. SANDRA LEGAN:** Thank you -- and one
8 last thing. In one of the papers, you look at
9 postnatal day 58, I think it is, and if you look at
10 mammary gland development and there's no difference
11 from controls in any of the dose groups -- or is there?
12 I can't remember.
13 Okay, this was only the 100-dose paper,
14 the '04. So my impression from reading the papers was
15 that these changes that occur that you see in mammary
16 gland development are transient. So they may be
17 delayed in early adulthood; but, you know, some time
18 after that like day 58 or something or maybe later, the
19 mammary glands look normal.
20 **DR. SUZANNE FENTON:** Well, yeah. Is
21 this a --
22 **DR. SANDRA LEGAN:** That's all, I just
23 wanted to hear what you is that a reasonable
24 conclusion, or is that through
25 **DR. SUZANNE FENTON:** In one study --

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1 **DR. SANDRA LEGAN:** the transient
2 effect of atrazine?
3 **DR. SUZANNE FENTON:** In one study, we
4 carried these animals out to like 90 days old. I mean,
5 it wasn't even a study; we just wanted to know what
6 would happen if we kept them longer. And
7 unfortunately, it's very difficult to do a whole mount
8 at 90 days. It's difficult to look at, and it's hard
9 to clear the fat pad; so I can't show you that. But I
10 think that this is not permanent for the life of the
11 animal. I think that small changes that take place
12 each cycle probably compensate for whatever happened
13 early in life over time.
14 But in this study, in the critical
15 period study, the Rayner 2005 study, we do have
16 dramatic effects on differentiation on these terminal
17 end buds after a 7-day exposure or a 3-day exposure.
18 So these are 67-day-old animals, so it's possible that
19 although we didn't see the persistence in the paper
20 that you're referencing -- again, I don't have it in
21 front of me, I'm sorry -- but we do definitely see an
22 increase in terminal end buds and lack of
23 differentiation in the exposed animals in this other
24 critical period study, and that I mean, we were able
25 to then breed the siblings to this and show that there

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1 was an impairment in lactation or weight gain in the
2 offspring or serious lactational effects.
3 So based on that, if you see the
4 differences at that point, I think they can translate
5 to an adverse effect. But I do agree that this is not
6 a persistent compound.
7 And one thing I didn't mention today is
8 that in our F2 pups, we did see decrements in mammary
9 gland development; but that was not significant once we
10 based it on their body weight. Because they were
11 smaller, we disregarded that change.
12 **DR. SANDRA LEGAN:** Uh-huh.
13 **DR. SUZANNE FENTON:** So that is a really
14 important consideration, and it's possible that these
15 are not permanent effects but that they were made
16 persistent until sexual maturity.
17 **DR. SANDRA LEGAN:** Right. And finally,
18 the atrazine isn't continually administered throughout
19 their postnatal life.
20 **DR. SUZANNE FENTON:** Right.
21 **DR. SANDRA LEGAN:** So if it is
22 transient, it may be because of the exposures.
23 Thank you.
24 **DR. STEVEN HEERINGA:** One last question
25 before we take a break from Dr. Mumtaz.

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1 **DR. MOIZ MUMTAZ:** I am Moiz Mumtaz,
2 ATSDR CDC.
3 Two quick questions. One, regarding the
4 parent complement of the metabolite and the fact that
5 most metabolites could be a common topic from other
6 compounds, is there any feel you have about
7 administered dose versus what could be there in terms
8 of either the concentrations of the proportion after
9 you perform these tasks?
10 **DR. SUZANNE FENTON:** Yes, that's a good
11 question. So it is true that other chlorotriazine
12 metabolites do produce three of these similar
13 metabolites, or chlorotriazine herbicides produces
14 three similar metabolites. That's one of the reasons
15 that we wanted to evaluate that mixture: because it
16 didn't just come potentially from one herbicide; it may
17 be coming from a family.
18 At the time we did these studies, we did
19 not have anyone that could measure internal dosimetry
20 for us. Since then, we have carried out two studies to
21 evaluate dosimetry of these exposures, both of the
22 mixture and of the parent compound, in pregnant and
23 lactating animals.
24 Those data have not been released from
25 the CDC, because the person who did the study left the

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1 CDC. They are going back through another quality-
2 assurance check to make sure that they can be released.
3 So hopefully, I will have that information for you
4 before the spring.
5 **DR. MOIZ MUMTAZ:** That's great. Risk
6 assessors always depend on weight of evidence, and if
7 you look at the way the species handle, you could get a
8 little more comfortable with it. But what's your view
9 about that being a good model for this particular
10 endpoint?
11 **DR. SUZANNE FENTON:** Yeah, that's a very
12 good question. So last year in November, I chaired a
13 session on mammary gland evaluation and risk assessment
14 in Oakland, California. We brought together 70 experts
15 in the field of both risk assessment and mammary gland
16 biology, and we had a round-robin assessment. It was
17 really double-blind.
18 There were seven labs chosen from around
19 the world to evaluate a set of slides from both rats
20 and mice. One of the compounds we used for this
21 assessment was atrazine. We used 100 mg/kg of atrazine
22 just as a model compound in both rats and mice. We
23 gave the sets of slides to all seven labs. They were
24 asked to evaluate the slides in whatever fashion they
25 saw fit. I didn't tell them how to evaluate the

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1 slides, but the slides were prepared the same way for
2 all the evaluations in one place.
3 So what happened at the end of that, we
4 had a round-robin evaluation at the workshop, and
5 atrazine was shown to have significant delays in both
6 rats and mice on day 21 in five of seven or seven of
7 seven of the evaluators, and then at day 45 in mice in
8 seven of seven evaluators. So no matter which way they
9 evaluated the glands, whether it was using morphometry
10 or whether it was using a subjective-scoring situation
11 -- and both were used almost equally -- it didn't
12 matter how they evaluated it; everyone saw the
13 developmental delay in both rats and mice at 100 mg/kg
14 of atrazine. And this work is going to be published
15 soon.
16 **DR. STEVEN HEERINGA:** Thank you very
17 much.
18 **DR. MOIZ MUMTAZ:** I do, I do want to
19 acknowledge the real life mixing in your type of test.
20 Ideally it's great to have a hypothesis to say it's
21 additive or realistic; but working from the public-
22 health perspective, I think it's a great deal of effort
23 to do something that's a real life mix. Thank you so
24 much.
25 **DR. SUZANNE FENTON:** Thank you.

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1 **DR. STEVEN HEERINGA:** I am going to
2 thank Dr. Fenton for her presentation and the Panel for
3 the questions; I think there probably are a few
4 remaining questions.
5 Dr. Fenton, are you here today, or are
6 you returning to--
7 **DR. SUZANNE FENTON:** All day.
8 **DR. STEVEN HEERINGA:** Okay.
9 **DR. SUZANNE FENTON:** I'll be here all
10 day.
11 **DR. STEVEN HEERINGA:** All day; okay,
12 very good. And so again, if a Panel member has the
13 opportunity to speak to you and there's any information
14 that's brought forward that would influence your
15 comments, please acknowledge that conversation.
16 But at this point in time, I'd like to
17 call a 15-minute break and, if we could, reconvene at
18 25 minutes after 10:00. At that point in time, we'll
19 have a short period of closure with the scientific
20 presentations and then turn to the public comment
21 period, and I believe that the, in order that the
22 office has scheduled the public comments, I think the
23 first session will be a fairly long session dedicated
24 to the Registrant. And so if Syngenta and that team
25 would like to get set up during the break, that would

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1 be great.
2 (**WHEREUPON**, a recess was taken.)
3 **DR. STEVEN HEERINGA:** Welcome back,
4 everyone, to the second half of our Wednesday morning
5 session on the FIFRA Science Advisory Panel meeting on
6 the topic of the Re-Evaluation of Human Health Effects
7 of Atrazine: A Review of Non-Cancer Effects and
8 Drinking Water Monitoring Frequency.
9 I have spoken with Steve Bradbury, and I
10 understand that I mislabeled Steve's title. He
11 actually is the Director of the Office of Pesticide
12 Programs; acting in some capacity, I'm sure, but he is
13 the Director.
14 [Laughter.]
15 **DR. STEVEN HEERINGA:** So at this point,
16 the EPA has indicated to me that they are satisfied at
17 this point that the points that they'd like to bring
18 across have been made, and we will have the opportunity
19 at the start of the Charge Questions for clarification.
20 And in the interest of time, I think
21 we're ready to move on to the period of public comment,
22 and the first scheduled public commenter is Syngenta
23 Crop Protection. And I think that Dr. Janis McFarland
24 will coordinate the introduction of the presenters.
25 I believe the way that we'd like to

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1 handle this, this is likely to be a multipart
2 presentation covering the different aspects of the
3 white paper and the topic at hand. We are scheduled
4 for 2 hours and 15 minutes, according to the SAP
5 Office. We will go up to lunch; we may break at lunch,
6 and I will work with you to sort of find a logical
7 breaking point. I don't expect that we could push it
8 all in before lunch and return.
9 So, Dr. McFarland, I'll turn it over to
10 you.
11 **DR. JANIS MCFARLAND:** Okay, thank you,
12 Mr. Chairman. I'm Janis McFarland, I'm the Head of the
13 Regulatory Affairs Department for Syngenta for the
14 NAFTA Region, U.S., Canada and Mexico. It's an honor
15 to be here today.
16 As my background, I started about 24
17 years ago as a metabolism chemist and throughout my
18 career have worked on many different pesticides and
19 been involved in various aspects of the science
20 regulation and stewardship of atrazine since late 1994.
21 On behalf of Syngenta, I'd like to
22 express our sincere appreciation for all of the hard
23 work and deliberation and science that's been
24 progressed and understanding by both the Science
25 Advisory Panels on atrazine as well as the work from

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1 the Environmental Protection Agency.
2 We are really excited about the work
3 we're going to be presenting today. There has been a
4 lot of progress in the areas of basic research and Mode
5 of Action.
6 And before we go into that, we did feel
7 that there was an underlying question that was actually
8 missing in some of the Charge Questions, and that had
9 to do with the assessment with the EPA making the
10 determination in Charge 6 of whether or not there is a
11 new risk assessment needed for atrazine, and also then
12 whether or not monitoring should be modified.
13 We felt that the area that was not
14 included that we would love to have advice from the
15 Panel and also additional advice from EPA would be
16 given weight of evidence of atrazine, the comprehensive
17 database as well as the state of the new science and
18 the basic research, is there a need to look at a
19 shorter exposure duration and, if so, type of -- the
20 shorter duration study, and if so, what type of study
21 should be designed or conducted to look at that shorter
22 exposure duration study.
23 We feel that the Cooper 2010 study with
24 the 4-day long evidence, intact long evidence study
25 that has been proposed for the new point of departure,

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1 we do realize provides very important information on
2 Mode of Action, basic research for atrazine; but we do
3 not feel that the study design is appropriate to
4 actually establish a point of departure.
5 We did put some of our initial
6 assessments and analyses of that study design in the
7 Docket yesterday, and it's under a Sielken & Associates
8 paper, and we also in the Docket today along with our
9 slide presentations have put in some information to try
10 to address some background information asked by the
11 Panelists yesterday. Some of that has to do with a
12 quick summary of metabolite exposure levels in water;
13 also, a statistical study of how robust -- when we have
14 about 300,000 samples of raw and finished and non-
15 drinking water samples and drinking water samples in
16 the atrazine database, and you look at either the raw
17 intake that could serve as drinking water or the
18 finished drinking water, what is the statistical
19 robustness of being able to estimate a peak. And we
20 feel very confident that the studies and comprehensive
21 databases are robust enough to actually estimate the
22 peak centile.
23 We also have, when we look at the
24 maximum levels ever -- and we started voluntarily
25 monitoring with frequent monitoring; we voluntarily did

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1 that for ten years prior to working on study designs
2 and monitoring programs with EPA in 2003, and we
3 generated almost 50,000 samples with that. We feel
4 very confident that no single maximum peak or no
5 duration, short-term duration exposure window that we
6 monitored in looking at both daily and then some
7 smaller daily sets but very frequent monitoring weekly,
8 that those maximum levels, single max daily in 4-day or
9 10-day rolling averages, have always been at levels
10 that are more than a thousandfold lower than our no-
11 effect levels that we're currently being regulated on,
12 which is the rapid for acute and the 6.25 mg/kg EPA
13 preputial separation study for the intermediate.
14 So we look forward to continuing to
15 progress the data and the basic research and look
16 forward to continuing to see the good progress that EPA
17 is making on the basic research, and we're looking
18 forward to telling you about that today.
19 And I wanted you to know as a company,
20 we are very committed to listening to the advice from
21 Scientific Advisory Panels and also to advice or areas
22 of uncertainty that EPA identifies and voluntarily
23 doing studies. In fact, what you'll see today is since
24 this re-review started, we've conducted more than 10
25 studies in this year in all aspects of completing the

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1 breast bud development work, in basic research Mode of
2 Action, in exposure areas, immunotoxicology areas. We
3 started pharmacokinetic work, comparison between gavage
4 and feeding and what type of exposures you'll get and
5 hepatocyte work.
6 And we are grateful for Dr.
7 Breckenridge, who is our Senior Toxicology Fellow at
8 Syngenta who is leading the scientific advancements in
9 that, and you'll be hearing from him, as well as we're
10 very grateful for all of the university scientists who
11 are helping to both advise and conduct those studies.
12 We will also be hearing from Dr. Hendley
13 and can answer some of the questions on any of the
14 statistical side or metabolite exposure profiles when
15 Dr. Hendley is on at the end of our session.
16 So with that, I'm going to turn it over
17 to Dr. Breckenridge. We again thank you so much for
18 the work and look forward to the next few days of
19 deliberations.
20 **DR. CHARLES BRECKENRIDGE:** Thank you,
21 Janis.
22 My name is Charles Breckenridge; I'm a
23 Senior Syngenta Fellow. I have been working on
24 atrazine since approximately 1994. I'm responsible for
25 the human safety assessment of the compound.

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1 We have today with us a team of
2 scientists who participated in the conduct of studies
3 over the course of the last couple of years. We will
4 start with first Dr. Russ Hovey, this gentleman second
5 to my right, who will present our research on the
6 breast bud development project.
7 Secondly, then, we will actually turn
8 over to the key theme of this meeting, which is the LH
9 surge and the adverse effects associated with impacts
10 of the LH surge suppression. But to start that
11 particular discussion out, and mindful that Dr. Covern
12 last meeting in April indicated that there was some
13 differences between rodent and primate and human
14 control mechanisms, we took the opportunity to invite
15 Dr. Plant, who's an expert in this field, to give us
16 perhaps a little more clarity on those differences and
17 how they relate then to the risk assessment process.
18 Dr. Handa will continue with some of the
19 research that we elaborated last time, and it's a
20 little bit unfortunate that the Panel changes in some
21 makeup so that we cannot necessarily go back and brief
22 everyone of what went before; but Dr. Handa will try to
23 catch everybody up with what we presented in April and
24 then how we have extended that onward.
25 We will then turn to some significant

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1 new work that we've conducted, and Dr. David Kim
2 from Syngenta will be summarizing this. This is PK
3 work and PBPK model development work. He is not at the
4 table at the moment, but he will join us.
5 And finally, Dr. Jim Simpkins will try
6 to put in context of adverse effect the impacts of LH
7 suppression, especially on ovarian function, but also
8 on sexual maturation in males and females and the
9 maintenance of steroidogenesis in adult animals.
10 I will close that session then, and we
11 will have one other speaker that will come up, which
12 will be Dr. Paul Hendley from Syngenta, who will be
13 discussing the water information.
14 So just so I can make certain in the
15 context of the complexity of the topics that we're
16 going to be discussing, I'm going to try to give you
17 highlighted conclusions. These are not obviously going
18 to be supported by actual data at this point, my
19 speakers will provide that; but I want you to be aware
20 of at least what the themes of the conclusory evidences
21 that we are showing here.
22 So in the first instance, you can see a
23 chemograph up in the top left panel, and we're simply
24 using this to remind ourselves -- and Dr. Hendley will
25 cover this rather extensively -- that Syngenta does

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1 have an extensive sampling data with 300,000 samples
2 approximately being well characterized, and I believe
3 Dr. Hendley will suggest some alternative strategies
4 that might be of interest to this SAP and some of the
5 Charge Questions that relate to that.
6 Secondly, then, we turn to Dr. Russ
7 Hovey, and there is no need to really extemporize on
8 the breast bud development project, because Dr. Fenton
9 has gone before and provided a description of her
10 research.
11 I guess I could just say at a high level
12 that in our hands and in an attempt to replicate some
13 of the work of Dr. Fenton, we have not been able to
14 demonstrate a breast bud development delay, and Dr.
15 Hovey will deal with that subject and present that data
16 to you.
17 Moving on, we now step back to the
18 question of the HPG and the HPA axis, and the first
19 speaker, Dr. Plant, will provide some discussion around
20 the differences between rodent, non-human primate and
21 primate neuronal control mechanisms, especially as it
22 relates to the LH surge and pulsatile generation.
23 That little cartoon up there is, you'll
24 see it reappearing in Dr. Plant's presentation, and
25 it's partially to orient ourselves to the differences

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1 in the anatomy and physiology and the functionality of
2 primates versus rodents.
3 The bottom line of that whole discussion
4 is that there is some substantial evidence to suggest
5 that the rodent model for LH surge control mechanisms
6 are not the same as in primates, and Dr. Plant will
7 elaborate on that; however, the pulsatile LH processes
8 clearly are similar, and we will discuss that in the
9 context of hazard endpoints.
10 The bottom line from that discussion
11 will actually be that perhaps the LH surge processes
12 such as we're studying in the rodent may not be
13 appropriate for modeling to human, and you'll see the
14 basis for that suggestion momentarily.
15 We will then turn back to some of the
16 basic research that Dr. Handa has conducted over the
17 course of four or five years working on Mode of Action.
18 And just to summarize what we had heard
19 in April, I believe it was fairly convincing evidence,
20 and even in work that we had not done but that had been
21 done in EPL's lab or EPA's labs, is that it does not
22 appear that the pituitary is a target of atrazine. The
23 evidence that Dr. Handa will show and Dr. Lee Tyree and
24 Dr. Cooper have presented is that the pituitary seems
25 to be responding to changes further upstream to the

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1 pituitary.
2 Dr. Handa has also spent considerable
3 time characterizing the generation neurons and their
4 characteristics under LH surge suppression, and all
5 things point to that, in fact, the effects are
6 upstream to the GnRH neurons as well. And just so that
7 we orientate that, perhaps those effects are in
8 preoptic area or other regions of the brain that
9 perhaps aren't as well represented in the primate.
10 Finally, when we get to the concept of
11 interaction between the hypothalamic-pituitary axis and
12 the adrenal axis, last time, Dr. Handa presented
13 evidence that, in fact, there seems to be a role of a
14 stress response or something like a stress response
15 that at least is mediating some aspect of the LH
16 suppression in the pulsatile LH model. Insofar as we
17 have shown that adrenalectomy actually reverses, it
18 prevents the effect of atrazine on pulsatile LH,
19 whereas it does not seem to impact the LH surge itself.
20 We also note from work that Dr. Handa
21 has conducted that the surge and the effect of atrazine
22 on it recovers quickly. Within 2 days after removal of
23 the compound you get partial recovery, and within 4
24 days you get full recovery. We would like to suggest
25 that that's probably connected to the kinetic profiles,

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1 which we will also demonstrate later.
2 We have turned beyond the effect on the
3 LH system to evaluating the adrenal response itself,
4 and last time you heard about atrazine activating
5 immediately corticosterone synthesis or release from
6 the adrenal gland with a very rapid ACTH response
7 accompanying that. We actually will report today that
8 we have verified that in fact, like males, by 28 days
9 the females no longer display that response; so short-
10 term acutely, females and males do respond acutely and
11 elaborate a cort response, which is characterized by
12 elevated corticosterone and progesterone but not
13 prolactin, and that effect appears to disappear with
14 repeated dosing.
15 We will relate that to the fact that we
16 have not been able to demonstrate any effect on immune
17 tox endpoint in both males and females; so the study we
18 are adding to the discussion we had last time is the
19 fact we have now completed a dose-response assessment
20 for females; the no-effect level is the high dose
21 tested in that study. So whatever is going on with
22 cort it's not actually having an effect, and it
23 probably is because it's a transitory response. The
24 NOAEL is 50 mg/kg on immune parameters in males and 25
25 mg/kg in females. The cartoon there is obviously wrong

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1 relative to the way the cort is displayed; atrazine
2 would induce their elevation rather than decline.
3 Finally, Dr. Handa will return to the aspects of the
4 HPG axis and then set the stage for a discussion of
5 substantially new research. We were mindful of the
6 research that was described by Dr. Cooper last time
7 when he gave a few indications of the characteristics
8 of the study that he had conducted: 4 days of
9 exposure; intact females of Long-Evans rat dosed with
10 atrazine beginning on the day of estrus, leading
11 through to sampling of blood for LH on the day of
12 afternoon proestrus 4 days later.
13 We have emulated that study. We have done an
14 intensive dose-response. We have conducted this study
15 in a very short time period of approximately two weeks
16 in a random fashion. We have doses of 0.75, 1.5, 3, 6,
17 10 and 50, and we will report today that in fact there
18 are no effects on LH surge at doses of 10 mg/kg and
19 lower, and that is perhaps contributory evidence to the
20 discussion we had yesterday in relationship to dose-
21 response modeling and those dose ranges.
22 We took that one step further. Realizing
23 that humans don't get bolus doses of atrazine-- what
24 they get is distributed doses that they drink in water,
25 if they get any -- and so we emulated that by doing a

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1 dietary feeding study, and this study was conducted at
2 three equivalent doses that matched up with our gavage
3 doses. These were attempting to achieve doses of 3, 10
4 and 50 mg/kg, and that translated to feeding levels of
5 30, 100 and 500 ppm. We report here that in fact there
6 is no effect of atrazine on the LH surge at 500 ppm in
7 young adult females animals, 13-week-old.
8 We believe that is related to kinetic
9 parameters, and Dr. David Kim will illustrate that,
10 because at the same time as we conducted the study on
11 LH surge, we had comparable animals set aside for
12 characterizing the PK kinetics of atrazine and the
13 three metabolites and Dr. Kim will elucidate that in
14 relationship to the toxicological endpoints.
15 In addition to that, these and other studies
16 will actually allow for a full elaboration of a PBPK
17 model. Dr. Tami McMullin had conducted and designed
18 and constructed a PBPK model. And I should say that
19 Syngenta was involved in funding that work, as she was
20 a graduate student at Colorado State University under
21 the mentorship of Mel Andersen. We are going to take
22 that model that she has tentatively developed and
23 extend it and enhance it. We believe that that will
24 become the basis upon which true internal dose metrics
25 can be calculated, and we also believe that it will

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1 then be possible to achieve the estimation of human
2 internal dose under conditions of actual human
3 exposure. So Dr. Kim will further elaborate that.
4 Finally, we turn back to the question of,
5 well, what does LH do and how much surplus capacity is
6 there, and how much consequence is there for a one-
7 standard-deviation reduction in the LH surge amplitude
8 or any other aspect of LH released, and Dr. Legan
9 yesterday talked about that excess capacity. We have
10 some discussion around that.
11 And in addition to that, then, we turn to the
12 more critical question is, what is the appropriate
13 endpoint to benchmark off of. In fact, you're going to
14 set a regulatory standard. Within the context of the
15 way the Agency regulated atrazine in regard to
16 carcinogenicity, we were within the traditional
17 framework analysis; that is to say, LH suppression,
18 extension of the cycle in rodents and the development
19 of tumors. Those were key events, and they were
20 concordant with each other in dose and time. And we
21 submit that in fact that's the procedure that should be
22 followed here, with a mindful coupling of the key
23 event, which would be LH suppression, to adverse
24 effect, and this will be the subject of Dr. Simpkins's
25 discussion as it relates to all of the data that exists

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1 on atrazine.
2 And actually, we heard yesterday that some
3 members of EPA thought there wasn't data adequate for
4 this purpose. We do remind the Panel that in fact for
5 the metabolites, we have conducted 90-day rodent and
6 rat studies. We have conducted all the acute studies
7 and immunogenicity studies, and EPA in fact has
8 conducted very nice studies on the metabolites and we
9 actually are going to be discussing some of that data.
10 This was Dr. Tammy Stoker's research.
11 So that there is information on the
12 metabolites, I don't believe that we can resolve the
13 question of which subcomponent is responsible. And in
14 2006 when EPA created their common mechanism group for
15 the triazine, we concurred with their decision that the
16 chlorotriazine, including other molecules that are of
17 that type, were an adequate representation of the risk.
18 We likewise believe and are in agreement with
19 the statements made yesterday that the conjugated
20 metabolites likely have no impact on the LH surge. We
21 have no actual direct evidence of that, and we probably
22 will acquire such evidence for a few of the major
23 metabolites relative to the LH surge. We do have
24 obviously differential information on that with respect
25 to aromatase, which we presented last time.

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1 And it was correctly stated yesterday in fact
2 there are metabolite differential sensitivities in
3 regard to, say, the activation of the adrenal axis.
4 DACT does not activate the adrenal axis. We heard that
5 from Dr. Cooper's lab and we believe that is very
6 important in the context of the kinetics, and you'll
7 see that.
8 So that's roughly what we are going to do in
9 the hazard side, and then we will return to the
10 characterization of the water.
11 With that, I'll stop, and I think probably
12 **DR. STEVEN HEERINGA:** Thank you, Dr.
13 Breckenridge. And I think just so that we're all on
14 the same page, because of the number and sort of depth
15 of many of the public comments in contrast to the way
16 I've managed this in some of the other meetings, I'd
17 like to go through the initial presentations,
18 particularly related to the toxicological effects, and
19 then we'll have a series of questions which will cover
20 those presenters, if that is satisfactory with the
21 Panel members. We will then turn to the water-sampling
22 issue probably after lunch and have questions on that.
23 If we can divide it up that way, I think that would
24 save us some time.
25 **DR. CHARLES BRECKENRIDGE:** Okay, thank

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1 you very much, Mr. Chairman, and I'll ask Dr. Russ
2 Hovey to identify himself.
3 **DR. RUSS HOVEY:** Good morning. My name
4 is Dr. Russ Hovey from the University of California at
5 Davis.
6 Can I please ask for the first slide,
7 sir, to be posted?
8 So I'm an Associate Professor with a
9 specific interest in mammary gland development and
10 lactation physiology, and I'm in Animal Science with an
11 appointment in the UC Davis Cancer Center.
12 So what I'd like to do this morning is
13 speak to you about some work that we've done looking to
14 try and understand, based on some previous work that
15 Dr. Fenton presented this morning, about possible in
16 utero exposure effects of atrazine on subsequent
17 mammary gland development in the Long-Evans rat. This
18 is work that is currently under review at Toxicology
19 Sciences. This is a collaborative study that was
20 supported by Syngenta. The animal side of the work was
21 conducted at WIL Research, the pathology and analysis
22 was done by EPL and statistical analysis by Sielken &
23 Associates.
24 So what I'd like to do is briefly
25 describe to you the stages of mammary gland

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1 development, and one of the things I point out -- it
2 seems like the slide doesn't conveying it properly --
3 but in the top left, the mammary gland originally
4 develops from the epidermis during embryogenesis, and
5 so the epithelial cells actually arise from the
6 epidermis and invaginate into the surrounding
7 mesenchyme.
8 And then the next slide on the right
9 would have shown you that during postnatal development
10 by prepuberty, as mentioned this morning, the ductal
11 development is concentrated around the nipple and is
12 positioned to advance to be a different process of
13 ductal elongation into the surrounding mammary fat pad.
14 And so in essence the mammary gland is a secondary
15 reproductive organ, in that its development is
16 coordinated with what you would see here during puberty
17 is the ductal extension and branching morphogenesis
18 actually occurs with the onset of ovarian function.
19 And so by the time of sexual maturation,
20 this is a whole mount depiction of the mouse mammary
21 gland; in the rat, you would see more lobular
22 development. But the point to be made here is that the
23 mammary gland is developed fully; it's undergone
24 branching morphogenesis and ductal elongation.
25 Now, having said this and as I pointed

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1 out, because the mammary gland is responsive to a
2 variety of different external influences throughout the
3 body, it's important to take into account that
4 development or function of the mammary gland, even in
5 the dam, can be influenced by her metabolic state, for
6 example, and her nutrition. And then in the progeny,
7 the course of mammary gland development likewise can be
8 influenced by factors such as nutrition, reproductive
9 development, as well as changes in the endocrine axis.
10 And as Dr. Fenton mentioned this
11 morning, a recent gathering of a variety of experts in
12 the field pointed out that if the mammary gland is to
13 be used as a tox endpoint, there's a lot of different
14 things that we need to pay particular attention to in
15 terms of making that type of analysis. This is a brief
16 review of some of those points, some of which are
17 specifically relevant to the work I want to present
18 today.
19 In our analysis, we have used the fourth
20 mammary glands. One particular point of emphasis was
21 that both histological and morphological analysis is
22 imperative for this type to work, quantitative
23 assessment of that morphological analysis is required,
24 and the things like reproductive development such as
25 stage of the estrus cycle needs to be taken into

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1 account.
2 Dr. Fenton mentioned taking into
3 consideration body weight as a covariant. I would
4 suggest, based on work 50 years ago, that needs to be
5 metabolic body weight, and adequate numbers of animals
6 need to be analyzed.
7 So in terms of revisiting this question
8 as to whether there's any in utero exposure effect on
9 subsequent mammary gland development, there's five
10 points that I'd like to bring to your attention based
11 on our previous work that's been done on this topic.
12 The first is, as has been mentioned
13 previously, that maternal dosing with atrazine can have
14 significant effects on maternal body weight. So this
15 is excerpted from Rayner, et al., 2005. You can see
16 there the maternal. The control dams, for example,
17 dosed between days 13 and 19 gained about 80 grams,
18 whereas dosing dams during that same period with 100
19 mg/kg of atrazine suppresses body weight gain by about
20 50 percent. Now, that's going to have significant
21 effect both on her ability to support the pups during
22 fetal development but also during lactation. And it
23 has been well acknowledged in the literature that a dam
24 will support normal fetal birth weight of her young
25 such that there won't be a difference, but her ability

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1 to support those pups during lactation will be severely
2 compromised.
3 So in our study, what we've done to
4 account for this is to actually use a pair-feeding
5 approach, whereby we pair-fed dams through the body
6 weight gain that was accomplished by the dams dosed
7 with 100 mg/kg of atrazine.
8 Another point with respect to this whole
9 morphological analysis of the mammary gland, it's
10 absolutely imperative that one carefully sample the
11 mammary glands in terms of making this morphological
12 assessment.
13 And so depicted here is images from the
14 previous studies that have been conducted regarding in
15 utero exposure to atrazine. What I'd like to bring
16 your attention to is the fact that if you are to make
17 any type of assessment of the mammary glands, it's
18 important that the whole structural network needs to be
19 intact.
20 And so my boxed areas here highlight the
21 fact that there has been some omission of certain parts
22 of the mammary tissue, and that can really have effects
23 both on quantitative as well as subjective analyses.
24 And so in our study, we have blindly removed any
25 samples that did not pass quality control. That led to

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1 the omission of about 10% of samples.
2 The other thing that was previously
3 mentioned was the fact that maternal dosing with
4 atrazine can also affect aging of vaginal opening of
5 the offspring.
6 As a result, I mentioned previously the
7 mammary gland is responsive to reproductive function;
8 so what we hypothesized was potentially that this delay
9 in vaginal opening in the progeny born to the dams
10 dosed with atrazine may have actually explained the
11 delay in mammary gland development that was previously
12 described.
13 And so the way we have accounted for
14 this is to sample progeny both at a fixed age, as has
15 been done previously and is widely done in the field,
16 but then also to sample daughters of progeny at the
17 same reproductive state, namely, to include a group
18 where we sample those animals at vaginal opening.
19 We have had some previous discussion
20 about the pros and cons of subjective analysis of
21 mammary gland development, and so in terms of using a
22 subjective scale, these are both samples that would
23 receive a score of 4.0 in the previous work based on
24 their matching corresponding groups, and we felt that
25 in this type of work it is absolutely imperative that

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1 all types of analyses need to be quantitative, taking
2 into account the methods that might be able to describe
3 any phenotypic changes.
4 And then finally in terms of looking at
5 any potential changes, another approach that's widely
6 utilized is to look at self-proliferation; in this
7 case, this is an analysis of early uptake in that
8 previous work. And in that work, it was previously
9 suggested that there's a significant difference in
10 terms of self-proliferation when it was subjectively
11 analyzed in terms of the early uptake.
12 But then subsequently when that was
13 actually quantified, there was no significant
14 difference. And so in our approach, what we have
15 sought to do is specifically quantify self-
16 proliferation and, consistent with what was found from
17 the round-robin discussion group, we have broken that
18 proliferation down into various important compartments
19 of the mammary gland, whether they be ducts, terminal
20 end buds or lobules.
21 So this is our experimental design. In
22 essence, we followed that that was implemented by
23 Rayner, et al., in 2005, and we used time, pregnant
24 Long-Evans rats, dosed them with either vehicle
25 control, low, medium or high doses of atrazine at 6.5,

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1 50 and 100 mg/kg/d between gestation day 13 and 19.
2 And as I mentioned, we also yoked a pair-fed group to
3 the highest dose of atrazine such that their intake was
4 controlled for that or yoked that consumed by the high-
5 dose group.
6 I'd point out that we had additional
7 animals in separate groups that were not involved with
8 these groups that we sought to do a cross-foster study
9 to try and account for any lactational exposure, and
10 cannibalism led to the omission of those animals; but
11 that was in separate groups within this study.
12 This is the maternal body weight change
13 both during gestation and lactation in those dams. So
14 on the Y axis, we have body weight change during the
15 respective period, and then the different treatment
16 groups on the X axis.
17 The light purple bars reflect the body
18 weight change during gestation, and as you can see and
19 as we expected, the high doses of atrazine led to a
20 significant suppression in maternal body weight gain,
21 consistent with previous reports. And as we planned or
22 expected to see, the pair-fed group also had a
23 suppression in body weight gain that was comparable to
24 that seen in the high-dose atrazine group.
25 And then in the darker bars this is

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1 their body weight change during lactation, and you can
2 see that there was no significant difference in terms
3 of body weight change during lactation in the different
4 treatment groups, although the pair-fed group during
5 gestation had a small but significant reduction in body
6 weight gain during lactation.
7 This is the experimental design in terms
8 of sampling of those F1 progeny. So on the top of the
9 line, I'd just like to draw your attention to a couple
10 of different experimental procedures that were
11 performed.
12 At PND4 the litters were normalized, 10
13 equals 10. They were weaned at postnatal day 21, and
14 then from postnatal day 25 the onset of vaginal opening
15 was monitored in all animals; and then subsequently
16 from postnatal day 50 through day 72 we monitored for
17 estrus cyclicity in those progeny that were remaining
18 in the study.
19 The sampling protocol was as follows:
20 daughters, one from every litter, were analyzed at
21 postnatal days 1, 21, 33, day of vaginal opening or as
22 mature adults, and we specifically controlled for
23 reproductive state by sampling all those females at
24 diestrus and at their first diestrus after their first
25 estrus after postnatal day 58.

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1 And the other thing I'd point out is
2 that we sampled on postnatal day 1 specifically to try
3 and examine any changes within the mammary gland before
4 there was any significant exposure to any compound in
5 the milk, for example.
6 And so the analysis we performed
7 involved two different approaches. One was a whole
8 mount analysis, whereby we conducted a morphological
9 assessment using various quantitative criteria, and
10 then we also examined self-proliferation via BrdU
11 uptake.
12 This was all performed in an operator-
13 blinded fashion, and as I mentioned, all samples had to
14 pass strict quality control in terms of containing all
15 aspects of ductal structures in the whole mounts.
16 We used a variety of different
17 quantitative approaches to make these morphological
18 assessments, and what I'd like to do is briefly talk
19 you through those. And these measures were used to try
20 and specifically capture all aspects of phenotypic
21 change that might occur during postnatal development.
22 One of those measures was ductal length,
23 which is from the nipple; you can see it intact here
24 right through to the external region of the ductal
25 network. Epithelial area was characterized basically

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1 to try and understand how much of the tissue was
2 epithelial.
3 The ductal area was polygonal assessment
4 of the entire ductal network. And then we also
5 manually tagged all end bud structures that met a
6 specific criteria in terms of their size and
7 appearance, and then that was automatically counted by
8 the computer. We also expressed a measure of
9 epithelial density by calculating epithelial area as a
10 proportion of the ductal area to try and capture any
11 changes within the mammary glands.
12 So what I'd like to do is talk you
13 through the results of the control animals; so this is
14 just looking at stage-specific changes within some of
15 these measures to validate our approach. As you can
16 see on the top left, this is the measure of ductal
17 length over time in different stages of postnatal
18 development.
19 As we would expect, there is an increase
20 in ductal elongation and extension over time, and this
21 is consistent with comparable changes in both ductal
22 area and epithelial area within the mammary glands.
23 The end bud structure, as was mentioned
24 previously, is a very unique and important structure in
25 the mammary gland, and it became apparent only after

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1 postnatal day 21, consistent with the assumption of
2 ovarian cyclicity, and was evident at all stages
3 thereafter.
4 And epithelial density, as we would
5 expect, maintained a relatively constant level
6 throughout the different stages, because it's a
7 function of epithelial area within the overall mammary
8 gland.
9 So with respect to our analysis of the
10 different treatment groups, this is now looking at the
11 different treatment groups across the X axis and the
12 various measures we made on the Y axis. We saw at
13 postnatal day 1 there is a small but significant
14 increase in the ductal length in the mammary glands of
15 progeny born to dams exposed with either 50 or 100
16 mg/kg of atrazine compared to the vehicle-exposed
17 controls.
18 And this wasn't evident in the pair-fed
19 group, suggesting that this may have been a response to
20 atrazine exposure in utero; however, there was no
21 effect in ductal length across any of the other stages
22 examined.
23 With respect to end bud incidence within
24 the mammary glands, this is depicting those measures at
25 postnatal day 21 through to adult; as I mentioned,

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1 these were not detectable at postnatal day 1. There
2 was no difference in any of the treatment groups with
3 respect to the incidence of end buds at either PND 21
4 or 33.
5 What we saw is that at vaginal opening,
6 there was a significant increase in the number of end
7 bud structures in the atrazine 50 group that was not
8 present in the atrazine 100 group relative to the
9 vehicle-exposed controls.
10 This is where it is important to note,
11 however, that our pair-feeding approach was valid,
12 because we actually saw that those progeny also had a
13 significant increase in the number of end bud
14 structures per gland. And then in the adult females we
15 did not see any treatment effect.
16 Likewise, we saw no difference in ductal
17 network area. This is the overall network area in any
18 of the treatment groups of any of the ages, nor did we
19 see any difference across any of the treatment groups
20 at any of the ages for either mean epithelial area or
21 mean epithelial density. And those figures are
22 available in the Docket packet.
23 Likewise, I mentioned we analyzed self-
24 proliferation measures, and we classified that both
25 with respect to lobular structures, terminal end bud

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1 structures and ducts. And this is a depiction of the
2 image analysis, and hopefully what you can see here is
3 that the red cells are specifically dividing in amongst
4 all of these negative yellow cells; so these have all
5 been automatically tagged by the computer.
6 And the terminal end bud structure here,
7 which is highly proliferative, you can see, as we would
8 expect, there is a lot more self-proliferation. And
9 this was determined by treating animals via tube 2
10 hours prior to euthanasia and then analyzing samples by
11 invasive chemistry.
12 In the control animals, as we would
13 expect, there was maximal proliferation at postnatal
14 day 21 when the mammary glands were growing; this is in
15 terms of BrdU positivity from the ductal structures in
16 the overall mammary gland. Similarly, a high level of
17 proliferation in all the end bud structures that were
18 detected at different stages of development absent at
19 postnatal day 1, and then subsequently there was also
20 proliferation detected within the lobular structures at
21 different stages of development.
22 With respect to self-proliferation in
23 the ductal structures, at PND 1 we saw that there was a
24 small but significant decrease in the ductal structure
25 proliferation in the animals only born to the high-dose

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1 atrazine dams. It was absent in the pair-fed group and
2 no difference at any of the stages of development.
3 In terms of end bud proliferation,
4 again, no significant difference in the proliferation
5 of end bud structures at postnatal day 21, 33, vaginal
6 opening. And then the variation we see in the
7 incidence of end buds here is simply a reflection of
8 the fact that those glands are so thick in those adult
9 animals that a histological approach failed to randomly
10 capture a lot of end bud structures through that
11 sampling method.
12 In terms of self-proliferation within
13 lobules, again, no significant difference at any of the
14 stages or in any of the treatment groups examined.
15 So in summary, our findings from the in
16 utero exposure to atrazine and its effects on the
17 mammary gland, we found no effect on any of the mammary
18 gland parameters examined when daughters were born to
19 dams exposed to 6.5 mg/kg/d.
20 We did observe a small increase in
21 ductal length at postnatal day 1 in the 50 and 100
22 mg/kg/d progeny that had resolved by PND 21; and that
23 this matched a small but significant decrease in self-
24 proliferation at PND 1 in the daughters born to the
25 high-dose group, but again had disappeared by PND 21.

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1 Our approach by pair-feeding was validated by
2 the fact that the increase we saw at vaginal opening in
3 the daughters born to the 50 mg/kg group was also seen
4 in the pair-fed progeny, and in conclusion our data do
5 not support previous suggestions in terms of atrazine
6 exposure in utero on an effect or delay of mammary
7 gland development in the daughters.
8 **DR. STEVEN HEERINGA:** Thank you very
9 much, Dr. Hovey. And at this point, again, we will
10 hold questions until we've heard the sequence of
11 presentations.
12 But, Dr. Breckenridge, if you'll
13 introduce your next speaker.
14 **DR. CHARLES BRECKENRIDGE:** Okay, so we
15 will proceed with our next speaker, and now we are into
16 the main core of our presentation relating to LH surge
17 and adverse effects relating to that, and Dr. Tony
18 Plant from the University of Pittsburgh will lead us
19 through some discussion on the differences between
20 rodent, non-human, primate and women.
21 **DR. STEVEN HEERINGA:** Thank you.
22 **DR. TONY PLANT:** So thank you, yeah. My
23 name is Tony Plant, I'm a Professor of OB/GYN at the
24 University of Pittsburgh, and I have used the monkey as
25 a model for human reproduction for all my career. What

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1 I would like to do today is outline to you some of the
2 differences that exist between the regulation of the
3 pre-ovulatory surge in the rodent versus the monkey
4 versus the human.
5 So this is a schematic of the
6 neuroendocrine axis regulating the ovary, which I think
7 you're all familiar with. I'm going to focus on the
8 hypothalamus. As you know, the hypothalamus, there
9 maybe one or two thousand neurons in there that secrete
10 GnRH, gonadotropin-releasing hormone, which in turn
11 drives the pituitary to secrete the gonadotropins, LH
12 and FSH, which in turn drives the ovary, the
13 steroidogenic functions of the ovary and also the
14 gonadogenic functions.
15 So we first look at the endocrine
16 changes in at least the pituitary-ovarian components in
17 the human shown here on the left; for the monkey shown
18 in the center and for the rodent on the right-hand
19 side.
20 What is shown in the top panel of all of
21 these is the time course of LH and FSH in blood;
22 throughout the first two panels, the menstrual cycle,
23 which in the human and the monkey on average is about
24 28 days; and then for the rat, which the estrus cycle
25 is 4 or 5 days. And then the gonadal steroids below:

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1 estradiol secreted primarily by the follicle, and
2 progesterone secreted by the corpus luteum.
3 So if we look at gonadotropin secretion
4 throughout the cycle, in all three species you can
5 conceptualize this as comprising a basal or steady-
6 state or tonic secretions through the greater part of
7 the cycle, through the greater part of the follicular
8 phase and through the greater part of the luteal phase.
9 And this is interrupted, again in all three species, by
10 this massive discharge of gonadotropin at midcycle.
11 This is the pre-ovulatory gonadotropin surge, and as
12 you know it eventuates in ovulation, again in all three
13 species.
14 The tonic secretion is regulated in all
15 three species by a negative feedback control from the
16 ovary, and the principal ovarian component in the three
17 species is estradiol; there are other hormonal factors,
18 but estradiol is the principal. This is a negative
19 feedback action, and that can be easily demonstrated by
20 ovariectomy at this stage of the cycle, which will
21 result in a profound hypersecretion of the
22 gonadotropins in all three species.
23 The positive feedback, or I should say,
24 the regulation of the gonadotropin surge, again
25 involves an ovarian component, and that ovarian

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1 component again in all three species is predominantly
2 estradiol. And estradiol exerts a stimulatory or a
3 positive feedback action at the hypothalamic-pituitary
4 level. It's somewhat difficult to conceptualize how a
5 steroid has both effects, and we really don't have the
6 time to discuss that; but it is a phenomenon.
7 Now to look at the hypothalamus. So the
8 reproductive neuroendocrinologists tend to divide the
9 hypothalamus into a rostral component, termed the
10 preoptic area, which sits here above the optic chiasm;
11 so that's where the optic nerves come into the brain.
12 And then if you move back caudally into the
13 hypothalamus, you come to what we call the mediobasal
14 hypothalamus.
15 And there's a nuclear group in that, the
16 arcuate nucleus or, in the human, the analog is known
17 as the infundibular nucleus. And as you know, the link
18 between the hypothalamus and the anterior pituitary is
19 an endocrine link.
20 And the GnRH from the hypothalamus is
21 secreted into this primary plexus of a portal
22 circulation and as a secondary plexus in the pituitary,
23 and these two plexi are linked by what are known as
24 caudal vessels, which run down the outside of the
25 skull.

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1 So if we first view tonic secretion,
2 it's not, as you would expect from most composite data
3 that I showed you, continuous and boring. In fact,
4 it's episodic. And this is shown here not for a
5 primate, not for a rodent; this is data from the sheep.
6 And the reason I show that is that the sheep lends
7 itself to an experimental approach where the
8 experimentalist can relate directly what GnRH is doing
9 in portal blood, shown here on the lower panel, and
10 correlate that to what the pituitary is doing by
11 measuring in this case LH in the peripheral
12 circulation.
13 Now, you can see that the secretion of
14 tonic gonadotropin is characterized by these dramatic
15 episodes of secretion, which vary depending on gender
16 and hormonal status and species anywhere between 20 to
17 30 minutes to 4 or 8 hours. But they are all
18 occasioned by this discharge or GnRH from the brain.
19 Now, the mechanisms that generate this
20 pulsatile GnRH release, the neurobiology of that is
21 unclear. And we talk about the GnRH pulse generator; I
22 think I've heard that term in the last couple of days.
23 This is really a physiological construct, but we really
24 don't understand the fundamental neurobiology
25 underlying that pulsatility.

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1 But it is the GnRH pulse generator that
2 generates these intermittent secretions of GnRH into
3 the portal blood, which then drives the pituitary to
4 secrete the gonadotropins. And from what we know,
5 we're not aware of major species differences across
6 mammals in the mechanisms that generate this
7 pulsatility.
8 Now, let's look at the surge. And here
9 I've listed on the left the processes involved in the
10 control of the surge in some species, and here the
11 corresponding parameter for rodents, non-human
12 primates, primarily the monkey, and the human female.
13 So if you first look at the location of
14 GnRH cell bodies or the cell bodies, GnRH cells that
15 project to the median eminence and are known as
16 neuroendocrine cells, these are exclusively in the rat
17 brain in the preoptic area. In the monkey and the
18 human, they are primarily in the mediobasal
19 hypothalamus.
20 In the role of the preoptic area, so the
21 rostral aspect of the hypothalamus, it's essential in
22 the rodents, it's non-essential in monkeys, and it's
23 non-essential in the human female.
24 The site of the estrogen-positive
25 feedback -- this is the feedback that stimulates the

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1 gonadotropin surge of events in ovulation -- it's in
2 the preoptic area of the rodent, it's in the mediobasal
3 hypothalamus-pituitary of the monkey, and there is some
4 argument in the human female whether the MBH is even
5 involved at all, but certainly pituitary feedback.
6 Another hallmark, a classical hallmark
7 of the LH surge in the rodent is that it can be blocked
8 by anesthesia, particularly barbiturate administered
9 just before the surge on the afternoon of proestrus.
10 This is not the case in the monkey. Deep barbiturate
11 anesthesia during the duration of the surge and before
12 does not block, and we don't know in the human;
13 experiment hasn't been done.
14 Now, the relationship to the
15 photoperiodic control in the light/dark cycle, it's
16 tightly coupled in the rodent, and it's weakly coupled
17 in both the monkey and the human. Is it associated
18 with the GnRH surge? Most definitely in the rat; also
19 true in the monkey, although it was argued for many
20 years, but it's certainly there. Whether it's present
21 in the human female is unclear.
22 And then the last aspect here, the
23 sexual differentiation of this preoptic area takes
24 place in the rodent such that the male hypothalamus of
25 the rat cannot support an ovarian cycle. This is not

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1 true in the monkey -- it's not differentiated to that
2 degree -- and probably not in the human.
3 So these are some of the axioms on which
4 our understanding of the rodent surge is based: it's
5 rigidly timed, as I said, by a daily neural signal that
6 is tightly coupled to a critical period during 24-hour
7 light/dark cycle; it's relayed to the pituitary by
8 discharge of GnRH in the hypophysial portal
9 circulation; it's generated in the preoptic area or the
10 rostral part of the hypothalamus; and the positive
11 feedback action of estradiol is exerted on the POA.
12 This 24-hour plot in the rodent brain
13 was elegantly demonstrated by Legan and Karsch Sandy
14 is a Panel member here -- where she took ovariectomized
15 animals and gave them a constant level of a
16 physiological stimulus for estradiol.
17 And this estradiol implant was
18 maintained for 12 days here, and you can see that each
19 day -- this is a morning sample, a noon sample, this is
20 a sample at 1700 hours -- you can see that every day
21 the rat hypothalamus fires its 24-hour signal and it
22 leads to a discharge, a pre-ovulatory-like discharge of
23 LH.
24 This is not the case in the monkey.
25 It's a complicated slide; but if you look on the middle

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1 panel here, where this is Knobil and his colleagues,
2 they have taken early follicular phase female monkeys
3 and implanted a physiological strength of estradiol
4 for, in this case -- I can't see from here -- but it's
5 12, I think, 24, 36 and 96 hours. So they're looking
6 at the effect of duration, and you can see that for a
7 surge to be induced in the monkey you have to maintain
8 this estradiol signal at a physiological level of 350
9 pg/ml for about 48 hours, and then all the animals
10 surge.
11 Now, in contrast to the rat, if you
12 increase the magnitude of this estradiol signal as
13 shown in this top left-hand panel, so now the estradiol
14 is only being imposed for 24 hours but the amount of
15 estradiol is super-physiologic, and you can see that
16 this leads to an acceleration in the surge and it
17 occurs 12 to 18 hours earlier. So it's not timed by
18 this 24-hour clock in the preoptic area that's linked
19 to the circadian system.
20 The role of the preoptic area now, and
21 that has been addressed in both rodents and monkeys by
22 a technique known as surgical deafferentation; it
23 involves the lowering of a surgical knife, known as a
24 Halasz knife after the Hungarian who introduced this,
25 so that you can surgically isolate the mediobasal

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1 hypothalamus from the more rostral preoptic area. You
2 can do this either an anterior disconnection, or you
3 can make it a 360 disconnection.
4 The alternative or an additional
5 approach to study the preoptic area is, you can lesion
6 it. And here you place stereotactically radiofrequency
7 lesion into the preoptic area and destroy the preoptic
8 area in that manner. Both these procedures in the rat
9 will interrupt cyclicity and block the positive
10 feedback action of estradiol, underlying the importance
11 of this preoptic area in the rodent brain.
12 In the monkey, that's not the case. In
13 these four studies -- or, the consensus of the evidence
14 is that it's not the case, and there are four studies
15 here. The first one used a Halasz knife and a complete
16 deafferentation of the mediobasal hypothalamus from the
17 anterior; this one used a preoptic lesion; this one an
18 anterior disconnection; and here, a preoptic lesion.
19 And in three of the four studies spontaneous LH surges
20 were observed, and in those animals that spontaneous
21 surges weren't observed, many of them showed an
22 estrogen-induced surge.
23 I just show you one for time, and this
24 is a preoptic lesion. The lesion is being
25 reconstructed here on the parasagittal section of the

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1 hypothalamus; so here's the landmark, the optic chiasm,
2 remember, above that lies the preoptic area, and this
3 lesion destroyed a large portion of the preoptic area,
4 including the suprachiasmatic nucleus, which sits just
5 on the optic chiasm. And you can see here, this lesion
6 had no effect on the cyclicity of this monkey LH
7 kinetic surges, follicular genesis and corpus luteum
8 and menstruation.
9 So that's led to the concept in the
10 monkey that this unit, neuroendocrine unit known as the
11 mediobasal hypothalamus-pituitary, is the control
12 system which dictates the control of the menstrual
13 cycle. And in contrast to the rodent, this region of
14 the hypothalamus is not involved.
15 So the question of whether there is a
16 GnRH surge in the primate has been now, I think,
17 unequivocally demonstrated by Steve and his colleagues,
18 and that's shown here, where they correlated GnRH
19 release in the median eminence on the top with LH
20 secretion measured in peripheral blood below.
21 And clearly, you can see there's a major
22 robust discharge of GnRH in the monkey, just as there
23 is in the rat. The duration, of course, in the monkey
24 is much longer. And this phenomena cannot be blocked
25 by barbiturate in the monkey; of course, it is in the

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1 rat.
2 Now, the GnRH pulse-generating mechanism
3 in the monkey appears to turn off during the surge mode
4 of GnRH secretion. And you need to remember that
5 because the human female appears to be further removed
6 from the monkey in that regard.
7 Now, the other aspect about the pre-
8 ovulatory GnRH surge in the monkey is that in contrast
9 to the rodent, it's not obligatory for a menstrual
10 cycle. And that was shown here initially by the work
11 of Knobil.
12 Again, this was published a long time
13 ago. Here, a lesion has been placed into the
14 hypothalamus of a monkey that's just abolished GnRH
15 release. And so post lesion this animal doesn't
16 respond to estrogen with a surge, although you've got a
17 nice estrogen signal, and tonic levels of gonadotropin
18 are undetectable.
19 And then investigators instituted an
20 invariant pulsatile stimulation of one pulse of GnRH
21 per hour for several months, and you can see that this
22 invariant intermittent stimulation drives follicular
23 genesis and, you know, so the increase in gonadotropin.
24 The follicle here causes positive feedback and you get
25 a gonadotropin surge and you get ovulation, as

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1 indicated by the pattern of progesterone, and this
2 cycle repeats until you stop the permissive infusion of
3 GnRH.
4 So here essentially there is no brain,
5 no neuroendocrine brain, in this animal; yes, it's able
6 to cycle. So you have to conclude that the site of the
7 negative and the positive feedback in this model is at
8 the level of the pituitary. There's no surge here.
9 Now, the human experiment is even more
10 compelling, because there are cases where the GnRH
11 neurons, which during embryonic development they might
12 migrate from the olfactory factor into the brain,
13 forebrain and into the hypothalamus.
14 In subjects such as Coleman's, which
15 have a genetic defect in a gene known as KOW, well,
16 this interferes with the migration of neurons; so the
17 neurons never get to the hypothalamus. So this is a
18 cleaner model than the monkey, and in several of these
19 studies -- and they are primarily by Crowley and Janet
20 Hall) in MGH, and this is some of their data -- those
21 look very similar to the Knobil study in the monkey.
22 These women that have hypogonadotropic,
23 hypogonadism due to GnRH deficiencies are treated in
24 the control group with an invariant -- and this is even
25 better studied in the monkey, because these doses of

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1 GnRH mimic the physiological GnRH and LH pulses.
2 And you can see -- I won't go over the
3 data -- but clearly, these women show spontaneous
4 cycles with this invariant stimulation; no GnRH surge
5 at midcycle, but clearly LH surges and follicular
6 genesis in ovulation.
7 In the other group, they decreased the
8 amount of GnRH being given to these women during this
9 period of -4 to 1 day around the surge, and you can see
10 that that has no impact. So they're actually reducing
11 the hypophysiotropic stimulus to the pituitary.
12 And they did that, because they had some
13 evidence based on indirect pharmacological data that
14 suggested in the human female, totally
15 counterintuitive, that the amount of GnRH during the LH
16 and FSH surge was actually reduced,. And certainly,
17 this data supports the idea that you can reduce the
18 GnRH stimulus without interfering with the cycle.
19 And then the other aspect about the
20 human female is that this pulse-generating mechanism
21 appears to continue through -- so this is the ascending
22 phase of a pre-ovulatory surge, very frequent sampling,
23 and this is the descending phase. And you can see
24 there is the beautiful pulses of LH and ALPHA subunit,
25 which indicate that this hypothalamic GnRH pulse-

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1 generating mechanism is still operational during the
2 surge.
3 So just to conclude, this is my sort of
4 schema of the rodent system. So the preoptic area is
5 critical. You have this 24-hour signal gated to the
6 photoperiod, which is relayed to the suprachiasmatic
7 nucleus, and for that to be manifest you need a
8 positive feedback action of estrogen here. In the
9 presence of estrogen the gates open, the clock works
10 and drives this system every 24 hours.
11 In the monkey and, as far as we know,
12 the human, of course, the preoptic area is not
13 involved. You don't have this positive feedback to
14 that area, and that positive feedback now in the
15 primate is in this MBH hypothalamic pituitary unit.
16 And you conceptualize that the human female may have
17 evolved even further and that the extent of positive
18 feedback of GnRH surge generation in the human female
19 is diminished and perhaps is not present.
20 So I would offer you that I'm not saying
21 that the rat is a bad model; but I think the mode of
22 secretion that you are studying for human relevance,
23 the LH surge in the rodent is not relevant to the human
24 situation.
25 What is relevant to the human situation

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1 is this hypothalamic GnRH pulse-generating mechanism,
2 which will permit the pituitary-ovarian axis to cycle
3 28 days and with it a pre-ovulatory surge.
4 Thanks.
5 **DR. STEVEN HEERINGA:** Thank you very
6 much, Dr. Plant.
7 Dr. Breckenridge?
8 **DR CHARLES BRECKENRIDGE:** Yes, thank you
9 very much; we will now proceed with going back to the
10 rodent model with Dr. Handa.
11 **DR. ROBERT HANDA:** Good morning; if we
12 could get that slide back up.
13 I'm Bob Handa, I'm a Professor in Basic
14 Medical Science and Neuroscience at the University of
15 Arizona College of Medicine. And I'll be spending my
16 time today speaking to you about our studies regarding
17 the mechanism of action of atrazine on regulating the
18 LH secretory patterns in the bag model of LH secretion
19 in the rodent model. These are studies that are in
20 collaboration between my laboratory, Syngenta and WIL
21 Research Laboratories in Ohio.
22 Basically, Dr. Plant has described the
23 hypothalamus-pituitary-gonadal axis, and so I won't
24 spend much time with that. What I would like to do is
25 review with you some of the data that I presented at

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1 the April SAP and do this relatively quickly and then
2 add on to that data some of the new datasets that we've
3 accumulated over the last several months.
4 So we know that the hypothalamus-
5 pituitary-gonadal axis regulates reproduction in the
6 rodent. We know that this is due to a group of neurons
7 that synthesize and secrete GnRH into the portal
8 vasculature and ultimately stimulate the secretion of
9 luteinizing hormone from the anterior pituitary
10 gonadotropes.
11 And we also know based on Dr. Plant's
12 presentation earlier that LH is secreted in two types
13 of patterns, a pulsatile or episodic release where
14 increases occur regularly throughout the day in the
15 rodent -- this is approximately every 30 minutes -- as
16 well as an LH surge type of pattern, and this surge is
17 a dramatic increase in response to elevating or rising
18 levels of estrogen and, as a result, this precedes and
19 is the cause of ovulation and luteinization of the
20 follicle.
21 So our studies that I will describe to
22 you today examine the mechanism of action of atrazine,
23 and from our previous studies we have known for several
24 decades now that atrazine can reduce the LH surge.
25 These are data taken from my laboratory, showing that

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1 estrogen- or progesterone- induced surges of LH in
2 ovariectomized female rats is inhibited by several
3 different doses of atrazine given for 4 days prior to
4 examination of the LH surge using repeated sampling
5 using a jugular canula to capture the peak of the LH
6 surge. These studies also show that in a series of
7 studies looking at pituitary sensitivity, we examined
8 pituitary sensitivity to a potent GnRH agonist, DL6
9 GnRH, which showed no effect of atrazine on that part
10 of the HPG axis, and we also showed that there were no
11 effects of atrazine on GnRH mRNA levels.
12 This is very difficult to see;
13 hopefully, you can see in the upper panel some green
14 neurons as well as some red-stained nuclei, if you
15 squint real hard. This is another group of studies in
16 which we examined the possibility that GnRH neuronal
17 activation was impaired by atrazine treatment, and what
18 you can see is that we used c-Fos, which is an
19 immediate early gene that is rapidly expressed by
20 neurons when they are activated, and we can demonstrate
21 that c-Fos is expressed in GnRH neurons, about 80% of
22 GnRH neurons in control animals; and that in the
23 presence of atrazine administration for 4 days, that
24 during the LH surge GnRH neurons are unable to express
25 c-Fos, suggesting that they are less activated and also

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1 suggesting that the site of atrazine action inhibiting
2 the HPG axis may lie upstream of the GnRH neuron.
3 Again, we also presented data at the
4 last SAP to show that if we remove atrazine from the
5 mix here and after treatment cessation and then try to
6 stimulate an LH surge, that within 2 days following
7 atrazine withdrawal that we can start to see the
8 reappearance of an LH surge in following estrogen or
9 progesterone priming, and that within 4 days following
10 removal of atrazine we can see the reappearance of a
11 full-blown LH surge, and that's shown on the left panel
12 here after 4 days of treatment cessation, and
13 accompanying that is the expression of C-Fos in those
14 GnRH neurons. And this pattern of recovery following
15 treatment cessation actually fits with the
16 pharmacodynamics of atrazine which Dr. Kim will address
17 in the next presentation.
18 Now, as I promised, I'll tell you a
19 little bit about pulsatile hormone secretion, and
20 again, as I presented at the last SAP, we can see
21 pulsatile hormone secretion, pulsatile LH secretion, in
22 the rodent by doing frequent sampling; these are
23 samples taken every 5 minutes over a 3-hour period.
24 And what you can see in the upper left
25 panel is a typical pattern of LH pulses in a rodent,

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1 and what you can see is that they occur approximately
2 every 30 minutes throughout the day. These are
3 ovariectomized female rats. We ovariectomized the rats
4 in order to release that estrogen negative feedback and
5 allow us to visualize those pulses for the activity of
6 the GnRH pulse generator better.
7 And what you can see is as we increase
8 the doses of atrazine, what you can see is that the
9 pulse characteristics begin to change such that by 200
10 mg/kg atrazine doses we find that in fact the pulses
11 are delayed in their appearance, they have a period of
12 over an hour now and that in fact they are increased in
13 amplitude.
14 And these characteristics of these LH
15 pulses are accompanied by similar changes in GnRH
16 secretion, and we've measured that using an in vitro
17 system where we perfuse hypothalami and examine the
18 secretion of GnRH from these hypothalami in vitro, and
19 again the same pattern appear in those GnRH secretory
20 rhythms.
21 So based on a number of studies that
22 have been reported showing that the possibility exists
23 that other hormones may impact the HPG axis and recent
24 studies from Ralph Cooper's lab and Steve Pruitt's lab
25 that suggest that atrazine might increase

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1 corticosterone in the rodent, we embarked on a series
2 of studies to determine in fact if the effects of
3 atrazine on HP -axis function might be secondary to the
4 effects on HPA axis.
5 So at this time, then, I need to
6 introduce a second and parallel neuroendocrine axis;
7 this is the hypothalamus-pituitary-adrenal axis where,
8 very similar to the HPG axis on the right, the HPA axis
9 secretes a neuropeptide, corticotropin-releasing
10 hormone, which drives the pituitary to synthesize and
11 secrete ACTH, or adrenocorticotropic hormone, and that
12 stimulates the adrenal cortex secretion of
13 corticosterone in the rat or cortisol in the human.
14 Now, this pathway is very responsive to
15 a stressor; so applying a stressor, you see a rapid
16 induction or increase in plasma levels of
17 corticosterone. And the hypothesis is then that
18 atrazine may be working to inhibit the HPG axis by
19 activating this neuroendocrine axis and thereby
20 inhibiting this through either corticosterone, which we
21 know inhibits HPG axis, or CRH, which we know CRH
22 neurons project the GnRH neurons and have been
23 implicated indirectly in activating GnRH neuronal
24 function.
25 The design of this experiment was

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1 described again in the last SAP, and that is animals
2 were treated with varying doses of atrazine ranging
3 from 6.5 to 100 mg/kg/d, and then they were sacrificed
4 by decapitation within 30 minutes of atrazine
5 administration by gavage.
6 In this study we utilized male Sprague-
7 Dawley rats, and they were sacrificed after either 1
8 dose, 7 doses, 14 doses or 28 daily doses of atrazine.
9 And this allowed us actually to examine not only the
10 levels of corticosterone but a whole series of other
11 hormones, and these are listed here. I will focus on
12 the corticosterone changes today; we went over many of
13 those other changes in the last SAP.
14 So these are the results of those
15 studies looking at corticosterone, and again I will
16 just remind you that when we administer atrazine and
17 look 30 minutes later, we can see elevations in plasma
18 corticosterone after the first administration by gavage
19 of atrazine, and that this is a 30-minute period post
20 gavage. What we see is after 7, 14 or 28 daily doses
21 of atrazine that this response has disappeared.
22 Now, we see a similar response in plasma
23 progesterone in males. Plasma progesterone is
24 predominantly secreted by the adrenal in males, and see
25 a response at the higher doses following the first

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1 administration of atrazine; but again, it's gone after
2 the 7, 14 or 28 doses of atrazine.
3 We've also measured plasma prolactin in
4 the same paradigm and we see no changes in prolactin,
5 suggesting that, as we brought up earlier, prolactin is
6 a stress-responsive hormone, and this suggests that
7 this is not a generalized stress response but is
8 actually targeted to somewhere in the HPA axis.
9 Then this is data from females following
10 28 daily doses by gavage, and what you can see is there
11 are no changes in corticosterone or progesterone; so
12 again, in females it appears that that rapid response
13 following the first exposure to atrazine has
14 disappeared by the 28th exposure to atrazine.
15 So this raises the question as to if
16 atrazine is regulating the HPA axis, and certainly it
17 could be utilizing corticosterone secretion to inhibit
18 the HPG axis acutely.
19 Where in the HPA axis might atrazine be
20 working, and I proposed a number of sites again at the
21 last SAP, in which we proposed that it could be acting
22 directly on the hypothalamus as a generalized stressor
23 might activate the HPA axis; and that if it did, that
24 it would activate these CRH neurons, which are found
25 within the paraventricular nucleolus of the

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1 hypothalamus, and thus we embarked on a series of
2 studies to test the activity of the PVN neurons, again
3 using c-Fos as a marker of cellular activity.
4 And I want to present the first of these
5 studies to you today, and that is that we know that
6 under non-stress conditions that there is very little
7 c-Fos expressed by neurons in the PVN. So in this
8 photomicrograph up here, you can see this is a section
9 taken through the PVN; the paraventricular nucleus is
10 this wing-shaped structure right here, this is the
11 third ventricle right there, and you can see very few
12 darkly stained nuclei in this preparation.
13 One hour following a stressor -- in this
14 case, it was a restraint stress -- what you can see is
15 the appearance of a number of darkly stained nuclei
16 within the paraventricular nucleus suggesting that
17 those neurons are activated, and this is represented
18 graphically over here in the non-stressed condition and
19 following stress.
20 And what you can see is 1 hour following
21 atrazine administration, you can see now this is a
22 blowup of that same area, the paraventricular nucleus
23 is here. And you can see a few c-Fos-positive neurons;
24 but in fact, there is no significant increase compared
25 to the 0 mg/kg treatment group.

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1 At the same time you can see that both
2 of the 50 mg/kg doses and 200 mg/kg doses increased
3 corticosterone secretion, and what this data suggests
4 is that if atrazine is increasing plasma corticosterone
5 levels, it is doing it downstream from the
6 hypothalamus.
7 Now, as I said earlier, we also had the
8 opportunity to measure a number of plasma steroid
9 hormones, and we did this using liquid chromatography
10 and a mass spectrometry, which is considered by many to
11 be the gold standard for measuring steroid hormones at
12 this time.
13 And what we saw was, in fact, no effect
14 of atrazine on a number of different hormones. In the
15 males, the androgen, androstenedione, testosterone and
16 dihydrotestosterone were not changed following 1, 7, 14
17 or 28 doses of atrazine. In females, the estrogens,
18 estrone and estradiol were measurable, as well as the
19 weak androgen, androstenedione, and none of those were
20 changed by atrazine administration.
21 In addition, at last April's SAP, Dr.
22 Steven Pruitt proposed that corticosterone can be
23 implicated in regulating a number of functions, and one
24 of these was immunological function; and he proposed
25 that, in fact, we would be able to very effectively

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1 examine the consequences of elevations in
2 corticosterone by monitoring immune function, and those
3 studies have been completed. Unfortunately, Dr. Pruitt
4 is not here to present them; so I'll take a stab at
5 that, although I'm not an immunologist.
6 But basically the results can be
7 summarized in a couple of statements. In male Sprague-
8 Dawley rats, we see no suppression of natural killer-
9 cell activity or spleen antibody-forming cell responses
10 at the 100 mg/kg body weight dose. We can establish a
11 no-effect level based on thymus weight reduction, which
12 occurred at the 100 mg/kg body weight dose but did not
13 occur at the 25 mg/kg dose.
14 And in female Sprague-Hawley rats, we
15 similarly see no suppression of NK activity or
16 antibody-forming cell responses at the 100 mg/kg body
17 weight dose, nor was there an effect of this dose on
18 thymus weight, establishing the NOAEL at 100 mg/kg
19 body weight.
20 So this raises the question of in our
21 studies that although we've seen increases acutely in
22 corticosterone and that still may drive the acute
23 inhibition of atrazine on the LH surge of whether or
24 not in fact it truly is involved, and we did the study
25 to test this and that is to remove the adrenal glands,

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1 the source of corticosterone, and then determine if
2 atrazine can still inhibit LH secretion either at the
3 pulsatile or the surge, the secretory patterns.
4 This is the experimental design for the
5 study we used. We had young adult female Wistar rats.
6 They were ovariectomized, and then 7 days later they
7 were cannulated in order for us to determine the
8 dynamics of LH secretion.
9 At the same time they were
10 adrenalectomized or sham-adrenalectomized, and then 3
11 days later at the same time as the adrenalectomy and
12 cannulation, we began then on a paradigm of atrazine
13 administration by gavage, and you can see 200 mg/kg
14 body weight or 50 mg/kg.
15 Sampling occurred then 3 days later, and
16 in the absence of estradiol-priming to visualize pulses
17 of LH or we treated them for 3 days with estradiol and
18 then examined estradiol and progesterone, and then
19 examined the LH surge in these animals.
20 So I'll submit to you the effects of
21 adrenalectomy on pulsatile hormone secretion in these
22 ov'eced female Wistar rats. What you can see is in the
23 upper left-hand panel, the typical pattern of LH pulses
24 that you see following atrazine administration, and
25 this is in the atrazine-treated, sham-adrenalectomized

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1 animal, and you can see these high-amplitude pulses,
2 which occur less frequently than normal.
3 And when we do the same examination in
4 animals that were adrenalectomized and atrazine-
5 treated, what you see is that atrazine has very little
6 effect on those animals and that, in fact, the
7 adrenalectomy returns the pattern of LH pulses back to
8 that of the control.
9 This is represented graphically down
10 here, in which you can see an increase in pulse
11 amplitude and an increase in pulse period in the sham
12 animals, whereas this is reduced to the control levels
13 in adrenalectomized animals, suggesting that at least
14 for pulsatile hormone secretion, corticosterone levels
15 may in fact mediate the effects of atrazine on LH
16 secretory patterns.
17 In contrast, if we look at the estrogen-
18 and progesterone-induced LH surge, again, treatment
19 with atrazine reduces the LH surge, the peak of the LH
20 surge, in a dose-responsive fashion, and adrenalectomy
21 has no effect on that inhibitory effect of atrazine
22 administration, suggesting that corticosterone or
23 products of HPA axis are not involved in atrazine's
24 effects in blocking the LH surge.
25 So a few key points to remember before I

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1 go into some of the newer studies that we've performed
2 over the past few months, we know that high doses of
3 atrazine can inhibit the HPG axis and at the same time
4 that they can activate the HPA axis.
5 We know that the HPG axis effects of
6 atrazine are transitory, and they're reversed after
7 cessation of treatment. And similarly, we know that
8 the HPA axis effects disappear by 7 days of exposure in
9 the male and by 28 days of exposure in the female; we
10 have yet to do the 7- and 14-day doses in the female.
11 We also know that some effects of the
12 HPG axis are secondary to changes in the HPA axis, such
13 as the pulsatile secretion of LH. But the induction of
14 the LH surge does not seem to be one of these that are
15 a consequence of changing HPA axis activity. We also
16 know that there are no effects of atrazine on androgen
17 levels in males or on estrogen levels in females, again
18 using LC/MS/MS.
19 We know that there no effects of
20 atrazine on immune function in males or females, and we
21 believe that the effects of atrazine on the HPG axis
22 are mediated centrally, whereas the effects on the HPA
23 axis seem to be mediated peripherally.
24 Okay. So let's return to examining the
25 HPG axis and some parameters of how atrazine might be

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1 altering LH surge. This study is here just to remind
2 me to tell you or to remind me to describe the way that
3 atrazine inhibits the LH surge. These are animals,
4 young adult female Sprague-Dawley rats.
5 We in this case have induced an LH surge
6 by ovariectomy and then hormone-priming, in this case
7 with just estrogen, and you can see there is very nice
8 increase in LH in the afternoon following 3 days of
9 estrogen administration. In this case, estrogen was
10 administered by implanting a pellet of estradiol
11 similar to that that Dr. Plant showed you where we find
12 a daily afternoon increase in LH.
13 If we administer atrazine for 4 days
14 prior to sampling, what we see is that it can inhibit
15 the LH surge, as shown in the blue bars; and again, we
16 can represent this by examining the peak LH regardless
17 of time or the area under the curve, and in both cases
18 they're significantly suppressed.
19 So we embarked on a series of studies.
20 This was described yesterday in one of the talks, and
21 this is a series of studies in which animals were
22 treated for prolonged periods of time with atrazine.
23 The upper panel shows the treatment design for Cohort
24 I, in which dams were treated with atrazine the
25 beginning of the day after finding a vaginal plug,

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1 which suggests that mating has occurred; so this
2 atrazine was begun at the time of conception or shortly
3 after.
4 And they were treated continually up
5 until the time animals, these moms, were weaned, and
6 then the pups were individually treated for 2 to
7 3 weeks following until the time of puberty until the
8 time of vaginal opening.
9 Another group of animals was continued
10 on for another 16 weeks up to 133 days of age, so these
11 were extensive periods of exposure to atrazine.
12 Animals were sampled at the time of vaginal opening
13 here by giving estrogen to induce -- by ovariectomy
14 followed by estrogen treatment to induce an LH surge.
15 Another group of animals was treated from the time of
16 weaning up to the same period of time, the peripubertal
17 period. And the last group of animals was treated for
18 2 weeks' time preceding the 133-day range.
19 What I want to first describe to you are
20 these groups that were treated up till puberty, and
21 then we induced an LH surge with an estrogen capsule,
22 and this will be followed then by examination of LH
23 surges in these animals at 133 days of age. I should
24 point out there were approximately 19 to 20 animals per
25 group in each one of these treatment groups and doses.

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1 Basically, what you see is animals dosed
2 from conception until weaning, shown on the left panel.
3 We can see that estrogen can very nicely induce an LH
4 surge in these animals, and there is no effect of
5 atrazine on any parameters of the LH surge up to 50
6 mg/kg body weight.
7 Similarly, animals dosed from weaning
8 until the peri-pubescent period also show very dramatic
9 increases in LH and there is no effects of atrazine
10 administration, suggesting at least in these younger
11 animals that they seem to be somewhat resistant to the
12 effects of chronic atrazine treatment on LH surge
13 suppression.
14 Similarly if we look at 133-day-old
15 animals, we find that the atrazine exposure from
16 conception to 133 days of age, we find nice surges in
17 response to estrogen priming but no effect of atrazine;
18 and similarly if we look at these young adult females
19 following 2 weeks of exposure to atrazine, we find no
20 effects of atrazine on the estrogen-induced LH surge.
21 So this raises the question as to
22 whether or not these animals are not responsive to the
23 LH surge-suppressing effects of atrazine. And this is
24 a slide that was actually produced by Charles
25 Breckenridge some time ago looking at the NOAEL levels

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1 on the left on the Y axis, and duration of exposure on
2 the X axis.
3 And if we put in the 50 mg/kg dose for
4 14 days, we actually fit that line pretty well. This
5 was used, actually presented in EPA's presentation in
6 the April SAP to describe this exposure duration, which
7 we thought was exposure-duration function as a result
8 of a NOAEL and exposure duration.
9 What we would submit was that in fact
10 this does not necessarily describe the long-term
11 effects of atrazine, and if we look at this Morseth
12 paper, what we find, in fact six months of atrazine
13 exposure, they had responses or inhibitory effects at
14 fairly low doses; but, in fact, it turns out that these
15 animals were actually 9 months of age by the time they
16 were sampled, and what we know from other studies is
17 that animals at 8 to 10 months of age have reached a
18 middle-aged period where in fact the LH surge and the
19 ability to generate an LH surge is actually
20 deteriorating; so what we can actually include in here
21 perhaps is a consideration of age of animal at the time
22 of testing, which may in fact confound the results of
23 these types of approaches or modeling.
24 So the last series of studies, what I
25 want to do is back up a little bit. We know that if we

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1 look at gavage dosing and we look at the ability of
2 atrazine acutely to inhibit the LH surge using a gavage
3 method, we know that in fact there does seem to be a
4 dose-response.
5 But we also know that this type of bolus
6 infusion of atrazine is probably not of physiological
7 importance when we consider the human condition, and as
8 a result we would see the plasma levels of atrazine or
9 chlorotriazines that would show this type of pattern,
10 whereas distributed dosing of the animal perhaps
11 through the diet may more closely mimic that which the
12 human is exposed to.
13 So we embarked on a series of studies to
14 examine and to compare these types of administration
15 paradigms on the LH surge in intact female rats. This
16 is the experimental design, it's very complicated; I'll
17 try and go over this with you slowly. But basically
18 what we did was used intact females that were
19 approximately 12 weeks of age, so they were young
20 adults.
21 They were monitored for estrus cyclicity
22 for at least two weeks prior to their use, and we only
23 used animals then that were showing regular 4-day
24 estrus cycles. At the day of estrus, then they began a
25 number of types of doses and routes of administration.

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1 The upper four groups show dietary administration at
2 three different doses of atrazine and the calculated
3 exposure level based on their food intake. And the
4 lower panels here show the doses of exposure by gavage:
5 0.75, 1.5, 3, 6, 10 and 50 mg/kg body weight.
6 Animals were monitored throughout this
7 period, and 4 days later when they were deemed to be in
8 the proestrus phase, they were sampled for LH using a
9 jugular puncture technique at four different times, two
10 that would represent, hopefully capture the peak of the
11 LH surge and one that would capture the baseline levels
12 and the post surge levels.
13 And some of these animals were then
14 continued to be monitored for use in the
15 immunotoxicology study that I presented to you earlier
16 in this presentation.
17 These are the results of those studies
18 looking at the effects of gavage treatment of atrazine
19 on the proestrus LH surge in these intact female
20 Sprague-Dawley rats. These numbers represent
21 approximately 19 to 21 animals per group, and what you
22 can see: there are significant increases over time,
23 and the highest dose of atrazine suppresses the LH
24 surge.
25 This is presented graphically in this

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1 histogram, again showing peak LH amplitude is
2 suppressed only at the 50 mg/kg dose; an area under the
3 curve similarly is suppressed only at the 50 mg/kg
4 dose.
5 Now, in the course of running these
6 studies, animals of course I told you were 4-day
7 cyclers. What we noticed is that in the highest dose
8 of atrazine administration by oral gavage, we saw a
9 significant increase in the number of animals that
10 became 5-day cyclers, and this suggested that in fact
11 we were not only inhibiting the LH surge but we were
12 having a physiological effect, in that the estrus cycle
13 was being prolonged.
14 And this raises the question as to
15 whether the drop in the LH surge that we report was
16 actually due to the fact that this group of animals
17 might have been slightly different, because they were
18 cycling at a 5-day interval. And as a result we
19 removed those and reanalyzed the data, and what you can
20 see is that in fact if we only include the 5-day
21 cycling animals, that in fact we still show the same
22 pattern of LH surge inhibition by atrazine.
23 Now, again, I told you earlier that we
24 also included a group of animals of which dietary
25 atrazine was included to try and match as closely as

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1 possible the levels that we used in the gavage
2 approach, and what you can see is when we did this and
3 we examined the LH surge in the dietary atrazine group,
4 we find no effect of atrazine on the proestrus LH surge
5 in these intact female rats.
6 And this matches very closely the
7 pharmacodynamics of atrazine, and Dr. Kim will again
8 show you some of these data in the next presentation.
9 And again, examining peak LH surge regardless of time
10 and area under the curve, we find no effect of dietary
11 atrazine administration on any of these parameters.
12 So some key few points to wrap up my
13 presentation, we know that short-term administration of
14 atrazine by gavage can reduce the estrogen-induced LH
15 surge in ovariectomized females, female rats. We know
16 that chronic atrazine treatment does not seem to alter
17 the estrogen-induced LH surge when tested peri-
18 pubertally or as young adults, at least at doses as
19 high as 50 mg/kg body weight.
20 But we know that 4-daily doses of
21 atrazine by gavage can produce the proestrus surge in
22 intact female rats, and it can increase the incidence
23 of 5-day estrus cycles, suggesting a prolongation of
24 the cyclicity. And lastly, we know that dietary
25 atrazine exposure does not seem to alter the proestrus

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1 surge of LH.
2 And all these lead to the conclusion
3 that we may need to be very careful in terms of length
4 of atrazine exposure, patterns of atrazine exposure in
5 terms of diet versus gavage when we try to infer what
6 atrazine might be doing to the LH surge.
7 **DR. STEVEN HEERINGA:** Thank you very
8 much, Dr. Handa.
9 **DR. CHARLES BRECKENRIDGE:** Mr. Chairman,
10 I believe we are perhaps running a few minutes behind;
11 but we do have one more presentation that will kind of
12 wrap up and add a pharmacokinetic component, if you
13 would bear with us to go --
14 **DR. STEVEN HEERINGA:** Yes, let's go
15 ahead and do that before lunch.
16 **DR. CHARLES BRECKENRIDGE:** Okay, thank
17 you very much.
18 **DR. STEVEN HEERINGA:** Mr. Breckenridge,
19 I have a question for you. Will your full team be here
20 later this afternoon?
21 **DR. CHARLES BRECKENRIDGE:** Yes, sir,
22 we'll be here all day.
23 **DR. STEVEN HEERINGA:** Okay, because what
24 I may do is move some of the actual questioning from
25 the Panel for clarification. There is a tremendous

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1 amount of scientific information that is being put out
2 here, but
3 **DR. CHARLES BRECKENRIDGE:** Yes, sir.
4 Okay, we'll be back.
5 **DR. STEVEN HEERINGA:** please go ahead,
6 Dr. Kim.
7 **DR. DAVID KIM:** Okay. So what I'll be
8 doing is presenting some results from three studies
9 that we conducted to characterize the pharmacokinetic
10 profile of atrazine and its chlorinated metabolites.
11 These studies were done in collaboration with
12 colleagues from the Hamner Institutes for Health
13 Sciences, and specifically Dr. Harvey Clewell and Mel
14 Andersen, both of whom were involved in the study
15 design as well as the analysis of the data and will
16 continue to work with us in developing PBPK model that
17 was referenced earlier.
18 So Dr. Rodriguez yesterday presented
19 some information, some data, on analysis of internal
20 dose, primarily total radiolabeled levels after
21 atrazine exposure at high doses, and we feel that this
22 is the right approach to take because ultimately by
23 looking at internal doses, what we are able to do is
24 better characterize the dose-response relationships,
25 and as well as reducing uncertainty in our risk-

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1 assessment processes.
2 By understanding pharmacokinetics, we
3 can also explain what the internal dose is under
4 different exposure scenarios as well as use that
5 internal-dose metric profile to understand or interpret
6 toxicodynamics, which I'll be returning to later on in
7 this presentation.
8 Ultimately, all this data that I'll be
9 presenting today can be used to support PBPK model
10 development, both in terms of parameterizing the PBPK
11 model as well as optimizing the PBPK model, and
12 ultimately using that PBPK model to perform animal-to-
13 human extrapolations on.
14 And it was referenced yesterday that a
15 PBPK model would be the preferred approach; we agree,
16 and we will aim to have a PBPK model based on new data
17 that we are presenting here available by early part of
18 2011.
19 So the studies that I'm going to be
20 summarizing address several gaps in our understanding
21 of atrazine pharmacokinetics, primarily with regard to
22 low-dose kinetics, different routes of different
23 mechanisms of exposure, gavage versus dietary, as well
24 as the metabolic rate constants that can be used to
25 parameterize the PBPK model.

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1 I'll be presenting data from rat and
2 human hepatocytes; and finally partition coefficients,
3 which give us some quantitative understanding of
4 distribution of atrazine in different compartments.
5 The three studies that I mentioned are
6 as follows. The first one is an oral in vivo PK study,
7 which was conducted at WIL Research Laboratories, and
8 the analysis was done at Covance Laboratories. This
9 study dosed at three different levels by gavage and
10 dietary, female Sprague-Dawley rats, and followed the
11 internal dose over a 4-hour treatment period and 4 days
12 of washout, 4 days of treatment and 4 days of washout.
13 The second study is an in vitro
14 metabolism study where we characterize the dissipation
15 curves of atrazine formation of its mono dealkyated
16 metabolites as well as DACT formation in rat and human
17 hepatocytes, and we plan to use this data to calculate
18 clearance values.
19 Study No. 3 was conducted at University
20 of Georgia in Dr. Jeffrey Fisher's lab, where we
21 measured the distribution of atrazine in different
22 tissues, and I will present that at the end.
23 So Study No. 1, I just want to orient
24 you to this fairly complex in vivo pharmacokinetic
25 study. We had 4 days of treatment, 4 days of washout.

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1 During the treatment days we gave animals dietary and
2 gavage relative administration, 3, 10 and 50 mg/kg.
3 The comparable doses are 30 ppm, 100 ppm, 500 ppm for
4 the diet. We attained an actual daily dose of 3, 9 and
5 43 mg/kg body weight over the treatment day period.
6 The black dots here represent the
7 intensity of the sampling schedule. And what you can
8 see here is that on day 1 we have a very intense
9 sampling schedule; we measured plasma levels every the
10 time points were something like 5, 10, 15, 20, 30, 45
11 minutes, and we did that so that we could best
12 characterize the fast kinetics that we expected to
13 observe in atrazine.
14 On days 2, 3 and 4, the rest of the days
15 we collected, we relaxed the sampling schedule; but we
16 did collect a lot of data, and all this data will be
17 used for optimization and evaluation of the model.
18 In total, we collected 1,800 plasma
19 samples, and if you multiply by 4 we've got over 7200
20 data points that we can use for PBPK modeling.
21 The four compounds that we traced in
22 plasma over the time course are as follows; this is the
23 figure that was presented previously where the atrazine
24 undergoes oxidative metabolism into its mono
25 dealkylates, DEA, DIA and ultimately forming DACT. I

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1 do appreciate and acknowledge the fact that there are
2 other metabolites; but for the purpose of this study,
3 I'll be presenting results from these four compounds.
4 So this is the raw data. There's a lot
5 of data. These curves are data points; they are not
6 model simulation-fitting data. So what we view or see
7 here is on the Y axis f plasma concentrations in
8 nanogram per mil at three different dose levels -- 3
9 mg/kg, 10, 50 mg/kg -- and then for four different
10 compounds.
11 I do want to highlight that the Y axis
12 differs by dose; it increases from 8 ng/ml to about 50
13 ng/ml, and it also increases as you go from atrazine to
14 DACT, suggesting that atrazine, the bulk of the plasma
15 samples contain DACT.
16 What we observed from these kinetic
17 curves is that atrazine DEA and DIA have very similar
18 kinetic profiles; they're rapidly formed, or absorbed
19 in the case of atrazine; rapidly converted to DEA; the
20 rapid metabolism with conversion into DACT. DACT also
21 has a similar profile, but the shape of the curve is
22 slightly different because of its slower formation and
23 degradation rates.
24 We see marked differences between gavage
25 and dietary doses. The red line here represents the

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1 plasma profile from gavage; the blue line here
2 represents the plasma profiles from dietary dosing.
3 The atrazine, DEA, DIA concentrations are in the order
4 of tenfold difference between gavage and diet dosing
5 both in terms of Cmax and AUC summary dose metrics.
6 But for DACT, the difference is approximately twofold.
7 To summarize the raw data that I've
8 showed you, I have plotted here Cmax and AUC by dose
9 and we have three doses, and what I want to highlight
10 here is that four different compounds that describe --
11 there is great difference in the concentration, the
12 dose metrics, Cmax and AUC you see between atrazine,
13 DEA and DIA; and likewise for DACT, but the difference
14 is on the order of twofold difference.
15 So I am not going to dwell on this; but
16 you have this in your handouts, and for those of you
17 who are quantitative-minded, here you go. But I do
18 want to highlight that the rats prefer to form DIA --
19 so the concentrations of DIA are higher than DEA -- and
20 that DACT predominates in terms of mass.
21 So I want to turn your attention to the
22 second study that we conducted. This was an in vitro
23 hepatocyte study where we, on wells we introduced
24 atrazine at two different incubation concentrations,
25 0.5 and 1.0 micromolar, not in the presence of DMSO; so

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1 we're looking at a system that is much more
2 physiologically relevant, as opposed to using an
3 artificial vehicle to introduce atrazine into the
4 hepatocytes.
5 We collected hepatocytes at different
6 time points. We had an intense sampling schedule early
7 on, and we relaxed it because we wanted to understand
8 the kinetic processes that are occurring, because we
9 expect atrazine to change its kinetic behavior very
10 quickly early on.
11 We compared the rates of degradation of
12 atrazine and formation of the metabolites for female
13 Sprague-Dawley rats, and we also obtained human
14 hepatocytes from a single female donor to do the
15 animal-to-human comparison.
16 So here are the results. This is for
17 0.5 m atrazine incubation, 1.0 m atrazine incubation;
18 the red line here represents data from the rat, the
19 time course profile for the rat; blue for the human;
20 you got a nanogram per mil on the Y axis and time on
21 the X axis.
22 You see that rats and humans at both
23 concentrations, incubation concentrations, atrazine
24 concentrations decreased very quickly. DACT formation
25 rates are comparable between the two species, and what

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1 we find is that there is interspecies differences in
2 terms of formation of the mono dealkylates where humans
3 prefer to form DEA, and rats prefer to form DIA.
4 And the results here, I do note that the
5 results from the human metabolism study are from one
6 individual; but the results here are comparable to a
7 recent publication that is in press by Professor Ernest
8 Hotchkins from NC State University, where he looked at
9 10 different individuals, and he looked at microsomes
10 not human hepatocytes; but he did find similar patterns
11 in form as we are observing here.
12 So again, this is a summary of the
13 metabolism study; I won't do all this, let's move on.
14 But what I do want to point out is that, as I said
15 verbally, that humans prefer to form DEA; rats prefer
16 to form DIA.
17 The final study was conducted at
18 University of Georgia in Dr. Jeffrey Fisher's lab, and
19 this study aimed to quantify the ratio of atrazine in
20 tissues versus saline solution. And this experimental
21 design was modified from previous work done by Jepson,
22 et al., and others, and it was based on a solid-phase
23 microextraction technique that really gave us better
24 analytical sensitivity.
25 Here are the partition coefficients we

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1 measured. These are the ratios of the concentration in
2 the tissue of interest relative to saline solution.
3 And what I want to point out here is that the values
4 that were used in previous PBPK modeling efforts by
5 Tami McMullin are consistent with the values that we
6 determined experimentally.
7 She used a model-fitting procedure to
8 calculate partition coefficients and found that a body-
9 to-plasma ratio of1.0 or 1.1 was adequate to fit the
10 data, and a liver-to-plasma ratio of 2.3 was adequate
11 to fit her data. We have measured a liver to saline
12 concentration ratio of 3.3, and for other muscle, which
13 represents a large portion of that body weight, has a
14 ratio of 1.
15 So what are the implications for PBPK
16 modeling? I have presented to you highly resolved,
17 time-resolved data for atrazine and its chlorinated
18 metabolites, high temporal resolution and
19 differentiating with four different compounds. I've
20 also shown you data that allows us to quantify the
21 rates of disappearance of atrazine formation
22 metabolites for rats and for humans that allow us to do
23 human interspecies scaling.
24 And finally, the partition coefficient
25 experiment that we conducted verified the previous

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1 modeling work done by Tami McMullin.
2 All this information is very valuable,
3 and we will be using this information to build a PBPK
4 model that will allow us to understand the internal
5 dosimetrics following different exposure scenarios and
6 also to scale between humans and replace the default
7 approaches of scaling by body weight.
8 I want to end with a few slides, just
9 three slides, that revisit the issue of how
10 pharmacokinetics can inform toxicodynamics. And we
11 never really do pharmacokinetics alone, although
12 interesting in and of itself. The purpose of our study
13 was to inform the findings from Dr. Handa's laboratory.
14 Just to summarize what Dr. Handa found,
15 at 4 days of treatment he found that levels of LH were
16 suppressed in the high-dose group, the 50 mg/kg gavage
17 dosing group; however, he did not find any difference
18 from controls when the rats were given atrazine by
19 diet. This is consistent with the plasma profiles
20 we've generated in our study.
21 Here concentrations of atrazine, DEA,
22 DIA and DACT, during the treatment we find large
23 discrepancies in both the maximum concentration and the
24 area under the plasma curve for gavage versus dietary.
25 And I do want to note here that one of the reasons why

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1 we conducted this comparison -- and I should have
2 stated this earlier -- was that we want to compare a
3 gavage dosing at a controlled laboratory experiment
4 with distributed feeding behavior or pattern, which is
5 more realistic when we talk about human exposure
6 patterns from drinking water exposures.
7 What we observed is that during the 4
8 days of treatment we see rapid uptake of atrazine;
9 large differences between gavage and dietary; and
10 likewise for DACT.
11 We also followed the concentration of
12 atrazine and its metabolites for 4 days after cessation
13 of treatment. And this gives us insight into what Dr.
14 Handa presented with regard to peak LH levels after
15 atrazine withdrawal, and what he found was that LH
16 levels increased back to control levels, levels that
17 are comparable to controlled values, within 4 days of
18 withdrawal of atrazine.
19 And we see that atrazine concentrations
20 and its metabolites decreased very quickly, and within
21 2 days they reached levels that were below the limit of
22 quantitation; by days 3 and 4, all concentrations of
23 these four are below the limits of quantitation.
24 So I want to summarize. In summary,
25 what we've learned from these in vivo pharmacokinetic

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1 and in vitro hepatocyte metabolism studies is that,
2 one, atrazine is rapidly metabolized; it's converted
3 into DEA, DIA, and there are interspecies differences
4 there; the peak plasma concentrations from gavage and
5 diet are very different, tenfold different for
6 atrazine, DEA, DIA, twofold different for DACT.
7 Peak concentrations are similar from the
8 gavage dosing from days 1 to 4. This holds true for
9 all four compounds, suggesting that is rapid uptake and
10 rapid conversion; however, for a dietary dosing, we
11 find that it takes a while for DACT levels to reach
12 what is called the pseudo-steady state. At days 3 and
13 4, you see less oscillation of that concentration.
14 Atrazine, DEA, DIA and DACT concentrations all are
15 below the LOQ values within 2 days of withdrawal.
16 From the human hepatocyte study, I just
17 want to point out that we have quantitative information
18 that allows us to calculate rates of formation and
19 disappearance of these compounds. We have results from
20 two different species, rats and humans, and we have
21 quantified animal-to-human differences.
22 And what this data will allow us to do
23 is, like I've said, support the PBPK modeling, which we
24 aim to work on the next few months here and provide
25 that to the Agency by 2011.

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1 Thank you very much.
2 **DR. STEVEN HEERINGA:** Thank you very
3 much, Dr. Kim.
4 **DR. CHARLES BRECKENRIDGE:** Mr. Chairman,
5 I appreciate the rapidity with which Dr. Kim was
6 speaking, and he was brought us quite up to the 12:30
7 mark.
8 We have one wrap-up to do, and we can
9 probably do that after; it would take about 15
10 minutes, so it's your call.
11 **DR. STEVEN HEERINGA:** And then we also
12 have the water.
13 **DR. CHARLES BRECKENRIDGE:** That is
14 correct, sir, so we are running a little bit behind.
15 **DR. STEVEN HEERINGA:** Okay. So let me
16 propose this. Let's take 45 minutes for lunch today,
17 and we will reconvene at 1:15. We will hear the wrap-
18 up from the Syngenta public commenters and also the
19 presentation on water sampling.
20 At that point in time, I'm going to move
21 on to the other public commenters, just to make sure
22 that it's going to be a long day, and that we will hold
23 comments for the Syngenta team. Again, a tremendous
24 amount of information here, I'm sure there's a lot of
25 interest. And I want to focus the time, but I also

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1 want to make sure that the other public presenters
2 aren't doing this at 8:00 o'clock tonight.
3 So we'll handle it. It might mean that
4 Dr. Breckenridge is going to do it; I don't believe
5 we'll be there. So that's the proposal at this point,
6 so let's rejoin at 1:15 and we'll finish up with the
7 presentations from the Syngenta team, and then we'll
8 move on to the other public commenters.
9 Thank you.
10 **(WHEREUPON,** a luncheon recess was taken.)
11 **DR. STEVEN HEERINGA:** Welcome back,
12 everyone. We are in the process of the period of
13 public comment for this FIFRA SAP meeting, and we have
14 heard a number of the component presentations from
15 Syngenta scientists and we have a few more
16 presentations to wrap up here.
17 And Dr. McFarland, if you would like to
18 introduce that, we'll try to move it along on time;
19 but, thank you.
20 **DR. JANIS MCFARLAND:** Thank you very
21 much.
22 We're happy to have Dr. Jim Simpkins
23 from the University of North Texas, who is going to
24 give the wrap-up in the toxicology section, and then
25 we'll follow right after that with Dr. Hendley covering

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1 the water monitoring.
2 And Dr. Hendley, there are some other
3 water experts that will be available for questions
4 later at the time, if the Panel has them.
5 **DR. STEVEN HEERINGA:** Thank you very
6 much.
7 Dr. Simpkins.
8 **DR. JIM SIMPKINS:** I'm Jim Simpkins,
9 Professor of Pharmacology and Neuroscience at the
10 University of North Texas Health Science Center. I've
11 been involved with the atrazine team since the early
12 '90s in an advisory capacity.
13 My charge today is to try to relate key
14 early events with adverse reproductive effects, and I
15 would like to start by pointing out that LH suppression
16 is not an adverse effect; it's a key early event that
17 may help us explain a variety of adverse reproductive
18 effects that may be occurring in animal models.
19 Those adverse events are depicted in
20 this slide in females only; that is, female rodents.
21 Effects on LH surge can lead to a change in fertility
22 by affecting ovulation and a variety of processes
23 related to ovulation.
24 In addition to that, changes in
25 pulsatile LH secretion can manifest themselves in

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1 females as a delay in vaginal opening, their surrogate
2 marker for puberty, or in adults in hypogonadism; in
3 males, the same kinds of changes and pulsatile LH
4 secretion result in a decline in testosterone
5 production that delays preputial separation, their
6 surrogate marker for puberty, and in adulthood reduce
7 sperm count and then a decline in weights of androgen-
8 dependent tissues. So those are the kinds of adverse
9 events that we will be looking at.
10 The pre-ovulatory LH surge depicted here
11 is driven by estrogens from the follicle and results in
12 a number of processes that could be affected if the
13 pre-ovulatory LH surge is affected.
14 Included in that is a pre-ovulatory
15 increase in progesterone, final maturation of the
16 oocyte, ovulation of the follicle or of the oocyte and
17 then formation of the corpus luteum, which maintains
18 progesterone secretion during the luteal phase of the
19 menstrual cycle.
20 In males, pulsatile GnRH secretion
21 drives, as Dr. Plant points out, pulsatile LH
22 secretion, and then that regulates secretion of
23 testosterone from the Leydig cells of the testis. A
24 reduction in pulse, amplitude or frequency can result
25 in a reduction in serum testosterone, a change in

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1 intratesticular testosterone and a resulting reduction
2 in the weights of androgen-dependent tissues.
3 Now, we searched the literature trying
4 to find scientific documentation of what Dr. Legan
5 mentioned yesterday, and that is the very large excess
6 capacity of the pre-ovulatory LH surge. And I will
7 present to you a few examples to put a context on the
8 statement that she made yesterday.
9 Here is an example of an in vitro
10 perfusion system of the ovary where the question being
11 asked is: What is the amount or the percentage of the
12 pre-ovulatory LH surge needed to produce full
13 progesterone production?
14 And in this study, Dr. Paluzzi
15 demonstrated that only about a third of that LH surge
16 is required to produce progesterone secretion that's
17 absolutely normal for this system.
18 In addition to that, these are work from
19 Dr. Ishikawa showing that in the barbiturate-blocked
20 rat -- and these are normally cycling rats in which the
21 pre-ovulatory LH surge is blocked with phenobarbital,
22 or pentobarbital in this case.
23 And then he doses with luteinizing
24 hormone and asks the question: What's the percent of
25 animals dosed that ovulate, and how many ova do they

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1 ovulate? What he was able to show is that a very short
2 LH surge induced by administration of exogenous LH is
3 needed for full ovulation and a full complement of ova.
4 I will point out to you the surge that
5 he is inducing with his injection of LH lasts much less
6 than an hour; the normal rodent pre-ovulatory LH surge
7 goes 4 to 6 hours, so full ovulation with a very
8 transient LH surge.
9 Dr. Phyllis Wise has demonstrated very
10 eloquently that as rodents, in this case Sprague-Dawley
11 rats, approach middle age, 8 to 10 months, the
12 amplitude of their pre-ovulatory LH surge is decreased
13 by half, and this was associated with disrupted estrus
14 in these middle-aged female Sprague-Dawley rats.
15 Another way to get at this excess
16 capacity of the LH surge is to look at biological
17 variability in normal pre-ovulatory surges, and we have
18 here two of many examples. This happens to be a study
19 in pigs, in which each of these animals displayed a
20 pre-ovulatory LH surge, each of them ovulated, became
21 pregnant and had a normal pregnancy and delivery.
22 So this is for that animal a normal LH
23 surge, and what you notice is the animal that has the
24 lowest surge versus the animal with the highest surge,
25 there is a fourfold difference in the amplitude of that

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1 surge.
2 All of them are successful surges, so
3 there is extreme excess capacity. These are the
4 results from a study that was cited several times
5 yesterday. This is Dr. Cooper's 2010 dataset. These
6 are the control-dosed animals, and what's depicted here
7 are the values: this is peak amplitude for the LH
8 surge, and this is fraction of the animals that are
9 showing that peak amplitude. And what we see is that
10 animals that have a surge of 8 ng/mL and animals that
11 have surges of 32 ng/mL, this is a fourfold difference
12 between the low and the high.
13 All these animals show evidence of pre-
14 ovulatory LH surge, progesterone secretion, uterus
15 weight increase; so these are having normal surges. So
16 there appears to be at least a fourfold excess of LH
17 that's being secreted in both of these examples.
18 Now, this is a summary of all that
19 information, simply indicating that there is excess
20 reserve on that pre-ovulatory LH surge.
21 Now I will bring you back to the data
22 that Dr. Handa presented earlier today, and this is
23 simply a re-presentation of the effects of bolus
24 exposure of animals to atrazine in response to gavage
25 administration for 4 days during their normal estrus

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1 cycle versus a distributed dose of atrazine, again over
2 4 days in normal estrus cycles.
3 And what he reported was high-dose
4 gavage administration of 50 mg/kg causes a significant
5 decline in peak amplitude and also area under the LH
6 curve, whereas an equivalent dose given in the diet,
7 and therefore a distributed dose, does not affect LH
8 secretion.
9 Now, a prediction from these data is
10 that gavage administration of atrazine ought to result
11 in high-dose reproductive toxicity but not lower doses,
12 and that distributed dose administration of equivalent
13 amounts of atrazine should be without reproductive
14 toxicity effects. And the next few slides that I will
15 show you I think demonstrate that point.
16 In female rats, what we have done is
17 taken a number of studies -- and I won't point them out
18 individually, but rather just talk about the patterns -
19 - taken a number of studies; in this case, this is the
20 Handa gavage LH data with a high-dose effect, nothing
21 at lower doses; and a variety of vaginal opening
22 studies -- I think five or six are depicted here -- and
23 we've put tick marks in green where there was no
24 treatment effect or pluses in red where there is a
25 treatment effect.

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1 And those are associated with the dose
2 of atrazine given by gavage, and the treatment period
3 is about 2 weeks in all these studies.
4 What you notice is that gavage
5 treatment, as predicted based upon the Handa gavage LH
6 data, results in high-dose reproductive effects
7 expressed as delays in vaginal opening, which is going
8 to be in contrast to the data that I show you in the
9 next slide, where dietary or distributed dose atrazine
10 was administered.
11 This is a two-generation reproductive
12 study conducted some time ago where the 0 generation
13 was exposed to atrazine 0, 10, 50 or 500 ppm, which
14 relate to the doses in the bottom left of highest 40
15 mg/kg; so about that dose that showed up in the Handa
16 study.
17 Animals were treated for 10 weeks, males
18 and females both, and then they were put together,
19 allowed to breed and the fertility index was calculated
20 -- that is, the number of breeders -- and the ratio of
21 successful pregnancies to breeders was determined.
22 And then gestation happened with
23 continued dosing. Pups were born, the number of pups
24 were counted, and then the F0 generation continued
25 treatment during lactation. The F1 generation then was

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1 treated, and went through the same procedure to look
2 for F1 fertility effects and number of live births
3 versus the number of pups.
4 Shown here again are the results of that
5 study. This is the Handa distributed dose or dietary
6 LH data with no effect on LH, and there was absolutely
7 no effect on F0 or F1 fertility index or on number of
8 pups born to those matings, suggesting that this
9 distributed dose was without reproductive toxicity.
10 Similar kinds of studies have been done
11 in male rats; regrettably, we don't have distributed
12 dose or feeding studies that have been done. So the
13 gavage studies, this is a Trentacoste published report
14 showing that with gavage treatment with atrazine --
15 these are from postnatal day 22 to postnatal day 47 --
16 there is a high-dose suppression of LH secretion;
17 similarly, high-dose suppressions in both serum
18 testosterone and intratesticular testosterone.
19 And then at the same doses that
20 testosterone levels were affected, weights of androgen-
21 dependent tissues were also less.
22 This is a series of studies also in
23 males using gavage -- and this is Tammy Stoker's data -
24 - that assess a number of atrazine and three
25 metabolites, DIA, DEA and DACT, which shows no effect

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1 on LH secretion. Although in each of these studies LH
2 was trending down, it simply was not significant,
3 largely because of variation in the data.
4 But what was observed with gavage
5 administration was significant effects on preputial
6 separation beyond puberty with atrazine and with all
7 three of the metabolites of atrazine.
8 A subsequent study was done because NOEL
9 was established in this study: 6.25 mg/kg/d had no
10 effect on preputial separation with any of the
11 compounds. And this is the dose of atrazine that's
12 used for acute LH suppression regulation.
13 Now, the summary of these data are here.
14 It does indeed appear that there is a large reserve in
15 the pre-ovulatory LH surge in a number of species. It
16 also is true that bolus dosing with atrazine shows
17 high-dose reproductive toxicity that is not evident
18 with distributed or diet dosing with atrazine.
19 Now, let me just finish by summarizing what you heard
20 late this morning and since lunch.
21 It appears, as Dr. Plant has pointed
22 out, that the rodent is not a good model for human risk
23 assessment related to events coupled to the
24 pre-ovulatory LH surge: the morphology is different,
25 the regulation is different; however, pulsatile LH

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1 secretion in all species may be relevant.
2 In addition to that, we need to identify
3 the key events that result in reproductive toxicity.
4 LH secretory events are clearly key events,
5 particularly pulsatile LH secretion. And I think we
6 need to strive for what was achieved in the cancer
7 assessment of atrazine, and that is that effects of
8 atrazine on LH secretion were preceding and related to
9 effects of atrazine on estrus cycle, which preceded the
10 appearance of tumors in those animals.
11 Third, there is a remarkable difference
12 in internal dosing that's seen with gavage
13 administration versus dietary administration of
14 atrazine, and we need to be aware of that in doing our
15 assessments. And it's noted that dietary
16 administration simply doesn't show reproductive
17 toxicity.
18 And then finally, PBPK modeling is going
19 to be critical for establishing internal doses that
20 allow us then to do comparison between rodents and
21 humans for exposure to atrazine.
22 I thank you.
23 **DR. STEVEN HEERINGA:** Thank you very
24 much; Dr. Simpkins' presentation, and I believe there
25 is one final presentation.

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1 **DR. PAUL HENDLEY:** Okay, if we can have
2 the slides, please.
3 While that's coming up, my name is Paul
4 Hendley. I'm a Senior Syngenta Fellow with Syngenta.
5 My colleagues from Syngenta are with me in the
6 audience, as is Dr. Harbourt from Waterborne
7 Environmental.
8 What I'm hoping we're going to be able
9 to see by the end of the presentation is four key
10 things. We're going to show that the magnitude of
11 atrazine residues are defined with high confidence, as
12 well as the distribution of those residues.
13 We're going to see that community water
14 systems can be characterized; they're highly site-
15 specific, each one is individual. We think there are
16 some additional approaches to defining chemograph shape
17 that are important to actually help us understand the
18 questions before the Panel.
19 There's also a couple of models about
20 SEAWAVE and the PRZM hybrid approach that are really
21 going to be very suitable to address the Question 4.3,
22 and they should be reviewed and refined.
23 Four key areas of the presentation: the atrazine
24 monitoring database; how to characterize community
25 water systems and their watersheds in order to consider

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1 program design; ways of thinking about chemograph shape
2 analysis in regard to sampling programs; and the
3 question of how do you extrapolate from 7-day data to
4 shorter-term averaging periods.
5 We'll start with the atrazine monitoring
6 database. And this is a slide showed in the April SAP.
7 It talks about the exceptional scope of the atrazine
8 surface water monitoring data.
9 Essentially, you can consider surface
10 water in two pools, the drinking water and the non-
11 drinking water. There's about 180,000 to 190,000
12 atrazine samples in the non-drinking water part, which
13 looks at water bodies, streams, rivers, lakes, the raw
14 water from the community water systems; it include USGS
15 programs, Syngenta programs, State programs and many
16 others.
17 In the drinking water area, we're
18 talking about finished water, and that's better
19 characterized if we consider three key elements: the
20 Safe Drinking Water Act, where over 4,400 community
21 water systems have contributed samples to the database.
22 There are finished-water-only samples,
23 and that makes up about 50,000 samples from that source
24 in the database recorded since 1993, typically recorded
25 at 4 samples a year.

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1 The Syngenta Voluntary Monitoring
2 Program, which ran from 1993 to 2003, looked at
3 community water systems with an atrazine history, and
4 over 130 or so community water systems were involved.
5 The key point here, raw or unfinished samples taken,
6 about 45,000 samples in the pool.
7 Since 2003, a mandated program, the
8 Atrazine Monitoring Program, has included every
9 community water system since 1997 to the present whose
10 annual average SDWA measurements exceed 1.6 ppb in
11 atrazine.
12 So everything up to 2003 and beyond has
13 been included that's been roughly over half the MCL --
14 again, very frequent monitoring focused on the growing
15 season, both raw and finished samples, and probably
16 27,000 raw and 27,000 finished.
17 This exciting table of statistics summarizes those
18 results.
19 They are in your record, we won't dwell
20 on them. The key point to think about here, this is
21 high frequency monitoring data. You can see some
22 unsurprising results: raw water residues are higher
23 than finished, for example.
24 But the key point here is that the
25 sample sizes are so large, and both for the entire pool

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1 and also for the sub-pools of static community water
2 systems and flowing community water systems, that the
3 confidence around what we know about the high centiles
4 and also, of course, in the light of the questions that
5 Dr. Portier asked yesterday about the distribution of
6 those residues, the entire distribution.
7 So the confidence we have on that is
8 extremely high. We understand the magnitude of peaks
9 that occur in the Midwest and the distribution of them,
10 as well.
11 The database is also valuable to
12 understand the sort of comments that Dr. Coupe made
13 yesterday about the trends with time. For example, the
14 data show us that the measured annual averages have
15 declined since 1994, and we explained last time that
16 was largely due to stewardship, best management
17 practices and label changes, with the good work done by
18 the farmers.
19 Importantly for what the Panel is
20 addressing, there are daily datasets. There are three
21 that all revolve around flowing water. There is a
22 community water system in Missouri that takes water
23 from the Missouri River that has good high sample
24 frequency.
25 You heard about the Heidelberg College

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1 data. The only thing I'd add to what Nelson said about
2 that is it's very relevant, because in fact 4 of the 44
3 community water systems highlighted in the whitepaper
4 actually draw their water from within those watersheds.
5 And in addition to that, we have the
6 Syngenta Eco Monitoring Program. Of course, as we
7 discussed last time, the size of those watersheds is
8 smaller than almost every community water system; but
9 they are a very good worst-case model to consider,
10 because they are so small because of the spikiness of
11 the residue pattern.
12 And of course, we're accumulating more
13 data all the time; since last April, we've got another
14 30 site years of daily data.
15 There is a dataset I think the Panel
16 needs to consider. It's a static water high frequency
17 dataset. It is a USGS dataset at Perry Lake in Kansas.
18 It's 1100 square miles, it's a big watershed in a big
19 lake. The daily sampling was done in the '90s.
20 It was about 5,000 samples were taken
21 over a 3-year period. The key thing here, these were
22 composite water samples; they were daily when something
23 interesting was happening hydrologically. It wasn't
24 every day; but the quality of the data is comparable to
25 Heidelberg, which is similarly not precisely daily

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1 sampling.
2 USGS did a bootstrap analysis along with
3 EPA on this, and they came to the conclusion that
4 looking at sampling at different interval frequencies,
5 reasonable measures of the actual high centile values
6 could be determined using a monthly sampling frequency,
7 and I have included a relevant table in your printout.
8 They did also some very cool stuff about the way the
9 plumes move through the reservoirs, and unfortunately
10 we don't have time to dwell on that.
11 So let's consider characterizing
12 community water systems. And Syngenta is accumulating
13 site-specific data to help us understand the
14 vulnerability and understand these systems.
15 There are two things to think about. The first one is:
16 what's the primary water system for a community water
17 system unit? If you are going to understand what the
18 residue patterns look like, you need to know that.
19 Surprisingly, it is not as simple as it
20 sounds. For those 44 community water systems
21 highlighted in the whitepaper, if you look at the
22 Government data, there are 73 potential sources of
23 water. So it requires careful data-mining and
24 interviewing and talking to the people who are involved
25 at the ground level to really understand what's going

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1 on at these locations.
2 And some of this can be complex, as I
3 showed last time. In some cases, you may collect the
4 water from a watershed, a creek; but they may store the
5 water in large reservoirs, which is subject for
6 dilution. So you really need to understand the true
7 role with a supply point, as well as the source
8 watershed.
9 The history of data-gathering in the AMP
10 and the VMP Program tell us an awful lot about these
11 site-specific phenomena. Among the 44 sites
12 highlighted in the white paper, it's a fairly good mix:
13 about 16 statics, 19 flowing, 3 very interesting
14 hydrologic ones in Louisiana where the hydrology is a
15 little unusual; and 6 of these pumped and stored
16 systems.
17 So the other thing you need to
18 understand is the watershed environment. And the good
19 news here is we've been doing a lot of work because of
20 the Atrazine Ecological Monitoring Program, and we have
21 a lot of data to help us through understanding the
22 environmental characteristics of the watershed.
23 In addition to what we've gathered for Eco, we've
24 delineated the watersheds for the community water
25 systems.

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1 We collect, of course, all the AMP
2 water-quality data and a lot of information from USGS
3 on flow information, et cetera, in addition to the very
4 high resolution, cropping, soils and PRZM modeling for
5 atrazine that's done for every soil in the country.
6 And we've shown you before the very high resolution
7 subfield scale: in fact, 10-meter grids, these 78
8 billion points across the U.S.A.
9 So what we will talk about now is the
10 chemograph shape analysis. And that phrase has been
11 used and mentioned, so we'll talk about it in a little
12 bit more detail. Our goal is to find, identify
13 community water systems that are possibly vulnerable to
14 short-tern atrazine peaks and identify where
15 appropriate sampling regimes apply.
16 There are various technical options for
17 that: you can look at empirical data; you can do some
18 theoretical calculations; there's existing flashiness
19 indices; and there's various models.
20 We talked about some of the empirical
21 datasets; typically, they are the daily ones. The
22 thing I would like to highlight here is that the
23 Heidelberg College and the Eco Monitoring Program have
24 not only chemistry data; they have flow data available
25 for the same periods, and I'm going to sort of show why

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1 that's important in a moment. NAWQA has some good
2 data, and also we've got tools for looking at local
3 rainfall with NEXRAD.
4 So if we are going to talk about what
5 does a chemograph shape look like, if you're going to
6 define that, we believe you need to think about the
7 number of peaks that exceed some threshold of X, how
8 long that threshold is exceeded, how big the peak gets
9 while it's exceeding the threshold and, in some
10 circumstances, you'd be interested in the interval to
11 the next peak.
12 And interestingly, under the ECOFRAM
13 process for ecological risk assessment that was set up
14 in the late '90s, software was designed specifically
15 for that purpose. And we have applied that software to
16 look at the Eco and the Heidelberg data with a range of
17 atrazine concentrations.
18 I'm going to show you an example with
19 one range: 15 parts ppb. And what you can see here is
20 that there are some Eco sites, then Heidelberg sites.
21 We have the number of years it was operating. We have
22 the area of the watershed, which goes from very small
23 to pretty large. And what this column says is 20
24 events exceeded 15 ppb at this site: 9 of those exceed
25 for 2 days, 4 of those exceeded for 3 days, and 1 for 7

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1 days.
2 For Rock Creek, there were 90 events
3 across 25 years, which is approximately 3.5 event a
4 year; but of those, about a third continued for 7 days
5 and continued to exceed for 7 days. The very largest
6 watershed had roughly 2.5 exceedances a year of the 15
7 ppb thresholds, but half of those continued for over 7
8 days.
9 So what we're seeing is that the
10 atrazine peaks are infrequent. The numbers of events
11 exceeding the threshold for 7 days or more increased
12 with watershed area, and we couldn't really distinguish
13 between the Eco scale and the small scale of
14 Heidelberg. And other data show that the magnitudes
15 are reduced for larger watersheds. That data shows
16 some very interesting data that supports the comment on
17 magnitude.
18 We don't have time to dwell on this; but
19 we did precisely the same analysis using the 80th
20 centile of flow as a threshold, and what that showed
21 again is the two largest watersheds, about 15%, 11% to
22 15% of their flow events exceeding that threshold
23 lasted longer than 7 days, whereas for the smaller
24 watersheds only 2% of the events had an extended
25 period.

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1 In other words, what these analyses has
2 showed is that both the chemical peak behavior and the
3 flow behavior for the Heidelberg and the Eco watersheds
4 to some extent show similar relationships between
5 duration and the watershed area. This isn't new; it
6 was reported by Baker in 2000. What that means is we
7 have a new tool available to us for considering peak
8 shape by using flow data.
9 Other approaches on chemograph shape,
10 flashiness indices have been published in the past;
11 Richards and Baker have them, there's a number of
12 others out there in the hydrology literature. All we
13 really need to draw from that is that the concept of
14 flashiness based on area has been exemplified in quite
15 a lot of cases as a way of looking at the question.
16 There are models. We have had a look at
17 them. We feel to be useful to understand chemograph
18 shape will require refinement in many ways to get it
19 down to a daily temporal scale and to a small watershed
20 scale. We don't think it's ideal for this purpose.
21 PRZM and SWAT are much cleverer models,
22 and they predict edge-of-field quite well; but PRZM has
23 been shown to over-predict drinking-water
24 concentrations, publications by Jackson, et al. And
25 SWAT does a much better job on hydrology, but both of

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1 their models require an awful lot of work, including
2 flow data, to parameterize the models.
3 So what we suggest is that empirical
4 analysis by the daily monitoring data or flow data,
5 which is much more commonly available than chemical
6 monitoring, is probably an efficient way of getting
7 into considering chemograph shape.
8 So the chemograph shapes differ
9 fundamentally between static and flowing water bodies.
10 We have shown that missing a peak in static water
11 bodies with 7-day sampling from Lake Perry is unlikely.
12 But some static water bodies can be overtopped by a
13 bigger event.
14 If so much water comes through that
15 there's multiple pond volumes, it will behave
16 ultimately like a flowing water body, and in your
17 handout there are some theoretical calculations that
18 show for different sized ponds where this occurs. Our
19 point is, if you look at static water bodies, you need
20 to treat one individually to see is it going to behave
21 like a static water body, or is it going to behave like
22 a flowing one.
23 And why does this matter? Why it
24 matters is, we tried to come up with a general
25 flowchart to help people think, pegs for thought, if

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1 you like, for thinking about chemograph shape. And
2 it's a preliminary guide, it won't replace detailed
3 individual understanding, and you will still have to
4 think about vulnerability in terms of environmental
5 vulnerability, the scale of the watershed and atrazine
6 use.
7 But imagine if you have a pool of
8 community water systems. You can say first which ones
9 are static by identifying the primary water source. Of
10 those, which are going to behave like true statics, and
11 which have the potential to behave like flowing water
12 bodies.
13 The true statics can be investigated on
14 the basis of size, and in fact we've already got the
15 data from Perry Lake validating the large series.
16 There's this odd category of the ones that store the
17 water in reservoirs, they are a separate group case-by-
18 case.
19 But for the flowing ones, we have a
20 concept or, if you like, a continuum: you've got area
21 going from very small to the whole of Mississippi;
22 you've got vulnerability towards flashiness going this
23 way, so it gets flashier as it gets smaller; and you
24 can place on this different types of hydrology, you can
25 place the daily datasets we have so we can think about

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1 the main context and put the results we get from the
2 data analysis of those to create an understanding
3 across the scale.
4 Here is the community water system, here
5 is the big Heidelberg and the small ones. EPA's
6 smallest flowing one is about here from that 44, and
7 their largest is here.
8 And imagine that we know something about
9 the 7-day peak width of this Maumee Reservoir. With
10 data-mining -- and this is an example -- you can put a
11 divider that says: on this side of the line, we know
12 7-day sampling is more than adequate; on this side,
13 what you need to do is a case-by-case analysis to think
14 about where the sampling and what regimes are
15 appropriate. And obviously, this requires data-mining
16 based on the available data.
17 Finally, the last question is about
18 extrapolating from 7-day sampling to shorter-term
19 averaging periods: two approaches, modeling and using
20 the existing daily data. PRZM hybrid approach was
21 presented to an SAP in 2007.
22 We won't dwell on the modeling; the
23 modeling essentially is parameterized to scenarios that
24 mean the edge-of-field predictions match what goes on
25 in a particular watershed for the community water

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1 system: you use local weather data for the year you
2 are looking at the peaks concerned and you have a rule-
3 based system, and the rule-based system takes your
4 measured values and your model values and it says, "Do
5 I have a measured value today?
6 If so, I'll use it. If I don't, was it
7 an event today? And if it wasn't an event, I will use
8 that number and add it to the science areas. If there
9 was no event, I interpolate the value for that day".
10 The important thing for that is it gives primacy to
11 measured values, it resets the estimates to reality,
12 and it will always increase the average concentrations.
13 So the other models, there is PRZM
14 modeling for atrazine everywhere. The USGS SEAWAVE
15 model appears to offer a lot of potential. It's very
16 thorough. It's based on some really solid research and
17 data from USGS. It requires flow data for calibration,
18 probably won't work for statics; but it does appear to
19 have a lot more potential because of the weight of
20 evidence behind it and some of the kriging approaches.
21 So our recommendation would be that we
22 need to fine-tune both PRZM hybrid and SEAWAVE for the
23 purpose required at the moment for EPA's current
24 purpose. But whatever model is used, the daily
25 datasets should be used with bootstrapping to really

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1 validate the approaches.
2 So I won't talk through this slide; we
3 did talk about conversion factors in great detail at
4 the April SAP. I apologize for those who weren't
5 there.
6 And I'll move to the key points. The
7 magnitude of atrazine residues are defined with high
8 confidence. We can confidently predict the highest
9 centiles and also address the question that the
10 probability of distribution for any peaks, whether they
11 are sampled or not sampled; we understand those very
12 well because of the size of the database. We have very
13 valuable daily data that can help us validate new
14 approaches.
15 A community water system
16 characterization requires accurate data-mining, because
17 each one is individual. It's critical to understand
18 the primary water sources and how water is handled.
19 But watershed vulnerability we're working on on two
20 fronts, and we're learning all the time between EPA and
21 ourselves.
22 There are some more approaches to think
23 about when you consider chemograph shape. There's
24 actually a software tool to do it, and we think that
25 daily flow data can supplement the chemical data to

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1 actually help understand the chemograph shape.
2 There's a flowchart that helps provide a
3 way of looking at the questions before the Panel, and
4 we would recommend that division into flowing and
5 static primary sources and watershed size is a good way
6 to start thinking.
7 PRZM hybrid and SEAWAVE approaches
8 should be refined for the purpose but appear to offer
9 great potential, and the daily datasets with their
10 bootstrap approach can come up with conversion factors
11 if needed, but probably most importantly as a tool to
12 validate any new models we develop.
13 And thank you for your time. And Mr.
14 Chairman, just for your information, if the questions
15 do come up, we do have some data addressing Dr.
16 Krishnan's question yesterday about TCT that we can
17 present, if asked.
18 **DR. STEVEN HEERINGA:** Thank you very
19 much, Dr. Hendley.
20 And again, as I indicated this morning,
21 in the interest of keeping our public comment on a
22 schedule, we will defer questions from the Panel to the
23 end of the public comment period, and I'll make sure
24 that everybody has an opportunity to present during the
25 afternoon here.

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1 **DR. JANIS MCFARLAND:** Thank you very
2 much.
3 **DR. STEVEN HEERINGA:** Thank you very
4 much, Dr. McFarland.
5 A lot of information, a lot of data
6 presented, and I think the Panel will take a little
7 time to absorb this; so hopefully, we'll get a chance
8 to study this, too.
9 At this point in time, I would like to
10 invite up our second public commenter, which is Dr.
11 Tyrone Hayes, and he is on behalf of and representing
12 himself and "other various scientists" is the way it's
13 listed, and I'll let him identify his colleagues.
14 Is Dr. Hayes' presentation loaded?
15 You're welcome.
16 Be sure to turn the microphone on, too,
17 Dr. Hayes.
18 **DR. TYRONE HAYES:** Okay. First of all,
19 I'd like to thank the Panel for the opportunity. My
20 name is Tyrone, and what I'm going to do today first of
21 all is talk a little bit about my ongoing research that
22 looks at reproductive effects of atrazine on
23 amphibians.
24 But then I've recently been joined by 39
25 scientists from 12 countries on 6 continents, and we've

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1 done an extensive review of the available literature on
2 the reproductive effects of atrazine across vertebrate
3 classes.
4 Three of those coauthors aren't listed
5 here, because I wasn't sure about the approval with
6 their Agencies for presenting this work; but perhaps
7 those names can be added later.
8 First of all, as a matter of disclosure,
9 I want to make clear where my funding sources have been
10 for my research on atrazine and for this work and, in
11 particular, point out that a little over ten years ago
12 I was funded by Novartis/Syngenta/EcoRisk; and to my
13 knowledge, at least two of my coauthors, Krista McCoy
14 and Frances Orton, were also either funded for or
15 funded by or worked in a laboratory that was funded by
16 Novartis/Syngenta.
17 The primary work that I've done on
18 atrazine has been on the African clawed frog, Xenopus
19 laevis. And a few years ago, actually initially while
20 working with Novartis and then Syngenta, we showed that
21 atrazine inhibited growth of the voice box or the
22 larynx in males that were exposed throughout the larval
23 period, which is roughly 2 months under the conditions
24 that we used.
25 This inhibition of growth of the larynx

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1 was an indication that the animals were demasculinized
2 or that their testosterone, the so-called male hormone,
3 was diminished or depleted. And we later on went on to
4 show that, in fact, when we dissected the animals, a
5 proportion, depending on the dose -- actually,
6 depending on the dose and the population -- but a
7 proportion developed gonadal abnormalities, including
8 hermaphroditism, such as the example shown here of an
9 animal that has at least three testis and three
10 separate ovaries.
11 We proposed at that time that the
12 mechanism of atrazine, a mechanism which had been
13 identified previously in other animals, was that
14 atrazine induced or upregulated aromatase, resulting in
15 the conversion of testosterone into estrogen,
16 ultimately resulting in the demasculinization effects,
17 such as the growth in the larynx, and the feminization
18 effects, such as the development of the ovaries in what
19 we presumed to be genetic males.
20 We showed in our original publication
21 that in fact when adult male African clawed frogs were
22 exposed to atrazine, there was a significant reduction
23 in blood levels of testosterone such that exposed males
24 had testosterone levels that were not statistically
25 different from unexposed females.

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1 And we published that work in a paper,
2 "Hermaphroditic, demasculinized frogs after exposure to
3 the herbicide atrazine at low ecologically relevant
4 doses". That was published in Proceedings of the
5 National Academy of Sciences, and in fact I presented
6 some of those data in the 2003 SAP on amphibians.
7 That paper left two questions
8 unanswered: one, were the hermaphrodites males with
9 ovaries or females with testis, which sounds like a
10 silly question except that African clawed frogs, like
11 most amphibians, don't have morphologically
12 distinguishable sex chromosomes.
13 So we didn't have the answer to that
14 question. They still don't, but we have some answers
15 now. And we also didn't know what happened to the
16 animals when they became adults, if they were
17 functionally affected or if, for example,
18 hermaphrodites went on to become females or if they
19 went on to become males or if they maintained
20 themselves as hermaphrodites.
21 Figuring those answers out, however, was
22 a project that would take 3 to 4 years, because that's
23 about how long it takes to get them to reproductive
24 maturity. We conducted that project and published it
25 recently, again in Proceedings of the National Academy

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1 of Sciences.
2 And among other things by the time we
3 got to publishing the paper, there are genetic markers
4 now that are available for identifying males and
5 females. So, for example, females express a gene
6 called DM-W that is only present on the W of a female
7 chromosome. In this particular population in the study
8 we just published, we found that a portion of the
9 males, once they reached adulthood, even though they
10 were genetic male, 10% of them turned into females.
11 So this is one example, and they really
12 turned into females. So these males, genetic males,
13 are capable of producing viable eggs and performing
14 just like a female would.
15 We went on in this paper to test the
16 remaining 90% of the animals that did not turn into
17 females. And in those cases we looked at a number of
18 things, such as their ability to mate with females,
19 which was significantly reduced.
20 We also showed that their fertility was
21 severely reduced. So control males normally will
22 fertilize upwards of 80% of a female's eggs -- each
23 female lays about 2,000 eggs -- whereas our atrazine-
24 treated animals have fertility rates that are as low as
25 15%, some 0, in part because they don't show

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1 reproductive behavior, but also in part because their
2 testis don't develop properly.
3 So, for example, this is a control --
4 and the room is a little light, so it's more difficult
5 to see -- but actually it's probably pretty obvious the
6 differences between the control and atrazine-treated
7 animals.
8 What you'll notice -- and I'll blow up
9 this section for you -- is that in the controls, the
10 testicular tubules -- I'm outlining one for you here
11 and one for you there -- are filled with all of these
12 dark areas, are the sperm that are developing inside
13 the testicular tubules, whereas if you look in the
14 atrazine-treated animals the majority of their tubules
15 are empty and just filled with cellular debris.
16 So there are maybe three tubules there
17 with observable sperm; but most of the tubules are, as
18 you can see, empty like these. So even if the animals
19 displayed the behavior, the fertility is low because of
20 an absence of sperm, most likely because of an absence
21 or a severe decline in testosterone, which we also
22 measured and showed in this paper.
23 Again, that was published in Proceedings
24 of the National Academy of Sciences just this year:
25 "Atrazine induces complete feminization and chemical

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1 castration in male African clawed frogs (Xenopus
2 laevis)".
3 The next two slides are some ongoing
4 work that is not yet published, but we're nearing
5 publication. In that, in repeating these experiments
6 that we just published, we were housing animals
7 together to repeat controls compared for animals with
8 animals treated with atrazine, and our attempts were to
9 look at differences between lineages, or families, if
10 you will, because we found that there are some
11 sensitivity differences between lineages of animals.
12 What we've now found is that there is a frequency of --
13 and here, I'll show you some more -- something that
14 I've never seen before: males actually copulating with
15 other males. So these aren't males that have turned
16 into females; these are genetic males -- well, I'll
17 show you that -- that still had testis, but they
18 behaved like females.
19 So just to show you how we have
20 characterized that for one group of animals I'm showing
21 you now, so this is one tub of 40 animals. My students
22 working on this project will just go down each day and
23 count the number of homosexual pairs, the number of
24 copulating males. So here is one day, here is the next
25 day, here is the next day. Ah, so sometimes it happens

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1 in controls.
2 And now, again, there are differences
3 between lineages. So some families have a background
4 of this behavior, and some don't. Of those families
5 that have some background, the incidence of male-male
6 copulations is greatly increased, significantly
7 increased when the animals are exposed to atrazine.
8 The other thing we've discovered is that
9 in these control groups, we've marked the animals with
10 electronic IDs. These are just random pairs of animals
11 that occasionally end up together in these tubs of 40
12 animals. In these atrazine-treated tanks, for example,
13 there are 40 animals in this tank. The ones that are
14 on the bottom are always the same. So there are about
15 12 males that always perform as the female.
16 Now, one other thing that may come to
17 your mind is that maybe it's larger males -- you know,
18 there are no females in the tank, so maybe it's larger
19 male subduing smaller males in the tank -- and in fact
20 that's not the case. So if you look at body weight for
21 these pairs -- and this is just one day, we grabbed all
22 the pairs out -- there are the animals that were on
23 top, and here are the animals that they were paired
24 with. The ones that are on the bottom are always
25 larger, which is interesting because females are

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1 typically larger than males in this species.
2 What's also interesting is if you take
3 blood samples from those animals, the ones that are on
4 the top have higher testosterone levels than their
5 counterparts on the bottom. But probably more
6 significantly, the ones on the top have no estrogen or
7 non-detectable estrogen in their blood, but the ones on
8 the bottom express estrogen levels that are not typical
9 of a female; but the estrogen-to-testosterone ratio is
10 typical of what you'd find in a female.
11 So in essence, we think what's happened
12 is these particular animals that didn't turn into
13 females made enough estrogen that their brains and
14 their behaviors were feminized; so they think, if you
15 will, that they're females. What's more is for some of
16 the animals when we dissect them -- and I'm sorry the
17 room is not darker -- these are testis, so these are
18 males, and all this is oviduct. So this is the
19 equivalent of a male with hypertrophied uterus,
20 something that I'd never seen in this species before.
21 So, again, we think what we've
22 identified now is within a population some males are
23 completely susceptible and make enough estrogen that
24 they completely turn into females, whereas other
25 genetic males are partially susceptible, they make

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1 enough estrogen to make vitellogenin -- in fact we've
2 shown -- to grow oviducts and did the female-typical
3 behaviors.
4 So to give you an idea of some of the
5 other work that we've done in this area, we have asked
6 whether or not these effects occur in other species of
7 frogs; so, in other words, we have asked questions like
8 whether or not this was a laboratory artifact.
9 In looking at North American leopard
10 frogs -- this was work that we published in Nature a
11 few years ago -- we showed again this partial
12 feminization as well; so this is the testis of an
13 animal exposed to atrazine in the lab, and these are
14 yolked eggs that are growing in this animal's testis
15 and bursting through the surface of the testis, an
16 effect that we've never seen in control animals in the
17 laboratory.
18 We've also asked questions like whether
19 or not the effects occur in the wild. And again we
20 have been able to show, if I can just show you the
21 histological section here; so I pulled out a section,
22 I'll blow it up and blow it up. We've identified
23 testicular oocytes in field-collected animals. And
24 we've also shown, in a paper we published in Nature
25 again, that these feminized males with eggs in their

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1 testis are 100% of the time associated with atrazine
2 contamination.
3 And just following up on that, we've
4 done an extensive 10-year study now where we followed
5 the North Platte, the Missouri, the Mississippi River
6 and some other sites of interest. The red shows the
7 areas of highest atrazine use based on sales.
8 And I've done this work in collaboration
9 with the U.S. Geological Survey, and we have three
10 papers in preparation now, including one that follows a
11 large pond that we were able to contaminate
12 experimentally and follow the population being
13 feminized and then recovering after the atrazine
14 degraded them and moved on, so to speak.
15 Now, that's all I want to say about my work and about
16 frogs.
17 But before I move on to the larger body
18 of work, I do want to do one sort of self-serving
19 thing. I want to set the record straight on one thing.
20 This is a quote actually from Alex Avery; but I've seen
21 it in many, many, many places, talking about my work:
22 " given the fact that Hayes refuses to share his
23 data," he wrote, " as EPA most recently confirmed in a
24 May 17, 2010 letter from Donald Brady, Director of
25 EPA..."

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1 This statement is not based in fact. In
2 fact, to my knowledge, I've never had any
3 communications with Donald Brady, and I certainly have
4 never refused to share data or make data available.
5 In fact, in 2003, or 2002 just before I
6 attended the SAP in 2003, Tom Steeger, who was in
7 charge of that SAP, wrote to me: "Tyrone, although
8 you're not required to provide EPA with any information
9 you have been very cooperative and have shared both the
10 raw data and standard operating procedures from your
11 research.
12 Additionally, you have spent a
13 (significant) amount of time helping the office of
14 pesticide(s) program(s) to understand the significance
15 of your data, and you have provided insightful reviews
16 of similar research efforts."
17 In fact, Tom Steeger spent 3 days in my
18 laboratory examining my samples.
19 Nearly a year later, a reporter from the New York Times
20 asked via email: "but one thing I am curious about is
21 whether or not Tyrone did provide the raw data." And
22 Tom Steeger, again a year later, replied: "
23 Tyrone did provide the EPA his data and standard
24 operating procedures. He has been very cooperative
25 with the Agency."

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1 So I'm not sure really where that
2 statement comes from; but I have been bothered by it,
3 and I wanted to set that record straight. Since 2003,
4 EPA has asked me for no SOPs and no raw data and no
5 other information. So I've never refused to share
6 anything. I am not really sure how or why that got
7 perpetuated.
8 What's more, what I want to point out is
9 that since, before and during my paper, a number of
10 authors had published work showing adverse reproductive
11 effects in frogs. And I want to read to you some of
12 the titles.
13 The first is "Response of the Amphibian
14 Tadpole Xenopus laevis to Atrazine During Sexual
15 Differentiation of the Ovary". The next one is "Form
16 and Prevalence of Intersexuality and Effects of
17 Environmental Contaminants on Sexuality in Cricket
18 Frogs".
19 The next one is "Effects of Nitrate and
20 Atrazine on Larval Development and Sexual
21 Differentiation in the Northern Leopard Frog";
22 "Atrazine concentrations, gonadal gross morphology and
23 histology in ranid frogs"; "Potential endocrine
24 disruption of sexual development in free ranging male
25 northern leopard frogs"; and as recently as 2010, "Low

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1 Levels of Herbicide Atrazine Alter Sex Ratios and
2 Reduce Metamorphic Success in Rana pipiens Tadpoles
3 Raised in Outdoor Mesocosms".
4 So my work is not the only work that's
5 shown; in fact, we weren't the first to show that
6 atrazine adversely affects reproductive development and
7 feminizes frogs. You can see that there are multiple
8 independent laboratories that in everything from
9 wildlife observations to mesocosms to laboratory
10 experiments, and at least four species have shown these
11 effects.
12 So while nobody has repeated my work
13 directly, similar and consistent effects have been
14 shown across independent laboratories in studies. I
15 quote Sir Austin Bradford Hill here, who in 1965, the
16 author of the so-called Bradford-Hill criteria for
17 establishing cause and effect, wrote: "I would myself
18 put a good deal of weight upon similar results reached
19 in quite different ways".
20 And that's what has happened with
21 atrazine in looking at the effects on amphibian sex
22 development.
23 What's more is Glenn Fox wrote in Eco-
24 Epidemiology: "The occurrence of an association in
25 more than one species and species population is very

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1 strong evidence for causation."
2 What I've just told you is that the
3 reproductive effects, the impact on sexual
4 differentiation by atrazine, has been shown not just in
5 multiple species of frogs but in multiple genera and
6 multiple families, including the Acridae the Hylidae,
7 the Bufonidae and the Ranidae; so at least five
8 families, not just species.
9 What's more is, I'm going to show you
10 briefly that my 39 colleagues and I have reviewed the
11 literature and shown consistent effects in fish and
12 reptiles; there are effects in birds, but they're not
13 strong effects and they require higher doses; and also
14 in mammals.
15 First off, I'd like to show you the
16 evidence that atrazine decreases testosterone and sperm
17 production, and this is after reviewing over 250 peer-
18 reviewed published papers in the open literature. So
19 here's testosterone decreased, in this case in goldfish
20 and here's a salmon. And these are ecologically
21 relevant doses, and you see a dose-dependent decrease
22 in testosterone levels in salmon.
23 So what we have seen now is that this
24 effect that I described to you in frogs of testosterone
25 decreasing not only occurs across species and genera

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1 and family, but it occurs across vertebrate classes.
2 So multiple independent laboratories in every
3 vertebrate class examined has shown that atrazine
4 decreases the male hormone testosterone.
5 What's more is if you look at Moore and
6 Waring's work on salmon -- and this is work that's done
7 in England -- the decrease in plasma testosterone seen
8 in salmon is associated with a decrease in the
9 expressible milk or sperm in response to female salmon.
10 So the same effect that we saw in frogs -- testosterone
11 decreases, sperm decreases, fertility decreases --
12 we're now seeing that same type of effect in fish by an
13 independent laboratory on another continent, in fact.
14 What's more is while putting this paper
15 together with my colleagues, even though I thought I
16 knew the atrazine literature very well, we discovered
17 something quite interesting.
18 So here's what I just showed you that we
19 just published. Here is a testes that's packed with
20 sperm. Here's a testes with dilated testicular tubules
21 and just cellular debris. That's the African clawed
22 frog work that I just showed you -- and this effect, by
23 the way, was produced at 2.5 ppb, animals exposed
24 throughout life.
25 This is work from my coauthor, Kestemont

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1 in Belgium, showing a very similar effect, in this case
2 in fish testis, where you're losing tissue and getting
3 empty spaces developing in the testis.
4 This is from my colleague in South
5 America working on caiman, so a type of crocodile,
6 where again you see densely packed sperm in the testis;
7 but when they're exposed to atrazine, you see these
8 dilated testicular tubules with a complete absence of
9 sperm.
10 And then finally multiple laboratories -
11 - this is one from Europe and one that's in Brazil, and
12 again coauthors on the paper we're working on -- showed
13 in rats, mammals, the same thing: sperm in the testis
14 unless they're exposed to atrazine.
15 So here you have an almost identical effect occurring
16 across vertebrate classes: from fish, amphibians,
17 reptiles and mammals.
18 What's more is we've shown in our most
19 recent paper that other androgen-dependent features are
20 absent or decreased in the atrazine-exposed frogs; so
21 the breeding glands, which you can see visibly or
22 histologically, are reduced in size. These are
23 androgen-dependent, and in the presence of atrazine the
24 decreased testosterone, you get a decrease in these
25 androgen-dependent glands.

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1 You see the larynx, so this is from our
2 paper again in African clawed frogs. You see a
3 decrease and an approach to a female-type larynx in
4 these animals exposed to atrazine.
5 This is from my colleague in South
6 America, again who's joined me on the paper, and here
7 he is measuring the clitoral penis length in caiman, or
8 crocodiles, that have been exposed to atrazine.
9 And again, you see this decrease in the
10 size of the androgen-dependent structure so that it's
11 intermediate between what you would find in an exposed
12 male and female; so again, consistent effects on
13 androgen-dependent secondary sex characteristics
14 following atrazine exposure, leading to this loss in
15 testosterone production and the destruction of
16 testicular tissue.
17 This is some work that was published on
18 rats showing a decrease in androgen, again in response
19 to atrazine. This is an independent study by Friedman,
20 et al., in 2002 showing a similar decrease.
21 And multiple papers have shown that
22 androgens are decreased in rats exposed to atrazine by
23 a variety of different mechanisms. And that literature
24 is all there, which I can make available for you.
25 This is unpublished data from Victor-

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1 Costa, one of my coauthors on this upcoming paper, and
2 what they're showing here is that atrazine exposure
3 causes a decrease in weight in the rats, and so there
4 is some debate about whether or not the smaller testis
5 was a result of the animal just being decreased in
6 size; but in this particular experiment, they've
7 allowed a recovery period free of atrazine.
8 So you can see the body weight recovers,
9 but the testis size -- and you can see what the testis
10 looks like there -- the testis size does not recover.
11 So it's not just a matter of the animals having a
12 decreased body weight, and that's why you see the
13 smaller testis; there's a direct sort of toxic effect
14 on the testis in these animals.
15 Here's other data from all the way back
16 in 2000 showing a decline in sperm number in rats that
17 are exposed to atrazine. So again, that is consistent
18 with the demasculinization or the loss of androgens in
19 atrazine-exposed animals.
20 Shanna Swan showed that in humans in
21 Columbia, Missouri that there is a statistically
22 significant relationship between the amount of atrazine
23 in the urine and low sperm count, low fertility and
24 inability of what she called sub-fertile men to get
25 their wives pregnant.

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1 Now, again, correlation does not equal
2 causation; but my point is that when you look at the
3 loss of testosterone, the loss of sperm and decreased
4 fertility that we've seen in fish, in frogs,
5 amphibians, in reptiles and in laboratory rodents, that
6 makes me think that there's probably a little something
7 to this finding that we should look at more carefully.
8 What I've done now is change the axes,
9 because what you're looking at now are the atrazine
10 levels in men in California who apply atrazine in a
11 paper published in 1993.
12 What you're looking at now are the
13 levels of atrazine for men who apply atrazine; so this
14 was just the field workers, these are the men who
15 actually apply it. These men have 24,000 times the
16 atrazine in their urine than is associated with low
17 fertility in men in Columbia, Missouri.
18 Of course, I usually tell my public
19 audiences when I speak these men have 24,000 times the
20 atrazine that we use to chemically castrate and make
21 hermaphrodite frogs. I could dilute their urine 24,000
22 times and use it to chemically castrate 24,000 buckets
23 of 30 tadpoles each.
24 I am particularly concerned, of course,
25 because most of the men who work in agriculture in

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1 California are Latino, 90%, some with life expectancies
2 of 50; so nobody knows anything about the reproductive
3 health of these men.
4 I'm particularly concerned, because if
5 you look at California, where we have the fifth largest
6 economy in the world, or at least reportedly, 1 in 10
7 jobs are in agriculture, 30% of the land is in
8 agriculture, we produce 350 agricultural products, 50%
9 of the U.S.'s food comes from California. We use more
10 pesticides than any other state, and 90% of the workers
11 are Hispanic.
12 If you look at the top 10 counties for
13 agriculture, the top 10 counties from pesticide use,
14 these are effectively the counties that make us the
15 fifth largest economy in the world. But if you plot
16 onto that the 30 poorest towns in California, look
17 where most of them fall -- and there's one in the
18 eleventh biggest agriculture count.
19 So the people who make us the fifth
20 largest economy in the world have the jobs and the
21 healthcare disparities, likely in part because they're
22 exposed to hazards -- not just atrazine, but other
23 pesticides as well. It becomes an environmental
24 justice issue, in my opinion.
25 So the other half of the equation --

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1 does atrazine turn on aromatase and induce estrogen,
2 which causes egg-yolk production and egg production in
3 frogs, and might that be associated with other things
4 that we worry about in mammals -- Suzawa and Ingraham
5 showed in 2008 that zebrafish exposed to atrazine
6 express aromatase and make estrogen in a dose-dependent
7 manner.
8 We have now been able to show, because
9 now we can identify genetic males and females in frogs,
10 that females express aromatase in their gonads, and
11 part of the reason why we were never able to find this
12 before is because if you look at the atrazine-exposed
13 animals, the genetic males that are still males don't
14 express aromatase; but the genetic males that are
15 either feminized or partially feminized express
16 aromatase as if they're real females, even though, as
17 you can see, that's a genetic male that's expressing
18 aromatase.
19 And I've showed you that they have
20 circulating estrogen levels, but only those that are
21 showing the feminized behavior.
22 Sanderson, et al., in a number of papers
23 show that if you take an adenocarcinoma cell and expose
24 it to atrazine, it will start expressing aromatase and
25 making estrogen. Similar work has been shown by Fan,

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1 et al.
2 This was a work that I coauthored in
3 another human cell line that if exposed to atrazine,
4 they express aromatase and make estrogen in a dose-
5 dependent manner. And Suzawa and Ingraham showed in a
6 number of other human cancer cell lines that they
7 express aromatase when exposed to atrazine as well.
8 So we're seeing an induction of
9 aromatase by atrazine across vertebrate classes: in
10 fish, in frogs, in reptiles, and now in mammals
11 including human cell lines.
12 The other interesting thing that we've
13 been able to show -- again, this has been in getting
14 this big paper together with my colleagues -- is that
15 here's my amphibians. These are leopard frogs with
16 testicular oocytes expressing eggs in their testis, an
17 effect that we never see in controls.
18 Now, people have given me a hard time
19 about using the word "never"; but here is my colleague,
20 Tillit, who did not coauthor the paper for us but
21 provided a figure. This is now in fish; so exposed to
22 atrazine, testicular oocytes developed in his recently
23 published study, and he never saw it in controls.
24 And now here's a colleague who joined me
25 on the paper, de Solla, who showed in turtles, now

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1 reptiles, testicular oocytes develop only when the
2 animals are exposed to atrazine; so again, similar
3 effects across vertebrates and, in this case, an effect
4 that you wouldn't expect to see in mammals, because a
5 mammal's gonads are sort of protected, if you will, by
6 the Y-chromosome in a very strong genetic mechanism.
7 And again, we've shown complete sex
8 reversal in genetic males exposed to atrazine, as I
9 pointed out earlier. And other colleagues -- and this
10 is from a second paper that we've all published
11 together now, 19 of us -- Suzawa and Ingraham showed a
12 dose-dependent loss of males in zebrafish exposed to
13 atrazine.
14 My colleagues, Oka and Iguchi, showed a
15 dose-dependent loss in males at ecologically relevant
16 doses; so you get more and more females as you're
17 exposed to atrazine. That's also been shown in
18 reptiles. de Solla showed that a male-determining
19 temperature in snapping turtles, you expose them to
20 atrazine and you start to get females when they should
21 all be male.
22 And another study in reptiles and
23 painted turtles shows the same thing at two different
24 temperatures: you increase the proportion of females
25 when animals are exposed to atrazine across the

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1 eggshell; so again, partial feminization and complete
2 feminization across multiple vertebrate classes.
3 In the case of prostate cancer, there
4 are at least studies that show that atrazine, when fed
5 to the mothers, will increase the incidence of
6 prostatitis and the severity of prostatitis when the
7 mother is exposed to atrazine.
8 You may know about the study that was
9 done in St. Gabriel, Louisiana at Syngenta, and I want
10 to read to you some things that were written in that
11 paper with regards to prostate cancer. They wrote:
12 "The increase in all cancers combined seen in the
13 overall study group was concentrated in the company
14 employee group." They wrote: "The increase in
15 prostate cancer in male subjects was concentrated in
16 company employees." They wrote: "The prostate cancer
17 increase was further concentrated in actively working
18 company employees." They wrote: "All but one of the
19 cases occurred in men with 10 or more years since
20 hire."
21 And finally: "Analyses restricted to
22 company employees also found that the prostate cancer
23 increase was limited to men under 60 years of age."
24 And again, correlation doesn't equal causation; but
25 when you have a model experimental system that would

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1 support atrazine as a possible cause, it would raise
2 concern for me.
3 That increase was 8.4-fold and concerns
4 me, because it's in an area known as Cancer Alley where
5 much of the neighborhood, so to speak, looks like this:
6 80% African-American.
7 With regards to breast or mammary
8 cancer, I was interested today to hear that
9 testosterone doesn't go down in rats, because that's
10 been shown before in other studies, and that E1 and E2
11 don't go up, because E2 and E1 definitely went up in at
12 least some studies in the published literature; so
13 there's an increase in estrogen just like we've seen in
14 fish, frogs, reptiles, now we're on to rodents.
15 I'm sure you know some studies have
16 shown an increase in the incidence of mammary tumors in
17 rats, and at least one study by Ueda showed that
18 "Atrazine treatment tended to increase the proportion
19 of estrogen receptor positive tumors and stimulated
20 cell proliferation in the DMBA-tumor(+) group". So
21 there's a mechanism there, an important mechanism.
22 A single study that I know of showed
23 with a P value less than 0.0001 that women whose well
24 water is contaminated with atrazine are more likely to
25 develop breast cancer. And again, there's a mechanism

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1 by which that might occur, because we know that at
2 least in some human cell lines, atrazine increases
3 aromatase expression and estrogen production.
4 And I'm finishing up here on this one.
5 In fact, Fan, et al., a paper that I coauthored, show
6 that atrazine acts on phosphodiesterase to increase
7 cycle gain P, leading to upregulation of aromatase.
8 That was shown by Sanderson, et al., before; but Fan,
9 et al., in two papers suggested that atrazine also
10 increases SF-1, another important transcription factor
11 binding in the nucleus.
12 Suzawa and Ingraham have interpreted
13 this differently and think that there are other
14 upstream genes that are turned on that lead to the
15 increase in SF-1 content.
16 My current graduate student has shown
17 that in breast cancer cells, some cell lines, atrazine
18 upregulates aromatase. And that's a significant
19 concern, because the local expression of aromatase is
20 very important in breast cancer.
21 Local expression of aromatase and
22 estrogen production may promote or will promote already
23 damaged cells; so while atrazine might not be a
24 carcinogen itself, by increasing aromatase expression
25 it potentially could lead to this increase in estrogen

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1 receptor positive tumors.
2 In fact, as you may know, the treatment
3 of choice right now for breast cancer is letrozole,
4 which blocks aromatase to decrease estrogen to prevent
5 those damaged cells from growing and spreading. It
6 doesn't make much sense when we're using 80 million
7 pounds a year of a chemical that does the opposite,
8 that turns on aromatase and increases estrogen in every
9 vertebrate class examined.
10 And I know that the Registrant gets
11 upset when I point this out, but Novartis Oncology
12 offers treatments for cancers that range from breast
13 cancer.
14 I can't imagine that there wasn't some
15 conversation when in January of 2000 a paper was
16 published that included one of Syngenta's funded
17 scientists, John Giesy, where he wrote: "The observed
18 induction of aromatase, the rate-limiting enzyme in
19 the conversion of androgens to estrogen, may be an
20 underlying explanation for some of the reported
21 hormonal disrupting and tumor-promoting properties of
22 these herbicides in vivo".
23 I didn't write that; that was work that
24 was done by one of the Syngenta scientists, Sanderson,
25 et al.

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1 Then in that same year in July 2000, a
2 marketing application for first-line letrozole
3 treatment of postmenopausal women was applied for by
4 Novartis. And then in November of 2000, that same
5 year, as you can see here, by November of 2000 Syngenta
6 simply does not manufacture or sell pharmaceutical
7 products.
8 And I'm not implying that there's any
9 kind of sinister plot or anything like that; but we
10 have this interesting chronological relationship where
11 in January of 2000 they discovered that atrazine
12 induces aromatase and potentially promotes breast
13 cancer; in July 2000, they at least apply for an
14 aromatase blocker to treat breast cancer; in November
15 2000, they stop selling atrazine, and then Syngenta
16 starts. I guess all I'm saying is it should be as easy
17 to get an aromatase inducer off the market as it is to
18 get an aromatase blocker on the market.
19 I want to end by pointing out, well, one
20 of the reasons that I feel passionate about this issue,
21 and one of the reasons that I point out is that 90% of
22 agricultural workers are Mexican/Mexican-Americans and
23 that the company that manufactures atrazine is in a
24 community that's 80% African-American.
25 These are the top 13 cancers that we get

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1 in this country. The ones in red now, 11 of the 13,
2 are the ones that African-Americans are more likely to
3 get relative to Caucasian-Americans. What I am going
4 to show you now, out of these 13, the ones that
5 African-Americans are more likely to die from relative
6 to Caucasian-Americans.
7 Is there a biological difference, or is
8 it that African-Americans are more likely to live in
9 communities where they come into contact with these
10 kind of environmental hazards?
11 Is it a biological difference, or is it
12 more likely that African-Americans and Hispanic-
13 Americans are more likely to work in occupations where
14 we come in contact with these hazards that are having
15 consistent effects in everything from fish all the way
16 up to human cell lines?
17 I think that my work on this aquatic
18 organism is indeed telling me something about this one,
19 and I think what we should be learning is that we
20 should use more sensitive model systems if we want to
21 protect the most vulnerable. Frogs may be more
22 sensitive because they live in the water and they have
23 permeable skin; but by using amphibian data, then you
24 protect the animals that are less sensitive and less
25 vulnerable.

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1 And in the same case, I think we need to
2 focus on more vulnerable components of our own species:
3 the unborn fetus and the minorities who live in and
4 work in areas where they are more likely to be exposed
5 to chemicals that are having, in this case, consistent
6 effects across vertebrate classes.
7 I didn't go into it because I knew Dr.
8 Fenton would go into it, but there are many other
9 effects in rats. There's the immune failure effects,
10 the prostate/mammary cancer effects that have already
11 been described. Atrazine causes neural damage when
12 pregnant mothers are exposed, and there are several
13 papers showing that. Atrazine has been shown to induce
14 abortion in rats that are exposed when they're
15 pregnant. Atrazine has been shown to cause prostate
16 disease in the pups when the mothers are exposed.
17 And as you just heard, atrazine impairs
18 mammary development, Dr. Fenton's work, which it's
19 interesting that there are studies that would suggest
20 now that there are no mammary problems, because if
21 that's the case, then why is it that in the second
22 generation you get impaired growth and development
23 because the mother that has been exposed is incapable
24 of making enough milk to support their offspring?
25 In fact, this is one of the studies that

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1 concerns me the most and that moves me the most,
2 because this particular animal, if I understand the
3 study correctly, was never exposed to atrazine. This
4 particular animal suffers from atrazine that his
5 grandmother was exposed to.
6 When I think about my little daughter,
7 and when I think about the fact that studies in Europe
8 now are showing that even after 10 years that atrazine
9 levels have not changed in the aquifers and in the
10 groundwater, that means that not only have we already
11 been exposed; our children will be exposed, our
12 grandchildren will be exposed.
13 And so when I think that there's even a
14 remote possibility that studies are suggesting to me
15 that my granddaughter's granddaughter could suffer from
16 atrazine that we are applying today, and we sat here
17 and didn't do something to prevent that from happening,
18 it moves me.
19 Sir Austin Bradford Hill also wrote:
20 "All scientific work is incomplete, whether it be
21 observational or experimental. All scientific work is
22 liable to be upset or modified by advancing knowledge.
23 That does not confer upon us a freedom to ignore the
24 knowledge we already have or to postpone the action
25 that it appears to demand at a given time."

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1 The data is stacking up: amphibians,
2 fish, reptiles, rodents, human epidemiology and cell
3 studies. It's getting pretty complete. And I would
4 suggest that it's time for action.
5 Thank you.
6 **DR. STEVEN HEERINGA:** Thank you very
7 much, Dr. Hayes, and I especially appreciate your
8 sticking to the allotted time. It's appreciated by the
9 Panel.
10 At this point in time, I'd like to move
11 to the next scheduled public commenter, who is Rod
12 Snyder, who is Director of the National Corn Growers
13 Association.
14 Rod? Rod Snyder here?
15 I guess he's not here. Let me move on,
16 then. We'll return if Mr. Snyder shows up.
17 The next scheduled public commenter,
18 according to scheduling arranged by the SAP Office, is
19 Jere White, who is the Executive Director of the Kansas
20 Corn Growers Association and the Kansas Grain & Sorghum
21 Producers Association. And I think Jere there -- I
22 recognize you -- is representing on behalf of the
23 Triazine Network, and the handouts are on their way to
24 the Panel members.
25 Mr. White, welcome.

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1 **MR. JERE WHITE:** Thank you, Chairman
2 Heeringa and members of the Committee. My name is Jere
3 White. I am the Executive Director of the Kansas Grain
4 & Sorghum Producers Association; also the Kansas Corn
5 Growers Association in central Kansas in a small
6 community called Garnett.
7 With me here today as part of our
8 Network panel is Dr. James Lamb, John Hall, Gary
9 Marshall from the Missouri Corn Growers Association and
10 Dr. David Bridges, and I'll start out our comments.
11 A little bit about the Triazine Network,
12 and certainly I have had the opportunity to meet a lot
13 of you in previous SAPs. I think we've been certainly
14 present at every SAP since 1994 dealing with atrazine
15 and always look forward to the experience.
16 We do believe that it is the SAP that
17 helps sort things out scientifically in the end, and
18 that's really what we're all about. The Network is
19 just simply a coalition, it's not a formal entity, and
20 we represent commodities including certainly corn and
21 grain sorghum but also citrus, tree fruit, vegetables,
22 grapes, sugarcane -- over 30 commodities grown in over
23 40 states.
24 We also represent general farm groups,
25 including Farm Bureaus at the State level, Farmers

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1 Union, American Agri-Women, a number of different
2 stakeholders and, of course, individual producers. We
3 were formed in 1995 to secure a scientifically based
4 outcome to what was in the EPA Special Review of the
5 triazine herbicides.
6 And in that capacity, we serve as sort
7 of a liaison between growers and the Agency and other
8 Agencies and also with the Registrant. So we take our
9 issues all directions and certainly have a vested
10 interest in doing so and continue to do so at this day.
11 A quick review of what I'd call triazine
12 in the new millennium, although obviously the
13 millennium isn't so new now.
14 June 27th, 2000 SAP, overseen by Clinton
15 EPA Administrator Carol Browner, eventually found that
16 atrazine is not likely to cause cancer in humans.
17 The Re-Review concluded on October 31st
18 in 2003, again in this case conducted principally under
19 Bush EPA Administrator Whitman, found a reasonable
20 certainty of no harm.
21 A Cumulative Risk Assessment on June 22,
22 2006 also found a reasonable certainty of no harm
23 associated with the use of atrazine in accordance with
24 EPA guidelines.
25 2003 SAP proceeding focused on the

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1 reports of atrazine's effects on amphibian reproductive
2 development and found that evidence submitted provided
3 an insufficient basis for any definite judgment.
4 And finally in 2007, EPA concluded that
5 it was reasonable to reject the 2003 hypothesis that
6 atrazine exposure can affect amphibian gonadal
7 development. The EPA also determined that there was no
8 compelling reason to pursue additional testing.
9 Let's move forward a little bit, July of
10 2009. If you were to go to the EPA website in 2009,
11 you would find -- and again, this was six months into
12 the current Administration -- that EPA reports to the
13 public that based on review of available scientific
14 studies, EPA has determined that atrazine is not likely
15 to cause cancer in humans.
16 This determination was based upon "the
17 best scientifically available data" and allowed
18 preeminent independent scientists, such as yourselves,
19 to ensure that the Agency was using the highest quality
20 data in its decision-making process. And for that, we
21 thank you.
22 Then things started to change. In
23 August of 2009, we were in a phase of what I would
24 characterize as the machinery beginning to turn. It
25 started with an NRDC report that focused on the

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1 activists' claims -- and certainly, I don't think that
2 the folks that were quoted and drivers of a lot of the
3 information in that report would deny that they were
4 activists; in some ways, we're all activists. It was
5 seeded to the New York Times.
6 NRDC takes credit on their website of
7 seeding the stories that New York Times ran, and
8 subsequently picked up or almost simultaneously picked
9 up by the Huffington Post.
10 Yet in that time, the activity of trial
11 lawyers -- and I couldn't find a good graphic for trial
12 lawyers, so I just used a skunk because it was
13 convenient
14 (Laughter.)
15 **MR. JERE WHITE:** --and you have all the
16 same churning and feeding off each other, and obviously
17 the EPA was under a lot of pressure.
18 Dr. Hayes just gave comments before the
19 Committee; but I'd like to share an email that he
20 shared with members of Syngenta's team the day before
21 the April SAP, and this is a quote from that.
22 He confirmed they'd entered Phase 5 --
23 and I'm not sure what that means, but I guess that's
24 where we're at. "Our destination will surprise you --
25 we enter our final approach." He chose the

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1 destination, he set the course, he paved the way, he
2 set the pace, and most importantly, he directed the
3 traffic.
4 Make no mistake about it. He did this.
5 Now, I don't necessarily agree, I don't even know what
6 the heck it means; but perhaps we'll sort that out in a
7 future SAP.
8 I would know that a lot of the things
9 that Dr. Hayes shared with you were the subject of
10 previous SAPs, by Panels very much like those that
11 you're part of today. In fact, some of you likely were
12 part of those Panels.
13 And even though some people might try to
14 suggest that somehow a Bush SAP was different than a
15 Clinton SAP, which is different than an Obama SAP, from
16 where we've sat over these years, the SAP was simply a
17 group of scientists trying to do the best they could
18 with the information that was made available to them.
19 I trust you're the same as they were under previous
20 Administrations; and again, we respect and applaud you
21 for your work in that area.
22 Then in October of 2009, EPA began to
23 respond to this machinery that I referenced earlier.
24 They announced a comprehensive scientific review with
25 four SAPs in FY10 -- and this in fact is the fourth SAP

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1 -- and two more announced in 2011.
2 I would point out, I guess based on the
3 previous presentation, it's good that one of those is
4 dedicated to amphibians, and the other is dedicated to
5 ag health. And certainly, we've made the point before
6 and I stand by it and my growers stand by it that if
7 there's a legitimate issue at the farm level, it's
8 certainly a legitimate issue for the people that I
9 represent and pay my way to be here.
10 We care about these things. We're
11 affected by it personally; my family has been affected
12 by some of these things. We don't take it lightly.
13 Upon consideration of the studies, EPA
14 referenced to initiate the new review of atrazine. So
15 if you go back to last October and you look at what
16 they said was driving it -- the media reports and some
17 of the studies that were there -- the fact is that the
18 February SAP dealt with the majority of those studies
19 and concluded that the overall quality of these studies
20 was relatively low, thus limiting their applicability.
21 But then if you take it a step further,
22 had the Agency followed its own process, typically in
23 the past before providing the information to other SAPs
24 to consider, it would have known that the new studies
25 were not useful on the regulatory decision-making

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1 process.
2 We believe that. There was a rush to
3 create a reaction to what was happening in the media,
4 and the reality is as we look at it at the end of the
5 process or towards the end of the process, at least for
6 the first year, it's good that we've done that because
7 you have addressed those issues, and in fact we're
8 moving on.
9 But what about this transparent process?
10 If you go back to the last SAP, Dr. Lowit at the tail
11 end of the Agency remarks made a comment that said that
12 they had been directed to form a small army with a very
13 large task in a very short timeframe.
14 When my constituents see that, quite
15 frankly, they don't understand. It's been part of a
16 special review since 1994. We didn't see the immediacy
17 of it. In fact, the work plan that's been laid out
18 does not suggest any immediacy.
19 The Agency has also testified before
20 Congress that the new review is being used in its
21 preparation for the scheduled 2013 re-registration of
22 atrazine. It's on a very long list of products, and in
23 fact if you look at, which I did just last night, the
24 Pesticide Registration Review Status, neither atrazine
25 nor triazines are listed as currently active.

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1 So where does this process fit? We're
2 not sure, but the Agency maintains that what it's doing
3 today is certainly not part of special review. Special
4 review is not concluded, but this isn't part of it.
5 The actions of a rush re-review process do not align
6 with the Agency's position on a re-registration process
7 that is still three years away.
8 We'd also say that if you look at this
9 specific SAP, we've had an extremely short timeframe
10 between the posting of questions on the Docket or on
11 the website and this meeting, and if you look at the
12 actual posting, which I believe occurred on a Friday --
13 the date escapes me -- the written responses were due
14 into the Docket the following Tuesday.
15 I'm not sure how that works for a
16 transparent and open process that invites all
17 stakeholders to participate. Thank God I'm sitting in
18 my seat and not in your seat. I can't imagine that you
19 don't feel very challenged to respond to the huge
20 volume of science that typically covers very different
21 disciplines.
22 I also want to share my final comments
23 that growers and others that have provided comments to
24 the SAP in the past in support of atrazine are now
25 being targeted by these trial lawyers -- that skunk

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1 from the previous slide -- through subpoenas for
2 massive records unrelated to any litigation that's
3 ongoing.
4 And in fact, among the group's
5 testifying before you today, three of those ag groups
6 have been served subpoenas since Friday. It's clear,
7 sending a message; we think it's very clear: if you
8 stand up for atrazine, you best be prepared to pay a
9 price.
10 And again, I did a slide yesterday
11 afternoon, I guess it was; it's out of date. One more
12 of the ag groups testifying today have been subpoenaed
13 since then.
14 And it's not just about what do you know
15 about something to do with the case. It has to do
16 with, for instance, any membership record between
17 Kansas Corn Growers and National Corn Growers. Doesn't
18 have anything to do with atrazine. Doesn't have
19 anything to do with any case in Holiday Shores.
20 But again, it is a burden that's being
21 placed on people that think they want to get into the
22 arena as a stakeholder on behalf of their constituents
23 in agriculture and on behalf of this product, and it is
24 obscene.
25 Finally, on behalf of the grower

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1 community that I represent, we do want to thank the
2 members of the SAP for your time and your effort. It's
3 been a long process. Ran into Dr. Fenner-Crisp in the
4 hallway the other day, and we commented that we've been
5 doing this a long time: her in different capacities, I
6 guess me in the same capacity.
7 It's been a tough job, there is still
8 work to do; but I can assure you that besides the
9 intimidation that agricultural organizations are
10 getting right now, beyond that, we'll see you next
11 time. We will be back.
12 With that, I'd like to turn it over to
13 the next presenter in our group, which is Dr. James
14 Lamb, and I'll let --
15 **DR. STEVEN HEERINGA:** Mr. White?
16 **MR. JERE WHITE:** Yes, sir.
17 **DR. STEVEN HEERINGA:** I wonder if I
18 could suggest something.
19 **MR. JERE WHITE:** Sure.
20 **DR. STEVEN HEERINGA:** People have been
21 sitting since a quarter after 1:00. I wonder, would
22 you be willing to take a 15-minute break and then come
23 back and do the three presentations?
24 **MR. JERE WHITE:** Absolutely.
25 **DR. STEVEN HEERINGA:** It's a little

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1 discontinuous, but you can pick up there and
2 **MR. JERE WHITE:** Yeah, we'll have four;
3 but, yes.
4 **DR. STEVEN HEERINGA:** so people won't
5 be fidgeting and leaving.
6 **MR. JERE WHITE:** That will be fine.
7 **DR. STEVEN HEERINGA:** So why don't we do
8 that, and we'll reconvene at ten minutes after 3:00 and
9 then continue with the presentations?
10 **MR. JERE WHITE:** Thank you.
11 **(WHEREUPON,** a recess was taken.)
12 **DR. STEVEN HEERINGA:** Welcome back,
13 everyone. At this point, we are in our period of
14 public comment for the FIFRA SAP meeting. We just
15 heard from Mr. Jere White representing the Triazine
16 Network; and I think, Mr. White, you are about to
17 introduce your fellow participants here.
18 **MR. JERE WHITE:** Thank you, Mr.
19 Chairman. At this point, I'd like to introduce
20 Dr. James Lamb. I'll let him brief the Committee on
21 his background.
22 **DR. JAMES LAMB:** Sure.
23 **MR. JERE WHITE:** And with that, Jim?
24 **DR. JAMES LAMB:** Hi. For those of you
25 who know me and wonder why I'm sitting here, we do have

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1 75 acres in production right now. For those of you who
2 don't me, I'm actually here as a toxicologist, not a
3 farmer. I've been working in toxicology, published in
4 reproductive and developmental toxicology, endocrine
5 tox and risk assessment since 1976.
6 I was Head of the National Toxicology
7 Program's Fertility and Reproduction Group for a few
8 years. I then came to the U.S. Environmental
9 Protection Agency, where I worked with some unnamed
10 people on this Panel. And I am currently the Center
11 Director at Exponent Center for Toxicological and
12 Mechanistic Biology.
13 So I was asked, actually, by this group
14 to talk about my review of some of the non-cancer
15 issues and, very specifically, it really came down to
16 talking about the EPA LH study that you heard about
17 earlier.
18 I'm going to talk a bit about the study
19 design and interpretation; an audit that we did of the
20 available data, which this is the study that's proposed
21 to be the basis for a change in the point of departure.
22 I'm going to talk about the levels of suppression
23 associated with adverse effects a little bit and
24 whether or not such changes should be treated as
25 adverse effects or not.

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1 Of course, what I'm talking about here
2 is the Cooper 2010, et al., paper. For full
3 disclosure, I've known Ralph for 30 years. He's much
4 older than I am.
5 (Laughter.)
6 **DR. JAMES LAMB:** And we've published
7 together, and I've had the pleasure of working with
8 him. I hope he talks to me after I'm done with this
9 talk, because there are certain things within the study
10 design that I think I'm recommending he go back and
11 take a look at before he submits it for peer-review
12 publication.
13 This is work that was done in 2003, 2004
14 and recently reported as an internal report. It is
15 described as a three-block study design. It is a
16 large, complex study; there was an awful lot of hard
17 work that went into generating the data.
18 They did administer atrazine by gavage.
19 It is looking for a potential sensitivity of a hormonal
20 change at the peak of the LH surge. It required, as
21 you can imagine, very precise timing of the animals;
22 and we can go through what he did to make sure that
23 that happened, and it was a lot of work and they are to
24 be commended for that.
25 What we did in our review is we started

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1 with the summary tables that they developed and worked
2 back to the handwritten data. Now, our review by
3 necessity was limited to the data submitted to the
4 Docket. So I think most of you have seen the files in
5 there. We were able to get our way back to handwritten
6 data that really helped us understand where the numbers
7 came from, from that summary table all the way back to
8 the handwritten notes.
9 There are still some questions we have
10 about that. That's not a criticism as much as it is a
11 recognition that it's hard to do this when you don't
12 really know exactly how to work your way through it,
13 and we weren't able to ask.
14 We reviewed a number of endpoints that
15 are listed here; you can read them, but it's the basic
16 endpoints of the study. But I'd like to talk a bit
17 about the design.
18 It's described as a three-block study.
19 There are eight dosing groups in these plus three sets
20 of controls; you can see them listed up here. There is
21 an overlapping approach to this. They started with
22 Block 1 with two dose groups.
23 Block 2 had three dose groups, which
24 included the lowest level in Block 1. And Block 3 had
25 three dose groups, which actually included repeating

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1 the lowest group in Block 2. So you had Blocks 1 and 2
2 with one dose-group overlap; Blocks 2 and 3 with one
3 dose-group overlap; Blocks 1 and 3 having no overlap.
4 I'm more inclined to describe this as
5 three separate experiments than I am a real block
6 design where you would have just distributed the dose
7 levels across the various blocks. It may or may not
8 matter to you. It seemed to make a difference even in
9 how some of the data might be interpreted, though.
10 Age, though, was not distributed equally
11 across the blocks or across the dose groups or the time
12 points. In addition to all these dose groups we've
13 talked about and the three blocks, there are also time
14 points because they're trying to time the LH surge
15 meticulously within 2-hour windows.
16 So they may not hit the peak exactly,
17 but they're trying to get it as close as they can based
18 on the previous day's estrus or proestrus smear;
19 however, in our audit of the data, I could not find
20 that they used the Block 3 controls in the analysis.
21 So I don't see anything that shows a pair-wise
22 comparison between the Block 3 controls compared to the
23 Block 3 animals, or that the Blocks 1, 2 and 3 controls
24 were brought together to compare against the dose
25 groups.

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1 There was a question I had about the LH
2 data. We could find the LH data for Block 3. There
3 are three columns listing LH data. The data, if you go
4 from the handwritten data up to the summary data, they
5 always come from one of those three columns or
6 occasionally a handwritten value.
7 There's nothing in writing that tells me
8 how. I am certain they had a rationale as to which
9 they picked. There were different dilutions, I can't
10 tell you really why they picked the numbers they did;
11 but I completely understand there's a reason why they
12 did. But you have three columns, so for auditing
13 purposes I can tell you the number is in one of those
14 three columns; but it's not always the same column.
15 We couldn't find the LH data, and I got
16 people with a lot better eyes than me. We couldn't
17 find the LH data for Block 1 or Block 2, so we couldn't
18 verify those raw data. The LH looks generally higher
19 in Block 1 than 2 or 3.
20 I don't think they're statistically
21 different because you've got one really low value in
22 that group, but they don't look the same across the
23 groups to my eye. So if you plot them, you might
24 wonder why then you would use all three controls
25 together and all three blocks together instead of one

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1 block at a time respectively. I think there's useful
2 data in there; I just don't think it's been analyzed
3 quite correctly at this point.
4 I found the number of data errors to be
5 quite low, and by that I mean there are some errors.
6 There are places where you can see in the summary table
7 the dose level is listed wrong for one of the time
8 points. It is wrong. When you go back to the raw
9 data, they moved it correctly to the wrong place. It's
10 included in the statistics.
11 It's an error. It's an easily corrected
12 error. There are things like that that you would
13 expect in moving thousands of data points around by
14 hand would happen; they're there, we saw probably less
15 than a dozen of these, but they're easily corrected.
16 There were three inclusion criteria that
17 we also looked at. Did they establish a 4-day
18 regular estrus cycle? We went back and looked at all
19 of these, which is why I had to bring my glasses today.
20 They did a great job of following the
21 estrus cycle. The coding was a bit unfamiliar to us,
22 but we ended up convinced that in almost every case
23 they had a 4-day estrus cycle. It was regular if they
24 included the animal in; but there are a couple of
25 places there where we think they made some errors,

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1 including animals that shouldn't be included.
2 They also used a bright line for uterine
3 weight increase of about a half a gram. Somebody
4 yelled at me that it was greater than 0.5. I really
5 couldn't tell, because I'm not sure they had a 0.500
6 animal in there; but they used a bright line, the
7 uterine weight had to be greater than a half a gram,
8 they seemed to follow that religiously.
9 They said that they had increased
10 progesterone factored into the inclusion criteria. We
11 sorted all of the data by progesterone levels.
12 "Increased" implies more than one level; there isn't
13 more than one level. There is no bright line that
14 jumped out of us, so I wasn't so clear that they have
15 three inclusion criteria; they may only have two. But
16 the two that they have, we felt that they applied them
17 appropriately.
18 My view is this study is best suited
19 towards exploring a Mode of Action. This is not really
20 a risk-assessment or a regulatory study. The 4-day
21 gavage exposure to animals very precisely timed is
22 going to give you very precise information about the
23 amplitude of the LH curve, of the LH surge.
24 It's not necessarily going to tell you
25 whether or not you're into an adverse effect, and they

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1 do have the complication now, too, of figuring out
2 whether they really have a pseudo-steady state with
3 these gavage or do they have four sequential dosings,
4 and how do they figure out how to take that to
5 extrapolate to humans?
6 So I think the gavage versus humans is
7 going to play a significant role in how to interpret
8 these studies.
9 As I say, we reviewed the data in the
10 Docket, we went through a number of these things. I
11 have a couple of tables in here. The bottom, I've
12 talked about the first four of these bullets; but the
13 fifth one is the range in ages not distributed across
14 the groups, and I have a chart here, which if you can
15 see the little screen on the left you can see that
16 these are colored bars.
17 But the bottom line is this says the
18 number of animals at 1800-hour time point -- I'm only
19 showing one time point -- the number of animals in each
20 of the groups. Now, the groups are control, Block 1, 2
21 and 3, and then each of the dose groups with, for
22 example, the overlapping dose groups treated
23 separately.
24 I'm giving you a sense of what the age
25 of these animals is and how they were distributed

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1 across the study, because we didn't see a pattern that
2 was very regular as far as the distribution across the
3 study.
4 In fact, there is an 8-week range in age
5 in this study. I'm not sure that's a huge problem, but
6 the animals are gaining weight; there's probably, what,
7 10 to 15 grams per week for these Long-Evans rats in
8 this age range.
9 So the gaining weight, the ones at the
10 beginning are going to be less mature and smaller than
11 the ones in the end; so comparing across these
12 complicates things a bit, I think.
13 It is interesting, though, the last 4
14 weeks really only came from the Block 1 group. So it
15 is an area where the Block 1 animals are very different
16 from the other animals. And there are, though, Block 1
17 animals in weeks 11, 12, 13 and 14, and it seemed like
18 they narrowed the age range as the study went on; it
19 got tighter as they did this more.
20 So in trying to think of this especially
21 as a block design, the dose levels are not really
22 evenly distributed across the blocks. The age is not
23 really evenly distributed across the blocks or even the
24 dose groups. Is there an effect of age or body weight
25 demonstrated in the control?

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1 We didn't test it, but I think it's
2 something that could easily enough go back and be
3 tested to see whether or not that's part of what might
4 be observed here.
5 I think that they need to go back and
6 use the Block 3 controls. I don't think there's any
7 reason not to use them, and there was nothing in there
8 that indicated that that was purposeful. I'm not sure
9 what happened.
10 But bottom line really in this is I
11 think it's an interesting study into the Mode of
12 Action; but does it predict or is it an adverse effect
13 compared to effects like ovulation, estrus cycle,
14 fertility or effects seen in males as well?
15 I don't think it is by itself an adverse
16 effect. It takes a substantial suppression and a
17 statistically significant difference in LH levels by
18 itself I don't think gets you to adverse effects. You
19 should instead be looking at either very severe
20 suppression or severe suppression that result in
21 effects in ovulation cycle or the males' effects on
22 preputial separation testosterone, accessory sex-organ
23 weight.
24 There are other studies that have been
25 described that do get to other endpoints and do show

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1 that I don't think anyone doubts their link between LH
2 and adverse effects. It's just whether or not it is by
3 itself such an effect. This is really more basic
4 research getting into time points.
5 So in the end you've got a large
6 assessment of atrazine looking at various hormones,
7 including the LH surge, at a particular time point. I
8 actually think the study would have been better -- it
9 might have been harder, but it would have been better
10 to have somehow done serial collections from the same
11 animal than to have done only terminal sampling. It's
12 not really a block design.
13 I think although there are relatively
14 few errors, there are things in the study as it is in
15 the internal report that I think need to be looked at
16 and corrected before it is submitted for publication.
17 And in the end I don't really think that the change
18 that they're describing qualifies as an adverse effect.
19 So, thank you for your attention.
20 **DR. STEVEN HEERINGA:** Thank you, Dr.
21 Lamb.
22 Mr. White.
23 **MR. JERE WHITE:** Thank you, Jim.
24 At this point, I'd like to introduce
25 John Hall. John is with Hall & Associates here in the

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1 D.C. area. He has worked actually with my real work
2 back in Kansas over the years as a consultant on water
3 issues. And I think he probably is the only confrere
4 in our group that does need to depart after we get done
5 as a group today.
6 **DR. JOHN HALL:** Thank you, Chair, and
7 good afternoon, everyone. My name is John Hall, and
8 I'm the founder of Hall & Associates.
9 By way of a little bit of background, I
10 have degrees in mathematics, environmental engineering
11 and law. With regards to the law degree, I was not
12 offended in the least regarding the skunk that was put
13 up on the earlier slide. I in fact tend to agree with
14 that characterization, unfortunately more frequently
15 than I would like.
16 Our group at Hall & Associates is fairly
17 unique. We address drinking-water and wastewater
18 issues, treatment issues for municipal, agricultural
19 and commercial interests all over the country and have
20 over 30 years' experience in doing this.
21 Our approach is not to point fingers.
22 We try to get in there where there's a difficult
23 problem and seek to integrate the needs of the various
24 interest groups to see if we can come up with a cost-
25 effective solution to a regulatory compliance problem.

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1 And that's what leads me here today to talk Safe
2 Drinking Water Act requirements, how they're changing
3 and how in fact these changes have a bearing on what
4 human health exposures might or might not occur in the
5 very near future with regard to atrazine.
6 Now, a little bit of background, I'm
7 sure everybody knows that there's Safe Drinking Water
8 Act. It's gone through a series of amendments over its
9 many years of implementations.
10 It started in '74, and in 1986 there
11 were major amendments that were instituted. Those
12 amendments focused primarily on bacteriological issues
13 related to surface-water treatment and disinfection,
14 and EPA had a set of rules come out on what's known as
15 the Microbial and Disinfection Byproducts Cluster.
16 The issue is interesting. I mean from a
17 public-health respective, I think all of us would
18 probably agree that little has done more to protect
19 public health in this country than disinfection. I
20 mean, you can get sick very quickly and very badly with
21 any type of untreated water, with the exception I
22 suppose of well water, which is less subject to
23 bacterial infection.
24 With that said, disinfection is not
25 perfect. It has some ancillary negatives associated

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1 with it, and they come up with disinfection byproducts
2 and the concerns that come up there.
3 So in 1996 further amendments got put in
4 place, and there were basically two major rules that
5 came out. One was the long-term surface water and
6 enhanced surface-water treatment rule, because
7 originally there was a surface-water treatment rule;
8 this was enhancement number 1, and then enhancement
9 number 2 which came out in 2006.
10 The bottom line of all of this is that
11 treatment technology mandates are changing across the
12 whole country, and they are changing in particular for
13 the types of systems that we're concerned with at this
14 SAP.
15 Now, to give you an idea of how the
16 requirements on stage 2 of surface-water treatments are
17 changing with regard to disinfection byproducts, you
18 can see that there are some timelines applicable for
19 various sized communities, anywhere from 100,000 --
20 they skipped the earlier states to start -- down to
21 10,000, they get the latest states to start.
22 Start doing what? Initiate
23 distribution-system evaluations: find out what kind of
24 problems they do or don't have with regard to
25 disinfecting byproducts, haloacetic acids, things that

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1 can form disinfection byproducts.
2 And then with regard to treatment
3 installation, there is a schedule here also. The
4 larger ones come in first April 2012, and then the
5 smallest communities are supposed to have their
6 situations dealt with by 2013.
7 The point I guess being right now it is
8 currently September 2010, and so these communities are
9 in the middle of their decisions as to what to do if
10 they have a disinfection byproduct-related problem.
11 Now, here's where the issue comes up.
12 As part of the white paper, we went back and evaluated
13 the systems that from 2002 to 2009 within EPA's
14 database that indicated there was an atrazine concern
15 related to the drinking-water source.
16 And let me explain this chart for a
17 second. This is the number of community water systems.
18 Community water systems that have what? Well, whether
19 or not they have packed carbon or granulated activated
20 carbon. Why are we looking at that?
21 Because we know if you have that in
22 place, it reduces the ability of atrazine, if it's in a
23 surface water, to get through to a finish water. So
24 this whole question of you look at raw versus finish
25 water comes up fairly importantly when you evaluate how

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1 these systems are doing with regard to atrazine,
2 trihalomethanes or other Safe Drinking Water Act
3 requirements.
4 Let me just run a line through, so you get
5 the idea. There's approximately 44 systems I believe
6 that are identified as community water systems in high-
7 exposure areas. Only one of those systems in this
8 first 8 that has no PAC and no GAC, only one of those
9 systems was in violation; it had 4 violations.
10 However, 6 of the 8 systems are in violation of
11 trihalomethanes and haloacetic acids. And then there's
12 the same 6 have other surface water- treatment
13 problems.
14 Then you look at another 27 of the
15 systems, some that have PAC but no GAC. Two of those
16 27 had again 4 violations each; but 14 of the 27 had
17 haloacetic acid/trihalomethanes disinfection byproduct
18 issues.
19 Then when you go to these systems that
20 have GAC or GAC impact, you see no atrazine problems,
21 and still some remaining disinfection byproduct issues.
22 Well, what's the issue on all of this?
23 Well, by 2013, these exceedances have to be addressed.
24 And in my experience -- oh, a second point before we go
25 to that.

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1 The number of atrazine problems is small
2 compared to the number of trihalomethane and
3 disinfection byproduct issues these systems have. That
4 does not mean you ignore atrazine, I want to be
5 perfectly clear about that; but it does raise the
6 question of does the same solution that is going to
7 take care of this problem address any residual issue
8 that may be associated with atrazine?
9 In my experience, these communities are
10 going to do one of three things, the ones that have
11 significant issues with their surface water. I mean,
12 you are in an agricultural land; so it should not be a
13 shock to anyone that you have elevated carbon levels
14 getting into a system, which then can allow the system
15 if it is using chlorine to cause a disinfection
16 byproduct concern. That shouldn't be a surprise.
17 But what we tend to find with these
18 systems, because they tend to be the smaller ones, one,
19 the first thing they look at is can they discontinue
20 use of the water supply they currently have. Why?
21 It's expensive to put in some of these treatment
22 technologies.
23 So if there's a nearby system they can
24 tie into that doesn't have this problem, they
25 discontinue. It's way cheaper to run a pipe than it is

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1 to put in a treatment technology and just continue to
2 operate all the time.
3 The next thing they look at is do they
4 have multiple water supplies. Is there another source
5 where they can blend or discontinue use of a particular
6 source under a period, say a high-runoff period when
7 you might get more of the carbon into the system, and
8 use an alternative source? It could be a well. Could
9 be just a better surface-water supply that's in the
10 area, the next thing that people tend to look at.
11 And then the third thing is they look at
12 carbon treatments. Why? These tend to be fairly
13 smaller systems. They're pretty much going to stick
14 with the chlorine-base disinfection.
15 It's not absolutely true, but by and
16 large it is what tends to occur. It's easier for them
17 to operate as opposed to going to any kind of
18 complicated UV-related system, which then doesn't leave
19 a residual within your collection line, which then
20 raises a concern to some people also.
21 So the bottom line is things are
22 changing and they're changing for the precise systems,
23 and there's only 3 out of the 44 have historically had
24 atrazine issues, whereas 22 out of the 44 have
25 trihalomethane issues.

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1 So the site-specific factors that one
2 would look at to influencing potable water-quality
3 supply in what's in the raw water and what's in the
4 finish water. These are the same factors that you
5 would have to evaluate to determine what is the most
6 cost-effective way to address the overall problem you
7 have in your system.
8 You don't say, "Oh, I just have an
9 atrazine problem; I'll put on my blinders and ignore
10 the rest of what's going on." You look at your overall
11 system and decide a solution. That's how you come up
12 with a cost-effective approach.
13 Well, some of the prior speakers, you
14 know have addressed a few of these issues; but they
15 deserve a little bit of re-emphasis. Surface-water
16 source, first and foremost, is the thing that causes
17 the quality of your raw water to be what it is, and
18 then that affects your finish water to a degree, to the
19 degree that you have no treatment in place.
20 The size of the drainage area, the
21 supply type, I think Dr. Hendley addressed the issue of
22 if you have a reservoir that has a considerable
23 detention time in it, you're not going to get as much
24 of a peak at all on any kind of atrazine exposure,
25 simply because you have a large water body that the

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1 peak runoff, if it's occurring, has been dampened into
2 a larger system. If you have a riverine system, and
3 particularly a smaller one, more variable; also more
4 variable on carbon input, not a shock.
5 And then alternative source options. In
6 terms of water-treatment facilities, the type of
7 disinfection is going to drive things, the nature of
8 the supply, and again whether or not you're using
9 activated carbon.
10 And even if you're not using it right
11 now, I can assure you that most of these systems, if
12 they stay in place, will likely be having activated
13 carbon as their option of choice in the future in order
14 to address the group of chlorines that are coming down
15 the road.
16 So this is our just basic concern in
17 what I consider to be a significant policy shift in
18 what I'll say is just a focus on raw water without
19 looking at the overall cost-effective activities that
20 are going on in these watersheds of concern; that this
21 focus fails to consider the differences in the water
22 supplies and what their water-supply management options
23 are, because they will in fact exercise these
24 management options to address these other problems.
25 Regardless of whether atrazine even exists, it's going

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1 to happen.
2 The parameters, numerous other
3 parameters may be exceeded in the raw-water supply,
4 which makes you have to look at multiple integration of
5 all of these issues when you are coming up with your
6 cost-effective option.
7 I am concerned that we are switching to
8 a worst-case supply focus here, and worst-case supply
9 focus on a single parameter, when in fact these systems
10 have to deal with multiple parameters. And going to
11 the worst-case points farther, I mean, we're looking at
12 3 out of 44 systems to drive an entire approach?
13 I wouldn't think -- and those are 3 out
14 of 44 in high-exposure areas. It just seems a little
15 bit of overkill to me, and without integrating the
16 other things that need to be considered.
17 With regard to water-supply treatment
18 issues, you always look at the site-specific factors to
19 figure out the cost-effective treatment decisions. And
20 actually, I shouldn't limit it to water supply. EPA's
21 TMDL Program, Total Maximum Daily Load -- I'm sure all
22 of you have heard more than you would like to hear
23 about that program over your careers -- that analysis
24 is all site-specific.
25 Simple, you would look at the case-by-

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1 case situations that are being encountered and decide
2 what is the particular solution, if it needs to be
3 implemented, to regulate the pollutants. You don't
4 apply one TMDL to all sources, it's just not done; it's
5 not the way the analysis goes forward.
6 So I think there is a nationwide impact
7 of shifting the regulatory focus from finish to raw
8 water. That's a major issue, it's a major policy
9 shift, and I would say that should be considered
10 carefully and I haven't really seen that it's gotten
11 the level of discussion maybe it ought to have.
12 And I guess I just want to end with the
13 last point, which is really maybe the first point.
14 Failure to integrate major changing Safe Drinking Water
15 Act mandates is a major oversight and where I see the
16 analyses are going.
17 I mean, really, if the treatment
18 technologies or other alternatives are going to come
19 into place regardless of what we are doing here today
20 with regard to this unit health exposure issue, we
21 really ought to know about that and integrate it into
22 our overall thinking before we decide that simply, for
23 example, more sampling is the solution to the problem,
24 when the solution to the problem, if you will, is
25 running off in a totally different direction.

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1 Thank you very much, and I appreciate
2 your attention.
3 **DR. STEVEN HEERINGA:** Thank you very
4 much, Mr. Hall.
5 Mr. White.
6 **MR. JERE WHITE:** I'd next like to
7 introduce my counterpart from Missouri, Gary Marshall.
8 Gary is not a scientist, but I believe he is going to
9 name his next hunting dog Data.
10 **MR. GARY MARSHALL:** That's probably
11 true, because I am one of the people that did receive a
12 subpoena last week. Even though technically I was in
13 Costa Rica, my office received the subpoena.
14 But my name is Gary Marshall, and I am
15 the Chief Executive Officer for the Missouri Corn
16 Growers Association. Mr. Chairman, good to see you and
17 members of the Panel. This is an ongoing process for
18 me, as well as for a number of you.
19 I've been involved in the special review
20 since 1996 and in the atrazine issue related to
21 Missouri since 1994 and prior to that, and in fact I
22 may have more experience in this room than probably
23 anyone else in actually applying the product afield.
24 So I in a previous life had a business
25 where we applied literally thousands of acres over a

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1 15-year period with herbicides like atrazine with
2 fertilizer, and so we have a lot of practical
3 experience of using the product. And as Jere says, I'm
4 not a scientist; but I feel like I know more about a
5 lot of the reproductive Mode of Actions of rats and
6 mice than I ever cared to know.
7 But I appreciate the opportunity to
8 visit with you just a few minutes and talk a little bit
9 about what we do and our concerns. And I guess the
10 first thing I should say is representing the 15,000
11 corn growers that I do in Missouri, I think I can speak
12 for them in that we have what I consider to be very
13 robust populations today of fish, of frogs, of birds,
14 of deer, turkeys.
15 You know, 50 years of experience using
16 the product atrazine -- and I realize the science that
17 we're talking about here and the minutiae that we're
18 able to deal with today -- but I deal in the real
19 world, 50 years' worth of applying products.
20 We started at 4 pounds per acre
21 whenever I started back in the '70s to a pound, a
22 pound-and-a-half or less than that today, huge amounts
23 of atrazine in the environment out there that have been
24 used, and no problems at all that we're seeing
25 associated with any of the animals or any of the plants

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1 or the ecosystems that we deal with.
2 Again, the reason I'm here is because
3 this herbicide allows our farmers to control weeds in
4 their fields, the pests. These weeds not only compete
5 for moisture, but they also harbor insects and other
6 diseases; we don't want them in the fields. Atrazine
7 is a cost-effective measure.
8 Perhaps the best illustration of that
9 that I can give you is to a producer in Missouri to
10 switch to an alternative product, first of all, you
11 have less efficiency; it doesn't work as well.
12 Secondly, you have increased costs. You combine those,
13 it's over $30 an acre.
14 We produce over 3 million acres of corn
15 in Missouri. That's a $100 million cost to our growers
16 if we would have to switch products: those 15,000
17 growers, a $100 million increase in costs. If you
18 change that, take it all the way across the United
19 States, on 90 million acres of corn you're talking
20 about a $2.5 billion hit to growers. And who
21 ultimately pays the price for a higher cost that
22 growers have? The consumers do.
23 So although this product doesn't go
24 directly to human food, it does go to animal feed, it's
25 exported all over the world, and in fact we use a lot

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1 of it today to help produce a gasoline-type product,
2 ethanol, that we use in our cars. So we have a lot --
3 I think the growers do -- of reason to be here.
4 Another thing that we've seen in the
5 last few years, glyphosate technology. If you're not
6 familiar with it, it's a new technology that has
7 allowed us to go away from some of the herbicides we
8 used in the past to help control weeds; but it's got
9 one problem, and that is it's been used so much so
10 extensively that we're starting to see some weed-
11 resistant species that are out there.
12 So for us, we need a product like
13 atrazine to be able to deal with these problem weeds.
14 It started for us in Southeast Missouri, it's spread
15 across the state three or four hundred miles to
16 Northwest Missouri. We need a product like atrazine to
17 be able to complement products like glyphosate.
18 And again, if you think that's an issue
19 for us, it is. Nationwide that's a billion-dollar
20 cost, $10 to $20 an acre to control those resistant
21 weeds. So it's a huge cost, and I know that one of the
22 other speakers is going to address that issue.
23 But as the science has evolved, so have
24 the growers in managing the atrazine that they have.
25 In the 1990s when I first got started in Missouri, we

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1 had numerous areas out of compliance for atrazine. In
2 fact, we had five major drinking-water reservoirs and
3 several streams out of compliance.
4 So we worked and we specifically put
5 together a group, and I think maybe we are one of only
6 two commodity associations that have a group like this
7 that works exclusively on water-quality issues.
8 We have ten people on staff, and that by
9 itself is a huge staff for commodity groups: ten
10 people doing nothing but working on water-quality
11 issues. So we put together projects with EPA funding,
12 with Department of Natural Resources in Missouri
13 funding, with USDA dollars.
14 We involve the University of Missouri,
15 and we put a number of grower dollars together to put
16 together ten years' worth of studies and of science.
17 Again, I'm not dealing in a laboratory
18 and looking at the probability of something happening
19 or using a model. We're looking at what actually
20 happens out in the streams, and I can tell you as a
21 result of those ten years' worth of studies, we were
22 able to work with the growers to help implement best
23 management practices on those fields, which resulted in
24 the delisting of every major water body, including the
25 Missouri and Mississippi Rivers in Missouri, that were

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1 out of compliance for atrazine. They're all delisted
2 today.
3 So we've been able to work with the
4 farmers, utilize the information, the best science, the
5 technology that we have, to be able to incorporate
6 things like conservation tillage, minimum tillage, no
7 till to help keep the products on the fields where
8 they're supposed to be and not get into the water
9 systems.
10 We utilized over 50 samplers, we had
11 dozens of fields, literally hundreds of producers
12 participated, and we've shown this data to thousands of
13 people, including one of the past EPA Administrators.
14 So we used and we not only looked at
15 various types of techniques; but we looked at rate
16 reductions, we looked at application of timing of
17 atrazine, tillage practices, split applications, a
18 number of different things. All of these helped us to
19 keep the product where it's supposed to be, which is on
20 the fields.
21 A part of conservation tillage allows us
22 to use things like buffer strips, integrated pest
23 management, better best management practices to be able
24 to keep those products there. Today, over 44 million
25 acres in the United States utilize conventional

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1 tillage. The reason they're able to do that, one of
2 the main reasons is the ability to use a product like
3 atrazine. It really works.
4 One of the results of using conservation
5 tillage and these best management practices, we've
6 reduced soil erosion. It was a huge problem in a state
7 like Missouri; we've reduced it by 90%. It's made a
8 significant difference.
9 A lot of the small streams that we deal
10 with in a state like Missouri -- and most of the corn
11 is grown along streams in our state -- but a lot of the
12 small streams have a lot more problem with turbidity,
13 with cloudy water, than they ever do with a product
14 like atrazine.
15 By using conventional tillage -- or by
16 conservation tillage, rather, we've been able to use
17 products like atrazine again to help keep those
18 products where they're supposed to be, on the fields.
19 They don't get into the water systems. We reduced that
20 turbidity and the problems in those streams.
21 For farmers, we also help reduce the
22 amount of fuel that we use, because we don't have to go
23 over the fields as often. So we reduce compaction on
24 the fields, the tilth of the soil is much better,
25 higher results there plus less expenses because we're

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1 not going over the fields quite as often as we did
2 before.
3 And besides that, we're providing great
4 habitat for wildlife; again, the fish and the wildlife
5 is excellent.
6 So I guess in conclusion with my short
7 presentation, I just want it noted that atrazine works
8 very, very well for growers across the United States.
9 It saves producers money, saves consumers dollars, and
10 it allows us to utilize conservation tillage and it
11 advances modern farming practices, and it helps improve
12 the environment.
13 Thank you.
14 **DR. STEVEN HEERINGA:** Thank you, Mr.
15 Marshall.
16 Mr. White.
17 **MR. JERE WHITE:** Lastly, we'd like to
18 introduce Dr. David Bridges. I need to make an
19 observation. I first met David probably a dozen years
20 ago at an SAP. He was a wheat scientist, and I was
21 doing exactly what I'm doing now.
22 He's now President of the university he
23 originally graduated from, and here I am in the same
24 role. So one of us did better with our career track
25 than the other, though without embellishing.

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1 **DR. DAVID BRIDGES:** Thank you, Jere.
2 Thank you for your time this afternoon,
3 and I will be judicious in my use of it; I know it's
4 been a long day.
5 My name is David Bridges. I'm President
6 of Abraham Baldwin Agricultural College and a Professor
7 in its School of Ag and Natural Resources and its
8 School of Science and Mathematics.
9 Much of my professional career was and
10 has been devoted to quantifying the impact of
11 pesticides, their use and the benefits derived from
12 such. Over the past 25 years I've worked with EPA,
13 USDA, Food and Drug Administration and many others to
14 try to accurately assess and value the use of
15 pesticides in the U.S. economy.
16 I don't have any slides (laughing).
17 In the early 1990s, a team of colleagues
18 and I began the process of conducting what was the most
19 comprehensive analysis of the use and benefits of the
20 triazine herbicides that had been conducted at that
21 time. Over the past six months, the team has
22 reassembled; unfortunately, many have moved on to other
23 things. But I chose to sign up for the fun again, and
24 we have almost completed another analysis of the use
25 and benefits of triazine herbicides in the U.S. farm

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1 economy.
2 I am fully aware that your charge, your
3 primary charge and responsibility, is not to sit here
4 and listen to me talk about benefits. I understand
5 that. However, I suggest and respectfully suggest to
6 you that your decisions cannot and should not be made
7 in a vacuum.
8 There are many other important issues
9 that impinge on the process. While you have been
10 asked to set the bar, you will consider the data that
11 is presented to you and the weight of the evidence and
12 the value of the science that has been submitted to
13 you. There are many other things that I think can
14 serve to play a role in the relative placement of that
15 bar: how low, how high.
16 Many of us at this table are scientists
17 or engineers or we're both, and by nature we seek truth
18 and we seek knowledge. But we hopefully also
19 understand that absolute certainty is very elusive,
20 very elusive. And what we may think is certainty today
21 may turn out to be something quite different tomorrow.
22 But there are a few matters in the
23 matter before us that are really pretty certain. After
24 50 years of safe use, the benefits of the triazine
25 herbicides, and particularly atrazine, is pretty

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1 certain. The benefits are certain. Most of us believe
2 the safety is certain.
3 Your task really becomes a very
4 difficult one. It is a task where you are asked to
5 trade certainty for multiple layers of certainty. And
6 incomplete science, should you make unnecessary
7 regulation, trade somewhat uncertain science for maybe
8 more uncertain science.
9 I want to share with you just a few
10 thoughts about use, reliance and potential impacts.
11 All of us know that atrazine is the most commonly used
12 herbicide in American history.
13 For more than 50 years since atrazine's
14 initial registration, atrazine has been used by more
15 American farmers than any other herbicide. It is
16 currently estimated that a half a million farmers a
17 year use triazine herbicides.
18 More than half of the U.S. corn crop is
19 treated annually, about 90% of the sugarcane crop and
20 three-fourths of the grain sorghum crop. Atrazine and
21 simazine have been used commonly on more than 30 crops
22 for more than 50 years. There is an element of
23 certainty that comes with time.
24 I'd also suggest that as you undertake
25 this very difficult task in a way that competing

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1 interests and the competing points about how strong the
2 science is or how unwavering it may be where others
3 tell you it is not so strong, it is doubtful, I'll
4 suggest to you that you should not underestimate the
5 recoil and the profound broad impact that your decision
6 will have on American agriculture and, indeed, on the
7 U.S. economy.
8 And most importantly, it will have a
9 profound impact on rural America. Most of us here
10 today come from rural America and are deeply concerned
11 about the economies and what is going on in the
12 heartland of America.
13 Impacts will be felt, and we can
14 categorize those who will be impacted into three
15 principle groups. Growers or farmers, I fully realize
16 that less than 2% of America's population spends its
17 time on the farm; but we all benefit from the 2% who
18 work on our behalf.
19 Consumers will be impacted; and finally,
20 the greater public at large. Your charge is important,
21 but your charge is inclusive. Your charge is to
22 protect all.
23 For growers, should atrazine no longer
24 be available, the following effects are almost certain.
25 Farmers will lose the herbicide that has been the

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1 mainstay of corn weed control for more than 50 years.
2 The combination of increased weed-control costs and
3 yield losses will seriously challenge profitability in
4 American farming.
5 To look at gross number, folks, the
6 margins in farming are small. The margins are small.
7 The increased costs and the lost yields will take a
8 large percentage of that profitability away.
9 Farmers will lose, at a time when they
10 can ill afford to do so, their most important weapon to
11 fight resistant weeds. Farmers will, at least in the
12 short term, become more reliant on glyphosate, a
13 product that is already seriously challenged with
14 respect to its future efficacy.
15 Farmers will face greater prevalence of,
16 like I say, resistant weeds, and they will do so
17 quickly. They will find it more difficult and more
18 costly to control those weeds in not corn and sorghum
19 and sugarcane but in the myriad of crops that they
20 rotate, too.
21 And I reiterate, should the product go
22 away, one thing is certain: farmers will use
23 herbicides. They will use whatever is available to
24 them, and in many cases those products will be less
25 effective, they will be more expensive, they will

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1 almost all certainly come without the benefit of 50
2 years of experience.
3 And they will almost all certainly come
4 with much less study, much less understanding and much
5 less certainty about the things that you've been asked
6 to consider the last two days.
7 Consumers, you, I and everyone else in
8 the room, who consume corn, sorghum, sugarcane, pork,
9 poultry, beef, fish, dairy products, your favorite
10 coffee at Starbucks across the street, will face
11 without a doubt a rise in food costs; and finally, the
12 public at large.
13 Your decision is not a carbon-neutral
14 decision. The loss of atrazine to the American farmer
15 will result in increased on-farm petroleum use and
16 therefore result in a larger carbon footprint for
17 American agriculture.
18 The loss of atrazine will reverse a 30-
19 year continuous trend in the adoption of conservation
20 farming practices. America's farmers are, by
21 definition and by necessity, America's penultimate
22 environmentalists and conservationists; they have to
23 be. So if atrazine goes away, conservation tillage
24 will decline. That means plowing will increase.
25 Soil erosion will increase, which means

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1 siltation of streams will increase, which means
2 sedimentation of streams will increase. Nutrient
3 loading to our surface waters will increase. The
4 biological diversity of farms will decline when tillage
5 increases. And a conservative estimate suggests that
6 as many as 48,000 jobs will be lost just in corn
7 production.
8 In closing, I know you will make your
9 decisions based on science. Many of you here at this
10 table have been here before. You will make your
11 decisions based on sound and convincing science.
12 Obviously, uncertainty -- and there is clean evidence
13 in this world -- leads to caution and precaution.
14 But make sure that the amount of caution and precaution
15 you take is appropriately weighed relative to the risk
16 associated with inappropriate regulation.
17 Make no mistake: caution on one
18 forefront represents risk on others. Facing limited
19 and mechanistically understood risk is better than
20 facing largely but totally unknown risk.
21 These herbicides are essential for
22 agricultural production, and massive change will occur
23 if the farm community faces unrealistic regulation.
24 Make sure you understand that is my caution and my
25 request of you.

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1 I won't repeat the following points
2 about conservation tillage; I believe I have made them.
3 But my sense is our estimates are -- and we have data
4 to show that it happened over the last few years -- is
5 that more herbicides will be used. You take atrazine
6 away, you take the other triazines away, more will be
7 used.
8 Can you sit here and say with confidence
9 that the alternatives are safer? How many alternatives
10 have a 50-year track record of use? How many
11 pesticides, how many other herbicides that farmers
12 might choose to use, have the record of study and the
13 level of understanding about mechanism and effect with
14 that of atrazine?
15 When faced with weak, little or no
16 evidence to condemn a product, or when uncertainty
17 abounds on one front, always consider, always consider
18 that some degree of certainty does come with more than
19 50 years of use.
20 I would say to you that the stewardship
21 on this product exceeds the level of stewardship on any
22 other pesticide registered in America. The Registrant
23 has been its steward; the farmers have been its
24 steward, as evidenced by adoption of best management
25 practice, reduction in rates and a variety of things

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1 that have sustained its use in the farm business for
2 many years.
3 Consider the weight of the other
4 evidence and the potential impact of unintended
5 consequences that could result from overly cautious and
6 errant decisions.
7 If I were in Georgia today, I would be
8 having a meeting or teaching a class. And I would say
9 to you this is far more than an academic exercise. It
10 is far more. The impact of your decision will be far-
11 reaching.
12 I think it is safe to say, and I will
13 stand behind this statement, that losing the triazine
14 herbicides will result in an unprecedented disruption
15 of the world's most productive agricultural system:
16 the production of corn in the United States of America.
17 Thank you for your valuable time, and I
18 wish you luck in your process.
19 **DR. STEVEN HEERINGA:** Thank you very
20 much, Dr. Bridges, the White and the Triazine Network
21 group.
22 We're going to move on to our next
23 public commenter.
24 And Mr. Snyder, we skipped over you
25 previously. Rod Snyder, are you here at this point

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1 from National Corn Growers Association?
2 Coming forward. So our next public
3 comment will be Rod Snyder, and comments are being
4 circulated to the Panel and will be available in the
5 Docket, too.
6 **MR. ROD SNYDER:** I will be fairly brief;
7 my good friends from Missouri and Kansas covered a lot
8 of ground here in the last few minutes.
9 My name is Rod Snyder, Director of
10 Policy for the National Corn Growers Association, and I
11 do appreciate the opportunity to testify before the SAP
12 today.
13 I am providing comments on behalf of
14 NCGA, which represents 36,000 members in 48 states and
15 more than 300,000 corn farmers that contribute to state
16 checkout programs across the country. These
17 opportunities to see about atrazine are important to
18 America's corn growers.
19 We are anxious to be heard, because so
20 much is at stake for our farmers and the rural
21 communities that depend upon the farm economy.
22 According to Don Coursey, an economist
23 at the University of Chicago, a ban on atrazine would
24 cost as many as 48,000 jobs, according to some new
25 research that came out this summer.

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1 Dr. Coursey also estimates atrazine's
2 annual production value to corn alone to be as high as
3 5 billion, not to mention losses for the growers of
4 sorghum and sugarcane.
5 Of course, no economic priority should
6 come before human health, we do all agree on that.
7 That is why EPA has relied on more than 6,000 studies
8 and the considered judgments of respected regulatory
9 agencies around the world to affirm the safety of
10 atrazine.
11 Yet, we find ourselves in the midst of
12 this very unusual, unplanned re-review of atrazine that
13 deviates considerably from EPA's longstanding
14 regulatory process. EPA and the Scientific Advisory
15 Panel have already repudiated the very studies EPA
16 relied upon to justify this re-review of atrazine,
17 noting that "The overall quality was relatively poor,
18 thus limiting their applicability".
19 Nonetheless, we find ourselves in the
20 fourth SAP in 12 months. On August 24th, just three
21 weeks before this SAP convened, EPA released a white
22 paper that was almost 700 pages long that included
23 summaries of more than 100 studies.
24 This white paper is complex and crosses
25 many disciplines. It was not until August 27th that

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1 EPA allowed stakeholders to know the exact questions
2 this Panel is being asked to consider. These questions
3 require a Panelist to make critiques of 17 preliminary
4 conclusions in questions that cross multiple
5 disciplines.
6 It seems imprudent to ask this Panel to
7 make rush decisions about science. For our part, it is
8 impossible for farmers and corn growers who are
9 currently in harvest to review one of the longest and
10 most complicated SAP white papers ever released.
11 We expect these scientific deliberations
12 to be both patent and transparent in a manner that
13 invites criticism. Unfortunately, this process has
14 been rushed, and we are concerned about the publication
15 of mountains of data and findings without adequate time
16 for the SAP, farmers or the general public to
17 intelligently analyze or respond.
18 So much is at stake here beyond just
19 atrazine, actually. We need EPA to maintain a fair and
20 balanced process for pesticide review so that all
21 stakeholders can have a high degree of confidence in
22 the resulting decisions. We hope you will consider the
23 precedent-setting nature of these decisions and the
24 American agricultural system that will be deeply
25 impacted.

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1 I thank you for your time.
2 **DR. STEVEN HEERINGA:** Thank you, Mr.
3 Snyder, and I will just add a comment that the Panel
4 sees the questions at the same time the public does, be
5 it the Docket. It's just a
6 **MR. ROD SNYDER:** It's good to know that.
7 I thought that.
8 **DR. STEVEN HEERINGA:** That's probably
9 neither here nor there for you, but it's
10 **MR. ROD SNYDER:** Thank you.
11 **DR. STEVEN HEERINGA:** Okay, thank you
12 very much, Mr. Snyder.
13 At this point in time, our next public
14 commenter is Mr. Scott Slaughter, who represents the
15 Center for Regulatory Effectiveness.
16 Scott?
17 **MR. SCOTT SLAUGHTER:** I'm Scott
18 Slaughter, and I am commenting today on behalf of the
19 Center for Regulatory Effectiveness -- and I apologize
20 for my cold and my hoarseness.
21 Sure, we got a subpoena, too; but we're
22 going to talk anyway.
23 Our comments address three points:
24 first, there are quality standards that govern EPA's
25 use of scientific studies and data; second, EPA should

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1 not use its draft 2000 BMD Guidance Document, because
2 the document says don't use it; third, EPA should not
3 use the 2007 and 2010 Fenton male rat studies, because
4 so many of the controls have unexplained prostate
5 inflammation.
6 With regard to the first issue, EPA
7 cannot use scientific data and studies unless they meet
8 certain statutorily required quality standards. Many
9 of these standards are required by something called the
10 Information Quality Act Guidelines.
11 These IQA Guidelines require that
12 studies and data used by EPA and other Federal Agencies
13 generally be accurate, reliable, reproducible and
14 transparent.
15 The U.S. Office of Management and Budget
16 is required under statute to ensure that EPA and other
17 Federal Agencies publish and implement these IQA
18 Guidelines. OMB has asked EPA to incorporate its IQA
19 Guideline standards into the charges that EPA gives to
20 expert peer-review panels like this one.
21 Let me read OMB's exact language to EPA.
22 This is in Appendix A to our written comments on --
23 yeah, go to page 3 of my written comments, series
24 written comments. I'm sorry, no, it's page 14,
25 Appendix 1, attached to my written comments.

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1 OMB told EPA, not for this SAP but in
2 the context of charges to another peer-review panel:
3 "Since the development of Agency Information Quality
4 (IQ) Guidelines required by statute, many Agencies have
5 been using charge language that tracks with the
6 standards of their own IQ Guidelines.
7 For example, such language often focuses
8 on whether or not the information in question is
9 accurate, clear, complete, transparently and
10 objectively described and scientifically justified."
11 We believe it may be useful for EPA to
12 follow a similar approach and incorporate some of the
13 language from your IQ Guidelines into the formulation
14 of the Charge Questions. We believe that EPA has not
15 done that for this SAP, so in our comments we have
16 tried to incorporate the IQA Quality Standards into the
17 review that you're doing right here.
18 Let me give you an example of how the
19 IQA Guidelines work in a context, in fact in a prior
20 SAP on atrazine. A few years ago, CRE and others
21 requested EPA not to use Dr. Hayes' atrazine studies
22 because they were not reproducible, in violation of the
23 IQA Guidelines. EPA and two SAPs eventually agreed
24 that the Hayes studies were not reproducible, and EPA
25 is not using them, is properly not using them to

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1 regulate atrazine.
2 We move on to our second issue. EPA's
3 Draft 2000 Benchmark Dosing Guidance Document is
4 another example of something that does not meet IQA
5 Guidelines. Therefore, EPA should not use it to
6 regulate atrazine.
7 However, EPA's cites the 2000 draft BMD
8 guidance Document, page 73 of its Issue Paper. This
9 draft document says on its front page, its cover page -
10 - and that's on page 3 of my written comments -- and I
11 quote; it says on the front: "Draft EPA. Do not site
12 or quote." "This document is a preliminary draft.
13 It has not been formally released by the
14 U.S. Environmental Protection Agency and should not at
15 this stage be construed to represent Agency policy. It
16 is being circulated for comment on its technical
17 accuracy and policy implications."
18 That, the document, speaks for itself
19 and should not be used in this context for any
20 regulatory purpose until EPA is willing to take the
21 caveats off the document and until EPA is willing to
22 designate it to be a final document and until EPA
23 itself is certain that the document is technically
24 accurate.
25 Third and finally, Dr. Fenton is

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1 coauthor of a 2007 Rayner study on rat prostates. The
2 Rayner article had significant prostate contamination
3 with regard to control prostate inflammation. In fact,
4 80% of the controls in some groups had prostate
5 inflammation.
6 That inflammation was not caused by
7 atrazine. The 2010 Fenton article that she discussed
8 today had control prostate inflammation; half the
9 controls had it.
10 Let me read to you what Dr. Fenton and
11 the rest of her authors said in 2007 about the control
12 prostate contamination in the controls and the general
13 summary they had in the 2007 study on the prostate-
14 inflammation issue.
15 This is recorded on page 5 of my written
16 comments at the bottom, and I quote: "The background
17 incidence of inflammation in the ventral prostate was
18 fairly high in that eight of 10 control animals
19 presented evidence of inflammation at PND120."
20 Eighty-percent is fairly high.
21 "Neutrophils were more prominent in the ventral
22 prostate in all dose groups, and were associated with
23 the higher overall incidence of inflammation in the
24 ventral prostate.
25 The incidence of inflammation in the

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1 ventral prostate was not treatment related and
2 presented a wider tissue distribution than the lateral
3 prostates. The severity of inflammation in the ventral
4 prostate was also not affected by atrazine exposure."
5 I'm still quoting: "At PND220, no
6 significant increases in prostate inflammation were
7 detected relative to controls, however, the incidence,
8 distribution, and severity of inflammation in the
9 ventral prostate were decreased compared to PND120.
10 The lateral prostates were not different from control.
11 There was no increase in incidence or severity of
12 prostate inflammation over time following atrazine
13 exposure."
14 I really think that the control
15 contamination and the control inflammation needs to be
16 explained before anyone uses this document for any
17 purposes or those studies for any purposes with regards
18 to regulation of atrazine.
19 That was it, and I will be happy to --
20 well, I guess I want to ask you a question now; but I
21 will later.
22 Thank you very much.
23 **DR. STEVEN HEERINGA:** Thank you very
24 much, Mr. Slaughter; and the Panel, in the Docket there
25 is a multipage document with appendices that--

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1 **MR. SLAUGHTER:** Yep.
2 **DR. STEVEN HEERINGA:** --was distributed
3 on behalf of Mr. Slaughter and the Center for
4 Regulatory Effectiveness.
5 Okay, we have two more scheduled public
6 commenters. In anticipation of the end of the
7 afternoon, if there are any other members of the public
8 who wish to make a public comment before this meeting,
9 I would encourage you very shortly to see the
10 Designated Federal Official, Joe Bailey, or the
11 Executive Secretary of the SAP, Ms. Laura Bailey.
12 At this point in time, I would like to
13 invite up Tyler Wegmeyer, who is Director of
14 Congressional Relations for the American Farm Bureau
15 Federation.
16 **MR. TYLER WEGMEYER:** Good afternoon. My
17 name is Tyler Wegmeyer, and I am the Director of
18 Congressional Relations for the American Farm Bureau
19 Federation. I am also a fourth-generation farmer
20 growing mostly specialty crops in western Loudon
21 County, Virginia.
22 The American Farm Bureau Federation is
23 the country's largest general farm organization. Farm
24 Bureau members grow, produce and raise the food, fiber
25 and energy sources that feed, clothe and fuel the U.S.

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1 and the world. Our farms and ranches are found in all
2 50 states as well as Puerto Rico, and we represent
3 producers of every size and scale of operation.
4 American Farm Bureau Federation welcomes
5 this opportunity to speak up on behalf of the benefits
6 of atrazine and what it means to American farmers.
7 Having access to important crop-protection products is
8 vital to the success of providing safe and abundant
9 food supply. I appreciate this opportunity to be able
10 to express our views before this Scientific Advisory
11 Panel.
12 At this time of continuing high
13 unemployment and national recession, when America is
14 running enormous trade deficits and our competitiveness
15 in manufacturing is being challenged, the American
16 farmer is providing a much-needed bright spot in our
17 economy. One reason for this bright spot, why American
18 agriculture remains so amazingly productive and
19 efficient, is the wise application of technology by
20 American farmers to agriculture.
21 You would think that at a time like
22 this, Washington's overriding interest would be to do
23 anything and everything to bolster the U.S. farm
24 economy. And yet, we keep finding ourselves fighting
25 off ill-considered proposals, such as the one in the

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1 purview of this Panel, that have the potential of
2 making farming more difficult, less efficient and more
3 expensive.
4 In our view, no move has been more
5 unhelpful than what appears to be a campaign against
6 the wise and appropriate use of agriculture technology.
7 The redundant re-evaluation against atrazine is a case
8 in point.
9 The campaign against this crop input
10 appears predicated on a set of claims that have been
11 examined and re-examined, and in each instance the
12 Agency has found in favor of continued use of atrazine.
13 We all remember the hysteria that was generated against
14 Alar in the 1980s and the damage it caused. The
15 campaign against atrazine is potentially more harmful
16 and with more widespread impact on more crops than Alar
17 ever was.
18 It is easy to see why this is so.
19 Atrazine is essential to corn growers, as well as to
20 sorghum and sugar growers. And corn is an essential
21 staple of animal feeds, impacting meat prices, as well
22 as a multitude of secondary food products. We look at
23 what is going on here, and we worry for America's
24 farmers in the rural communities that depend on them.
25 We are concerned when a wholly redundant

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1 regulatory re-review is launched against atrazine on
2 such an accelerated time scale. The stream of data
3 being poured out for this SAP is extremely difficult to
4 manage in the artificially compressed schedules you
5 have been allotted to carry out your meetings.
6 The members of this SAP are also being
7 asked to evaluate this new data while turning away from
8 the more than 6,000 studies that were considered by EPA
9 when it completed a dozen years' worth of work in
10 approving atrazine as safe to use, a process completed
11 just a few years ago in 2006.
12 We have to wonder why this Panel is
13 being asked to hurry up and make scientific judgments
14 under a whole new scientific terminology called points
15 of departure.
16 We also wonder why no one seems to be
17 taking stock of atrazine's documented benefits to the
18 environment. One of these clearly is in the increasing
19 amount of acres using no-till practices, a practice
20 that stores carbon in the soil and for which atrazine
21 is an important component.
22 Our Farm Bureau members in all 50 states
23 look at the EPA's recent actions with dismay and
24 frustration. Farmers are deeply concerned that this
25 process will result in unjustified restrictions or

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1 elimination of an important crop-protection tool.
2 Again, we appreciate this opportunity to
3 submit our comments. Thank you.
4 **DR. STEVEN HEERINGA:** Thank you very
5 much, Mr. Wegmeyer. Sorry, I had your name wrong
6 before; that's the way I had it on my sheet. We'll
7 correct that in the final.
8 Finally, in terms of scheduled
9 presenters, I would like to invite up Rebeckah Freeman
10 Adcock, who is Director of Government Affairs for
11 CropLife America.
12 Turn on the mic.
13 Welcome.
14 **MS. REBECKAH ADCOCK:** Thank you to the
15 Panel and to EPA for the opportunity to comment. My
16 name is Rebeckah Adcock, here today representing
17 CropLife America. CropLife America's member companies
18 proudly manufacture, register and distribute crop-
19 protection products to American agriculture. Our
20 members work with farmers and ranchers every day to
21 ensure that crop-protection tools are registered
22 properly and used correctly.
23 America's abundant, affordable food
24 supply depends on the availability of safe, effective
25 crop-protection products. Moreover, our collective

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1 ability to feed the world centers on the efficiency and
2 ingenuity of modern agricultural technologies like the
3 products used to protect crops and animals from pests.
4 It's critically important to remind
5 ourselves of these fundamental points, because in
6 recent months we've seen serious deviations from the
7 regular order, transparency and scientific integrity of
8 EPA's risk-based pesticide review process.
9 From CropLife America's point of view,
10 the legality and scientific validity of the Pesticide
11 Program has been profoundly distorted by unsupported
12 science, sensationalized journalism and political
13 expediency.
14 Even so, in the interest of science and
15 process, CropLife America would like to address one of
16 the EPA's charges to the SAP; specifically, the
17 question of whether the Agency should consider
18 monitoring end results for raw surface water when
19 assessing the potential human health effects associated
20 with exposure to pesticides in finished drinking water.
21 We believe the answer is no, it is not
22 appropriate to use pesticide levels in raw water for
23 this purpose. While monitoring data can be an
24 effective reality check for modeled estimates of
25 residue potential in surface and groundwater, pesticide

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1 concentrations in raw water are not an effective
2 measure of the potential for risk to humans from
3 exposures to pesticides from consuming drinking water.
4 To that point, the U.S. Geological
5 Service also recognizes that finished water supplies
6 are the best measure of pesticide concentrations for
7 evaluating human exposures.
8 In a joint monitoring program conducted
9 by USGS and EPA investigating pesticide concentrations
10 in raw water and finished drinking water from surface
11 water sources, USGS concluded that "Finished water
12 samples provide the best practical measure of pesticide
13 concentrations that a supplied population is exposed to
14 in drinking water".
15 The Safe Drinking Water Act requires
16 monitoring of drinking water that is representative of
17 the water that the public actually consumes. For that
18 reason, the Act in its implementing regulations
19 expressly provide that monitoring for the health
20 effects of synthetic organics like atrazine should be
21 confined to finished water and that sampling should
22 occur within the community water systems that actually
23 serve consumers.
24 Safe Drinking Water Act regulations also
25 set out monitoring and sampling requirements intended

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1 to ensure that the best scientific methods are used to
2 collect and analyze the drinking-water data. Again,
3 the regulations dictate that sampled water should come
4 from water that consumers actually drink.
5 Raw water, again, while potentially
6 important to study for residue modeling and ecological
7 considerations, is not drinking water. And it is
8 neither consumed by nor provided to the public by
9 community water suppliers.
10 Monitoring of raw surface water is
11 employed only in limited circumstances under the Safe
12 Drinking Water Act. As a matter of fact, raw-water
13 monitoring occurs only when a community water supplier
14 seeks to be exempted from existing monitoring
15 requirements for a particular contaminant.
16 Specifically, where regular monitoring has over
17 successive periods consistently shown no detection of
18 the contaminant in the samples taken, a community water
19 system may conduct monitoring of the surface raw-water
20 sources as evidence that further monitoring for the
21 contaminant is not necessary.
22 In the case of atrazine, EPA has
23 undertaken a rigorous, transparent and comprehensive
24 human health risk analysis, including the adoption of
25 drinking water standards as required under the Safe

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1 Drinking Water Act.
2 In adopting health-based standards for
3 drinking water, EPA is required to identify a Maximum
4 Contaminant Level Goal, or MCLG, and the law requires
5 that the MCLG must be set "at a level at which no known
6 or anticipated adverse affects on the health of persons
7 occurs" and "which allows for an adequate margin of
8 safety inputs".
9 Using the best available science,
10 supporting studies and data, EPA has concluded that an
11 annual average of 3 parts per billion of atrazine in
12 drinking water represents the appropriate MCLG. In
13 other words, that's the level at which no known or
14 anticipated adverse effects on human health will occur,
15 factoring in a large margin of safety.
16 EPA next sets an enforceable standard
17 for a permissible level of a contaminant that is set as
18 close to the MCLG as is feasible. This is called the
19 Maximum Contaminant Level, or MCL.
20 For atrazine, the enforceable MCL is set
21 at the same level as the MCLG, an annual average of 3
22 parts per billion.
23 Data-collection regulations provide that
24 monitoring of drinking water for atrazine may be
25 performed on finish water within community water

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1 systems, and to that end public water suppliers are
2 required to do quarterly monitoring for atrazine down
3 to its level of detection.
4 That detection level is, as most of you
5 know, several orders of magnitude below the actual MCL
6 or MCLG. In the event that the MCL for the contaminant
7 is exceeded in finished drinking water, additional
8 monitoring can be ordered and has in some cases been
9 ordered by EPA.
10 In summary, the Charge Questions before
11 the SAP with regard to atrazine monitoring are confined
12 to the issues of drinking water quality, which is
13 necessarily an examination of human health effects that
14 flow from the actual consumption of finished water that
15 is consumed by the public.
16 CropLife America believes that science
17 and the law dictate the SAP's assessment of these
18 issues and that this assessment should necessarily be
19 focused on finished drinking water and not raw water.
20 To date, the re-review of atrazine has
21 provided neither a sound new process nor any
22 substantive basis for revisiting or revising EPA's
23 monitoring protocols or drinking water standards for
24 atrazine.
25 We strongly urge the SAP to provide

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1 recommendations to EPA based on the sound science that
2 is already the foundation of the Safe Drinking Water
3 Act, including the mandated atrazine monitoring of
4 finished water at sampling points within the known
5 distribution centers of community water suppliers.
6 Our comments should also be received as
7 more than just concerns about the specific charges
8 within this special review of atrazine. Much more is
9 it stake. CropLife America knows that the work of this
10 SAP may well determine whether the Pesticide Program
11 further descends into the scientific abyss, regulating
12 based on unsupported science, activism and politics, or
13 whether your recommendations guide EPA back to the
14 light of FIFRA's transparent, scientific-based review
15 and the rigorous process and standards established by
16 the Safe Water Drinking Act.
17 Thank you.
18 **DR. STEVEN HEERINGA:** Thank you very
19 much, Ms. Freeman Adcock.
20 Ms. Freeman Adcock, will you be
21 providing copies of your comments to the Docket?
22 **MS. REBECKAH ADCOCK:** It is my
23 understanding that our Science and Reg Team is going to
24 actually provide more extensive written comments based
25 on my brief comments.

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1 **DR. STEVEN HEERINGA:** Okay, sure.
2 **MS. REBECKAH ADCOCK:** And we'll make
3 sure that we get something to you by the close.
4 **DR. STEVEN HEERINGA:** As long as they're
5 in before the close of the meeting
6 **MS. REBECKAH ADCOCK:** Absolutely.
7 **DR. STEVEN HEERINGA:** we'll be fine
8 with it.
9 **MS. REBECKAH ADCOCK:** Thank you.
10 **DR. STEVEN HEERINGA:** Thank you very
11 much; again just a technicality, things arrive after
12 the close of the meeting.
13 Okay. At this point in time, we have
14 completed public comment from all of the scheduled
15 public commenters, and I want to thank everyone for
16 being so focused in their presentations.
17 We made the decision, I made the
18 decision to defer Panel questions to the presenters.
19 What I'd like to do at this point, we have at least 30
20 to 45 minutes that we can use to address comments or
21 questions of clarification to any of the public
22 commenters that we heard this afternoon; some of them
23 may have had to leave already. I think unfortunately
24 Dr. Handa may have had to leave.
25 But I would like to do it in an order.

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1 I am not going to close the period for public comments
2 this afternoon; I will leave it open until tomorrow
3 morning, because I know there's a lot to digest.
4 But if you have something that is
5 specifically related, a question or clarification,
6 something you didn't understand or you wanted to
7 explain in a little more detail for one of the public
8 commenters who presented this afternoon and
9 particularly if it relates, of course, to our Charge
10 Questions.
11 There are a lot of interesting issues of
12 general science or related science that I'm sure we
13 could get into, but I would prefer that you save those
14 for separate conversations and focus on questions that
15 would relate specifically to the Panel's deliberation
16 on the Charge Questions.
17 Any members of the Panel, I guess you
18 would have to indicate who you'd like to call up, and
19 rather than create a round-robin, let me start in
20 reverse order. Any questions for Ms. Adcock?
21 For Tyler Wegmeyer?
22 For Mr. Slaughter, the Center for
23 Regulatory Effectiveness?
24 Any questions for the Triazine Network
25 team, Mr. White and colleagues?

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1 Ken, Dr. Portier, has a question for Mr.
2 Hall. Mr. Hall, are you still here?
3 He may have been in town okay. This is
4 I think it's well, what I will ask Ken to do is maybe
5 to speak with Mr. White, and if it's again something
6 that needs to be fully disclosed to the Panel, he'll
7 bring it back and mention it publicly during the
8 meeting tomorrow.
9 Any questions for Mr. Snyder?
10 Questions for Dr. Hayes?
11 Dr. Hayes here yet?
12 Very good. Okay, any questions for Dr.
13 Hayes on his presentation?
14 Dr. Hayes, are you going to be here
15 tomorrow morning first thing?
16 **DR. TYRONE HAYES:** I will.
17 **DR. STEVEN HEERINGA:** Okay. Thank you
18 very much.
19 Any questions for the reversed order,
20 and again probably in terms of new information
21 presented to the Panel in terms of studies and data,
22 the Syngenta Crop Protection Group, questions for any
23 members of the Syngenta panel?
24 And again, I'll leave this open
25 overnight. I know all of the public commenters can't

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1 be back here tomorrow; but if there are questions or
2 issues that come to mind as you study the materials
3 tonight, we'll have a chance to ask those first thing
4 in the morning.
5 Dr. Portier has a question for Dr.
6 Hendley.
7 Paul Hendley?
8 This would relate to the water sampling
9 and monitoring.
10 **DR. KENNETH PORTIER:** Thank you for
11 coming up, Paul.
12 In looking at your presentation, there's
13 so much data here and you've been doing a lot of
14 modeling, and as I was listening to your presentation I
15 was trying to answer some of my think of the question,
16 and that is with all of the information you have.
17 All the models you have, are you at the
18 point where you'd be able to answer a question for a
19 particular community water system whether the incoming
20 water supply would meet a criteria that it would exceed
21 a certain level? Say we set a certain level for a
22 certain number of days. Would the models be able to
23 estimate the probability of exceeding that kind of a
24 duration amount event?
25 **DR. PAUL HENDLEY:** This is Paul Hendley.

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1 I think the answer is we're getting
2 there. I think assuming it's a community water system
3 from the -- I'm from the VMP Program, for which we have
4 a lot of history.
5 Assuming we have the information from
6 the current day history and this year's data, I believe
7 that if you look at the fact, we can very well define
8 what the maximum event peak that we might not have
9 sampled would be and what the distribution of those
10 peaks might be in the context of the weather and the
11 environment and stream flow; we have the tools to do
12 that. I think the dots haven't quite been joined up
13 yet to do that, but the probability is there.
14 With 50,000 sort of raw and finished
15 samples coming from the VMP and AMP Program, the
16 distribution of residues that will occur in Midwest
17 watersheds is well understood.
18 The knowledge we have about and this is
19 where I think the important insight that came recently
20 is thinking about using the flow rather more, the flow
21 that's happening at the site will connect those two
22 pieces of information.
23 **DR. STEVEN HEERINGA:** Thank you, Dr.
24 Hendley, and again I apologize for referring to you by
25 the wrong name.

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1 Dr. Akana.
2 **DR. SUSAN AKANA:** I'm sorry, did you say
3 Dr. Robert Handa is here?
4 **DR. STEVEN HEERINGA:** I believe that Dr.
5 Handa is here; but he needs to leave shortly, so if you
6 have a question for Dr. Handa, I'll --
7 **DR. SUSAN AKANA:** Only quick questions.
8 Dr. Handa, as you know, I'm very
9 interested in the adrenal response that you see with
10 the atrazine. Do you know anything about the adrenal
11 weight or machinery of the adrenal gland that's been
12 treated with atrazine?
13 **DR. ROBERT HANDA:** I don't believe we
14 measured the adrenals; I would have to ask Charles,
15 Charles Breckenridge.
16 **DR. SUSAN AKANA:** Also in your studies
17 with the GnRH neurons, that was collected at 1830,
18 something like that?
19 **DR. ROBERT HANDA:** That was collected at
20 about the time of the peak of the LH surge. Now, we
21 had to guess on that.
22 **DR. SUSAN AKANA:** Uh-huh.
23 **DR. ROBERT HANDA:** So I believe it was
24 about an hour before lights out, which is about the
25 time, give or take an hour, that our colony shows the

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1 peak of the LH surge.
2 **DR. SUSAN AKANA:** I was quite taken with
3 the very small response of the CRH rats in the PDN. By
4 any chance, did you look at any other CRH bodies in the
5 mediobasal hypothalamus?
6 **DR. ROBERT HANDA:** No, we didn't. We
7 went on to another study where we've looked at CRH
8 heteronuclear RNA to try and identify CRH cells
9 specifically and haven't identified any increased CRH
10 heteronuclear RNA.
11 **DR. SUSAN AKANA:** Oh, I'm thinking
12 specifically in brain sense, like amygdala or BNST?
13 **DR. ROBERT HANDA:** No.
14 **DR. SUSAN AKANA:** The distributed CRF
15 system.
16 **DR. ROBERT HANDA:** Right. No, we
17 haven't.
18 **DR. SUSAN AKANA:** Thank you.
19 **DR. STEVEN HEERINGA:** Dr. Handa, I
20 believe there's also a question from Dr. LeBlanc and
21 then a question from Dr. Legan.
22 **DR. GERALD LEBLANC:** I have a question
23 regarding a couple of slides you had up there. I'm
24 just going to read the heading for the first one --
25 that is, "Atrazine does not alter estrogen-induced LH

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1 surge in the peripubescent animal" -- and then the
2 following slide was the same thing but in the adult
3 animal. And I assume that your conclusion that there
4 was no effect was based on that total profile of the
5 induction of LH over that time course.
6 **DR. ROBERT HANDA:** Right, and we also
7 analyzed the data in terms of peak amplitude,
8 irrespective of when the peak was, as well as area
9 under the curve.
10 **DR. GERALD LEBLANC:** But looking at
11 specific time points, there seems to be in many
12 instances in both slides where there's a nice dose-
13 response of LH suppression with atrazine dose.
14 **DR. ROBERT HANDA:** So as it turns out,
15 there is an occasional point that may have been
16 different by post hoc. It's kind of hard to say that
17 we should analyze by post hoc. If the two-way analysis
18 is at variance or one-way analysis is at variance, it
19 doesn't show up significant overall.
20 **DR. GERALD LEBLANC:** Thank you.
21 **DR. STEVEN HEERINGA:** Dr. Legan.
22 **DR. SANDRA LEGAN:** I have a question
23 about a study that you did with the intact breast you
24 gave atrazine 4 days in a row starting on one day of
25 the cycle and then to see if it affected cyclicity,

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1 was it? And you measured the LH surge?
2 **DR. ROBERT HANDA:** Right.
3 **DR. SANDRA LEGAN:** The LH
4 concentrations, and then you mentioned you had a graph
5 with bars. As the dose increased to the 50 mg/kg dose,
6 you had about 25% of the animals in that group had
7 delayed their cycle to go to well
8 **DR. ROBERT HANDA:** Exactly.
9 **DR. SANDRA LEGAN:** they were a 5-day
10 cycle instead of a 4-day cycle.
11 **DR. ROBERT HANDA:** A 5-day cycle, right.
12 So --
13 **DR. SANDRA LEGAN:** And that was
14 determined how?
15 **DR. ROBERT HANDA:** On every morning the
16 animal is smeared. If they showed a proestrus surge or
17 a proestrus smear, they would be sampled for LH. If
18 they did not, we would wait till the next day and then
19 they would be sampled. And that's the only group, in
20 fact, where a significant number of animals we had to
21 delay the taking of the blood samples till the
22 following day.
23 **DR. SANDRA LEGAN:** And did you combine
24 the LH levels from the 4- and the 5-day rats in all
25 your data?

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1 **DR. ROBERT HANDA:** We did that in two
2 ways. We analyzed the data for the 4 and 5 days
3 combined, and that was the following slide after that,
4 as well as the 4-day cyclers only to see if there was
5 an impact of having to wait the extra day on the
6 effective averaging, and there was no difference in
7 terms of their profiles.
8 **DR. SANDRA LEGAN:** So there was no
9 difference in the LH profiles between the animals that
10 had 4-day cycles and the animals that had 5-day cycles
11 **DR. HANDA:** Well, we only had a few. We
12 only had --
13 **DR. SANDRA LEGAN:** Yeah, 5 animals out
14 of 20, maybe?
15 **DR. ROBERT HANDA:** Yeah, so we compared
16 4- and 5-day cyclers with 4-day cyclers alone.
17 **DR. SANDRA LEGAN:** I see, because so
18 that it comes up to mind that I guess if I were doing
19 it, I might not combine the 4- and 5-day cyclers unless
20 I could statistically determine that they were not
21 different.
22 **DR. ROBERT HANDA:** Right.
23 **DR. SANDRA LEGAN:** And there's an end of
24 maybe if you had 20 per group, which you started
25 with...

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1 **DR. ROBERT HANDA:** Right, there were --
2 **DR. SANDRA LEGAN:** there would be --
3 **DR. ROBERT HANDA:** -- about 19 in that
4 group at the end, and so I believe there were 5, 5 --
5 **DR. SANDRA LEGAN:** Five that --
6 **DR. ROBERT HANDA:** -- that were delayed
7 and became 5-day cyclers.
8 **DR. SANDRA LEGAN:** -- delayed and --
9 **DR. ROBERT HANDA:** -- and became 5-day
10 cyclers.
11 **DR. SANDRA LEGAN:** -- 14.
12 **DR. ROBERT HANDA:** Right.
13 **DR. SANDRA LEGAN:** You could still do a
14 **DR. ROBERT HANDA:** We could do an
15 analysis on those alone, you know; it was much easier
16 to do the 4 days alone and see if there was in fact any
17 difference.
18 **DR. SANDRA LEGAN:** So the reason I'm
19 asking is because yesterday I mentioned that this drop
20 in the this effect of atrazine in attenuating the
21 amplitude in the LH surge is maybe only critical if the
22 LH surge amplitude is low enough to have adverse
23 sequelae, such as lengthening cycle.
24 So if the animal has too low an amount
25 of LH, obviously, they will not ovulate, and they may

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1 you know, the follicles are still producing estrogen
2 and they may have an LH surge the next day, which you
3 saw.
4 **DR. ROBERT HANDA:** Right.
5 **DR. SANDRA LEGAN:** So I guess your data,
6 would you say that your data indicate that in the LH
7 surge attenuation that you saw in that dose group was
8 about a 50% drop? If you look at the numbers, whatever
9 the LH peak was in the one group, it was about half of
10 that.
11 **DR. ROBERT HANDA:** It was, it was a
12 little over half.
13 **DR. SANDRA LEGAN:** Okay. So 55-
14 **DR. ROBERT HANDA:** 50% --
15 **DR. SANDRA LEGAN:** 60%, so you could
16 go 60?
17 **DR. ROBERT HANDA:** -- yeah, somewhere in
18 that range.
19 **DR. SANDRA LEGAN:** So we have a 40% --
20 and there's been data presented and you know well that
21 that's enough for fertility in the rat so that supports
22 do you think that supports the possibility that
23 atrazine might have another effect that ultimately is
24 deleterious than only, maybe including even, but not
25 solely the drop, the 50%, say, drop or whatever in the

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1 LH surge amplitude?
2 **DR. ROBERT HANDA:** Well, I've thought
3 about that a lot in terms of what that would mean. And
4 again, coming into mind the fact that we don't see a
5 tremendous drop in the surge and why that some animals
6 would be delayed.
7 And frankly, I don't know for sure why
8 they would be delayed in their cycle; I could only
9 guess. They appeared to have normal, perhaps, you
10 know, decreased in amplitude like the rest of the
11 group.
12 But certainly they were sufficient
13 enough that you would expect they would be on the
14 physiological end of things that they would show normal
15 cycles.
16 **DR. SANDRA LEGAN:** Uh-huh.
17 **DR. ROBERT HANDA:** So again, there may
18 be something else appearing; we don't know.
19 **DR. SANDRA LEGAN:** Thank you.
20 **DR. STEVEN HEERINGA:** Thank you very
21 much.
22 Dr. Breckenridge, I just acknowledge
23 you.
24 **DR. CHARLES BRECKENRIDGE:** Thank you
25 very much; Charles Breckenridge, Syngenta.

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1 There is rather extensive literature on
2 the cycle-disrupting effects of atrazine as it
3 progresses through to mammary tumor development in a
4 constant estrus state; so clearly, high doses of
5 atrazine will lengthen the cycle, and so it may well be
6 that these animals in this duration are actually on the
7 edge of the cycle-disruption effect.
8 I mean, we don't this certainly is
9 consistent with those other studies both by Dr. Cooper
10 and by us.
11 **DR. STEVEN HEERINGA:** Dr. Cooper has a
12 question for Dr. Handa.
13 **DR. RALPH COOPER:** Yes, I just wanted to
14 I guess get your opinion, given all the studies that
15 you've done looking at the interrelationship of the HPA
16 axis and atrazine and stress, and what's your opinion
17 of the possibility that the situation in an
18 experimental study where there is higher levels of
19 stress where the effects of atrazine might in fact be
20 blunted? Do you think that's possible?
21 **DR. ROBERT HANDA:** I am not sure I
22 understand your thinking; there may be in fact elevated
23 levels of stress, which the chronic atrazine would then
24 decrease.
25 **DR. RALPH COOPER:** Or it would make it

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1 more difficult to see the effects of atrazine.
2 **DR. ROBERT HANDA:** You would expect,
3 then, that you would see a difference compared to the
4 vehicle treated controls, and we don't see a
5 difference, in fact. So they're almost identical after
6 7, 14 and 28 days of administration of atrazine. So I
7 would expect that would not be the case.
8 We can also look at the absolute values
9 of corticosterone, and we know from a number of studies
10 historically where the levels of corticosterone should
11 be approximately, about 2 to 5 Ug/g. And they seemed
12 to be in that range for both males; and the females are
13 always a little higher, and they seemed to be in the
14 normal range for females as well.
15 **DR. STEVEN HEERINGA:** Dr. Krishnan, do
16 you have a comment for Dr. Handa, a question?
17 **DR. KANNAN KRISHNAN:** In the slide where
18 you plotted the NOELs for atrazine, the Cooper study,
19 et al., from Cooper 2010 wasn't there; it doesn't fit
20 the pattern. Do you want to comment on that?
21 **DR. STEVEN HEERINGA:** Dr. Breckenridge?
22 **DR. KANNAN KRISHNAN:** Yes.
23 **DR. CHARLES BRECKENRIDGE:** Charles
24 Breckenridge, Syngenta.
25 That was more like a historical slide we

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1 were bringing up in the context of the design for the
2 developmental study. That was really the reason why we
3 did the developmental study, because we recognized that
4 the duration of treatment was confounded with age.
5 And so in some ways, that slide is
6 perhaps needing a bit of clarification. It really
7 wasn't duration-indicated. In the higher dose groups,
8 those are really short duration, 2, 3 days.
9 And as you went on in fact, in the
10 Morseth 1986 was in fact continuous dosing for at least
11 six months. So the whole intent of the study that we
12 did with the developmental effects or investigating
13 potential developmental effects was to elaborate
14 whether in fact at a particular age a 2-week exposure
15 would produce the same effect as a 90-day consecutive
16 exposure, and that's effectively why we had recovery
17 groups in there.
18 We were fully anticipating to see a
19 response at 90 days and we did not, and that was
20 somewhat surprising to us. In fact, we didn't see, as
21 you might have noticed, 2 weeks of dosing at 90 days
22 didn't produce an effect.
23 Yet, 1 week of dosing at that same age
24 did. And so that is a bit perplexing to us, and we'll
25 be doing some investigations to further understand

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1 whether in fact there is a falloff, especially in young
2 animals, of duration of treatment as you first
3 introduce the compound versus continue that duration
4 for some time.
5 So, in fact, we didn't put Dr. Cooper's
6 data on that slide. We didn't put our data on that
7 slide, either. But it was more historical slide coming
8 from the December SAP and I think reiterated by the EPA
9 in one of the early ones this year.
10 **DR. STEVEN HEERINGA:** Dr. McManaman.
11 **DR. JAMES MCMANAMAN:** I'll let Dr. Handa
12 go away. I have a question for Dr. Hovey.
13 **DR. STEVEN HEERINGA:** Thank you, Dr.
14 Handa. I understand you have a plane to catch, so
15 **DR. ROBERT HANDA:** Thank you.
16 **DR. JAMES MCMANAMAN:** Yeah, I need some
17 clarification. It's slide 12, it's the maternal body
18 weight change. There are asterisks indicate two
19 different things on this slide, so the pair-fed versus
20 the control, or is it statistically significant, or is
21 it the pair-fed versus the 100 mg/kg/d? Which one is
22 it, because it's not clear?
23 **DR. RUSS HOVEY:** Yeah, sure. So the
24 question relates to significant difference associated
25 with the pair-fed group. And so that was a comparison

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1 of the pair-fed animals to the 100 mg/kg group.
2 The reason we made that comparison was
3 because that was what they were yoked to, whereas the
4 atrazine-dosed females were compared against the
5 vehicle dose control. And in addition, the pair-fed
6 group was significantly different from the vehicle
7 exposed control group as well.
8 **DR. JAMES MCMANAMAN:** And that was both
9 during lactation and during gestation?
10 **DR. RUSS HOVEY:** No, so during gestation
11 there was a -- let's pull the slide up.
12 So during gestation, there was a
13 significant reduction versus the high-dose atrazine.
14 So the question becomes why was there even a more
15 pronounced decrease in body weight gain.
16 What we think was going on there is that
17 there perhaps is a different mechanism at play in terms
18 of these animals that are being forced to restrict
19 their food intake by matching them to the atrazine
20 group, whereas the atrazine animals are, if you will,
21 voluntarily restricting their intake.
22 **DR. JAMES MCMANAMAN:** So is there any
23 concern about difference in metabolism between the
24 atrazine-treated group versus the control group?
25 **DR. RUSS HOVEY:** Between the atrazine-

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1 treated group and the control group?
2 **DR. JAMES MCMANAMAN:** Right. It would
3 appear that one explanation would be it's the atrazine-
4 treated group are more metabolically inefficient;
5 therefore, their weights did not decrease as much as
6 the pair-fed.
7 **DR. RUSS HOVEY:** Yes, so I don't think I
8 can comment on any sort of metabolic efficiency of
9 those animals, per se. I think we were looking at it
10 the other way, and that is that both animals are
11 undergoing a metabolic stress, if you will, obviously
12 not demonstrating as much maternal body weight gain as
13 the control animals would.
14 **DR. JAMES MCMANAMAN:** One more question.
15 This is on slide 18, and that is the whole mount
16 analysis. There's an indication that the pair-fed
17 versus the atrazine 100 are significantly different.
18 The atrazine 100 have fewer end buds than the pair-fed
19 group, is that correct?
20 **DR. RUSS HOVEY:** That's correct.
21 **DR. JAMES MCMANAMAN:** Okay. The
22 analysis that was given, provided by Syngenta in the
23 papers that we received, the statistician said that
24 there was no difference. Does your conclusion differ
25 from his, or is there a mistake there?

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1 **DR. RUSS HOVEY:** Oh, I'd have to defer
2 to the original analysis on that. We didn't notice
3 that, so we certainly will check if we do have an error
4 in that report; but I believe as we represented it here
5 is correct.
6 **DR. JAMES MCMANAMAN:** Okay. So given
7 that there is a statistically significant difference in
8 the number of end buds, would you then conclude that at
9 the 100 mg/kg atrazine that there is an effect on the
10 mammary gland properties?
11 **DR. RUSS HOVEY:** Now, can you repeat the
12 question in terms of which treatment you're comparing?
13 **DR. JAMES MCMANAMAN:** Well, if we're
14 comparing the pair-fed, which I agree with you is an
15 appropriate control; but if you compare that with the
16 100 mg/kg atrazine, which would be the proper
17 comparison, then you see a statistically significant
18 difference in the number of terminal end buds at the
19 date of vaginal opening.
20 **DR. RUSS HOVEY:** So I guess my comment
21 would be that in fact the pair-fed animals, by virtue
22 of them having a dam that was matched for a decrease in
23 maternal body weight gain during gestation, the fact
24 that they demonstrated an increase in end bud number at
25 the time of vaginal opening relative to the vehicle

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1 treated controls suggests that there was a in utero
2 effect, if you will, or a carryover effect from that
3 maternal treatment due to body weight restriction.
4 **DR. JAMES MCMANAMAN:** Well, I would
5 agree with that. But also, then you're leaving out the
6 comparison to the pair-feds.
7 **DR. RUSS HOVEY:** Uh-huh.
8 **DR. JAMES MCMANAMAN:** And that would
9 seem to me the more appropriate comparison.
10 **DR. RUSS HOVEY:** So it suggests that
11 there is potentially a different mechanism at play in
12 terms of the fact that the 100 and the 50 mg/kg doses,
13 I'm not showing a dose-dependent response.
14 **DR. JAMES MCMANAMAN:** Well, clearly,
15 there was not a dose-dependent response on this yet.
16 But you did mention that diet and nutrition can affect
17 mammary gland development.
18 **DR. RUSS HOVEY:** Uh-huh.
19 **DR. JAMES MCMANAMAN:** And presumably if
20 we're factoring in body weights here, that they've had
21 the same restriction of diet because they've reduced
22 their intake; therefore, it would seem that it can't
23 completely explain everything by reduced weight.
24 **DR. RUSS HOVEY:** Right, nobody's
25 consistent with even, you know, our observation during

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1 gestation in terms of the fact that the forced
2 restriction of food intake did not lead to an identical
3 maternal body weight change.
4 **DR. JAMES MCMANAMAN:** I have one more
5 question, sorry. So you note -- I think it's back on
6 that previous -- about weight that the 50 mg/kg
7 atrazine was statistically different, basically lower
8 in body weight compared to the control.
9 **DR. STEVEN HEERINGA:** Dr. McManaman,
10 which slide are you looking at?
11 **DR. JAMES MCMANAMAN:** This is slide 12.
12 **DR. STEVEN HEERINGA:** 12, thank you.
13 **DR. JAMES MCMANAMAN:** Yeah.
14 So is that consistent finding in all the
15 studies, because I believe in one of the other studies
16 that we received -- I know it by I think it's Coder A,
17 I believe, or Coder I can't remember which one it was;
18 but there was no difference in the weights of the 50
19 mg/kg. So I'm wondering, is there some explanation for
20 why this one was different and the other one was not?
21 **DR. RUSS HOVEY:** Without going back to
22 the original data, one suggestion is that this is a
23 representation of the maternal body weight change
24 during the whole dosing period.
25 **DR. JAMES MCMANAMAN:** Okay.

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1 **DR. RUSS HOVEY:** And that may account
2 for your question.
3 **DR. JAMES MCMANAMAN:** Right. Thank you.
4 **DR. STEVEN HEERINGA:** Thank you, Dr.
5 McManaman and Dr. Hovey.
6 Dr. Akana.
7 **DR. SUSAN AKANA:** On the same slide, I'm
8 interested in their pair-fed controls. Rats normally
9 eat in a diurnal rhythm; so with pair-fed control, how
10 did you give them their food, diurnally or in one lot,
11 or did you yoke it to a diurnal pattern of the
12 controls?
13 **DR. RUSS HOVEY:** So if I may, I will
14 defer to Dr. Coder from WIL Research, who conducted the
15 animal side of things.
16 **DR. STEVEN HEERINGA:** Sure. Dr. Coder,
17 your full name for the record, please.
18 **DR. PRAGATI CODER:** Pragati Coder, WIL
19 Research. I am a Senior Toxicologist in the
20 Developmental and Reproductive Toxicology Department.
21 The pair-fed group was one day behind in
22 gestation, so they were mated a day after the 100 mg
23 group and were pair-fed the diet the 100 mg/kg group,
24 the mean amount that they consumed on the previous day.
25 But the diurnal consumption was not 100. It was given

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1 to them as a lump amount at the beginning of the day.
2 **DR. SUSAN AKANA:** Okay. And then a
3 general question to this data, is this a study that
4 originally had a design of cross-fostering?
5 **DR. CHARLES BRECKENRIDGE:** That's
6 correct, there's two additional groups that were
7 maintained as separate groups going into the study.
8 So --
9 **DR. SUSAN AKANA:** And this is the one
10 where there was a sad failure of survival of the cross-
11 fosters, is that correct?
12 **DR. CHARLES BRECKENRIDGE:** Correct.
13 **DR. SUSAN AKANA:** Did this take place in
14 the same experimental room as the other dose studies,
15 the atrazine?
16 **DR. CHARLES BRECKENRIDGE:** I will defer
17 to Dr. Coder on that.
18 **DR. PRAGATI CODER:** Yes, it was.
19 **DR. SUSAN AKANA:** And if you rack your
20 brain, do you see any conceivable reason for the
21 failure for fostering, because I would consider that a
22 red flag for the housing for the whole entire room.
23 **DR. PRAGATI CODER:** They were housed in
24 the same room. Animals were initially assigned to the
25 same control in high-dose group. It was after

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1 parturition was complete on lactation day 0 that we
2 tried to foster the pups. We routinely foster rats in
3 our facility and unfortunately don't do it as often
4 with Long-Evans.
5 We tried several different things to
6 facilitate the fostering. Initially, what we tried to
7 do was foster the entire litter. Unfortunately, in a
8 GLP compliant situation, we have to record observations
9 on every pup, and in an electronic database system it's
10 difficult to foster a half-and-half model that was done
11 on previous studies.
12 So when the whole litter was taken, it
13 was quite obvious within minutes that the dam would
14 immediately begin to cannibalize the pups.
15 So the next thing we tried was since we
16 were mainly interested in the female pups in this
17 study, we tried to maintain the male pups with the
18 original dam and tried to put the female pups in the
19 nest, laid them with the male pups to facilitate maybe
20 a better chance of fostering. That didn't work,
21 either.
22 We even tried things like rubbing the
23 pups against the dam prior to putting them in the cage,
24 which didn't work. We tried even vanilla extract on
25 the snout of the dam to see if that might remove the

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1 scent of the pups or prevent them from being able to
2 identify self versus non-self, but that didn't work,
3 either.
4 **DR. SUSAN AKANA:** What was the duration
5 of time over the fostering attempts? Like were you
6 trying to foster over, say, three or four days, you
7 know, among the gestation dates or
8 **DR. PRAGATI CODER:** The entire study I
9 believe was staggered maybe over five or seven days.
10 Pretty much by the end of the second day we knew the
11 fostering was not going to work, and in order to
12 conserve the remaining groups and group sizes, we had
13 to make a terminal decision about those groups.
14 **DR. STEVEN HEERINGA:** Thank you very
15 much, Dr. Coder, Dr. Akana.
16 Yes, Dr. McManaman.
17 **DR. JAMES MCMANAMAN:** So I have a
18 question as a follow-up of Dr. Akana's question. One
19 difference between the Syngenta study and Dr. Fenton's
20 study was that the animals are housed in Dr. Fenton's
21 study on a 14/10 light/dark cycle versus the 12/12.
22 It's my understanding that differences in light/dark
23 cycles can significantly affect responses, and I would
24 like to get your response to that concern.
25 **DR. PRAGATI CODER:** All the LH surge

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1 studies were on a 14/10 light cycle in our facility,
2 too. From the moment of animal arrival.
3 **DR. JAMES MCMANAMAN:** Okay, but that's
4 not what's reported. It's reported as a 12/12, I
5 believe.
6 **DR. PRAGATI CODER:** I will have to look
7 into the discrepancy--
8 **DR. JAMES MCMANAMAN:** Okay.
9 **DR. PRAGATI CODER:** --but I am 100% sure
10 they were 14/10.
11 **DR. JAMES MCMANAMAN:** Right.
12 **DR. STEVEN HEERINGA:** Dr. Lee.
13 **DR. HERBERT LEE:** I have a question for
14 Dr. Hendley.
15 **DR. STEVEN HEERINGA:** Yes, Paul Hendley.
16 You should let him stay up front, I guess.
17 **DR. HERBERT LEE:** So you sort of glossed
18 over this, but you presented it in the materials for
19 the Docket. There is a summary of results for the
20 Perry Lake sampling frequency analysis in terms of
21 looking at different -- it says "10,000 trials of
22 selected fixed frequency sampling" right here; this is
23 slide 11. I was wondering how you did the sampling?
24 "Fixed frequency" implies something to me that I don't
25 think you can do 10,000 trials of, so I'm perhaps

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1 misunderstanding.
2 **DR. PAUL HENDLEY:** Well, Paul Hendley
3 speaking.
4 So this is actually from a 2001
5 publication; this is not analysis Syngenta did. This
6 is a publication that I believe actually was a
7 combination of authorship from USGS and EPA.
8 I believe that they used some Monte
9 Carlo-style approach to pull the 10,000 sets of samples
10 from what, as far as I can tell from the literature,
11 were constructed 365-day time series.
12 **DR. HERBERT LEE:** Okay, thanks, I'll
13 follow up with the reference.
14 **DR. PAUL HENDLEY:** We'd be happy to
15 supply that.
16 **DR. STEVEN HEERINGA:** Dr. Legan.
17 **DR. SANDRA LEGAN:** Thank you. I have a
18 question for Dr. Plant.
19 **DR. STEVEN HEERINGA:** Dr. Plant, please.
20 **DR. SANDRA LEGAN:** My question relates
21 to your last slide. At the end of your talk, you put
22 the control mechanisms up and how estrogen feeds back
23 to the hypothalamus. On one side you talked about the
24 rat; on the other side about the primate, possibly
25 human.

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1 And my question is you have estrogen
2 positive feedback in the rat going to the preoptic area
3 where the GnRH neuron cell bodies are. And of course
4 in the monkey it goes to the mediobasal area of the
5 hypothalamus.
6 And that was kind of your main summary
7 point, along with all your other data, that kind of led
8 to the conclusion that the LH surge -- the positive
9 feedback, actually, of estrogen on the LH surge is
10 probably not the best or maybe not be the best endpoint
11 to look at in terms of being able to take this forward
12 and extend our conclusions to adverse possible effects
13 in humans.
14 And I just want to ask if you looked at
15 it a little differently and estrogen, since the GnRH
16 neurons, they have only estrogen receptor data, and
17 changes in the complement of those receptors are really
18 unrelated to either negative or positive feedback
19 actions of estradiol in the rodent; I don't know about
20 the primate offhand.
21 So estrogen positive feedback isn't
22 directly probably on the GnRH neurons. It's indirect
23 through any number of other areas of the brain, and
24 there in the background Draft Paper it alludes to the
25 catecholamine, catecholaminergic neurons, dopaminergic

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1 neurons. And as many of us understand, there's a
2 number of neurotransmitter systems involved.
3 So if you redrew your diagram and you
4 had estrogen positive feedback from higher centers
5 feeding ultimately to wherever the GnRH neurons are in
6 whichever species you happen to be looking at, do you
7 think it could be possible that the rat is an okay
8 model?
9 I mean, and that main difference that
10 remains would be the clock, you know, the time-of-day
11 gating of the surge through from the SCN and so forth.
12 So what do you think about that? Is that a
13 possibility?
14 **DR. TONY PLANT:** I think it's possible,
15 but I think that at the contemporary thinking of the
16 rodent world -- and I don't study the rodent -- but
17 that is that the kisspeptin and the tachykinin-b story
18 where people like Robert Steiner, Janice Simpair and
19 Cordova, the kisspeptin neurons mainly in the brain
20 generally are located in the AVPV, which is an area
21 above the optic chiasm here.
22 **DR. SANDRA LEGAN:** Uh-huh.
23 **DR. TONY PLANT:** They have estrogen
24 receptors, and there's also kisspeptin neurons in the
25 arcuate nucleus. They express also tachykinin-B and

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1 dynorphin; they're called candy neurons. Bob Goodman,
2 your colleague, characterized the term there.
3 But these neurons have estrogen
4 receptors, and all the data in the rodent suggests that
5 these neurons in the AVPV above the optic chiasm are
6 the site or a major site of the positive feedback
7 action of estradiol.
8 That fits very nicely with Goodman's
9 classical studies in the rodent, where you put
10 estradiol either in this region of the preoptic area or
11 in the NBH.
12 **DR. SANDRA LEGAN:** Uh-huh.
13 **DR. TONY PLANT:** And he found that the
14 only sort of surges in the rat when estradiol was
15 implanted here and not in the mediobasal hypothalamus.
16 So the contemporary stuff on the kisspeptin story fits
17 very nicely with the classical stuff.
18 And in the context of the primate, all
19 the classical work there eliminating the preoptic area
20 suggests that that is not involved in the regulations
21 of surge.
22 **DR. SANDRA LEGAN:** Right. But are there
23 kisspeptin neurons --
24 **DR. TONY PLANT:** No, no, there are
25 kisspeptin neurons.

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1 **DR. SANDRA LEGAN:** Then where are they
2 in the primate?
3 **DR. TONY PLANT:** As I say, they're --
4 **DR. SANDRA LEGAN:** They're inside the
5 MBH?
6 **DR. TONY PLANT:** No, the kisspeptin
7 neurons are in the preoptic area; now, my colleagues
8 will argue that the kisspeptin neurons in the primate
9 brain may not be homologous to the AVP in the rodent
10 brain. But there are kisspeptin neurons in the
11 preoptic area. There's also kisspeptin neurons in the
12 arcuate nucleus.
13 But I think the fundamentally important
14 studies are the studies in the human female, where the
15 GnRH neurons in the Coleman's patients never get into
16 the hypothalamus.
17 And yet, those women, if you give them
18 this uninterrupted intermittent GnRH drive, will cycle
19 spontaneously, will have normal pre-ovulatory surges.
20 And therefore, you have to exclude the entire
21 hypothalamus as being a site of positive feedback; it
22 has to be the pituitary.
23 **DR. SANDRA LEGAN:** Uh-huh.
24 **DR. TONY PLANT:** And coupled with Janet
25 Hall's data that the pulse generator still operates

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1 during the midcycle surge, and her pharmacological data
2 which suggests the amount of GnRH during the surge, the
3 LH surge in the human female, is actually less than
4 during the follicular phase, the most parsimonious
5 hypothesis is that in the human female all you require
6 and all you have for running the menstrual cycle is
7 this intermittent pulsatile pattern of GnRH, which is
8 driven by the mediobasal hypothalamus.
9 **DR. SANDRA LEGAN:** Uh-huh. Thank you.
10 **DR. TONY PLANT:** Probably by the candy
11 neurons.
12 **DR. SANDRA LEGAN:** Okay, thanks.
13 **DR. STEVEN HEERINGA:** Okay. Well, thank
14 you very much, Dr. Legan and Dr. Plant.
15 At this point in time, I think that I
16 will leave the period of public comment open.
17 Dr. Breckenridge, I will permit you a
18 comment here.
19 **DR. CHARLES BRECKENRIDGE:** Please. Just
20 for convenience, Dr. Plant would like to leave
21 early morning, and also I think Dr. Handa leaves
22 tomorrow as well, plus I believe the topics are breast
23 bud development.
24 So if there could be any questions
25 relating to that, we would like to give them, Dr. Hovey

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1 and Dr. Plant, an opportunity to answer them tonight,
2 or if you think it's a high likelihood --
3 **DR. STEVEN HEERINGA:** Right.
4 **DR. CHARLES BRECKENRIDGE:** -- you'll
5 have a discussion on these matters tomorrow, I don't
6 believe Dr. Handa can be here at all. Dr. Hovey, it
7 would inconvenience him for sure.
8 **DR. STEVEN HEERINGA:** Understood. I
9 think that as a courtesy here, looking at the Panel
10 members, are there other critical questions of
11 clarification for Dr. Plant or Dr. Hovey?
12 **FEMALE:** Dr. Kim?
13 **DR. STEVEN HEERINGA:** Dr. Kim will be
14 here tomorrow, is that correct? Okay.
15 I guess I would say that looking around
16 the room that we're satisfied that the key questions
17 that we feel need to be answered from those
18 presentations have been addressed, and we do have the
19 presentations and the information.
20 I assume, Dr. Breckenridge, if there's a
21 critical matter of fact that we could come back through
22 you and before the close of the proceedings.
23 **DR. CHARLES BRECKENRIDGE:** That's
24 correct, and I have Dr. Simpkins to help me with any
25 particular neuroendocrine type of question.

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1 Okay, thank you.
2 **DR. STEVEN HEERINGA:** In that case, what
3 I'd like to do today is bring the proceedings to a
4 close; but before I do that, I'll turn to the
5 Designated Federal Official.
6 Joe, do you have anything to say?
7 Okay, nothing today.
8 Again, I want to thank everyone who
9 participated today. A tremendous exchange of
10 information; as I always say, I learned a tremendous
11 amount and look forward again to picking this up
12 tomorrow morning.
13 We'll leave the period of public comment
14 open so that if the Panel comes up with any other
15 critical questions, if you prepare your responses to
16 the Charge Questions or review some of the information
17 that's been presented in the public comment period,
18 we'll have a chance to address that.
19 I think we'll also have a chance for the
20 EPA to provide any closing remarks or summaries,
21 including any rejoinder to things that may have
22 occurred in the public comment period, and then we'll
23 move on to the Charge Questions.
24 And so thank you, everyone, for your
25 participation today, and we'll see everyone tomorrow

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1 morning at 8:30.
2 (WHEREUPON, the proceedings recessed at 5:12 p.m.)
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