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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

ENVIRONMENTAL PROTECTION AGENCY

CONFERENCE CENTER LOBBY LEVEL

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ARLINGTON, VIRGINIA 22202

SEPTEMBER 16, 2010

8:30 A.M.

1 FIFRA SCIENTIFIC ADVISORY PANEL
2 MEETING
3 SEPTEMBER 16, 2010
4 **DR. STEVEN HEERINGA:** Good morning
5 everyone. Welcome back to the third day of the FIFRA
6 Science Advisory Panel Meeting on the topic of the
7 Reevaluation of the Human Health Effects of Atrazine:
8 Review of Non-cancer Effects and Drinking Water
9 Monitoring Frequency.
10 I'm Steven Heeringa, I'm the Chair of
11 the Panel for today. This afternoon, I have an
12 obligation at NIH and Dr. Portier is going to step in
13 this chair and then I'll be back tomorrow morning.
14 I think at this time, if we could just
15 quickly go around the table one more time just to have
16 the Panel give their name and affiliation and we'll get
17 underway.
18 **DR. KENNETH PORTIER:** I'm Ken Portier,
19 Director of Statistics at the American Cancer Society
20 in Atlanta.
21 **DR. JANICE CHAMBERS:** I'm Jan Chambers,
22 I'm a professor at the College of Veterinary Medicine
23 at Mississippi State University.
24 **DR. CAREY POPE:** Carey Pope, Oklahoma
25 State University.

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1 **DR. JOHN BUCHER:** John Bucher, National
2 Toxicology Program.
3 **DR. DANIEL SCHLENK:** Dan Schlenk,
4 University of California, Riverside.
5 **DR. RICHARD GREENWOOD:** Richard
6 Greenwood, University of Portsmouth, UK.
7 **DR. KANNAN KRISHNAN:** Kannan Krishnan,
8 University of Montreal, Canada.
9 **DR. MOIZ MUMTAZ:** Moiz Mumtaz, ATSDR
10 CDC.
11 **DR. NELSON HORSEMAN:** Nelson Horseman,
12 University of Cincinnati.
13 **DR. JAMES MCMANAMAN:** And Jim McManaman,
14 University of Colorado.
15 **DR. KATHERINE ROBY:** Kathy Roby,
16 University of Kansas Medical Center.
17 **DR. BARRY DELCLOS:** Barry Delclos, FDA,
18 NCTR.
19 **DR. SANDRA LEGAN:** Sandy Legan,
20 University of Kentucky.
21 **MR. WESLEY STONE:** Wes Stone, United
22 States Geological Survey.
23 **DR. RICHARD COUPE:** Richard Coupe, US
24 Geological Survey.
25 **DR. HERBERT LEE:** Herbert Lee,

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1 University of California, Santa Cruz.
2 **DR. BETTE MEEK:** Bette Meek, University
3 of Ottawa, Canada.
4 **DR. SUSAN AKANA:** Susan Akana,
5 University of California, San Francisco.
6 **DR. PENELOPE FENNER-CRISP:** Penny
7 Fenner-Crisp, Private Consultant, Charlottesville,
8 Virginia.
9 **DR. ELLEN GOLD:** Ellen Gold, University
10 of California, Davis.
11 **DR. SHELLEY HARRIS:** Shelley Harris,
12 University of Toronto and Cancer Care Ontario.
13 **DR. GERALD LEBLANC:** Jerry LeBlanc,
14 North Carolina State University.
15 **DR. STEVEN HEERINGA:** Thank you very
16 much, Panel members and before we begin, may we return
17 to our Designated Federal Official for the meetings,
18 Mr. Joe Bailey.
19 **MR. JOSEPH BAILEY:** Thank you, Dr.
20 Heeringa. Good morning, everyone, welcome back. I'm
21 Joe Bailey, Designated Federal Official for the
22 meeting. Just a couple of reminders that first of all,
23 this is a Federal Advisory Committee Act Meeting, which
24 means that the Panel's recommendations that are
25 presented to EPA are advice and recommendations only.

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1 And that any policy and regulatory decisions further
2 down the road are strictly the Agency's decisions after
3 taking into consideration advice the Panel gives. And
4 the other thing is all the presentations from
5 yesterday, I was hoping I would be able to get them in
6 the docket so they're available to everybody, but there
7 are some technical glitches, so they're not there yet.
8 But hopefully we'll get them there today and everybody
9 will have access to them. So again, welcome and thanks
10 for being here this morning.
11 **DR. STEVEN HEERINGA:** Thank you, Joe.
12 Just to remind us we are in the period of public
13 comment for this SAP meeting and we had concluded
14 yesterday with presentations by a number of public
15 commenters, but I agreed to leave the period of public
16 comment open through this morning in the event that the
17 Panel members had additional questions for any of the
18 public presenters yesterday. Have any additional
19 questions, again of clarification that would bear on
20 the charge questions or our proceedings, Dr. Akana, who
21 would you like to ?
22 **DR. SUSAN AKANA:** I believe it would be
23 Dr. Breckenridge from Syngenta.
24 **DR. STEVEN HEERINGA:** Possibly Dr.
25 Breckenridge and your colleagues who are here this

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1 morning, if you would just like to come forward 'cause
2 I anticipate that...
3 **DR. CHARLES BRECKENRIDGE:** Mr. Chairman,
4 before I proceed with answering some question of Dr.
5 Akana, could I correct a statement that we made
6 yesterday in relationship to the life cycle for the
7 breast development?
8 **DR. STEVEN HEERINGA:** Yes, please do.
9 **DR. CHARLES BRECKENRIDGE:** Okay, so the
10 question was what duration of life cycle may be used in
11 that study, and I think the statement was that we used
12 1410. 1410 is correct for all the ALIC serves that we
13 did. The breast development study was unique in that
14 we were trying to replicate the conditions of Dr.
15 Fenton's work.
16 And so we obtained animals from Charles
17 River labs in Raleigh, just as she had done, and we
18 learned that Charles River labs maintained their
19 animals on a 12/12 schedule. And because we were
20 bringing those animals into the study on gestation days
21 four, five, six and seven, this was necessary for the
22 staggered nature of the design of the study.
23 We elected to keep those animals on a
24 12/12 schedule rather than switching a schedule to a
25 14/10. So as practice in the lab, we have a regular

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1 14/10 schedule.
2 But for this particular instance, we
3 didn't want to disturb the animal in the sense of a
4 period where in fact we would be applying test material
5 within a very short time of their receipt at the
6 laboratory. So we were incorrectly stating the life
7 cycle in the breast development study yesterday.
8 **DR. STEVEN HEERINGA:** Thank you very
9 much, Dr. Breckenridge. Dr. Akana.
10 **DR. SUSAN AKANA:** Concerning the life
11 cycle, what time of the day in life cycle were the
12 gavages administered?
13 **DR. CHARLES BRECKENRIDGE:** Okay, so
14 there are many studies here and I will I guess I'll
15 refer to the latest ones. That is to say the studies
16 where we investigated the dose response function for
17 the intact animal model. And under those conditions,
18 the lights were turned on at 5:00 AM in the morning,
19 and the dose was administered just after lights were
20 turned on.
21 **DR. SUSAN AKANA:** And the question I'm
22 somewhat concerned about is the atrazine diets. The
23 diets that have atrazine in it. As you know, rats eat
24 normally in a circadian fashion and they eat about
25 maybe 20% of their food in the light cycle and the

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1 remainder in the dark, and generally in about two
2 manners.
3 Now the atrazine diets are they actually
4 palatable, do you have any sense of that? And do you
5 have evidence to believe animals are eating in a normal
6 meal pattern?
7 **DR. CHARLES BRECKENRIDGE:** Okay, thank
8 you very much. Yes, we were mindful of the fact that
9 the animals at high doses tend to consume less food
10 than controls, and that might in fact be part of
11 response to the body weight effect that we're getting
12 in the early stages of the dosing by diet.
13 We obviously used other data sets to try
14 to match the PPM concentration in diet so that we could
15 achieve the targeted dose as you remember in the high
16 risk group, for instance, we were looking to achieve 50
17 milligram per kg equivalent over the entire 24-hour
18 food consumption period. We fell somewhat short of
19 that in the toxicity study. It was 40 milligrams per
20 kg and we were slightly better in the PK component
21 which is about 43, 44 mgs per kg.
22 In addition, we also were aware of the
23 diurnal pattern of food intake, so what we in fact did
24 was we had a 14-10 schedule on this study and we did
25 food intake for each block of time. And when we

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1 finally submit that report, you'll see what the dose
2 consumption was in the dark versus in the light.
3 And in regard to the dietary study,
4 especially as it relates to the kinetics component, we
5 started the compound administration the night before
6 the first day of blood collection, so that effectively
7 we had an entire night of dosing when we started to
8 collect the first blood samples for the PK component.
9 So in summary then, we basically
10 calculated individually daily doses. But we do know
11 the dose in half-day segments with 14 hours light, 10
12 hours dark. We would have had preferred it to be a
13 12/12 cycle.
14 But again, since that was the standard
15 model, we always use for the LH surge, we didn't want
16 to change that variable just to get a better or equal
17 representation. And I guess I should say that we
18 didn't quite see as strong a pattern as a 20/80 percent
19 shift between the light and dark but there clearly was
20 an impact.
21 **DR. SUSAN AKANA:** So if there was an
22 approximate diurnal rhythm in eating, there's probably
23 a diurnal rhythm in corticos drug?
24 **DR. CHARLES BRECKENRIDGE:** Yes.
25 **DR. SUSAN AKANA:** Thank you.

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1 **DR. CHARLES BRECKENRIDGE:** I guess I
2 could just add one really interesting fact that we
3 noted in the data as we were looking at food intake,
4 because we standard every animal to a four-day cycle
5 and every panel entered the study out on constant day
6 on a day of estrus it imparted scalloping the food
7 intake pattern because as I understand it, estrogen
8 actually modifies food intake and behavior in the
9 animal.
10 And that scalloping food intake
11 persisted through the entire 28th day where we had the
12 immuno tox phase, it was delightful to actually see
13 what happens when you standardize animals on a
14 physiologic parameter that impacts some other variable.
15 **DR. STEVEN HEERINGA:** Dr. McManaman.
16 **DR. JAMES MCMANAMAN:** Yeah, I also have
17 a followup question regarding the diet. I noticed that
18 the day of vaginal opening in your study where they
19 were dosed during gestation was significantly longer
20 than that of Dr. Fenton and I was wondering, do you
21 have any comments about possible explanations for that,
22 is there that much variability in this particular
23 strain of rats and day of vaginal opening? Do you know
24 what the variability is?
25 **DR. CHARLES BRECKENRIDGE:** We have only

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1 investigated the Long Evans rat at one time in the
2 Coder study, and we did that explicitly matching with
3 Dr. Fenton's work. We have done and not only us, but
4 it's been reported on vaginal opening delays in various
5 case studies with the Wistar. We had a couple strains
6 of Sprague-Dawley. It is typically recorded that there
7 is a day or two shift in the vaginal opening on high
8 dose but I don't know if I can answer your question
9 with variability.
10 **DR. JAMES MCMANAMAN:** Well, it was
11 noteworthy that the atrazine dose did not affect
12 vaginal opening in your study as it did in her studies.
13 So that's my point.
14 **DR. CHARLES BRECKENRIDGE:** Okay. We
15 misunderstood. I guess most of those studies are
16 typically focusing on the non-gestational post delivery
17 and so the bulk of the evidence is actually in animals
18 treated from birth onward and that is clearly the way
19 you're saying it affects this, but this was the first
20 time that gestational effect was recorded.
21 **DR. JAMES MCMANAMAN:** So another
22 possible difference between the two studies might be
23 the way the animals were housed. They were all housed
24 singly. In your study, were they housed in plastic or
25 wire mesh cages?

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1 **DR. CHARLES BRECKENRIDGE:** They normally
2 do these studies in plastic to create an environment
3 specific behavior, so yes, plastic.
4 **DR. STEVEN HEERINGA:** Dr. Chambers.
5 **DR. JANICE CHAMBERS:** I have a couple of
6 follow-up questions on the kinetic study also. Was
7 there any residual solvent in the food that was used in
8 the dietary aspect of this study?
9 **DR. CHARLES BRECKENRIDGE:** No, we did
10 not use solvent variants just a mixture I believe. I
11 might have to verify that.
12 **DR. JANICE CHAMBERS:** Also, do you, for
13 the gavage study, those were not fluid fed animals, is
14 that right?
15 **DR. CHARLES BRECKENRIDGE:** That's
16 correct
17 **DR. JANICE CHAMBERS:** And do you have
18 any idea what the amount or proportion of absorption of
19 the atrazine in either the gavage or the dietary
20 studies was?
21 **DR. CHARLES BRECKENRIDGE:** I think
22 someone else can better address that question.
23 **DR. DAVID KIM:** So you're asking, after
24 X amount of atrazine mixture given to the animals via
25 gavage, how much of it hasn't absorbed? We'll be able

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1 to quantify that when we get into the PK model and when
2 we start summarizing the data but what we do know is
3 that within five minutes we're seeing atrazine enter
4 the systemic circulation.
5 So there's rapid intake into the
6 systemic circulation. We did some pharmacy mass
7 balance studies and have conducted in the past. But 1
8 percent after oral intake, 1% parent material is
9 measured in this. A lot of it is converted into
10 metabolites because of past effects. So we'll be able
11 to tease out all these factors that affect uptake when
12 we get the PK model.
13 **DR. CHARLES BRECKENRIDGE:** And just to
14 add further to that, in regards to the oral gavage, you
15 note that the when we're tracking the twelve 'o clock
16 thriving metabolite largely dose concentrations fall to
17 a non-detectable within a duration of time, and that is
18 presumed then to reflect the ending of the absorption
19 phase of that bolus dose. It's a much more difficult
20 question when you're dealing with dietary because that
21 dose has been distributed over time.
22 And so what you're getting to see is
23 just a snapshot of what is in at that time that the
24 animal's blood sample is taken. So it's a little bit
25 more hard to characterize is there a differential rate

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1 or something of the diet versus the bolus dose. But I
2 think we can say from the bolus dose experiments that
3 absorption seemed to be complete within a short time
4 after the dose administration. We're not surprised
5 that they'll make that statement to the dietary level.
6 **DR. JANICE CHAMBERS:** And one last
7 question, do you know if there's any microbial
8 metabolism of the atrazine in either route?
9 **DR. CHARLES BRECKENRIDGE:** I think we've
10 heard some or read some reports that suggest that that
11 is true. We're interested explicitly in eco lab report
12 that this hydroxyatrazine found in the rodent plasma
13 and I believe some of the docket chilled EPA suggest
14 that that was the case. We're not aware of a
15 physiologic process within the animal that would permit
16 that reaction to occur.
17 And so we suspect that if it's being
18 detected in plasma or urine samples, its one of two
19 things, microbial or in fact it's a flaw in the
20 methodology because in fact the sometimes hydrolysis
21 reactions can happen and we have observed that even
22 with parent compound under storage conditions will
23 hydrolyze.
24 And so we are not yet resolving whether
25 in fact reports of hydroxy in plasma are in fact

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1 reflecting true values or other processes that might
2 lead to that premise.
3 **DR. STEVEN HEERINGA:** Dr. McManaman
4 **DR. JAMES MCMANAMAN:** Yeah. I would
5 like to follow up on that. Did you measure the
6 concentration of atrazine or its metabolites in a peak
7 material?
8 **DR. CHARLES BRECKENRIDGE:** In these
9 specific studies we have not, but we have done chloro-
10 radiolabel studies in the past and it is typical that
11 we have 80% of total label in urine, 20% in the feces.
12 **DR. STEVEN HEERINGA:** Okay. At this
13 point, I think, I would like to thank the Panel for
14 their questions oh Dr. Greenwood.
15 **DR. RICHARD GREENWOOD:** Richard
16 Greenwood. Just one quick query. On your figure six,
17 you've provided plots of the atrazine metabolites
18 **DR. STEVEN HEERINGA:** Which presentation
19 was this, Richard?
20 **DR. RICHARD GREENWOOD:** So this was the
21 one of the Syngenta September 9th
22 **DR. STEVEN HEERINGA:** Oh, it was one of
23 the submissions.
24 **DR. RICHARD GREENWOOD:** Submissions,
25 yeah. A series of figures all those figures based on

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1 joining the points together
2 **DR. CHARLES BRECKENRIDGE:** To clarify,
3 is this Dr. Kim's presentation?
4 **DR. RICHARD GREENWOOD:** This is one
5 which--it's a paper that you put on the docket from
6 you, Dr. Kim and Dr. Pasqual.
7 **DR. STEVEN HEERINGA:** Can you describe
8 the preliminary results from these studies on atrazine
9 update in the final report?
10 **DR. DAVID KIM:** Are these plasma
11 profiles or metabolite profiles?
12 **DR. STEVEN HEERINGA:** The 19 page...
13 **DR. DAVID KIM:** I could take you around.
14 And so those are, the reason why it
15 looks fairly smooth is because we collected plasma
16 samples with very intense sampling schedule. So those
17 are dots which represent sample points that are
18 connected. It's not a result from a model fitting
19 exercise.
20 **DR. RICHARD GREENWOOD:** The other
21 question, it's in the washout studies it looks almost
22 like for most of the time, there's a linear loss rather
23 than an exponential loss becoming exponential at later
24 times. Is that because of the--you've got less points
25 in that area to define it or is that what you observed?

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1 **DR. DAVID KIM:** Okay. Yes. We have
2 quite a few samples during the washout period. We
3 collected, I believe okay, I don't have the numbers
4 off the top of my head but that would be in the report.
5 We have more than ten data points essentially to
6 characterize washout. It looks linear because of Y-
7 axis's lot scale.
8 So it's a lot in the near decay. It's
9 seems like there's a, it's a linear decay based on the
10 lot linear curve--at the high dose because the
11 concentrations are elevated. It may even look like
12 there is a two phase washout.
13 **DR. RICHARD GREENWOOD:** Thank you very
14 much.
15 **DR. STEVEN HEERINGA:** Dr. McManaman.
16 Okay, I'll allow this question, but I need to wrap it
17 up. Please go ahead.
18 **DR. JAMES MCMANAMAN:** So I wanted to get
19 a clarification. When you said that was a tracer study
20 that you find a 80:20 ratio, is that with gavage or is
21 that with dietary treatment? My question was about
22 dietary, how much goes in through the dietary?
23 **DR. CHARLES BRECKENRIDGE:** I'm sorry. I
24 didn't understand that. Yes, these are gavage studies.
25 We have not done that type of study in the dietary.

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1 **DR. STEVEN HEERINGA:** Dr. Krishnan, Dr.
2 Mumtaz?
3 **DR. KANNAN KRISHNAN:** In the same PK
4 report on February 8, I was also concerned that you
5 limit the LH suppression to a threshold level without
6 mentioning either C-max or AUC of the atrazine
7 equivalents. Was there any calculation based on any
8 comparison done based on the AUCs in these gavage
9 versus diet study?
10 **DR. CHARLES BRECKENRIDGE:** In the
11 relationship between what is observed in blood versus
12 what is observed with the LH Suppression, we went into
13 those experiments with the premise that in fact it
14 would be area at the curve above a threshold that would
15 actually drive the LH suppression.
16 We were somewhat surprised that in fact
17 it appeared not to be the area under the curve, and
18 that the differences between the diet and the gavage
19 treated animals appeared to be, have all mostly been
20 accounted for by c-max.
21 So there was about a tenfold difference
22 there as David had pointed out yesterday and yet only a
23 twofold when we're considering dimethyl chlorotriazine.
24 So I don't quite know yet how to get a resolution on
25 what is the component of the blood level that's driving

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1 the GnRH effect.
2 But one would have to presume that it
3 has to last for some duration. That was my initial
4 assumption and that comes largely from the viewpoint
5 that high doses in young adult animals, you need
6 several days of dosing to accomplish the phenomenon and
7 if you apply that single dose that doesn't do it and
8 therefore somehow c-max isn't quite enough to, to
9 muster.
10 And so it's still experimentally
11 unresolved and I don't have any information yet how to
12 resolve that.
13 **DR. KANNAN KRISHNAN:** Another question
14 about the material that wasn't presented was that it
15 relates to the fraction of DCT residue, it was a slide
16 that was supposed to be given to us yesterday based on
17 the monitoring data?
18 **DR. STEVEN HEERINGA:** This was a single
19 loose slide. Dr. Hendley.
20 **DR. PAUL HENDLEY:** You're going to yes,
21 okay. So you want clarification on the content of the
22 slide?
23 **DR. KANNAN KRISHNAN:** Yeah. I looked at
24 the average atrazine level being 80 some percent and
25 the DACT, DIA, DEA, there is between 2% to 6% so the

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1 rest of it above 10 some percent would be the hydroxy
2 data?
3 **DR. PAUL HENDLEY:** No. This refers
4 specifically to the component of chloronitrotrizine
5 mixture. So these are samples that will run from the
6 three years when every sample, monitoring sample was
7 taken, was analyzed for all the chlorinating components
8 without a large pool of samples.
9 We're referring here to the high end of
10 a distribution, the dose exceeding 15 parts per billion
11 of total chlorotriazines. And in the case of raw
12 samples, that was 87 samples from the so called raw,
13 and then the relationship there the average atrazine
14 percentage in that total chlorotriazine was 87%, and
15 the remainder was made up of the chlorinated DACT, DIA
16 and DEA.
17 So this is referring purely to the
18 chlorinated triazines. And of course the key thing
19 here is the high TCT occurrence occurs typically in the
20 spring when there's a runoff event when atrazine is
21 freshly applied. Which is why in the higher
22 concentration residue pictures, you will always see the
23 high concentration of atrazine that makes up the vast
24 majority of the TCT mixture.
25 **DR. KANNAN KRISHNAN:** Thank you, because

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1 I was looking for something that wasn't there.
2 **DR. STEVEN HEERINGA:** Dr. Mumtaz.
3 **DR. MOIZ MUMTAZ:** This question is for
4 Dr. David Kim. In the implications of PBPK modeling,
5 you say that this model can be used to reduce
6 uncertainty. So what is the basis of what you have in
7 terms of what we showed, a general statement of what
8 people can anticipate when using the model?
9 **DR. DAVID KIM:** Right. So it's a very
10 good question, that's a very broad question. So let me
11 try to gather my thoughts and I think that the
12 statement about the PBPK model and the reason why PBPK
13 model has not been used to do the animal rat to human
14 extrapolation currently is because the existing model
15 has a lot of uncertainties with it.
16 So one of the points that was made in
17 EPA's documents was that you model under predicts the
18 plasma profiles for atrazine and metabolites, and this
19 is based on Tami McMullins' 2007 publication, which was
20 an initial model based on in vivo data.
21 So there remains uncertainty with regard
22 to understanding the, predicting the plasma profiles
23 into that. What I meant by reducing uncertainty is
24 that based on the data that I have, both from in vitro
25 and in vivo experiments, I'll be able to address some

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1 of those uncertainties with optimizing parameters in
2 that PBPK model and replacing it with better with lots
3 more data.
4 **DR. MOIZ MUMTAZ:** So you're going over
5 specific data that you have?
6 **DR. DAVID KIM:** Yes.
7 **DR. MOIZ MUMTAZ:** In that, in that lab
8 that would help you?
9 **DR. DAVID KIM:** Right. As well as
10 experiments, information that we have garnered in the
11 in vitro asset study as well as one of the issues with
12 regard to previous models was that the dosing was done
13 at a 150mg/kg, very high dose, but what Tami observed
14 in her plasma profile was a two phase plasma curve.
15 And at lower doses, we're not observing that.
16 So we will be able to address what the
17 kinetic profiles look like at lower doses which are
18 more realistic compared to what human, human scores.
19 **DR. MOIZ MUMTAZ:** All right, this sounds
20 good. Let me just follow up on this second.
21 **DR. STEVEN HEERINGA:** Dr. Breckenridge.
22 **DR. CHARLES BRECKENRIDGE:** Yes, Mr.
23 Chairman. Actually, anticipating questions relating to
24 the McMullin model versus our data, I prepared a one-
25 page summary of that and perhaps it's a good basis for

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1 the discussions if you would like to hear that as to
2 how the model at this, at the moment will be modified
3 to...
4 **DR. STEVEN HEERINGA:** But in terms of
5 the Panel is that something--if we can do it fairly
6 quickly. Let's go ahead.
7 **DR. DAVID KIM:** So this is a handout
8 that was given to you this morning. I'll just walk you
9 through, there's four steps in this process and this is
10 something that Dr. Harvey Poole and I, as well as Dr.
11 Breckenridge, discussed yesterday.
12 Let me start off with the McMullin which
13 has uncertainties that EPA has pointed out and are
14 valid points as well as end points that we concurred
15 with. It has a lot of uncertainties primarily because
16 of the gut, the discretion for gut absorption.
17 So what was used to describe gut
18 absorption was a fast, slow and zero order gut uptake
19 and this is because of the two phase, two keys that was
20 observed in the plasma profile data. I'll be beginning
21 with that model. I'll be simplifying it.
22 Let's break down the gut model --
23 simplify the gut absorption model to have just a single
24 absorption rate because that's what we seem to be
25 observing with plasma profile data.

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1 The specific primers that we find PBPK
2 model which you see under circle number 2 step number
3 2, the partition coefficients as well as the clearance
4 values will be replaced with in vitro information that
5 I presented to you yesterday.
6 In addition to the fine model of
7 hypothalamus and pituitary compartments representing
8 those two tissues, and I did not show this data
9 yesterday, because they haven't been analyzed, but in
10 this PK experiment, at the end of blood collection for
11 each individual we collected the brain, separated the
12 hypothalamus and pituitary, and we are currently
13 quantifying levels of atrazine and some metabolites.
14 So what you will see in the final report
15 is a time course profile for those two compartments.
16 That refined model will be then--will review
17 predictions with that model with in vitro inputs to
18 assimilate the time course, in vivo time course data,
19 we'll do this iteratively until we have an optimum
20 model for your review.
21 **DR. STEVEN HEERINGA:** Thank you very
22 much, Dr. Kim. At this point I want to thank all of
23 the public commenters who contributed to the session
24 yesterday and again this morning. Dr. --I forgot.
25 I've got to cut off questions, I'm sorry.

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1 **FEMALE:** One quick comment to Dr. Kim is
2 if you're going to look at the concentration of
3 atrazine in tissues, don't forget the adrenal.
4 **DR. STEVEN HEERINGA:** It's a tough part.
5 As a statistician try to manage these scientists. We
6 deal with uncertainty all the time in here.
7 Okay, thank you very much everybody for
8 your contributions.
9 At this point in time, I'd like to bring
10 the period of public comment to a close and I'd like to
11 invite the scientific staff of the EPA back up to the
12 head of the table. I think as I indicated yesterday,
13 before we turn to the charge questions, I'll turn to
14 Dr. Lowit I believe for any wrap up that they would
15 have or potentially any rejoinder to proceedings of the
16 last half day. So please, you can move forward.
17 **DR. ANNA LOWIT:** Good morning. I
18 believe we have one quite a couple of things we wanted
19 to say, there was some clarification that Dr. Cooper
20 was going to make, and then I just have a couple of
21 comments I was going to make. So if someone could tee
22 up Dr. Cooper's slide, I'll start with that.
23 **DR. RALPH COOPER:** This is just to
24 address some of the things that took place yesterday.
25 I felt that some clarifications might be helpful in

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1 dealing with some of what might appear to be
2 discrepancies but are not.
3 And one tick off the technical comment
4 about the control animals, we're still confused a
5 little bit about that. All the control animals are
6 included in there, and we're trying to figure out which
7 data set. I think if we're using a statistical
8 analysis Dr. Lin's comments might not even apply. But
9 still I think it's important that we share everything
10 we have and we'll try to make sure that we find out
11 what that issue is.
12 The other thing that Dr. Lin, on bullet
13 two up there, brought up was that the broad range of
14 dosing. That might appear to be broad but I think that
15 we generally aim to use young adult female animals that
16 are ninety to 120 days. That study included animals
17 that the outside range taken from the example used and
18 by the example that was given from Sielke & Associates.
19 The range and age of animals were 77 to
20 126 days. These are all, met the criteria of cycling
21 and I'm not 100% certain whether they were included in
22 the data analysis. But if it was in the 1800 data
23 point, then they would have been--point being that, of
24 those animals there were close to a hundred animals in
25 that study, in that particular time period, sorry. And

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1 that 85% of them were from 84 to 105 days.
2 There were 6 animals in the control in
3 the high dose that were outside that range. On the
4 aging side and on the opposite. I think the point is,
5 is that even with this range of ages, which is within
6 the young adult female range, it was still
7 statistically difference statistical differences in the
8 LH and I think that may underscore the robustness of
9 that kind of response as opposed to introducing
10 variability.
11 To bullet number one up there, I think
12 it's important that we recognize that Dr. Handa's study
13 looking at the intact female animal dosed for four days
14 starting on the day of actual estrus versus pro estrus
15 with Sprague-Dawley rats.
16 And I just wanted to point out again
17 that-- let's go one quick slide down. You see the
18 Cooper, et al. study in 2000, we compared Sprague-
19 Dawleys with Long Evans. In the top bar you're
20 familiar with that figure. Long Evans on the left,
21 Spragues on the right, four days exposure.
22 These are very active mice and animals.
23 And the Spragues are certainly more sensitive, I'm
24 sorry, the Long Evans are certainly more sensitive than
25 the Long Evans, less sensitive than the Long Evans.

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1 And I think that one of the reasons why we I don't
2 think this is responding.
3 One of the reasons we wanted to look at
4 the intact animal was to see if we could, if that dose-
5 response was going to be different. This isn't working
6 up here.
7 So we used the Long Evans animals and I
8 think that may account for the differences in response
9 seen, this is the Gentner versus the Cooper et al.
10 study. Even in the Handa data, you saw he had a
11 suppression in LH in the intact animal, again arguing
12 that animal, the high dose anyway, that that animal,
13 the intact animal may be more sensitive, for lack of a
14 better term, model to use in this, and if you're going
15 after the most sensitive strain or sensitive species, I
16 think these are issues that we have to keep in mind.
17 And my last point is that as brought up
18 by Dr. Legan in the discussion, I just want to mention
19 that we too found, on the bottom bullet there, is dose
20 increased in the four day studies. The number of
21 females that achieved what we set out as pro-estrus
22 criteria was significant.
23 We feel we're saying that as we raise
24 the dose, we did see it affect within that one cycle on
25 the number of animals we went through. We excluded

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1 those from our analysis because we felt we didn't want
2 to push the data in a direction that it was through the
3 LH suppression that we were getting an extension of the
4 cycle.
5 I thought it was just we were comparing
6 apples and oranges, so we try to keep all animals that
7 were deemed pro-estrus by our criteria and then look at
8 the hormones. So it was kind of funny in the sense
9 that we're making it difficult for ourselves to find an
10 effect. So again, I just want to point that out, and I
11 think Dr. Handa's had the same type of response.
12 And then the last thing was that dose
13 may not and we are 100%--I am. I am 100% agreement
14 that suppression changes in LH alone are not going to
15 be, within a single cycle, would not necessarily bode
16 an adverse outcome, but I think it clearly show that
17 these are precursor changes that might predict that
18 you're going to run into trouble either after a little
19 longer durations or a little more time. That's all.
20 **DR. STEVEN HEERINGA:** Thank you, Dr.
21 Cooper.
22 **DR. LOWIT:** I guess, are there any
23 questions on that for
24 **DR. STEVEN HEERINGA:** Quick questions on
25 Dr. Cooper's presentation. Dr. Legan.

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1 **DR. SANDRA LEGAN:** I have a question
2 because in the Cooper, et al. analysis, you said you
3 have the last point you made about the proportion of
4 animals that were actually--that met your pro-estrus
5 criteria decreased. So the ends, in table one are
6 these the correct references, this is what's recorded
7 in the Cooper study. So...
8 **DR. STEVEN HEERINGA:** We seem to have
9 too many pieces...
10 **DR. SANDRA LEGAN:** In some of the lower
11 dose groups, that's not the right data. In some of the
12 lower dose groups, you still have, I mean the ends are
13 two's and five's and in the higher, like in the 25 mg
14 group, they're all above 8 and a 75 mix. So it's hard
15 to see from here. Can you help out?
16 **DR. STEVEN HEERINGA:** Dr. Legan, could
17 you give the reference of the paper just for the record
18 here?
19 **DR. SANDRA LEGAN:** This is part of the
20 Cooper et al. data that were submitted, and there is a
21 section in there where there is a summary report. And
22 this is table one in that report.
23 **DR. STEVEN HEERINGA:** Thank you.
24 **DR. RALPH COOPER:** It's not the if you
25 look at that data, the way we put the study together.

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1 And again, I have to agree with Dr. Lamb's analysis.
2 This study was not set out to be an LH surge
3 sensitivity time study. We are actually, in that case,
4 looking at shifts in steroidogenesis over the day of
5 vaginal pro-estrus with response to this and we also
6 measured the LH, and if you look at the data, and this
7 is why we left two animals at 200 at whatever dose and
8 two animals at...
9 We started measuring LH baseline, and so
10 we looked at the 1200 to 1400 groups and I think those
11 are the ones where the concentrations are baseline.
12 And then as the surge started to appear, we wanted to
13 make sure that we had a sufficient number of animals in
14 there.
15 So we went, we called it loading up
16 those time points when we get the animal to come
17 through the cyclicity, we identified the animals, the
18 four day rat, we then had the tables where we assigned
19 them to the different groups. I told the, our
20 technical staff to please make sure that we cover the
21 peak, all right.
22 So we never, to be totally honest with
23 you, went back and filled in those baseline groups for
24 certain doses. Okay. So that explains it. And
25 frankly speaking, I don't think it would make much of a

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1 difference. Unless we suspected there was a shift at
2 the peak height, in other words an earlier onset. And
3 that's possible.
4 We didn't explore that, the data
5 wouldn't suggest that. And then, of course, on the
6 other side, the delay, there would be a delay. And
7 again, from the 1800 dose responses, I didn't really
8 feel a delay would be something we could pursue, and we
9 had sufficient animals in those dose groups, at least
10 the higher dose groups, to say that, no, the hormones
11 in all groups are going down in 2000.
12 So that's why, and again, that's just I
13 don't see that as the ends aren't there, but I don't
14 think it was necessary for us to go back and fill them
15 in.
16 **DR. SANDRA LEGAN:** I see. Thank you,
17 but it was just that that, those data, it's hard to see
18 the point you made before from this table and that's
19 why I asked for the clarification. That clarifies it.
20 Thank you.
21 **DR. STEVEN HEERINGA:** Thank you very
22 much, Dr. Cooper. At this point, we have quite a
23 number of charge questions, okay. Dr. Roby, you
24 haven't had any questions.
25 **DR. KATHERINE ROBY:** Just a follow-up

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1 then. You said that that study was originally designed
2 to look at steroidogenesis on pro-estrus? Do you have
3 any results from that study that you could share,
4 especially with regard to the current shifting in the
5 cycle from a four to a five day? I'm interested in
6 that.
7 **DR. RALPH COOPER:** This is again, a
8 historical memory of the committee. No.
9 The answer is this. We were looking at
10 the HPA and we've presented all that data on HPA in the
11 April meeting and we saw clear effects on the adrenal
12 axis that we're trying to link to changes, the
13 unraveling of the HPG over those four days and it was
14 agreed that the, that achieved exposure due to change
15 in the HPA, but more work was needed to make that
16 possible. So, what the ovaries steroids, you see
17 progesterone in the data set there, that one unusual
18 number there, but no. And estradiol really doesn't
19 change much.
20 **DR. STEVEN HEERINGA:** Dr. Lowit.
21 **DR. ANNA LOWIT:** Just a couple of
22 comments because there are a lot of questions in the
23 morning starting to hit your way. This is sort of
24 bringing us back to where we started a couple of days
25 ago. We're in the process, we're a significant amount

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1 of the way through now of a re-evaluation of atrazine
2 building upon the 2003 risk assessment.
3 The goal of this is to complete science
4 evaluation, so the risk managers can begin to move
5 forward as to whether or not there needs to make
6 changes to the water monitoring scheme. And that, that
7 re-evaluation of the science is going to be complete in
8 2011.
9 So we will see you again one more time
10 for human health because I believe that the eco team is
11 a different group of people minus Nelson. We'll see
12 you again one more time next year, not clear when that
13 would be. The hope is spring time.
14 It's unclear that was looking to the
15 summer yet, but the goal is spring time and we'll just
16 pretend that spring is anything from March to June,
17 plus the months. I just want to sort of put a reality
18 check on some of the things we've heard for the last
19 few days.
20 Our review, we believe is up date as
21 July 15th. We've heard a lot of new data in the last
22 few days and that looks very encouraging. But
23 particularly as it relates to developing PPBK models,
24 as I count the months this morning. If we were to have
25 an April SAP at least five months to do experiments,

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1 build models, write papers, and submit within the
2 agency in time for us to review about it.
3 So just a reality check, we're very
4 encouraged by the efforts by Syngenta to pursue PPBK
5 model. The science evaluation for atrazine is always a
6 living, breathing thing, but in 2011, we will have a
7 limited, we will say we're going to make some new check
8 decisions.
9 Depending--its very aggressive schedule
10 to do that kind of modeling in five to seven months
11 time frame. So as you think of after deliberations you
12 can keep in mind our regulatory needs. There are some
13 that are fairly immediate in the next--in the coming
14 months literally.
15 But the atrazine reviews always is
16 living and breathing, so continue to stay updated on
17 the literature over time. So even in 2011 we may stop
18 the current reevaluation, the science review never
19 stops truly.
20 So as you think about deliberating on
21 some of the things you've heard, if you can keep those
22 two temporal times in mind that there are immediate
23 needs and then there are also long term improvements to
24 the atrazine knowledge base.
25 **DR. STEVEN HEERINGA:** Thank you very

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1 much, Dr. Lowit. At this point in time, I think I would
2 like to move on to the first of the charge questions
3 which relate to the epidemiologic literature on
4 Atrazine and I guess Dr. Christensen is going to read
5 this question into the record.
6 So we'll read the questions into the
7 record and then I'll call on the lead discussant and
8 then we'll turn to the associate discussants and then
9 open it up to the Panel.
10 **DR. CAROL CHRISTENSEN:** Hi, good
11 morning. The first charge question. Question No.1.1
12 reads, please comment on the sufficiency of the
13 agency's non-cancer epidemiology reviews with respect
14 to identifying the major strengths, limitations of each
15 study.
16 **DR. STEVEN HEERINGA:** That's the
17 shortest FEPA question I ever heard read into the
18 record, thank you. Doctor Gold, right to the point.
19 **DR. ELLEN GOLD:** Good morning. I have
20 rather lengthy comments so within the time, what I'm
21 going to do is make a few general introductory
22 comments, you asked for some comments on some specific
23 papers I'm going to keep those pretty--try to keep
24 those pretty brief in greater detail in my written
25 comments.

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1 And then I've work in this just the same
2 as section three so they are organized by--help out
3 from this basically. And so I'll see summarize my
4 comments for each of the print out in the epidemiology
5 and then I'll turn it over to my colleagues to indulge
6 further.
7 So to start out with I have a few
8 general comments. First of all the overall EPA critic
9 has been really thoughtful and comprehensive in
10 reviewing the epidemiology literature for non-cancer
11 outcomes in relationship to potential atrazine
12 exposure.
13 Second it is very easy to criticize
14 human studies which do I have the ability to control
15 exposures and outcomes and behaviors as well they are
16 holding on the studies.
17 But it is important to know that it is
18 not impossible especially the non-cancer outcome with
19 sufficient resources to measure the outcomes and
20 exposure well or at least better than some these
21 studies of man in human individuals.
22 Third I think we believe that the
23 ecologic study should be considered in this summit, in
24 the lower class of studies from cohort and case control
25 studies of individuals like exposures and outcomes

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1 because they are largely using aggregate data on
2 exposure and outcome and normally we considered
3 suggestive for purposes of hypothesis or for purposes
4 of hypothesis generation.
5 And finally I would note that a number
6 the comments that what follows here that I'll make here
7 were also made in the February 2010 SAP comments and
8 some of them did not appear to have been heeded and
9 included in this issue paper so I'm going to make them
10 again and hope that and encourage you to incorporate
11 some of the advice from earlier this year regarding the
12 evaluation of the epidemiologic studies.
13 So without further ado I'll dive in to
14 the individual studies, so I guess I'm going to try and
15 keep it brief. So the first section dealt with female
16 reproductive and you ask for comments on the first few
17 studies, the first three there are from the
18 agricultural study.
19 And yeah I'm going to just extract and I
20 might going to read all on my comments, largely I agree
21 with the assessment, but I think there are some things
22 that should have been noted, for example the low
23 participation rate in the agricultural study for these
24 outcomes, which raises the potential for participation
25 bias, hypothetically women, hypothetically women with

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1 more adverse reproductive outcomes might have been more
2 likely to participate or those that were more concern
3 about pesticide exposures. So you might have seen an
4 effect when there really wasn't one.
5 Also this was an issue we raised in
6 February that the representativeness of this study
7 population presents questions not only from the
8 participation rate point of view but it 97% White.
9 And fairly well educated so that
10 generalizability of the findings is limited in number
11 one and number two, it's not really possible to look at
12 the effect modification by race ethnicity or lifestyle
13 or their health factors which might be really
14 important. I think we're learning more and more that
15 those kinds of interactions are important.
16 So those comments I think apply to all
17 three of the studies, three analysis for two of our
18 papers and the Saltanga paper. There was one incorrect
19 so I mean also note a couple of minor things, the
20 single word changes but they're important ones.
21 So in the paper to date that dealt with
22 agent menopause on page 31, the hazard ratio of 0.79
23 for atrazine exposure does not constitute a greater
24 association which is the term used. Then for they're
25 not for hormonally active over toxic pesticides which

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1 was 0.77 because the closer you are to one, the less
2 the association is okay, so that needs to be corrected.
3 Let's see, the EPA critique is correct
4 in pointing out that a non-standard question was used
5 to assess menopause and perimenopause in the pesticide
6 exposures assessment specifically atrazine exposure.
7 And the timing of exposure relative to the outcome has
8 not been really addressed.
9 The issue paper however also mention
10 that again that the participation rate was low
11 potential for bias--for participation bias and also the
12 generalizability and lack of ability to look at that
13 modification I mentioned before.
14 And then with regards to the Saldata
15 paper, the issue paper says that these results were
16 depicted only graphically. But I think you can tell
17 from the graph that the adjusted dot ratio is in excess
18 of one and then it appears that the confidence in this
19 does not improve. I think it's worth mentioning that
20 because on page 354 it's says these associations was
21 not statistically significant, it may not be exactly
22 right and then all the other one limitation.
23 So let me summarize then the female
24 reproductive section, so these were the three papers in
25 that section. I think that pointed out the limitations

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1 already, so I don't need to repeat these and the ones
2 that I'd like to add about representativeness,
3 generalizability and that sort of thing.
4 So furthermore I'd say well the
5 agricultural health study included a study sample
6 likely pesticides exposure and that's make sense to
7 examine as a potentially high risk population. It
8 really was not designed to address these research
9 especially related to reproductive health.
10 And other epidemiologic studies have
11 been better designed to asses these outcomes, the
12 menstrual cycle outcomes, age of menopause. And some
13 of them have even infected biological samples that have
14 been stored and could be analyzed to asses the atrazine
15 exposure and might have better representativeness and
16 certainly have better diversity in the study sample in
17 the agricultural health study.
18 So I'm just encouraging the agency to
19 consider finding resources of value--. So you talked
20 about looking at future comments versus in the next few
21 months, finding resources to evaluate data and samples
22 from these other studies that would not only make the
23 findings more generalizable but the designs and the
24 data from these other studies would prove the
25 examination of potentially important modification by

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1 the ethnicity, lifestyle, health factors etcetera and
2 which are important to consider.
3 Finally, the concern expressed in the
4 critic regarding the adequate control of physical
5 activity I think is overstated from age of menopause.
6 I don't know of any literature that suggests it's
7 important. But the key factors for that particular
8 outcome are smoking, parity, education level for all
9 kinds of symptoms.
10 Okay so that's it for female
11 reproductive and there is one setting on male
12 reproductive this long study, just one study which was
13 a test sort of cross section on case critical study.
14 And like the agricultural health study the study sample
15 which was derived from the multi-center study of future
16 families is almost entirely White.
17 That's limiting again generalizability
18 and the ability to examine interactions, the
19 participation was quite low which she acknowledges.
20 These are the common problems seen in characteristics
21 in human population, but it has the advantage of being
22 hypothesis driven and employed biomarkers both of the
23 exposures and outcomes, these are all strengths.
24 I thought that there was I mean this is
25 another one word correction on page 362, it says the

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1 study was of none persistent pesticides or anything she
2 was pretty clear with it was persistent. Sorry--in the
3 document it says persistent and she says non-
4 persistent.
5 So anyway this is the single study in
6 relation to atrazine exposure to reduce hormone quality
7 is very suggestive with the important strengths being
8 hypothesis driven and using biomarkers and exposures in
9 the outcomes, but have no really limitations that I've
10 just mention. So really this is something I really
11 needs to be addressed in future studies.
12 So the next section was on fetal and
13 perinatal outcomes then going to summarize my comments.
14 Again the EPA critic did a good job starting with the
15 Arbuncle paper which from the Ontario farm family
16 study.
17 So what I would add to what the EPA says
18 its unclear how they at least to me, maybe I missed it
19 how they handled most of the pregnancies from the same
20 woman which would represent a lack of independence
21 which violates the most statistical test and some I
22 mentioned how those were handled.
23 I also think that papers should
24 emphasize that the associations of preconception
25 atrazine exposure with early spontaneous abortions were

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1 noticed in magnitude and most of them are statistically
2 significant.
3 And again this is a one word comment,
4 the term risks is used but they really will divide,
5 slightly different and we might have over estimated
6 that. There was also the Savitz paper which I thought
7 again you did a good job at evaluating that, I'm not
8 sure that I have much to add except that again this was
9 one that had a very modest participation rate.
10 So in summary the studies of the
11 relation of atrazine in fetal and perinatal outcomes
12 were suggestive with largely positive that's
13 statistically non-significant association which were
14 modest in magnitude and a number of limitations were
15 noted.
16 In addition I would add that there was
17 sort of lack clarity in how the independence of
18 multiple pregnancies from the same woman were handled,
19 the lab data on specific herbicide exposure and
20 potential for participation bias.
21 So the next section was on birth defects
22 and I'm really going to summarize these because three
23 of the five studies were ecologic and as I said we feel
24 like those ought to be in a separate category and
25 really can't. They really aren't looking at the

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1 individual maternal exposure and at best, they're
2 suggestive and I think that's the major thing about
3 those.
4 There were two studies two new study a
5 provocative study, so the first one looked at residence
6 near corn fields and said that atrazine is largely used
7 in corn fields and not on soy beans which was the other
8 comparison group.
9 I will just note that the sample study
10 used here was quite small for several types of the
11 birth defects and the likelihood the chance could have
12 resulted in findings are to be mentioned because there
13 were multiple statistical tests for each individual
14 defects and no adjustments was made for this multiple
15 comparison from the key diode that was considered.
16 And one other comment is that while the
17 others indicate that atrazine is largely used on corn
18 fields and not in soy beans. That they didn't really
19 address--well they didn't talk about other agriculture-
20 -agrichemicals like fertilizer nutrients that are
21 preferentially applied to corn fields. But they didn't
22 really say anything about other pesticides that might
23 be used in corn fields, so this is sort of an
24 uncontrolled uncommented on confounder.
25 Then there was the Waller case control

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1 study, so this has the advantage of looking at
2 individual women. However they did kind of use an
3 ecologic measure of exposure which you noted in your
4 critique which was fine, but I would say in addition,
5 there was again certain minor things that the issue
6 paper lists variables that looked like they were
7 different, significantly different between cases in
8 controls that did control for them, but there some
9 other ones that were not noted in the issue paper like
10 marital status, race and income, so this is like those
11 ought to be mentioned.
12 When we summarized them by birth defects
13 studies three of them use considerably less than
14 optimal ecologic designs so that atrazine exposures and
15 outcomes were noticed that started individual level
16 which is the major limitation. The other two studies
17 can only be considered suggestive because one did not
18 examine the individual maternal exposures to atrazine
19 and the other used a largely ecologic measure rather
20 than an individual measure of atrazine exposure.
21 The additional limitation has included
22 multiple statistical testing that might have resulted
23 in statistical significance due to chance alone because
24 the key values were not adjusted for the multiple
25 testing. Not accounting for other exposures that might

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1 explain observed effect in the Ochoa-Akuna study. And
2 not adequately describing or accounting for confounding
3 variables in the Waller study.
4 So next we have the adverse birth
5 outcome studies. Again I thought the EPA did a great
6 job in their critique. I'm just going to say
7 additional comments beyond what they've already said in
8 their paper.
9 I thought for example in the Ochoa-
10 Akuna, this is the second one that is out there. She
11 also--one of the strengths of this so this was a
12 historical cohort study and one of the strengths was it
13 had a relatively large sample size, but also they have
14 a limitation that again an individual maternal tap
15 water consumption was not obtained which might have
16 resulted in this classification of exposure.
17 Then there is the Villanueva Cross
18 Sectional Study, again EPA noted the appropriate key
19 strengths and limitations. I would say that the issue
20 paper should also note the findings are suggestive of
21 elevated odds of low birth weight which was not
22 statistically significant. And small for gestational
23 age which is found in pregnancy who's third trimester
24 overlap with high atrazine period. And similarly for
25 preterm delivery since first trimester overlap with

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1 these periods not statistically significant though.
2 But probably the most important premise
3 in my hand is that none of the analysis in this paper
4 were adjusted for variables that are often influential
5 in these outcomes such as maternal smoking, educational
6 level of parent, you see that in the issue.
7 So there we have the ecologic study of
8 number--So here what I would add is that the analysis
9 assumed that the relative ranking of communities with
10 regard to drinking water contaminants remain the same
11 throughout the study period. And the study population
12 again was larger in White maybe the result is not very
13 generalized at all.
14 And again ecologically it did not look
15 at individual maternal drinking water exposures and
16 only control for some important in compounding
17 variables on a community level not in the individual
18 level.
19 I don't think that I have anything to
20 add about the Jabrowski paper and then the final AgCal
21 study paper on birth weight. The only thing I would
22 add there is that the number of low birth weight
23 infants who are preterm infants was too small to assess
24 the individual pesticide exposures and the technique
25 what difference as well as the adjustment for the

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1 finding.
2 So in summary the five studies that was
3 done, adverse pregnancy outcomes range from ecologic to
4 population base case control in historical cohort
5 designs. The ladder having strengths for a better
6 individual assessment to exposure to atrazine in large
7 sample sizes and adjustment for multiple compound
8 variables to asses the independent affect of atrazine
9 exposure although individual maternal water consumption
10 was not assessed to determine likely individual
11 exposures better.
12 So the findings are suggestive in
13 relation to atrazine exposure to small for gestational
14 age but two of the non ecologic designs focusing on
15 verbally only examine pesticides and not specific for
16 atrazine.
17 And then finally we have respiratory
18 effects papers. So first the paper by Hoppen and again
19 these studies in the agricultural health studies
20 suffers from the same limitations that I've mentioned a
21 couple of times before about participation in micro
22 generalizability, lack of ability to look at effect
23 modification.
24 And as noted in the issue paper, they
25 did a subsequent paper on this topic that they actually

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1 stratify on the type of asthma and controls for
2 additional confounding on dose significant
3 relationship.
4 Then there was a cause in cross-
5 sectional study, I would only add that the sample size
6 here is really small and would not have provided
7 adequate statistical power to detect the equal
8 differences if specific chemicals were evaluated in
9 these associations were controlled or broken down and
10 similar criticisms of the Kimjinski study.
11 So in summary of the respiratory effects
12 finding studies, these three cross-sectional studies in
13 the relationship of pesticides to respiratory
14 impairment has--I think limitations including
15 inadequate sample sizes to provide adequate statistical
16 power to detect meaningful tendencies associated with
17 specific chemicals, adequate with controlling for
18 confounding and any observations were actually modest
19 in magnitude and that's it for that question.
20 **DR. STEVEN HEERINGA:** Thank you Dr.
21 Gold. I think we understand that you have more
22 detailed comments but you've covered all the high
23 points. Dr. Bailar is our first associate to discuss
24 it.
25 **DR. JOHN BAILAR:** I don't have a lot to

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1 add except when I state otherwise. My comments
2 regarding these three closely related charge questions
3 refers--just to the epidemiologic part of the EPA
4 draft. I think EPA has done a good job of improving a
5 graph that was already pretty strong.
6 As always, revisions have brought out a
7 need for few more changes but I think they can be dealt
8 with rather handling. I have written elsewhere and I
9 think that I commented at the February meeting about
10 four problems common to all major public issues
11 regarding quantitative data.
12 The first is that the data are vast and
13 in the case of atrazine, they're getting vaster.
14 Second is that the data tend to be highly complex in
15 the number of disciplines involved in the problems
16 attacked and the methods used, the settings and so
17 forth.
18 Third, they're generally of poor
19 quality. And fourth, they're not what we want anyway.
20 For example, we may have high dose life time animals
21 ingestion studies, but we're really interested in low
22 dose human exposures by en large. All four of these
23 apply with some force the data relevance of atrazine
24 and EPA has struggled hard to resolve the problems.
25 It's not easy to do that.

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1 I've had the benefit of reading Dr.
2 Gold's more extensive written comments. I generally
3 agree with her about the individual studies and I'm not
4 going to repeat those remarks. At this point, I would
5 like to make a minor remark of Sir Austin Bradford Hill
6 used the first name Bradford and the last name Hill.
7 He was not to investigators named Bradford and Hill.
8 He was not one investigator with a hyphenated last
9 name. I've seen this misspelled at least two places in
10 the EPA draft and in at least one of the slides that we
11 have seen here not from EPA.
12 It appears that little is known about
13 human fertility related to atrazine exposure. If this
14 is in fact the serious data gap, if I haven't missed
15 anything, that gap should be noted in the EPA draft.
16 I'm not sure that such studies are needed, but if they
17 are undertaken, I believe that they should focus on
18 them with very high exposures.
19 In several of the reports, atrazine was
20 studied along with other pesticides and results for
21 atrazine had been presented in comparison with the
22 results for all pesticides together. This is
23 incorrect.
24 The result of such an analysis is to
25 reduce the apparent strength of the evidence to some

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1 effect. The comparison should be between atrazine and
2 all other pesticides in that study. It may be that the
3 original authors often or always report the wrong
4 comparisons in a way that cannot be corrected but EPA
5 should at least be heard.
6 My last comment here is that SGA has
7 many causes and more than one cause if in fact there
8 are any might be affected by pesticide. Lack of
9 agreement amongst studies maybe a result of multiple
10 mechanisms.
11 For example, atrazine might have a
12 direct effect on fetus at some time or in some settings
13 and work through the mother's endocrine system or the
14 father's and the possibility of multiple mechanisms or
15 some of these specific outcomes. I think it needs a
16 little bit more attention. Thank you.
17 **DR. STEVEN HEERINGA:** Thank you Dr.
18 Bailar, Dr. Harris.
19 **DR. SHELLEY HARRIS:** Good morning.
20 First I'd like to congratulate the EPA for looking at
21 that immunologic literature and including it in this
22 process. It's really nice to see. Again, I'm not
23 going to duplicate Dr. Gold's comments, she's done
24 carefully through each study line by line. You can see
25 that in the report. But so I was planning to focus on

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1 a little bit more on the methods that were used for
2 this review.
3 First of all, states that EPA in the
4 document states that the database is strong and I think
5 I would disagree with that. I think it need--the human
6 study should start with 29 papers and reduce that to 19
7 papers for various reasons. And I calculate there's
8 probably 38 papers of cancer code concept. Hopefully
9 we'll be seeing it on a later date. And because these
10 19 papers represent many different outcomes of interest
11 I'd say that actually the database is quite weak.
12 Imagine the cancer database would be
13 stronger and but also unfortunately more relevant for
14 men and picturing out women. As I said, Dr. Gold had
15 reviewed each paper and I may mention out one paper at
16 the end of my comments. I won't duplicate her comments
17 and I'll just focus a little bit on the methods.
18 So general comments in methodology on
19 the inclusion criteria for the review itself, I see on
20 a page--but first of all I think EPA should include a
21 list of references as an appendix. Includes all the
22 studies that were found in the literature review itself
23 and the reason for exclusion, so at that at a later
24 date, you can justify that you can handle a relevant
25 human literature and you've excluded various studies

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1 for consideration for the various reasons.
2 On Page 324, on the Syngenta methods of
3 the 29 papers, there was a comment that to remove that
4 did not measure atrazine or triazines independently and
5 I thought this is a pretty interesting comment because
6 ecologic states were included and studies which
7 included measurements of triazines are proxies of
8 atrazine exposure, being a proximity to fields, the
9 residential proximity as measures.
10 And so I wondered how this was defined,
11 the measurement of atrazine, the exposure measurement
12 is defined and how that's applied to the different
13 studies so that they would be included in your review.
14 Is that something that needs to be justified for the
15 right way?
16 Another comment not related to
17 epidemiologic studies in cells, but to the process was
18 that of the studies that were obtained, 46 of those who
19 were exposure assessment or dose assessment studies I
20 would believe and for this, for the after review that
21 make sense to exclude those.
22 But I think in the future SAP meetings
23 especially the cancer meeting, we need to see those
24 studies. So at some point, there needs to be a review
25 of all the human exposure and absorb those studies and

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1 it needs to be attached along for the epidemiologic
2 panelist as well as the tox, although we can't
3 ultimately know the risk assessment.
4 Also comment on the ecologic studies.
5 The inclusion of them into this process, Dr. Gold
6 mentioned again, they should perhaps be considered as
7 separate category and I would concur with that as well.
8 I would suggest that for the review of the individual
9 epidemiologic studies, that some type of scoring system
10 might be developed so that each paper can be scored as
11 to quality and so.
12 Once this is gone through the inclusion
13 or exclusion criteria, the methods can be reviewed as
14 you've done and shown in the appendix and it can be
15 scored for quality, so that at some point later, if
16 they're going to be influencing the risk assessment
17 process that would at least have a waiting system that
18 would be felt.
19 It may also these will have more than
20 one person score these types of papers and do that
21 independently. And as epidemiologists, we've built
22 numerous types of methods to do this and that analysis
23 and those types of things and it'd be nice to see it
24 applied in this process and it also be nice to see it
25 apply to some of the talks and studies as well. We'll

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1 comment on that in Section 3.
2 Okay and just one final comment, Dr.
3 Gold went through and reviewed all the individual
4 studies. But a comment about the Arbuncle study and it
5 seems that EPA has largely ignored the study or
6 discounted it for being fairly old or published many
7 years ago and also for the exposure assessment and I
8 might argue that the exposure assessment was a little
9 more valid in that study for at least predicting the
10 occurrence of potentially more significant exposures in
11 women, and so the other studies that was sized specific
12 with the ecologic studies.
13 So I think that it may be that those
14 studies should be discussed appropriately and that wrap
15 my comments with that.
16 **DR. STEVEN HEERINGA:** Thank you Dr.
17 Harris. This point in time, I'd like to hopefully put
18 out to other members of the Panel who would like to
19 comment on Question 1.1. Okay. Question 1.1, I'd
20 suggest let's move on with Question 1.2 and we'll go
21 through the subparts and maybe see if that needs
22 clarification on both. So doctor Christensen if you
23 would read from the record. Dr. Gold just a moment, do
24 you want to consider the parts A and B separately or
25 together?

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1 **DR. ELLEN GOLD:** I think we're doing it
2 separately.
3 **DR. STEVEN HEERINGA:** You're doing them
4 separately, okay. So read 1.2.
5 **DR. CAROL CHRISTENSEN:** Okay Question
6 1.2 Part A, please comment on the scientific
7 information that does and does not support the Agency's
8 conclusions as described in Section 3.0 with respect to
9 the characterization of quality and the limitations of
10 the non-cancer epidemiologic database and its utility
11 in hazard characterization, dose response analysis,
12 quantitative risk assessment.
13 **DR. STEVEN HEERINGA:** Dr. Bailar, lead
14 this one?
15 **DR. JOHN BAILAR:** I tend to agree with
16 EPA in its analysis and conclusions supplemented by Dr.
17 Gold's incisive comments regarding the individual
18 studies. So I'm not going to dwell on that. Instead
19 I'm going to offer some generic comments on three
20 broader issues that deal with interpretation of the
21 integrated hold the data.
22 This is not a place for a short course
23 and statistics but this matter stand out in the
24 discussions and analysis of the effects of atrazine.
25 I'll review them briefly because I think that you need

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1 more explicit acknowledgment and discussion in the EPA
2 draft. These extend across the whole sets of studies
3 and are not limited to the interpretation of single
4 studies where EPA does often discuss these problems.
5 First the general failing in most
6 studies have toxic effect is the lack of sufficient
7 attention the matters of statistical power. Lack of
8 evidence, showing an effect is simply not the same as
9 evidence showing a lack of effect.
10 The EPA draft could be stronger if it
11 discussed the likelihood, that critical negative
12 results might be reversed by better, stronger and
13 especially larger studies whether in humans or animals.
14 The second broad problem is that there's
15 often insufficient appreciation of the multiple
16 comparison problem. This problem is widely recognized
17 as it applies to single studies but it applies with
18 equal force through any collection of paper through
19 other sets of independent of results.
20 There have been a lot of studies related
21 to health effect of atrazine, each with a lot of end
22 points and a lot of analysis. At the usual 5% level of
23 statistical significance and scientific analysis, an
24 average of 1 in 20 tests, where there is in fact no
25 effect will be labeled statistically significant.

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1 This 5% of approach or 95% in the case
2 of confident analysis has been very productive for many
3 decades across all science where important results can
4 be evaluated in a broad context with prior knowledge
5 and sometimes by the collection of new data.
6 The multiple comparisons problem is
7 pervasive and hard to deal with in reviews that cover
8 large numbers of reports. The question in such reviews
9 is not whether some result is statistically significant
10 but whether the overall pattern of results labeled
11 significantly lies outside the expected range.
12 Very roughly speaking, if the literature
13 reviewed reports 100 tests of data whether there is no
14 real effect, one should expect about 5 will be
15 statistically significant. You wouldn't be surprised
16 to find two or three, seven, maybe eight, but if there
17 are say ten or more of the reported key values that are
18 statistically significant, or if some of the ones even
19 with the smaller number have very little key values,
20 there maybe an effect present. Some effects may be
21 addressed.
22 I urge EPA to review that critical quasi
23 findings in its atrazine report and comment at greater
24 length on the plausibility that such findings are the
25 result of multiple comparison.

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1 One more point is that statistical
2 confidence balance and key values measure the effects
3 of random error and random error only bias always,
4 always increases the uncertainty. So the calculated
5 key values are too small, confidence balance are too
6 narrow and we don't know as much as we think these
7 measures tell us. Bias can be made rather small in
8 designed laboratory studies, but it's a major threat to
9 conclusions in other settings.
10 These three points can be summarized of
11 saying that negative findings do not always mean
12 there's no effect and positive findings could not
13 always mean that such an effect is operating. This is
14 as true for laboratory studies as it is for
15 epidemiology.
16 Educated scientific judgment cannot be
17 replaced by reliance on mechanical rules plays a real
18 effect. I understand the pressures to replace judgment
19 as much as possible with objective measures but it
20 would be helpful to have more explicit acknowledgment
21 of points where judgment and formed by statistical
22 analysis still has an important role.
23 In short, these three problems need more
24 attention in the EPA draft. A specific comment on page
25 37, line 18 of the EPA draft says that there is no

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1 national birth defect registry in the U.S. I think
2 that CDC has in fact operated a very broad base
3 registry for many years. Are there reasons why it has
4 been used in geographic studies of atrazine?
5 The rationale for very frequent sampling
6 of water needs to be strengthened, but 1% peak in
7 concentration will occur in a random 1% of samples
8 whether they're taken hourly, daily, monthly or others.
9 If there is a need for frequent data at specific sites
10 rather than overall, that need should get a special
11 attention.
12 While exposures may be of short
13 duration, the effects might be expressed over much
14 longer periods. Now this is widely recognized or
15 answered, it might rule for hormonal disturbances in
16 the mother.
17 For example, I would not focus
18 exclusively on trimester of gestation. Last, it still
19 includes the data for gastric juices and of thalasemia,
20 both are abdominal wall defects but they're entirely
21 different conditions almost certainly brought about by
22 different attributes. Thank you.
23 **DR. STEVEN HEERINGA:** Thank you, Dr.
24 Bailar and our first associate discussant so far today,
25 Dr. Gold.

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1 **DR. ELLEN GOLD:** So again I think EPA
2 did a really good job in Section 3 and the Section is
3 very well considerate and carefully written. As the
4 synthesis Section 3.3 is very well done and highlights
5 the significant limitations of literature, so I'm not
6 going to repeat those. And I'm just going to summarize
7 what additions I think need to be included.
8 So the issue of paper should also add
9 the number of the studies including the agricultural
10 health study; A) a notable potential for a participant
11 biased given a little participation, B) lack of
12 diversity in the study sample which likely results in
13 lack of representative in some sample and has lack
14 generalizability of the findings; C) use of ecologic
15 designs that do not assess individual exposures in
16 outcomes, D) multiple statistical testing that might
17 result in statistical significance and the chance of a
18 if the key values are not adjusted for the multiple
19 testing; E) not accounting for other exposures that
20 might explain the observed effect and; F) lack in some
21 studies have use the standard measures of the outcomes
22 so that this classification are imprecision of the
23 outcome assessment have occurred.
24 So as noted, as I've said earlier, the
25 issue that we should encourage the use of other study

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1 samples and other data sets and biological samples
2 which are evaluated menstrual cycle characteristics and
3 adverse male and female reproductive birth and
4 respiratory effects with better study designs and
5 outcome measures, the notes that were reviewed
6 including the agricultural health study.
7 **DR. STEVEN HEERINGA:** Dr. Harris.
8 **DR. SHELLY HARRIS:** Just a very short
9 comment on page 58 specifically the EPA's conclusion.
10 The EPA states that the epidemiology and toxicology
11 databases can be used to gather to better and inform
12 hazard identification and hazard characterization, but
13 for the purposes of quantitative risk assessment, the
14 experimental toxicology data particularly In-Vivo data
15 from Iraq will be used for endpoint selection and dose
16 response assessment.
17 And I think these are the conclusions
18 that you're referring to in the question. And I would
19 say instead of the epidemiology database, I fully agree
20 with that and I think that studies that they study do
21 not blend a tremendous amount of support for more
22 hypothesis generation and characterization.
23 **DR. STEVEN HEERINGA:** Thank you Dr.
24 Harris. And the third comments from members of the
25 Panel on this particular question. What I would like

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1 to do is to wrap the question 1.2 up before our break,
2 next if you would read part B question.
3 **DR. CAROL CHRISTENSEN:** Sure. Okay,
4 question 1.2 part B, please comment on scientific
5 information that does and does not support the
6 integrative analysis and conclusions, contained in
7 Section 4.0 of the document, with respect to the
8 similarities, differences, and uncertainties of the
9 experimental toxicology in epidemiologic findings.
10 **DR. STEVEN HEERINGA:** Dr. Harris, please
11 answer this one.
12 **DR. SHELLY HARRIS:** Well I had a very
13 different answer on Monday compared to what I have
14 today after all the presentations yesterday. So this
15 is like a moving target. And when I reread the
16 question and looked at--that we've been asked to
17 characterize the uncertainties of the experimental
18 toxicology database and the epidemiologic database, so
19 I wonder if this better suit towards the end of the
20 meeting. But I will do my best as an epidemiologist to
21 discuss in the toxicology findings as well for the last
22 a couple of days.
23 Okay first of all, to be able to
24 incorporate the epidemiologic data into the assessment
25 process and integrated with the toxicology database, we

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1 need well designed observational studies that test
2 hypotheses which are developed in part on the adverse
3 effects observed in animals and understanding of the
4 toxicological mode of action. And this is basically
5 what is stated in the document.
6 Today, we are assuming and sometime may
7 and I'm sure I'll be corrected later if I'm wrong, that
8 atrazine or a mixture of the relevant metabolites by
9 repeated exposures attenuates the LH surge in animals
10 and when this attenuation is significant and this can
11 result in some types of adverse reproductive effects in
12 animals and that's the assumption I'm going on now.
13 And also another assumption I'm making
14 and the hypothesis on Monday, I'm not sure now, is that
15 the mode of action that's relevant in humans. And
16 we've heard evidence to the contrary, I think the
17 Syngenta presentation by Dr. Tony Plant yesterday. So
18 the assumption I'm making again with the mode of action
19 is relevant. And I have a very good qualifier as well
20 as that I was not here at the April SAP meeting of the
21 review of the detox data.
22 And I'm not a toxicologist with
23 expertise to actually assess whether mode of action in
24 rats is irrelevant for humans and I really don't have
25 expertise to address the uncertainties in the

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1 toxicological database.
2 What I can say that it doesn't appear to
3 be a clear consensus regarding the end points and
4 effects on those databases from the presentations
5 yesterday and from the EPA document.
6 So having all those qualifiers, so
7 basically what EPA knows is to do this to integrate the
8 epidemiology and experimental toxicology, we need a
9 strong experimental toxicology database. We need this
10 toxicological mode of understanding and for the
11 purposes of this meeting; it's the attenuation of LH
12 surgical and multiple exposures. I'm looking for nods
13 of agreement here and an epidemiology database.
14 And so what we've observed is that we
15 have this well, I'm calling it very strong experimental
16 toxicology database, hundreds of studies. But clearly
17 there are some issues with say Coder 2010 study a
18 comment yesterday, animal selection and study design is
19 not well suited to risk assessment, best suited to
20 exploring mode of action pressures and this Dr. Lamb's
21 presentation.
22 So to compliment the toxicology
23 database, we need human epidemiologic studies which
24 have the specifically design to evaluate relevant
25 outcomes which can be biologically justified based on

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1 mode of action. We need to see significant
2 improvements in the epidemiologic literature.
3 Some of the reproductive health effects
4 which have been discussed in the last couple of days
5 observed in animals are acute in nature and occur
6 relatively short periods of exposure including the life
7 menstrual cycle characteristics, longer in the cycles,
8 and maybe the precursors of the attenuation of LH
9 search and we can design perspective studies to
10 evaluate these outcomes or precursors in humans. And
11 they have been conducted at relatively low cost as
12 compared to some of these largest scale cohort studies
13 looking at long term cancer outcomes. So that is a
14 suggestion we'd like see those types of studies
15 conducted in humans.
16 To achieve the exposures and doses and
17 measurements that are relevant to our meeting exposures
18 are repeated over time and not a single occurrence, the
19 type of studies that we would propose may need to be
20 conducted neither occupational of cohorts or limit in
21 residing farms because we don't believe or I don't
22 believe that will be seeing the doses necessary to
23 serve the effect with humans unless they're
24 occupational exposures or exposures that occur greater
25 than general population exposures via drinking water

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1 sources, that type of thing.
2 And then in these types of studies,
3 ideally we would obtain some kind of information on
4 current or strong exposures, the questionnaires,
5 records or diaries, at the same time collect
6 information on sort of dose estimates over time which
7 could include biological samples and analyzed for
8 atrazine parent compounds relevant in metabolites,
9 conjugates et cetera and this will help us merge these
10 two, the experimental toxicology in the human
11 databases. And this type of information is obviously
12 far more reasonable for risk assessment.
13 So we have none of that unfortunately,
14 what we do have is an experimental epidemiology
15 database are not experimental an observational
16 epidemiology database of 19 non-cancer studies that are
17 currently available. And as I said, this database is
18 small. So even though in the document, it states that
19 it's a fairly large database so I don't agree with
20 that.
21 So epidemiologic data relevant for
22 female reproductive health outcomes maybe obtained from
23 the existing cohorts which are designed for other
24 purposes and perhaps used in hypothesis generating
25 fashion, but really should the expected data will be of

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1 sufficient quality to be useful for risk assessment of
2 outcomes that differ from those of the primary
3 hypothesis.
4 And so as an example of this, the
5 primary outcome of interesting agricultural health
6 study, I think you'll have historically have had
7 cancer. And so the methods of exposure assessments
8 that were designed to be relevant for those cancer
9 outcomes is actually long latent periods, some
10 consideration for frequency, seasonal and duration of
11 exposure over the years, other factors that might
12 affect those exposures such as protective clothing and
13 equipment use.
14 Those kinds of questions were designed
15 with the intent of looking at cancer outcome, I think
16 namely is the cohort setting of course if we're going
17 to look at other chronic and acute outcomes but the
18 primary focus is cancer.
19 So we really can't expect to have the
20 answer to very specific questions about reproductive
21 outcomes from studies that were designed for other
22 reasons or other purposes. And this is not opposed to
23 some of the agricultural health study, but this is just
24 a statement of how the data can be used.
25 The two studies published by far in 2004

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1 and 2006, looking at menstrual cycle characteristics
2 and delayed menopause make use of this cohort but
3 aren't really severely limited by the availability of
4 the irrelevant exposure of the data.
5 I do not consider an ever, never
6 analysis and then corresponding results of all sorts of
7 odd ratios particularly useful other than for
8 hypothesis generation. They provide no information of
9 time frequency duration or magnitude of dose and all of
10 these measures are important for the incorporation of
11 any kind of epidemiologic data and various assessment
12 processes.
13 And based on what I've heard about
14 experimental toxicology, we need to be looking at lower
15 level of multiple exposures over time in humans and
16 this is important for epidemiologic studies when we
17 design duration of exposure is extremely important.
18 So in ever and never analysis, you just
19 need a comment on ever never analysis and if folks are
20 not used to those terms in epidemiology an ever never
21 analysis could be--if you smoke one cigarette of your
22 lifetime you have been exposed to a cigarette and is
23 that a relevant measure for a cancer outcome.
24 No, so the question might be, have you
25 smoke ten or more cigarettes a day for ten years, ten

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1 years prior to your diagnosis, not so relevant exposure
2 measurement if it was classified as a dichotomous
3 variable ever and never.
4 If we're looking at reproductive
5 outcome, you might ask someone if he smoked ten
6 cigarettes a day over the past month and that's the
7 relevant question to be asking if you're going to
8 analyze it as an ever, never exposure.
9 And I would suggest that ever and never
10 being exposed to pesticides is just not useful
11 information for us to say to be incorporated into risk
12 assessment. Particularly when these ever and never
13 classifications due to all pesticides as a group or to
14 herbicides, insecticides, or fungicides separately,
15 again, I don't think they are particularly useful
16 information.
17 As we move towards categories of
18 classifications or groups of pesticides such as
19 triazines or phenoxies or whatever they maybe the
20 information becomes more important.
21 So as we move from individual exposures
22 in animals to multiple exposures over time and
23 mixtures, and humans who are trying to move from
24 mixtures, the exposures of the life stages down to
25 exposures to individual chemicals and isolating those

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1 effects with appropriate data collection techniques, so
2 both of the two fields will merge at some point.
3 I have more comments. I'm just trying
4 to find them here. I mentioned this comment before but
5 on other cities that reporting including ecological
6 studies of group data, I don't believe should be given
7 much consideration in the analysis because of the
8 exposure assessment issues and compounding issues.
9 And also in the EPA report I think that
10 we need to make a distinction between ecological
11 studies and ecological approach and there's a lot of
12 confusion in the terminology that's used for exposure
13 assessment. When we talk about ecological studies, we
14 talk about looking at differences in rates over time or
15 occurrences at certain outcomes over time in group
16 level data.
17 We can take an ecological approach to
18 exposure assessment in observational studies but we
19 signing exposures to individuals regardless if they
20 represent the kind of needs. So if we are looking at
21 water contamination data or you asked yesterday about
22 drinking water, we assigned some kind of mean value
23 based on your residence, your location, your supply of
24 water, that's still scientific individuals.
25 So that's an observational study, not an

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1 ecologic study even though it might be some ecological
2 measures to come up with assignments for exposures.
3 And again, I think we should give more weight to those
4 types of studies when we're looking at the individual.
5 Okay so I'm not going to include all
6 these comments today. I have created a bit of a table
7 that looks at the experimental studies--the
8 experimental toxicology and epidemiology, and some
9 issues about the role integration of the two. And just
10 a few comments and I'll include them in the report.
11 But basically I won't compare the two databases. We
12 have hundreds of toxicology studies and 19 epidemiology
13 studies.
14 Exposures in the toxicology are
15 ultimately were originally single exposures, multiple
16 exposures are of the same dose over short periods of
17 time, and now this is moving now over life stages,
18 whereas in the human data, we have exposures that occur
19 over lifetime, they're not consistent, between stages
20 or within stages and they change quite significantly.
21 We have issues about--when we look at
22 said quality; epidemiologists have a number of
23 procedures that is to go through a score study quality
24 and to come up with the cumulative test scores and we
25 can use this information to weigh these studies

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1 appropriately in risk assessment.
2 I'm not sure if the same exists for
3 toxicology and how many folks go through and identify
4 which are the most important studies to base their
5 endpoint analysis and that type of thing.
6 There are a number of comments I have on
7 modes action whether the rodent is a good model or not,
8 I'm sure that it will be discussed further in this
9 meeting. And I will not go through the different areas
10 of female reproductive health and male reproductive
11 health, and the four areas that were identified
12 earlier.
13 But I will say that we have numerous
14 toxicology studies and generally only one reasonably
15 relevant epidemiology study in each category and they
16 all suffer from the form of exposure, measurement, and
17 lack of specificity of the chemicals being looked up.
18 So I'll include that in the report but
19 following just a couple of comments and I think it was
20 encouraging yesterday the presentations because what we
21 see that we really need is more information on
22 pharmacokinetics and pharmacodynamics in humans and a
23 very good review on the exposure in absorbed dose
24 assessment studies within this as well to be able to
25 connect the toxicology and epidemiology literature.

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1 And I think that those are coming certainly, so that's
2 good to say. And I think I'll keep it at that.
3 **DR. STEVEN HEERINGA:** Thank you Dr.
4 Harris. Dr. Bailar.
5 **DR. JOHN BAILAR:** Several additional
6 points. I'm concerned about the handling of studies
7 with substantial numbers of results below the limit of
8 detection. But can in fact be a lot of useful
9 information such as findings even if they account for
10 mostly observations.
11 And especially, when interest is focused
12 on the highest exposures anyway as they are with
13 atrazine. At the very least, one can do a rough test
14 by first assuming that all the below limit values are
15 in fact zero, then assuming that all of the upper end
16 of the no defect range.
17 If these two analyses are in rough
18 agreement about the most important conclusions, the
19 report can say so. There are of course much more
20 sophisticated ways to approach below limit of data but
21 again this is not the place for textbook.
22 I have two examples, the last paragraph
23 on page 32 and the last one on page 36. I thought also
24 in the docket in sections 3.3, the synthesis of that
25 epidemiologic data was particularly well done. And I

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1 agree with the conclusion that this time the
2 epidemiologic database concerning the non-cancer health
3 effects of atrazine exposure is not sufficiently robust
4 or mature enough to support causal inference.
5 However and I'm not sure that the answer
6 is more research on either human epidemiology or animal
7 studies of apical effects. In the end, I think this
8 committee should make some generic recommendations to
9 EPA about the broadest research needs and directions.
10 A lot of time, effort, and money has been spent on a
11 lot of different approaches to epidemiologic study that
12 atrazine had helped.
13 And Dr. Lowit has usefully reviewed
14 where we stand. The available data did not settle the
15 issues. No smoking gun has been found. I do not see
16 any strong epidemiologic evidence of health effects of
17 concern at exposure levels of concern.
18 What I see at this time in the
19 epidemiology is about what I would expect to see from a
20 lot of studies in which investigators have tried hard
21 to find the effects where there maybe none. I would
22 not even describe the epic results as even strongly
23 suggested.
24 I recognize and share the concerns about
25 effects not yet established. Concerns based largely on

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1 laboratory findings but I suspect that further records
2 in epidemiology will just produce conditions of
3 equivocal findings.
4 Also, I'm doubtful about the value of
5 additional water studies as support for the scientific
6 findings though they may have value in the context of
7 monitoring regulation. But none of those are more
8 imperative water studies if they're relevant to human
9 health effects, that this whole matter needs stronger
10 analysis in the EPA draft.
11 Is there a need for continuing research?
12 Definitely yes, and I believe that it should be focus
13 on mechanisms in humans with supporting laboratory
14 studies and with special attention to the exposure
15 levels of relevance to human populations.
16 I must stress this need for doses for
17 exposures that maybe ultimately relevant to human
18 apical events. I'm not against high dose studies in
19 light of the low dose effects and high dose studies
20 that are clearly negative are like would mean no effect
21 of lower doses either.
22 But keep in mind that statistical power
23 will be a major consideration in low dose research and
24 studies must be designed to have enough power to detect
25 outcomes of interest. Except for my skepticism about

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1 new water studies, this seems to be pretty much for
2 EPA's account.
3 **DR. STEVEN HEERINGA:** Thank you Dr.
4 Bailar and Dr. Gold.
5 **DR. ELLEN GOLD:** I'm not sure if I have
6 a lot to add but I'll be brief or just try to be brief.
7 I think we've talked a lot about how well EPA did in
8 integrating the findings and noting certain
9 manifestations of the findings in the epidemiologic
10 studies.
11 I guess given some of the potential
12 modes of action that might be different in animals and
13 humans it's not unexpected that we might see different
14 findings that we can't try to explain at the moment.
15 And again I would encourage some other
16 existing databases on humans who try and look at some
17 of the outcomes and some of the exposures I've
18 mentioned before. And I wanted to say something about
19 the male reproductive study phase one.
20 I mean we've noted all these limitations
21 which were significant but I would also note that the
22 effect was pretty strong. Sample studies were kind of
23 small and so I have like confidence limit that did
24 include one. And so some of the findings are
25 consistent with what we heard yesterday in terms of the

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1 testimonies. So this seems like an adequately derived
2 design studies.
3 And because of the data, the human data
4 on small for gestational age and perhaps low birth rate
5 and prematurity are suggestive and not inconsistent
6 with the animal findings.
7 I wanted to address Dr. Harris' point
8 about ecologic study design versus ecologic data, and
9 well I agree largely with her, if you have to put
10 ecologic study designs in a separate category as
11 hypothesis generating and that it is useful to use
12 ecologic exposure assessment for individuals.
13 I think it's even more useful if you can
14 actually get some assessments of drinking water habits
15 and measuring drinking water of humans. And so I sort
16 of stratify to rank them let's say that way. So I
17 would encourage that as well.
18 I just have one or two more points. The
19 conclusion in- so I'd like to address the absurd uses
20 of the toxicology versus the epidemiologic data. So
21 the conclusion in the issue here first things
22 appropriate that the experimental toxicology data and
23 not the epidemiologic data are best suited for dose
24 response assessment of this at this time.
25 And both the epidemiologic and

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1 toxicological databases can be use to inform hazard
2 rate and implication and characterization agree with
3 that.
4 But it would also seem contrary to what
5 is stated in the issue paper that the epidemiologic
6 findings can be used for endpoint selection when
7 studies are well designed. I mean it's not the case
8 right now but in future, I would want to exclude that
9 possibility even difficult if these studies are not
10 achieving the unattainable perfection. Because if you
11 don't have experimental data but you have a well
12 designed epidemiologic study, I think they can be used
13 in this way.
14 And so this has been the case
15 historically that response to outcomes for which
16 experimental data were not yet available but human
17 studies have suggested health outcomes associated with
18 the exposures that needed to be explored experimentally
19 to understand potential mechanisms and biologic
20 possibility, to also provide a sufficient information
21 to undertake preventive efforts including the absence
22 of experimental data, about physiologic mechanisms or
23 whatever. So I would disagree with that point.
24 So I think that the issue paper is
25 largely correct in its conclusions that the animal data

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1 are likely to be relevant to humans although other
2 modes of action have play a role in humans, and the
3 human epidemiologic data are suggestive for adverse
4 reproductive and birth defects.
5 So again, I would encourage the EPA to
6 collaborate with other federal agencies that have
7 funded human studies of these types of outcomes, that
8 have assessed them better than in some of the studies
9 that we reviewed here, and then have biologic specimens
10 stored that could be evaluated for exposure assessment.
11 Thank you.
12 **DR. STEVEN HEERINGA:** Thank you Dr.
13 Gold. I thank the epidemiologic group for their well
14 organized and concise presentation. Comments from
15 other members of the Panel on this particular question.
16 Yes, Dr. Bucher.
17 **DR. JOHN BUCHER:** So I just wanted a
18 little clarification from that the group answer because
19 I think I heard two different perspectives on the value
20 of further epidemiology studies for atrazine. And I
21 would just state from my standpoint I agree more with
22 Dr. Gold's perspectives than Dr. Bailar had boasted.
23 As you put that question together that you can
24 reconcile those views or come up with single and
25 clearer message.

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1 **DR. ELLEN GOLD:** Thanks, I'll do my
2 best. But I also conclude that it's not bad if you
3 have a little bit of disagreement and some explanation
4 or a little disagreement.
5 **DR. STEVEN HEERINGA:** Alright absolutely
6 and I think just importance of views but the extent
7 could be rectified fine but if not if you want to sort
8 clearly explain why there are the differences. Dr.
9 Fenner-Crisp.
10 **DR. PENELOPE FENNER-CRISP:** The question
11 of the agency and know that there was a delay in the
12 presentation of the cancer epidemiology because there
13 was some unfinished work on egg health. Are there any
14 ongoing non-cancer studies within the egg health study
15 construct?
16 **DR. STEVEN HEERINGA:** Dr. Christensen.
17 **DR. CAROL CHRISTENSEN:** Yes this Dr.
18 Carol Christensen, within a non-cancer concept by
19 understanding it that much of that work if any by the
20 co-investigators with the NIEHS.
21 **DR. PENELOPE FENNER-CRISP:** I know.
22 **DR. CAROL CHRISTENSEN:** Yeah and so they
23 have sort of active research interest in both
24 respiratory health and female productive health.
25 However, I do know sort of eight priority hypotheses of

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1 in the investigation about atrazine specifically, but
2 as they kind of go on and look at different test study
3 solutions and other exposures there maybe other
4 atrazine findings that we have them working closely
5 with those investigators and that's why there is
6 nothing outstanding, you know, sort of in the works.
7 **DR. ELLEN GOLD:** You're aware of
8 anything planned or ongoing sponsored by anybody else
9 on the planning or anything else?
10 **DR. CAROL CHRISTENSEN:** No.
11 **DR. STEVEN HEERINGA:** Dr. Christensen,
12 what about the National Children Study, EPA, do you
13 still have the reports on that particular study, will
14 atrazine be one because my understanding on the ongoing
15 other radical redesign and managerial changes on the
16 study that they were anticipating in or blood and other
17 samples, samples are essential?
18 **DR. CAROL CHRISTENSEN:** Yeah, at this
19 time, personally, it's really familiar working with the
20 design protocols. I do understand that they are taking
21 biological specimens overtime so there'll e banks and
22 certainly the potentially over time to put this little
23 piece, it may be with many different questions
24 including relevant questions here.
25 **DR. STEVEN HEERINGA:** Dr. Gold and Dr.

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1 Fenner-Crisp.
2 **DR. ELLEN GOLD:** Yes, so we do have
3 aside from the national children study in our place and
4 they are just beginning there.
5 **DR. CAROL CHRISTENSEN:** Yeah.
6 **DR. ELLEN GOLD:** And one thing because
7 of the way they designed it, they're trying to recruit
8 women who may become pregnant so that the actual return
9 of investments has been small so far so there may be a
10 need to reassess and redesign. They've just started
11 it.
12 **DR. STEVEN HEERINGA:** That's the longer
13 terms. Doctor Fenner-Crisp.
14 **DR. PENELOPE FENNER-CRISP:** Is atrazine
15 or the triazines and their aggregates still on the
16 NHANES monitoring list?
17 **DR. ELLEN GOLD:** Yes, atrazine is
18 included in the NHANES Program. I have to double check
19 on other triazines, but I know I just need to I know
20 there are measures of exposure obviously, potential
21 category and
22 **DR. STEVEN HEERINGA:** Thank you, that
23 thought also crossed my mind too.
24 **DR. ELLEN GOLD:** Included in the
25 database.

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1 **DR. STEVEN HEERINGA:** Dr. Lowit.
2 **DR. ANNA LOWIT:** I was just
3 anticipating, I was sensing that you were going to ask
4 for one more round and I've had a clarification. As
5 you before you close this question.
6 Dr. Harris said at the beginning of her
7 discussion of part B caveated her comments with her
8 expertise which makes sense. And I want to make sure
9 that as we move through the more animal based
10 toxicology studies, questions and comments related to
11 Cooper study and the animal relevance of the the human
12 relevance of the LH 20's and the animal that we circled
13 back, that to
14 **DR. STEVEN HEERINGA:** I have a similar
15 thought and in other words that, for exactly that
16 reason that Dr. Harris pointed out and as we go through
17 these other issues is in fact a response on the
18 epidemiologic cycle to try to add that to me, and
19 obviously in the report, we'll try to integrate it, but
20 as we go in sequence, we'll be sure to try to capture
21 and then presenting her additional thoughts that might
22 come from the epidemiologic team.
23 Well, at this point, I'd like to call a
24 break and again, thank three of our epidemiologists for
25 an excellent job at this point. Let's take 20 minutes

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1 and we begin here at after 10 minutes.
2 **(WHEREUPON,** a Break was taken.)
3 **DR. STEVEN HEERINGA:** Okay let's find
4 our seats and we'll begin again. At this point, we're
5 ready I believe. I'd like to move to question 2.0,
6 review of studies on mammary gland development. Dr.
7 Lowit, will you read question 2.1.
8 **DR. LOWIT:** Okay question 2.1, please
9 comment on the quality, strengths, and limitations of
10 the mammary gland development study for Rayner et al
11 (2004, 2005) and Coder (2010) studies. Please discuss
12 in your comments factors that could lead to different
13 findings. Please comment on the Agency's conclusion
14 regarding studies on atrazine.
15 **DR. STEVEN HEERINGA:** Dr. McManaman,
16 start.
17 **DR. JAMES MCMANAMAN:** So I have this
18 broken out into the three components of the charge
19 questions. The first is to comment on the quality,
20 strengths, and limitations of the mammary gland
21 development study by Rayner and Coder.
22 So I will go through each one of the
23 studies beginning with Rayner 2004. In this study on
24 this is little review but they did this Long-Evans rats
25 that were dosed with 100 mg/kg of Atrazine once a day

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1 by gavage vehicle else were housed on a 14/10 life-arc
2 cycle and at birth, half the dose from each treatment
3 were cross clustered with the other half of pups that
4 were originally in that letter to give four
5 experimental groups.
6 A group that was treated with vehicle
7 and main vehicle, a group that was treated with
8 atrazine during gestation and then with cross pups with
9 control pups with those clustered treated with control
10 for vehicle and then cross pups with atrazine pups in a
11 group that receive the atrazine during gestation and
12 cross pups with the atrazine pups.
13 So basically, they found that at the
14 specified times, each group has analyzed for body
15 weight, date of vaginal opening, weight at vaginal
16 opening as the cycle, mammary gland properties.
17 They've found significant effects of atrazine on the
18 age of vaginal opening and they found decreased body
19 weights of the pups set with day four in the atrazine
20 group.
21 The mammary gland properties, they
22 found--they used a developmental score to assess the
23 mammary gland development and they found significant
24 effects in the pups that were cross sponsored on the
25 atrazine moms at post natal day four and 22. And there

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1 was also a decrease in the labeling index at these
2 times.
3 They also looked at expression of aroma,
4 taste and epidermal growth factor receptor and found
5 decrease to aroma, taste post natal day 33 and in the
6 pups from the atrazine that were cross-sponsored on the
7 atrazine moms. And increase EGFR and I think four pups
8 cross-sponsored them as well as the atrazine cross
9 pups.
10 The strengths of this paper is that
11 there were multiple time points, where the experimental
12 design which multiple time points were evaluated and
13 cross fostering approach. In addition, there was
14 technical expertise in the conduct of the experiments
15 and that they were able to cross foster which is
16 difficult for this strain of rats. And well I guess
17 that's the main point about that.
18 The Limitations for this one and for
19 this paper and for the subsequent paper of 2005 was the
20 subjective mammary gland scoring system. And also
21 there were limitations in the conclusions which covered
22 the age of a utero exposure.
23 They concluded that it was primarily
24 related to the neuro exposure to atrazine whereas cross
25 sponsored data set suggested there were significant

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1 lactation effects on the other treatment and that there
2 was no discussion on mechanism. So those were the two
3 limitations on that.
4 Rayner 2005 was intended to find the
5 sensitivity, window of sensitivity during gestational
6 exposure. They dosed again, with like 100mg/ kg and
7 they did do a limited dose response curve here. Here,
8 they changed the protocols, so now they were giving
9 atrazine twice a day, 50mg/kg to give a total of one
10 day, 100mg and they evaluated the groups at days 13 to
11 15 gestation, 15 to 17, 17 to 19 and 13 to 19 to
12 identify the critical periods of atrazine exposure, and
13 both the F1 and F2 offspring.
14 Again, they examined maternal end feel
15 weight via vaginal opening, weight of vaginal opening
16 and use of mammary glands scoring system, in this day
17 however, they used a objective approach and that they
18 measured the length of the epithelial tree and they
19 measured the area of the epithelium and they looked at
20 postnatal days 4, 22 and 25, for the 13 and 19 group
21 and postnatal in 46 and 47 for using the objective
22 approach and they looked at postnatal day four through
23 67 for the subjective scoring system and they also
24 measured organ weights and there was no difference in
25 the groups. And significantly they found that the F2

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1 pups there were differences at the postnatal day four
2 and postnatal day 11 in the weights of the atrazine
3 treated groups. This is not a cross foster study.
4 The strengths were the experimental
5 design to identify the specific periods of gestational
6 development, they were sensitive to atrazine and the
7 inclusion of experiments designed to test the effects
8 on the F2 generation.
9 Methodology was also a strength, they
10 used objective measurements of ductal growth and the
11 epithelial size and again used multiple time points.
12 Another strength is the reproducibility again they
13 found the same days of vaginal opening in their study
14 and they found the same effects of atrazine treatment.
15 The limitations were that they continue
16 to use the mammary gland scoring the subjective mammary
17 gland scoring system and there's concern among the
18 group that there might be that the methodology of the
19 scoring system may force identification differences
20 where differences really don't exist.
21 So there were some concern about that
22 but I think that Dr. Fenton addressed some of these
23 issues or try to address some of these issues in the
24 sense that the multiple investigators were using the
25 subjective scoring system and they get consistent

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1 results.
2 And then finally, the last limitation
3 was that there was a lot of care feeding although they
4 recognized that atrazine was causing a decrease in gram
5 weight, they didn't put in the care feeding controls.
6 So now the next one is the Syngenta 2010
7 which is a combination of Dr. Coder and Hobie. Again
8 they used Long-Evans rats. In here there was a
9 variation between what the chem group used. They used
10 these animals that were on 12/12 cycle, my third cycle
11 which potentially is a compounding variable here.
12 Animals were dosed with atrazine, at right doses of 100
13 mg/kg by gavage, this is once a day compared to the
14 twice a day that the previous Rayner used and they were
15 dosed on gestational days 13 to 19.
16 They used an objective image analysis
17 approach to characterize mammary gland development
18 post-natally and significantly their planning crossed
19 fostered experiments where they started to do standard
20 ratio in cannulization.
21 So they measured the body weight,
22 vaginal opening and mammary gland development, they
23 tried to make this as close as possible to the Rayner
24 studies and significantly they found no difference in
25 vaginal opening in their study, the same strain of rats

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1 but no difference. The dammed body weights were
2 significantly reduced during gestation and lactation.
3 And the body weights by treatment with atrazine.
4 The body weights of the high-dosed
5 atrazine in the fair-fed groups were similar during
6 gestation. They were different from the control. The
7 body weights of the high-dosed atrazine and the fair-
8 fed groups were also significantly less than that of
9 the control during lactation.
10 But significantly the fair-fed group had
11 a lower body weight than the high dose atrazine group
12 and this is all through lactations, so there was hardly
13 any change in body weight in the fair-fed group whereas
14 the atrazine group did increase and consistently
15 maintained a higher body weight during that period.
16 They evaluated end numbers in BrDU
17 labeling values at a variety of different times of
18 course roughly corresponding to those of the Rauner
19 study and found that there were differences at
20 postnatal day four in the high-dosed atrazine group in
21 terms of end-bud numbers and a BrDU labeling.
22 Respectively they end bud numbers were greater than the
23 controls in the fair-fed group. In the high-dose group
24 and the BrDU labeling and the high-dose group was
25 lessen out the controls.

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1 They also found that end-bud numbers
2 were different at the day of vaginal opening. With
3 end-bud numbers in the fair-fed group were greater than
4 the controls of the high-dosed atrazine group.
5 Interestingly, the Hobie papers states that the
6 atrazine at the 50 mg/kg group were also greater than
7 the controls but that was not the conclusion of the
8 public letter paper that was in our docket.
9 So the strengths of these were that
10 those response designs with fair-fed controls were
11 significant strength of the Howder paper and then the
12 use of the extensive objective extensive use of
13 objective image analysis approaches rather than these
14 subjective approaches used by Rayner.
15 Limitations for the methodology in terms
16 of life target cycle and the possible stress effects as
17 exemplified by dam aggression and cannibalization.
18 Further there were different, there was it could be a
19 lack of reproducity in body weight effects of atrazine.
20 This particular study found that there was an effect, a
21 significant decrease at the 50 mg/kg level whereas in
22 another study within this packet Coder C-study found
23 that there was no difference between the 50 mg/kg on
24 body weight of the dams.
25 Now the difference between these two

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1 studies is that the Coder D, the one I'm just referring
2 to was that's a Long-Evans study and the Coder C-study
3 was Sprague-Dawley study so there's some question about
4 whether atrazine does have an effect on body weight in
5 their strength specific.
6 Furthermore, another limitation with the
7 conclusions that there was no effect--the no-effect
8 conclusion when it was clearly possible effects of
9 atrazine on end-bud numbers had postnatal day four,
10 that there were no effects of postnatal day four and
11 there were also effects at the day of vaginal opening
12 on both the 50 and the 100 mg/kg groups.
13 And there's no discussion with
14 significant differences in body weight during lactation
15 between the fair-fed and the high-dose groups. So
16 those are the evaluations of the strengths and
17 weaknesses.
18 So I move to the next question which is
19 to discuss your comments regarding factors which could
20 lead to the differences in findings. I've already
21 alluded to this, the Fenton group used a 14/10 cycle
22 and the Coder group use 12/12 and there was also
23 concern that the Coder study, the animals were stressed
24 and we've heard that atrazine produces corticosterone
25 increases and so potentially there's an undoubting

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1 factor here as that the animals were already stressed,
2 you would not see the effects of atrazine, the same
3 effects that the Rayner studies saw.
4 Regarding the agency's conclusions of
5 these studies I think that both studies show
6 significant effects on mammary gland development, but
7 differences in procedures, differences in the results
8 and differences in possible adverse effects as stress
9 of the Coder study prevent concrete recommendation
10 regarding the use of the mammary gland to investigate
11 adverse outcomes of atrazine at this time and I think
12 that if you want to use this we have to have additional
13 studies.
14 **DR. STEVEN HEERINGA:** Thank you very
15 much. Our second discussant is Dr. DelClos.
16 **DR. KENNETH BARRY DELCLOS:** I think that
17 strengths and weakness has been pretty well covered in
18 the last statement. I think the differences clearly
19 not totally due to quantitative methods used by Coders
20 since Rayner also for the vaginal opening delay which
21 is not found in the Coder studies and also where Rayner
22 did use the quantitative measures in the mammary gland
23 area for example as mentioned by the treatment only
24 differences.
25 The differences in the quantitative

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1 versus subjective measures have already been covered as
2 those are potential question stressed with the animals
3 I'm about to mention yesterday.
4 One thing included for study did fall
5 over the Rayner study is for its rat strain dosing and
6 life cycle as one difference that was mentioned. The
7 other control variable with difference in diet and it
8 is stated in the real report we were doing were based
9 on the diet using the previous studies injected with
10 atrazine with probable weight comes with the different
11 strain of diet used in the previous study and the one
12 with the current study was not expected to impact
13 animal health of the outcome of the study.
14 I don't necessarily agree with that the
15 absence of data because both of these diets are natural
16 ingredient diets of fiber where it is particularly high
17 in soy content, very variable phytoestrogen levels.
18 It's true both with both of the diets but they do
19 different analysis, they differ in the fat source that
20 the fiber using the animal fat and the 502 using corn.
21 But there has been a lot of--over the years bounded
22 with the rule of the soy content of the diet.
23 The phytoestrogen content in the diet is
24 exactly ten points so they only see data that lies
25 comparative study for the EPA and for the sharper

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1 studies what can--with your appropriate answer and came
2 out with the recommendation that the levels of the
3 phytoestrogen should be tapped to a lower 350 mcg/g I
4 believe 350 parts per million which cleans the animals
5 even with that 30-40 milligrams of isoflavones per
6 kilogram per day.
7 Then the some weight--and phytoestrogen
8 has been what's interesting in the animal studies to be
9 used, so they're expecting the very endpoints of
10 serving both that vaginal opening and mammary glands.
11 And I also noticed this stuff that the--in the earlier
12 that the total vaginal opening will be different for
13 the maternal studies.
14 It was difficult to compare across
15 laboratories like this. There's going to be variation
16 of course with that of the Coder study that the vaginal
17 opening time did fall within the rate where Rayner were
18 in significant differences delay of vaginal opening.
19 So I think, you know I don't know
20 whether the phytoestrogens have an effect on atrazine
21 or it has been looked at, I don't know if what we're
22 aware of, but I think it's something that should be
23 considered.
24 And I think that EPA, it's my feeling
25 that they require the reporting of phytoestrogen levels

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1 in the diet. It's certainly something if you're
2 currently clear cross studies on mammary gland that you
3 should be aware of and control force of about the same
4 diet should have been used and it's a potential--and
5 the thing is there's many reports and there's
6 disagreement in the literature on this effect of so why
7 the time determines the time of vaginal opening and so
8 forth that their maybe a strain difference of--there
9 are also a sporadic reports in the literature where
10 people move from one institute to another and somewhat
11 lose their effect and they attribute to the diet, so I
12 think it's a really important profounder in charging
13 the studies.
14 And I agree that as from the last
15 discussant, it indicated that the studies are not ready
16 for--I agree with the agency's inclusion that they're
17 not ready for the risk presented. That's all I have to
18 say.
19 **DR. STEVEN HEERINGA:** Thank you Dr.
20 Delclos. Dr. Horseman.
21 **DR. NELSON HORSEMAN:** So I'm not going
22 to comment on the strength and weaknesses. I just have
23 a general comment I want to make, so I think Jim
24 covered--this guy the strains in particular very well.
25 So there's a fundamental issue here that I think that

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1 runs through this stage.
2 Neither of its various posts that breast
3 milk is good, and breast cancer that where the phone
4 number over these studies only address bigger than
5 smaller. And the outcome that's supposed to be
6 negative as smaller, and I don't see any reason to
7 believe that to be a legitimate outcome and particular
8 it's pointing out by Fenton in her presentation, the
9 issue of precocious mammary gland by augment which has
10 then recently reported as a potential human health
11 issue by trying to bear on his colleagues maybe
12 relevant. And here the paradoxes that bigger is a
13 negative outcome.
14 So I think just that the fundamental
15 level that the biggest weakness in this entire set of
16 studies lies on the presupposition that you can
17 automatically suppose that the more development at this
18 particular stage or at this individual stages, it is a
19 positive outcome and less development has made about
20 that.
21 Particularly it was regarded to
22 gestational studies. The most normal state at the
23 handling gestation for the mammary gland is
24 underdeveloped. This is a very small underdeveloped
25 only, slightly branched the mammary gland system.

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1 So I think that this--and when you come
2 back to sort of the summary of both of these sets of
3 studies, I think you'll not agree with this notion and
4 to maybe think about how we might be able to use the
5 mammary gland but be able to require examining these
6 fundamental assumptions first. That's my main comment.
7 **DR. STEVEN HEERINGA:** Thank you Dr.
8 Horseman. Dr. Leblanc.
9 **DR. GERALD LEBLANC:** I never ceased to
10 be fascinated by the frequency with which to hop in
11 labs typically one from Academia or the government and
12 the other being a supported lab addressing the same
13 question if you happen to seemingly despair results.
14 I've concluded that one of the reasons for this is that
15 the academic or the Government Labs are typically
16 seeking to discover new information or the industry
17 labs are seeking to confirm, to refute, or to address
18 alternative interpretations of the existing data. The
19 results that we get a series of checks and balances
20 from which hopefully the best science emergence and the
21 agents have been mixed on decisions.
22 In this case, we have the Rayner
23 studies, and Rayner et al. discovered basically that
24 atrazine were administered at a 100 mg/kg either
25 prenatally or postnatally, negatively impact with

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1 mammary gland development.
2 The screens or the paper have been well
3 covered by my colleagues and I am not going to go into
4 that but I'd like to add a couple of points. One being
5 that this Rayner effort really represents three
6 studies. The two that we were asked to evaluate, and
7 then the Enoch studies which used a 100 mg/kg atrazine
8 as positive control.
9 And all three studies cooperate. They
10 all provide the same basic information with respect to
11 effects on mammary gland development.
12 This study has also provides the well-
13 tested atrazine effect that has increased the vaginal
14 opening supporting the efficacy of the treatments. The
15 measure used, scoring had been cited by my colleagues
16 as a weakness to the study and I agree that the
17 subjective nature of scoring can be viewed as a
18 weakness to the studies.
19 But I think it's important to also
20 recognize that it can be recognized as strength because
21 this really provides a holistic or an integrated
22 measure of mammary gland development rather than
23 looking at individual parameters in isolation.
24 The Coder studies sought to replicate or
25 extend upon the relevant aspects of the Rayner study.

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1 And again, the strengths and the weaknesses have been
2 well covered--I'm going to look at this quickly to see
3 if there's anything here that hasn't been discussed.
4 They've all well been covered. I'm not going to repeat
5 myself.
6 Since it presumed the tenth of the Coder
7 Study was to confirm, refute or extend upon the Rayner
8 Studies, I do find it surprising that a different
9 analytical methodology was used to assess mammary gland
10 development.
11 And the least I've learned to expect is
12 that both the qualitative scoring and the quantitative
13 movement or analysis would have been using this study
14 compared to provide us some interstudy comparison which
15 we could then expand to the Rayner studies which this
16 clause had done.
17 I consider it possible that small
18 difference between treatments if controls existed
19 anymore from metric analysis. Just looking at the data
20 that we had in the report, we can see differences, and
21 while these differences were deemed non-significant and
22 apparently not significant, it's certainly possible
23 that in combination they would have in fact the scoring
24 in the Rayner studies.
25 If the EPA may consider requesting that

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1 the registrant have the slides generated in the Coder
2 study scored using the same scheme required by Rayner,
3 ideally the slides are to be scored of the same
4 histologist who scored the Rayner slides. This will
5 provide some direct comparison of results. There have
6 been two methods and this will be very informative.
7 Despite the different methodological
8 approach as used in the Rayner and the Coder studies,
9 several disease decision results exist at the atrazine
10 dose with is a 100 mg/kg.
11 Both studies reported a decrease in the
12 maternal animal weight, they both report a decrease in
13 pup weight, they both report an effect on live births
14 or death ones, and they do both report an effect on
15 mammary gland development.
16 The major discrepancy is that the
17 effects observed on mammary gland development are not
18 consistent with respect to magnitude and temporalities.
19 This difference may be due to the different methods and
20 analysis used which again, are views for a comparison
21 of the two methods, how to use the slides generated in
22 the Coder study.
23 **DR. STEVEN HEERINGA:** Thank you Dr.
24 Leblanc. Dr. Lowit.
25 **DR. ANNA LOWIT:** Thank you. I basically

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1 agree with everything that has been said so far and I
2 have just a few things that haven't been mentioned.
3 Yesterday, it was brought up by Dr. Coupe that they
4 made an effort to assess mammary gland development in
5 animals after vaginal opening on the same day at the
6 estrous cycle, and I think there's a lot of variability
7 in the data and I think in the adult numbers afterwards
8 in other measurement, hormonal measurements and the RU
9 measurements and so forth so I think that it might have
10 helped in the future if they do all their studies that
11 after vaginal opening, you have to check the animals on
12 a given date on the estrous cycle.
13 I found a couple of errors in the draft
14 paper in terms of their citations of that papers and I
15 have those in my written accounts. The only other
16 thing I want to add is I agree with the comments of Dr.
17 Leblanc that it would have been really nice to see the
18 comparisons between studies on the subjective scoring
19 using that method.
20 But my final comment is that what struck
21 me about these studies was that when they looked in
22 adults after and close to postnatal days 50 or 60.
23 There are some dates when I think each study looked at
24 mammary gland development, it had reverted. It was no
25 different from controls that happened.

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1 So even though there are--I think most
2 studies actually did find similar things in terms of
3 some delay in mammary gland development, it's
4 temporary. And I think they have to keep in mind that
5 atrazine treatment was also temporary.
6 It was limited to up to a period during
7 gestation or in postnatal or early postnatal, live
8 birth during lactation. And then it stopped. So once
9 it stops, once they're weaned, that postnatal day 21,
10 40-50 you know a couple of months later, things have
11 normalized.
12 It appears, I'm not--I mean they're not
13 frequently have points, there's just one in each study.
14 But it is a temporary phenomenon then maybe that's of
15 course affected, it was atrazine-caused and there's
16 something going on there. That's all, that's my
17 comment.
18 **DR. STEVEN HEERINGA:** Thank you very
19 much doctor. Other comments from our panel members
20 with regard to this question? Dr. Akana.
21 **DR. SUSAN AKANA:** In most of this view,
22 the endpoints have been morphological or structured and
23 I'm a physiologist, so I say--where is the functional
24 output for this?
25 And as one goes with milked mouse, you

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1 can do these studies. And in Rayner study, they're both
2 on lactation challenges primarily focused on mom. But
3 the study designed, and they touched it on yesterday,
4 there was a possibility of measuring the--well she did
5 it. She weighed the depth and the liters after
6 separation that when they review grouped after 20
7 minutes of--well that's on the 20 minutes of lactation
8 will be weighed a liter.
9 Now at this age, infant mice or infant
10 rats do not excrete. They don't pee and poop on their
11 own. They need moms in relation to do it. So, what
12 they have is what milk they took in. Now, there was
13 reportedly no treatment difference in the weight gain
14 per liters. And I mentioned yesterday, however the
15 pups were less than atrazine-treated groups.
16 Therefore, they must have done it for milk.
17 So, I think there is a possibility of
18 exploring that kind of functional outlook from the
19 mammary gland. And there are a number of devices you
20 can use to collect milk from anesthetized females, so
21 there are possibilities.
22 **DR. STEVEN HEERINGA:** Thank you Dr.
23 Akana. Dr. Horseman.
24 **DR. NELSON HORSEMAN:** If I might just
25 make two comments on things since I'm not wise pretty

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1 well, I don't know, but we don't advise pretty
2 regularly whereas that we either correct that that can
3 be done and it is a functional outcome.
4 We might come back to that later. I do
5 think I want to because by virtue of the way these
6 papers are presented and these studies are presented,
7 the concept of delay of mammary gland development is
8 intrinsic and we came to adopt that language when we
9 talk about these studies, and I think it's important to
10 challenge that notion. And I'll just give you one
11 specific case beforehand; Jim will be able to elaborate
12 on this.
13 So, why should it inherit MTV mammary
14 gland retrovirus? If you compare them with the
15 equivalent mice that don't inherit that or it might be
16 infected with that retrovirus, are always going to
17 score higher on any of these tests that we're talking
18 about here. Well, it's just simply observation
19 morphology or in measuring these things.
20 And so, it would be hard to say that
21 tumor virus is a better outcome than not having tumor
22 virus, right, and I think at some basic level. And so
23 the notion that this delay--that we adopted the
24 assumption of the delay is a negative outcome, I think
25 it is problematic.

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1 **DR. STEVEN HEERINGA:** Thank you. Dr.
2 McManaman.
3 **DR. JAMES MCMANAMAN:** So, I have just a
4 couple of thoughts regarding the effects of the
5 atrazine. It occurs to me that it's quite profound
6 given that what we heard yesterday about the
7 pharmacokinetics, that when you stop dosing at
8 gestation on day 19, that you can have an effect
9 several weeks later.
10 What I understand is that most of the
11 atrazine and metabolites, the area under the curve of
12 the data should have resulted in a clearing of the
13 active components within a few days after birth, yet we
14 still see an effect of both studies at the date of
15 vaginal opening on a number of end buds.
16 So, I think that has well, it's not, I
17 don't know how useful that is in terms of risk
18 assessment. I do think that it has a profound
19 biological question, it outraces profound biological
20 question so it's then how does that happened because in
21 tumor, I believe there is nothing left to induce these
22 changes. So, there has to be something happening early
23 on. And with that is a conundrum.
24 Furthermore, from what I've read, the
25 limited amount of information about how much atrazine

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1 is actually in the milk is not well established. And
2 the data that I saw suggests that with using a tracer
3 study that about 2% of the atrazine that was induced by
4 the buds ends up in the milk.
5 So again, it raises questions about how
6 much atrazine is really there and what effect it's
7 having. Is it a gestational effect? Is it a
8 lactational effect?
9 And the questions are there were some
10 more questions and issues than they sought to address.
11 So, I think we know very little and I think about how
12 it affects the mammary gland and I'm--well, the data
13 don't support the use of the mammary gland at the
14 moment, I think the data support further study, because
15 I think that it has profound implications.
16 **DR. STEVEN HEERINGA:** Dr. Bucher
17 **DR. JOHN BUCHER:** First, the disclaimer
18 on Dr. Fenton works in my division, and I know that she
19 indicated the other day, we have an ongoing project to
20 look at the relative sensitivity and accuracy of the
21 subject of scoring mechanism versus this quantitative
22 scoring mechanism.
23 But I would agree with Dr. LeBlanc. I
24 don't think I have seen anything yet or I would
25 challenge I guess the group to produce data that would

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1 suggest that quantitative scoring system that was used
2 is in fact more sensitive or more specific or more
3 accurate.
4 And until that has been shown, I am not
5 sure that the subjective system should be discarded as
6 it really has been and has a serious weakness as the
7 new case that's characterizing it in the document.
8 So, I think that this is really
9 important with respect to those levels in the Enoch
10 paper that generated changes in mammary development.
11 They are very, very low with respect to the combination
12 or a mixture of studies. Clearly the atrazine wasn't
13 tested on its own and with those low levels in the
14 Enoch studies has been.
15 But I think that this is something that
16 the panel should be fairly specific on, if you believe
17 that the sensitivity and accuracy of the quantitative
18 approach has been shown to be superior than this data.
19 But I'm not sure I've seen the data to suggest that
20 yet.
21 **DR. STEVEN HEERINGA:** Dr. Horseman?
22 **DR. NELSON HORSEMAN:** I'll just comment
23 that--I don't necessarily believe that the
24 quantitative, the objective--they both end up being
25 quantitative in the sense that you assign quantities,

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1 the subjective scoring either is intrinsically more or
2 less valuable. I think they do.
3 They require a lot of different
4 approaches from the beginning in terms of how
5 individuals actually gather the data and we heard a
6 discussion about how people are trained and support to
7 gather the data which at that end, it's important that
8 they are different all the way up to the statistical
9 analyzing of the data.
10 And nonetheless we didn't discuss in
11 detail the statistical handling of these scoring data.
12 And I don't consider myself the internal legitimate
13 statistician, but I was not convinced that the most
14 robust statistical techniques were used there.
15 So there are layers of issues I think in
16 deciding preference of either the objective or the
17 morphology measurement base approaches versus a scoring
18 base approach. And maybe the argument that the one is
19 better than the other one, I would agree.
20 There is no reason to say that, but the
21 way they are handled obviously in this particular
22 studies, these measurements that the Coder study did
23 were handled in a much more apparently rigorous manner
24 from both measurement statistical sense, but that
25 doesn't make the approach more or less valid.

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1 **DR. STEVEN HEERINGA:** Dr. Fenner-Crisp.
2 **DR. PENELOPE FENNER-CRISP:** I just want
3 to follow up a little bit on John's last comment and it
4 was pointed out by Dr. Fenton yesterday that the
5 process by which the criteria were selected and are
6 applied is quite consistent with general evaluations of
7 pathology period, including some efforts to look at
8 severity of whatever the phenomenon is, which is a
9 reflection of this.
10 So, I was a little disconcerted by the
11 under currents of dismissiveness of using this kind of
12 technique when it kind of just bases of all of MTV's
13 data evaluations and a whole lot of other pathological
14 evaluations for studies of all of them.
15 So, the long history of having this kind
16 of process in which entities have agreed upon
17 appropriate criteria and that they agreed upon this
18 foreign mechanism and then do an internal and an
19 external peer review.
20 So I found it a little disconcerting
21 that you might want to just abandon that approach.
22 **DR. STEVEN HEERINGA:** Dr. McManaman
23 **DR. JAMES MCMANAMAN:** Yeah I don't think
24 that was our intention to suggest that it was--if one
25 had to say, how could we reconcile differences then and

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1 I think that was the way I interpreted the charge is
2 that--if one has to evaluate in a blinded way and just
3 is able to use image analysis in which you have--
4 there's no Gestalt effect, you know.
5 And that is a very objective way that
6 would lead to less bias--potentially less bias, whether
7 this leads to a greater accuracy or not, I don't know.
8 But personally, I do the same kinds of studies that Dr.
9 Fenton does them in a sense that I look at them first
10 and find out what is the difference and then try to
11 come up and see viable lead determinants and try to
12 seek, you know to try to quantify that.
13 So in a way, I personally lean towards
14 the Fenton approach but I'd also do the image analysis
15 and it's difficult to try to match those things, but
16 clearly I wasn't able to just--if one had to evaluate
17 it from strictly an objective view the subject you've
18 approached that Dr. Fenton uses is if you were going to
19 try to have other laboratories reproduce this it's
20 harder to reproduce than the objective image analysis
21 approach.
22 So I think that it's a relative
23 weakness, it's not an absolute weakness. Furthermore,
24 the difference between the way a pathologist evaluates
25 samples in a way that Dr. Fenton's group evaluates

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1 samples appears to be and that pathologist had
2 historical values for differences in a group.
3 And Dr. Fenton appears to take each
4 study and look for differences. And that's a different
5 means of analysis than what a pathologist would do. So
6 I think that--well that maybe just a practical way of
7 handling that.
8 I don't know if that is the best way so,
9 I would have to say thank you to Dr. Fenton--should be
10 encouraged to use historical data as a way of looking
11 at what's a four and what's a one and then from there,
12 try to finish one--each experiment into a one and four
13 paradigm.
14 **DR. STEVEN HEERINGA:** Dr. Bucher and
15 then Dr. Portier.
16 **DR. JOHN BUCHER:** So just one
17 clarification just to remind you that, Sue didn't say
18 that they included historical slides in the result.
19 Slides have each study so that there could be a sort of
20 a collaboration back to increase .
21 **DR. STEVEN HEERINGA:** Dr. Portier would
22 like to move on.
23 **DR. KENNETH PORTIER:** It's an
24 interesting discussion always to me, the qualitative
25 scoring and quantitative measurement. And what the

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1 argument want--suggested by actually having the Coder
2 slides score means that you can necessarily look at the
3 two.
4 And when I was looking at the--thinking
5 of the Rayner studies, I kept thinking what if they
6 have four or five measurements but they have done a
7 multivariate analysis.
8 They haven't looked at--because there's
9 some kind of latent structure here that would actually
10 lend itself to grouping, kind of like the coding and so
11 there's still some--it's very large and interesting
12 statistical analysis that could be done.
13 I did review the analysis of the data--
14 the scoring data and while the scoring is qualitative
15 and then they use any of methodology, they sum the
16 scores over individuals and litter to come up with an
17 average score for the mother. And then they went on
18 and did end over.
19 And I think that's probably pretty
20 standard approach. I don't think there's going to be--
21 in view of this that coming out of that approach.
22 **DR. STEVEN HEERINGA:** Well, very good
23 discussion on that. I'll thank the discussants and the
24 associates for the organization of the presentation.
25 At this point, I think I'd like to move

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1 on to Charge question 2.2. Of course if other issues
2 arise back to 2.1, feel free to bring them in. But at
3 this point Dr. Lowit, if you can read the charge
4 question 2.2 into the record.
5 **DR. ANNA LOWIT:** In three of the studies
6 considered in Question 2.1 (Rayner et al 2004 and 2005;
7 Coder 2010), effects have only been observed an
8 Atrazine dose of 100mg/kg/day. In contrast, Enoch et
9 al. (2007) report delays in mammary gland development
10 as low as 0.09 mg/kg/day following exposure to atrazine
11 and mixture of several metabolites/degradates (DEA,
12 DIA, DACT, hydroxy-atrazine).
13 The Agency's review of this mixture
14 studies provided in Appendix A (Section A.10). Please
15 comment on the Enoch et al. study and the degree to
16 which the Agency's review accurately reflects the
17 strengths and limitations on the study. Please include
18 in your comments a consideration of the study design of
19 the mixtures experiment and how this designed impacts
20 the interpretation of results.
21 **DR. STEVEN HEERINGA:** Dr. Mumtaz will
22 discuss it.
23 **DR. MOIZ MUMTAZ:** I'm aq chemist by
24 training and became a toxicologist so I just then use
25 chemicals in the nervous systems and it was being

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1 required to become a toxicologist.
2 So I'm more quantitative in the massive
3 extracts of the chemical. So then I came to EPA, I
4 realized to begin with mixtures of chemicals and so I
5 want to commend EPA for taking up this issue into
6 mixtures because often just because their complexity is
7 in born, that specific mixtures is shunt and it stay
8 with similar chemicals.
9 So my comments are the structures to top
10 it before the goals of this assessment. What are the
11 issues that make up this assessment and the common
12 relate it on the Enoch study, hopefully the rest of the
13 panel members will add to it.
14 So the goals of chemical risk assessment
15 in general could be multiple. It could be just
16 protecting public health. It could be ecological
17 health. It could be determining available levels, or
18 just improving the methodology or technology involved.
19 In case of mixtures, it could be just--to show that
20 mixture risk assessment is not an issue because a lot
21 of plant when you do a single chemical risk assessment
22 involving the community--what about mixtures, so it
23 could be just that and at least that it use the other
24 than the said sides.
25 We deal with hundreds of chemicals and

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1 most of the time they find that at the low levels we
2 find chemicals and it's also important to look at
3 mixtures of chemicals.
4 But, it is just to show that being a
5 group we have addressed it on selective community,
6 where population is important. But the goal of these
7 insights here was to look at how they can improve the
8 frequency of standings, it was to get a risk assessment
9 of exposure. I believe that's my understanding of the
10 assignment we have here.
11 So this consist of chemical mixtures
12 goes through the process of hazard identification, it's
13 for your assessment, those response and then this kind
14 of question that John will lead some of that tomorrow
15 or later on this afternoon.
16 We'll see how that went to catch
17 everything into it and generate recommendation. And
18 they all recognize that exposure to chemicals is not
19 for a single chemical but all these mixtures of
20 chemicals.
21 To evaluate the mixtures risk
22 assessment, often a 104 is potency made dose or
23 response attitude which is but that assumes that the
24 slow interactions of humans between the chemical system
25 they go to the process in the human body or in an

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1 animal body system.
2 But interactions do occur and there's a
3 lot of data to show that. That interactions in a
4 volatile system do occur because there are limited hot
5 place that human or animal body can dispose of
6 chemicals. And so we shall consider the role of
7 interactions in the joint process in the human mixture
8 risk assessment.
9 That at least to--hypothesis has been
10 raging to say, "Hey, if there are--these three can
11 cause present the same mode of action." That could be
12 possibly be of interactions and if that is the case, if
13 there's a limitation, that will recommend--that was
14 involved, it could either go down or you could it could
15 just not create limiting there could be--and that shows
16 separate enzymes so that there are--it could be more
17 than anticipated.
18 So, the consideration of interactions
19 helps us do the hypothesis testing for uses of
20 chemicals. While doing so, we should also consider
21 that the exposures occur either simultaneously or
22 sequentially and I'm stating all these issues about
23 mixture risk assessment because later on when we look
24 at the study, these are the issues we need to address.
25 I'm really happy that as toxicologist, we are moving

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1 away from genetic toxicity studies and we try to infer
2 data from such studies about mixtures. Then they don't
3 have the steps to go toward or there are levels to
4 address to get exposed.
5 But for a well designed facts of this
6 study towards improved paucity or risk assessment, it
7 prove teamwork as a that issue then improved the
8 experimental toxicologist, scientist, competition and
9 modelers and discuss systems as can be similar to this
10 part of a panel development. People have different
11 backgrounds in terms of scientific backgrounds and how
12 they are trying to enter their goal at.
13 And you might not agree today or in the
14 next meeting that what we're doing is right, but
15 ultimately when we get the answers then a consistent--
16 it could be the right one. Until then, we have to
17 depend on less than, I believed design studies and that
18 brings us to the Enoch et al. study.
19 This study was designed in context of
20 enlargement with preliminary exposures. Mammary gland
21 development as an indirect indicator of cross studies,
22 areas, mixture with appropriate proportions on them one
23 week was tested at three different concentrations of
24 0.09, 0.87, 8.72 in per kilogram levels, and an
25 appropriate positive and negative produced.

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1 This study addresses issues that
2 include, but limited to this specific mixture. They
3 don't administer dose. It is the same study of
4 simultaneous exposure to allergen and the three known
5 metabolites. There was no consideration given to the
6 genuine concentration of chemicals or the metabolites
7 as a functional scientific basis.
8 This was a mixture of component
9 chemicals of assumed similar mode of action. And if I
10 had looked at these structures of chemicals I would
11 have hypothesized that those additivity would be the
12 case in this part of the recognition.
13 I happen to have the knowledge because I
14 know that levels of low and the mode of actions were
15 similar. If the mode of actions were different, it
16 could have been a depression but that's just essential
17 right now about what you are doing in the study.
18 So as I mentioned, mammary gland
19 development was started as the part of the emphasis of
20 the endpoint. That dose response is a function of a
21 hundredfold change that we speak, as captured by the
22 EPA report. So it shows this endpoint or the weight
23 that was varied was really not sensitive to a
24 hundredfold the dose response was really not as good as
25 atrazine.

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1 But there was no correlation established
2 between that internal dose of the chemical and the
3 mammary gland development. So we don't know what are
4 the availability of this mixture as it was administered
5 to lodge.
6 We don't know how much of it is really
7 absorbed into the system and then what happens to the
8 proportions of this three or four chemicals during that
9 time period and that's something that really I just
10 want to leave on this afternoon.
11 Depending on the several components of
12 this chemical, Richmond was really causing these
13 effects, the proportions would change and then later
14 exposures also changes because some of this
15 metabolites, which were put in this mixture both from
16 multiple chemicals, so this might not really represent
17 what our patients are being exposed to or the rest in
18 this case are being exposed to.
19 And come to other points of what the
20 mixture itself even though we know this mixture will
21 identify it in the environment. This is a relative
22 mixture because we're looking at atrazine and its
23 metabolites. In any farm situation, we are exposed to
24 herbicides, pesticides, fertilizers, and bunch of
25 chemicals.

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1 So even though we are testing these
2 mixture and its doses, that has really help us identify
3 the real problem of the environment as in the concept
4 of public health.
5 I know that, CDC's in its studies go for
6 that. The USGS analysis of water shows that there's
7 bunch of chemicals present, I mentioned to you about
8 the herbicide and pesticides and nitrates in the same
9 sample of water.
10 So, that's something to consider. And
11 also, just because the chemical are present, it doesn't
12 mean that it's close through and it's something
13 standard and has been exceeded.
14 But CDC's enhanced data show that most
15 of us sitting here where they have more than 160
16 chemicals in our bodies, so by studying this limited
17 mixture, we are not trying to identify the sole problem
18 of what is happening in the environment but we have
19 specific and limited to the interpretation of this
20 particular mixture.
21 It has an interaction profile on
22 atrazine, and other chemicals present and what are the
23 causes that produce or relevant.
24 I'm going to stop here and let the panel
25 members comment and then we have some conversation on

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1 that.

2 **DR. STEVEN HEERINGA:** Thank you Dr.

3 Mumtaz. We'll go back to Dr. Akana.

4 **DR. SUSAN AKANA:** So this model design

5 of this study was made difficult to fit in with the

6 earlier types of studies. So I have two minor, minor

7 comments that might help frame something. And they're

8 both maternal factors.

9 The strains of rats that have been used

10 are the Long Evans and the Sprague Dawley and there is

11 literature that there's a difference on how the

12 maternal strains treat their young. And it looks as if

13 the Long Evans rat is more attentive on a number of

14 maternal behavior results.

15 Now, why is that significant? The whole

16 body of literature now, people giving micro meaning on

17 maternal behavior, the thing when we helped the

18 retrieval contact with siblings and mothers.

19 And they actually have a powerful

20 influence on programming my favorite access, the HPA

21 access, but that does--and there are some very

22 interesting evidence of the maternal that you really

23 have to strain the pup. The pup carries that on to

24 group pup, so it's transgenerational behavior. So if

25 you're looking at the long evidence strain and this

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1 might explain why there are some difficulties
2 supporting across different labs with a different
3 strains.
4 My second minor comment is that when you
5 order pregnant rats in, most vendors refuse to ship
6 them on their conception onward, towards or they say,
7 if you receive shipment you have a danger of losing
8 their pregnancy.
9 So as I understand it, with Dr. Fenton
10 in general, he had ordered in pregnant dams to be
11 shipped on gestation day tenth and if I understand
12 correctly, in the other studies, they come in on
13 gestation date of four, five, six, or seven I think Dr.
14 Coupe has said.
15 There are some studies saying that the
16 day of the shipment of a pregnant rat has an influence
17 on her maternal behavior because of the destruction in
18 early development. So, paying attention to the
19 strength and what day they had shipped might be the
20 nuance factors that have been blurring back some of the
21 interpretations.
22 **DR. STEVEN HEERINGA:** Thank you Dr.
23 Akana. Just a note to everybody on the panel, make
24 sure you hold the mic close and speak up even though we
25 just--really reason a good sound here in the back of

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1 the room to take. So, I just have to mention to all of
2 us to make sure that we project close to the mic.
3 Thank you Dr. Akana. Dr. Chambers?
4 **DR. JANICE CHAMBERS:** Thanks. My
5 interpretation of the strengths and weaknesses of the
6 study, I guess we're a little different from the two
7 other perspectives, so you got really the points. I
8 also agree with Moiz that doing mixture study perhaps
9 are more relevant.
10 And so I do commend that authors who's
11 doing that. However, there are a number of critical
12 points that the result of the EPA has pointed out, the
13 body weight of the pups in the mixture study were
14 increased but the atrazine which presumably is the
15 positive control were decreased.
16 This is included both. In the 4-0 type,
17 it addressed the point that earlier Dr. Akana about the
18 milk and the stuff or something that can be 60 or I
19 think that they would--that would be a legitimate
20 increase. So the increase evaluations are not toxicity
21 so I don't know how they interpret that.
22 Also, a thought has crossed my mind you
23 may or may not want to pay any attention to is if
24 there's any credibility to the other studies which
25 resort here in earlier that there's not lot of question

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1 much about the idea of low gestational age, kind of
2 close. You know, that is to correlate things to
3 increase in pup weight so there's just there between
4 the heavy such as they are the results in this.
5 I also kind to have questions in
6 experimentalist about whether atrazine should be
7 considered the positive control that still is an
8 experimental compound, I think. And these people are
9 still trying to gather data on that.
10 So if that's really a true positive
11 control, I kind of question that database is good
12 enough on that. Now, the mixtures, I guess one of the
13 things that is concerning about the study is the
14 incredibly low dose levels of which they got mammary
15 gland changes. And if those are true, that mean you
16 need to rethink your risk assessment.
17 There is one compound in this mixture
18 though that is not present in the other studies and
19 that's hydroxyatrazine which is an environmental
20 degradant, not a metabolite.
21 I'm not mainly in the metabolite. And
22 so if that were really the compound that was doing
23 something then that could explain why this very low
24 concentration result show something, but again I don't
25 think there's any database on what hydroxyatrazine

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1 might do.
2 Again, two internal ways to increase in
3 the mixture study not in the atrazine so they didn't
4 match the so called positive control. I don't know
5 anything about how variable this sort of measure is,
6 the control was rather low one occasion and in the same
7 range or some of the detrimental effects and some of
8 the mixture studies. So I don't know how you interpret
9 the validity of the animal group when the controls were
10 low on one occasion.
11 Dose responses as you guys pointed out
12 was not always present in the mixture study. If this
13 very low doses are real and worthy of consideration in
14 risk assessment process, because they are so much lower
15 than all the other studies that exist right now.
16 I think that really needs some
17 replication before you take that into the risk
18 assessment process. I'm a little uncomfortable with
19 the positive control that is so much higher in
20 concentration than the others to set certainly in
21 effect in pharmacokinetics with the animals involved.
22 And that's probably all the comments I had.
23 I think it is medical certainly on the
24 standpoint of being an environmentally relevant mixture
25 but it had the compounds that we don't know anything

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1 about. This, I think a little more verification
2 certainly replication if you're going to consider these
3 valid doses across the population.
4 **DR. STEVEN HEERINGA:** Thank you Dr.
5 Chambers. Dr. Krishnan?
6 **DR. KANNAN KRISHNAN:** It seems like
7 there's going to be as you would expect some
8 replication on comments. I was trying to eliminate the
9 words I heard and then however repeating but I'm not
10 coming up with anything. And I appreciate it so I'm
11 just going to go to comments that I have.
12 Initially, both of the other two, the
13 study design is fine even it's objective which is
14 essentially to rattle with the effects of composite
15 mixture here and focusing on an environmentally
16 relevant DCT mixture.
17 Furthermore, she said the doses where
18 designed to relate to the environmental acronyms in
19 terms of proportions and consultations which is
20 actually much better than most of the other mixture
21 studies that I have seen are far evaluated. But in
22 trying to use this are evaluated for the purpose for
23 which it was not, that there's no way evaluating it for
24 a different purpose.
25 Well, the side comments are currently

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1 clear and I concur with the evaluation with the agency
2 in terms of the shortcomings particularly the enclosed
3 from the hydroxy metabolites and the lack of individual
4 dose response information and possibly the scoring
5 process to evaluate the mammary system as well.
6 This tallying would have been
7 strengthened if the findings were--or if such findings
8 were ordered for other mixtures, let's say different
9 compositions affecting of temporal and spatial
10 reference are--there were those response information
11 for each of the compliments are the reproducibility of
12 these findings was there in other studies evaluating
13 the same endpoint of these kinds across levels.
14 Usually even just with the atrazine itself are within
15 the specific metabolites are--and if there was any
16 measure of internal dose or other parameters explaining
17 the basis of such an extraordinary low. Such effects
18 had low doses because possibly some interaction might
19 explain it.
20 So the thing that concerns me the most
21 is that there is no support from any of the other
22 search studies particularly even just with atrazine at
23 such low doses. Because giving atrazine individually
24 will result in essentially the same research with the
25 exception of hydroxy metabolite and you said that the

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1 proposal of the metabolites within the mixture is going
2 to be different, well, there's going to be temporal
3 changes.
4 And that's not in need to atrazine.
5 This kind of--once you give a chemical resulting in a
6 mixture, and chemical metabolite, it's not in each
7 atrazine, it's going to happen with every other
8 chemical that we know of, know all at most.
9 So considering these kinds of production
10 of metabolite and chemical mixture from atrazine
11 administration versus this mixture study, we should be
12 able to make some comparisons and conclusions to
13 strengthen the possible use and consideration about the
14 study. But I just don't gone away with the existence
15 of the weight an evidence for that.
16 So even though the study of weights is
17 concerned because the recorded didn't find such low
18 doses as being most cooperative.
19 The fact that individual dose response
20 at any of the compounds here are not known the mode of
21 interaction is not known, the internal doses were not
22 known which could actually shed some light about why
23 they don't expect to have or why the outcome was so at
24 such doses and in the absence of other studies that
25 such low doses collaborating or replicating these

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1 observations and concurrently with the agencies
2 inclusively regarding the non-use of this data set as
3 well as my colleagues who has worked with this.
4 **DR. STEVEN HEERINGA:** Thank you Dr.
5 Krishnan. Dr. Meek.
6 **DR. BETTE MEEK:** Well, there's not very
7 much left to say. I just wanted to make a couple of
8 points in the context. These are really a couple of
9 observations additional to as noted by the agency and
10 others related particularly to the limitations and
11 design relevant to testing the mixture which then
12 enables extinction of effects on the individual
13 chemicals that these are the--because I think that
14 point is going to be well made.
15 My comments relate to how you would use
16 a net layer like this in the context where we have
17 evidence in this assessment and it's important to
18 consider always the weight of evidence, the selection
19 of relevant studies as a basis to select those that are
20 critical explanation, dose response analysis, and that
21 includes consideration not only of the quality of
22 individual studies including internal consistency but
23 also the collective weight of evidence into finding
24 critical dose response in relationships.
25 So effects observed by one group with

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1 doses that are not consistent with the lead of evidence
2 should not be due to the influence selection of the
3 critical dose response in relationships or the point of
4 departure. That doesn't mean of course if you don't
5 raise questions that should legitimately be addressed
6 in an additional study.
7 Also, for individual studies, we
8 normally look for particularly in a critical study to
9 define the dose response relationship. It's always
10 desirable to have several complementary measures that
11 is left and they don't know that the issue is so much.
12 It's one better than the other or more sensitive than
13 another, it's really looking for a kind of a
14 accumulation of data that gives us confidence in the
15 results that we're observing.
16 Particularly where some are subjected
17 and again, this is a basis to measuring true
18 consistency of the observations. And so the pathology
19 findings that we normally look at, we look at it in
20 relation to the other results and studies as well, so
21 more than one kind of level or challenges is always
22 helping.
23 So again, for weight of evidence,
24 consistency of the result of an individual study with
25 those from other investigators considering assumed

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1 types of effects is absolutely an important
2 consideration and I think perhaps, maybe it would be
3 helpful and perhaps that the transparency if there were
4 some priority delineations of some of these generic
5 criteria in terms of how we look at weight of evidence
6 in determining critical studies with dose response
7 analysis. That's it.
8 **DR. STEVEN HEERINGA:** Thank you Dr.
9 Meek. Dr. Mumtaz, we'll come back to you.
10 **DR. MOIZ MUMTAZ:** That there's one thing
11 I thought was missing is that if you could look at
12 these various chemicals and you can always subtract
13 with the analysis contradiction in toxicology to see
14 what kind of potential this can cause because it's not
15 that we can act upon in terms of regulating it but just
16 to make the rate of evidences already mention so that
17 we can see these various metabolites, what kind of
18 product that they have and I know there's a big
19 competitions in toxicology at EPA and that would agree
20 with this report, but that would support that too.
21 But as everyone agreed, it's this one
22 story that we are looking at that should be sized if
23 there's one replication to be able to duplicate what
24 we're doing, so that's very important and the weight of
25 evidence is easier to--at lower levels as you already

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1 have been able to point it out. Thank you.
2 **DR. STEVEN HEERINGA:** That's a good
3 comment. I think in conjunction with the--mentioned
4 this morning, a sort of shorter term and longer term
5 recommendations and others--it's a longer terms but
6 important. Dr. Horseman.
7 **DR. NELSON HORSEMAN:** I think what I'm
8 hearing and what I think is a reasonable recommendation
9 is that this study per se isn't useful but it's clear
10 that it presents some challenges. Given the fact to
11 this very low doses and then the observation of effects
12 of these low doses, and the nature of this mixture
13 which I think Dr. Chamber has pointed out is
14 interesting because of the inclusion of
15 hydroxyatrazine.
16 So the notion that this thus need to be
17 followed up, I think these could be emphasized because
18 I don't think this is going to go away, right? So this
19 will come up again in the future.
20 So both replicating this study somehow
21 with--made you better informed or evolved sense of what
22 the endpoints might be and including endpoints that
23 could be directly related to this because I think we
24 need to keep that touchstone as well.
25 But also including physiological

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1 endpoints as Dr. Akana pointed out, so in dealing with
2 the challenges of this study I think at some thought it
3 needs to go into how the study should be designed
4 obviously, but those are some of the issues that ought
5 to be followed about.
6 **DR. STEVEN HEERINGA:** Thank you Dr.
7 Horseman. Comments from other members of the panel on
8 Question 2.2? Okay, I think that, Dr. McManaman.
9 **DR. JAMES MCMANAMAN:** I have one small
10 comment. In the charge it says that there were no
11 effects other than it's a 100 mg/kg/day and I think the
12 cover study shows that at 50 there was a significant
13 effect at the least on one parameters. So I think that
14 that needs to be amended or at least taken into
15 consideration. Thank you.
16 **DR. STEVEN HEERINGA:** Dr. Akana
17 **DR. SUSAN AKANA:** A comment on the
18 heavier pup weight on the early postnatal day in the
19 sixth week.
20 I actually think that's a hint that this
21 might be a model at these low doses of childhood
22 obesity where you see a heavy child and then at late
23 period normal weight and then heavier weight in
24 adulthood.
25 And, I do not find this necessarily

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1 inconsistent with other studies with a small chested
2 SGA, small pup or--because in models of neonatal
3 metabolic program, too big to--that's the problem if
4 you're not on the optimal curve both have long, both
5 are bad and have potentially bad outcomes in adulthood.
6 So I do not have a problem with seeing atrazine or even
7 mixtures at different doses producing heavier or
8 lighter pups, both are a problem.
9 **DR. STEVEN HEERINGA:** Dr. McManaman.
10 **DR. JAMES MCMANAMAN:** I agree totally.
11 It's well-known and she feel that low birth gestational
12 weights shift and might end up to have larger--it will
13 be larger with time and the idea is if there's a
14 rebound effect and I want to note that in the cover
15 study, during lactation, the dams on the atrazine were
16 heavier, 100 mg/kg, atrazine were heavier than the pair
17 of that controls again suggesting a potential metabolic
18 effect which would be consistent with the heavier pups
19 that are noted in this study. Thank you.
20 **DR. RALPH COOPER:** I just wanted to kind
21 of chime in on to Dr. Chamber's comment in stressing
22 the presence of the hydoxyatrazine mixture study. I
23 think it's a really important component of any future
24 studies and also just to comment about the idea of
25 doing mixture studies and one of the points in the,

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1 that by choice, with this mixture study, you can't
2 really determine which one, which pair are subset and
3 it is important.
4 That reminds me of a review in the
5 applications for PCB's projects and some proposals
6 would be talking about looking at congeners of PCB's
7 individually and try to figure out which one is most
8 important, one would then wish too, they're important,
9 and if there's a tendency to critic this as, well
10 you're missing potential interactions that could be
11 important because some PCB co-engineer shall be working
12 together. And the other flipside would be proposals
13 that we're proposing to study.
14 I thought I heard mixtures and there
15 would be a tendency for critics to say that would be
16 willing to make sure as you may be missing the
17 individual components that are most important, so I
18 think the same thing applies to this mixture study.
19 We're looking at environmental relevant set of
20 compounds that are apparently are in the water that are
21 there together that potentially a person is being
22 exposed to a drinking water. So I think that is in my
23 mind the strength of this study.
24 **DR. STEVEN HEERINGA:** I think it's a
25 productive morning and what I'd like to do is take a

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1 lunch break. Let's take a little over an hour and come
2 back here at 1:15. Can you do that? I appreciate the
3 progress we've made. Thank you.
4 **(WHEREUPON,** a lunch break was taken)
5 **DR. STEVEN HEERINGA:** Okay, let's plan
6 to resume. Welcome back everyone. I had indicated
7 that I wasn't going to be here all afternoon, and it
8 turns out I'll be here half. It will change the plans
9 and Dr. Portier will take over at about three o'clock.
10 We have completed at least the initial
11 discussion, Charge Question 2.2 and I believe we're
12 ready to move on to Question 2.3. If you could read
13 that into the record please.
14 **DR. CAROL CHRISTENSEN:** In light of
15 Panel discussion on Questions 2.1 and 2.2, please
16 comment on the manner on which the Agency has proposed
17 to use the mammary gland development studies in the
18 hazard assessment for atrazine.
19 **DR. STEVEN HEERINGA:** Dr. Horseman.
20 **DR. NELSON HORSEMAN:** A short answer is
21 yes. So our comments, so the Agency has proposed with
22 as little evidence on mammary gland development studies
23 that were summarized in the Issue Paper and presented
24 during the meeting based upon the analysis made in
25 response to Questions 2.1 and 2.2 that we did for

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1 lunch.
2 This does seem to be an appropriate way
3 of handling these studies currently. However, these
4 conclusions should not be construed to suggest that the
5 mammary gland is not either legitimate target for
6 further analysis and the recommendation does not
7 undermine the notion but there are good reasons to
8 believe that the mammary glands and the mammary gland
9 functions are important concerns for environmental
10 agents.
11 It remains true that particular features
12 of mammary gland development suggested as a valid and
13 potentially sensitive target for environmental agents
14 and I think Dr. Fenton made this case in a number of
15 ways.
16 These features include the fact that the
17 mammary gland development occurs at several distinct
18 phase of life including prenatal, puberty during
19 gestation and during the mother's pregnancy and during
20 lactation, and even during aging. And this distinct
21 phase of development offer opportunities to probe
22 agents that might have an effect. And also the point
23 should be made that the breast is a very frequent
24 target of cancer.
25 In addition, something we haven't talked

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1 about here too much is the importance of breast milk
2 for healthy development of the young, which is an issue
3 that was talked about in the epidemiology studies, and
4 the importance of breastfeeding for the healthy
5 metabolism of the mother are recently I think better
6 recognized but I think very well recognized and
7 documented in the literature. So it makes us aware of
8 this important area.
9 The aforementioned comments argue that
10 developing accepted methodologies and standard
11 operating procedures that would inform useful end
12 points related to mammary gland development and
13 physiology will be important.
14 It would be important for these methods
15 and procedures would address actual lactation end
16 points, and Dr. Akana's comments anticipated I think
17 what I'm going to say, and we'll do this both
18 qualitatively and quantitatively.
19 And this goal seems to present some
20 obvious challenges and it's interesting I think that
21 the studies here didn't make a lot of attempt to
22 address these kinds of real functional end points and
23 its characteristic I think of the law of literature.
24 However, very precise and comprehensive
25 lactation end points are routinely measured and used

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1 for specific goals, and here I'm thinking about an
2 invariance.
3 I think there's a legitimate analogy or
4 lesson to be learned because very small differences in
5 lactation outcomes can have very major economic
6 consequences there and therefore, there are approaches
7 routinely used that can monitor these small differences
8 in a physiological or a functional or an end point that
9 can be legitimately scored as adverse or outcomes.
10 So it should be possible to use this
11 rich literature and methodological resource to develop
12 approaches and standard operating procedures to
13 characterize the effects of environmental agents such
14 as chemical catalysts like atrazine on mammary gland
15 outcomes, and these methods should and could take into
16 account the importance of gathering both experimental
17 data and mapping that on human functional end points
18 related to the breast and breastfeeding that can be
19 meaningfully integrated.
20 Breast cancer outcomes are not on the
21 scope of this SAP but remaining vigilant about breast
22 cancer outcomes is obviously still important. And so
23 it seems that the Issue Paper, it concludes that the
24 few available mammary gland studies do not represent
25 sufficient body of evidence to be used in risk

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1 assessment.
2 It seems there's a correct way of
3 handling these studies. The suggestive evidence in
4 these studies does however argue with developing useful
5 and standardized methods for assessing the mammary
6 gland at a functional level that will be important in
7 the future. So I think that's -- I'll pass it on.
8 **DR. STEVEN HEERINGA:** Thank you, Dr.
9 Horseman. Dr. Delclos.
10 **DR. BARRY DELCLOS:** I have very short
11 and simple comments, I think. I agree with EPA's
12 determination that mammary data should be included as
13 part of the characterization. It was not used in risk
14 assessment. There's somewhat conflicting data limited
15 to the dose response data and the mode of action
16 information.
17 As discussed, many of the effects of
18 triazine over a failure of effects of the F2 generation
19 in each replication and long-term consequences need to
20 be evaluated.
21 The mixture of effects potentially
22 important, there's no clear mechanism to determine
23 those effects. Reported effects are particularly
24 significant because they're effects of developmental
25 exposure in current doses lower than is reported for

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1 the LH surge. Well, not if we're using quantitative
2 risk assessment. They should not be missed.
3 **DR. STEVEN HEERINGA:** Thank you, Dr.
4 Delclos. Dr. LeBlanc.
5 **DR. GERALD LEBLANC:** Data on mammary
6 gland development are informative with respect to
7 characterizing the hazard associated with atrazine
8 exposure. However, the existing data are insufficient
9 to warrant consideration in identifying the point of
10 departure for atrazine.
11 The single study is available that
12 reports on NOAEL for mammary gland development, that's
13 the Coder study, but I have reservations about making
14 regulatory decisions based on a single, unreplicated
15 study. As is often the case, these studies and
16 particularly the Enoch mixture study open new lines of
17 inquiry that should be pursued in future
18 considerations.
19 With respect to the mixture study, I see
20 three possibilities to explain results of the study.
21 One, the observed results are an artifact, that there's
22 some inherent flaw in this study design. The other is
23 that one or more active metabolites are contributing or
24 are responsible for the toxicity.
25 And here, we may be seeing additivity

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1 and presumably, this would be dose additivity among the
2 metabolites, the active metabolites. Or there's some
3 interaction among the metabolites resulting enhanced
4 toxicity, i.e. synergy.
5 From my experience, the likelihood of
6 significant interaction among these compounds would be
7 slim, and by significant here, I mean interaction
8 resulting in an order of magnitude increase in toxicity
9 of one of the constituents.
10 So I don't think synergy is a major
11 consideration here. Certainly, additional study should
12 be considered to address the possibility that the
13 results are now artifact, that there is a flaw in the
14 study design.
15 And that last possibility that there are
16 the existence of active metabolites should also be
17 pursued in future studies. I would concur with other
18 Panel members in that hydroxyatrazine would be a
19 candidate that should be considered here since the
20 hydroxy metabolite presumably isn't produced at
21 significant quantities in vertebrates.
22 So in the rodent studies where atrazine
23 is administered, hydroxyatrazine would not be
24 contributing to toxicity, so it may be the
25 environmental degrade that could be responsible for the

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1 enhanced toxicity that was seen in the Enoch study.
2 This should the considered.
3 **DR. STEVEN HEERINGA:** Thank you Dr.
4 LeBlanc. Dr. Legan.
5 **DR. SANDRA LEGAN:** Basically, I think --
6 my colleagues have stated in a very articulate manner
7 many of the things that I would at this point mention.
8 I think they've done a good job and I agree with them
9 that the Agency's manner of handling this is not to use
10 these studies, these very mind-blowing studies in risk
11 assessment at this time and that there needs to be
12 further issues addressed as my colleague said.
13 **DR. STEVEN HEERINGA:** Thank you very
14 much. Dr. McManaman.
15 **DR. JAMES MCMANAMAN:** Well, I agree. I
16 think that the data shows that the mammary gland is not
17 a direct target of atrazine due to the lack of dose
18 response. And consequently, it should probably not --
19 the mammary gland effect should not be used as a way of
20 looking at risk assessment.
21 However, having said that, it is
22 interesting that we can now -- we can show from a
23 variety of different pieces of evidence that because it
24 is not a direct target yet there's still an effect, it
25 suggests that perhaps the entire mode of action of

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1 atrazine needs to be reexamined and that there may be
2 other targets that have not been considered.
3 For instance, there is some evidence of
4 interaction with neurons in the hypothalamus, and I'm
5 wondering --
6 I would urge the Agency to consider
7 looking at other sites as direct targets, which then
8 could -- their activity or alterations in our activity
9 could affect the mammary gland or the HPA axis or the
10 HPG axis. So I'm thinking that what we've seen today
11 is we've seen an analysis of the indirect effects of
12 atrazine exposure and not the direct ones, and we still
13 don't know what the direct targets are.
14 **DR. STEVEN HEERINGA:** Thank you, Dr.
15 McManaman. Comments from other Panel members on this
16 particular question? Yes, Dr. Akana.
17 **DR. SUSAN AKANA:** I absolutely concur
18 with Dr. McManaman that the hypothalamus would be a
19 very likely site to find some changes with circuitry
20 put in place in early gestational or postnatal base
21 which could very much give you the very late outcomes
22 you see in adults.
23 **DR. STEVEN HEERINGA:** DR. Fenner-Crisp.
24 **DR. PENELOPE FENNER-CRISP:** Well, we
25 were asked explicitly what to do about it because you

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1 haven't reviewed it yet and that's been for review.
2 Tom and I would recommend that after you review the
3 Coder study that you put it in the same bin as these --
4 use it as a matter of hazard identification but it
5 wouldn't be ready for quantitative risk assessment in
6 there.
7 Female: Which study was that again?
8 **DR. PENELOPE FENNER-CRISP:** The Coder
9 study that Syngenta had on their mammary gland.
10 **FEMALE:** That study is in its -- well,
11 it's part of the learning package.
12 **MALE:** It was considered in 2.1.
13 **DR. PENELOPE FENNER-CRISP:** I understand
14 that, but you haven't received it and reviewed it.
15 Now, we have. We actually got it. Did you get that?
16 So although you didn't ask, I'll bring that right over
17 here.
18 **DR. STEVEN HEERINGA:** Dr Horseman, I
19 think you said it was in --
20 **DR. NELSON HORSEMAN:** I just want to
21 mention, that one was considered in 2.1.
22 **DR. STEVEN HEERINGA:** Other comments or
23 suggestions? Dr. McManaman and Dr. Akana on the
24 hypothalamus, the data we heard yesterday about primate
25 versus rodent, that same conclusion would apply. Dr.

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1 Akana?

2 **DR. SUSAN AKANA:** I would limit myself

3 to rodent studies sometimes.

4 **DR. JAMES MCMANAMAN:** Considering that

5 there's really no data about the primates regarding

6 this, I would say I would have to limit it to rodent

7 studies, too. But nonetheless, there is -- it's well-

8 known that the hypothalamus plays a key role in mammary

9 gland function. Ask any woman who's trying to

10 breastfeed right after giving birth and things are not

11 just working quite right at that time, and so it's

12 difficult.

13 So I think that there's a lot of data

14 showing the functional relationships between

15 hypothalamic activity and breast function and it should

16 not be excluded.

17 But I think that there is a good amount

18 of data in animal study showing that alterations on

19 hypothalamic activity can affect mammary gland -- late

20 term mammary gland function, as well as the

21 aforementioned metabolism effects observed with

22 atrazine.

23 **DR. STEVEN HEERINGA:** Dr Akana?

24 **DR. SUSAN AKANA:** On this section, I

25 think there might be some data in primates by Susan

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1 Smith and Kevin Rowe and I shall find those references.
2 **DR. STEVEN HEERINGA:** Thank you. I just
3 sort of wanted to make -- Dr. Horseman?
4 **DR. NELSON HORSEMAN:** Just one quick
5 comment on that if I can -- if I think I understand the
6 original question. I think there is probably a better
7 mapping of the physiology of hypothalamic and neural
8 control of mammary gland development, milk gland and
9 all of that between the rodent and the human than there
10 is for the regulation of the ovarian cycle in terms of
11 the role of-
12 **DR. STEVEN HEERINGA:** Thank you. I was
13 confused on that.
14 **DR. NELSON HORSEMAN:** Right. It may be
15 a closer map than in the other case.
16 **DR. STEVEN HEERINGA:** Thanks. I think
17 that's valuable for me and maybe for some others in the
18 room, too. Okay, at this point, we -- I'll turn to EPA
19 to see if there's -- a few of you I think have a pretty
20 clear response on these questions.
21 **FEMALE:** Very good. Thank you.
22 **DR. STEVEN HEERINGA:** So we move on to
23 the next question, which I have as Question 3.1 and if
24 we could read Question 3.1 into the record. Now, just
25 to -- let me check with the Panel. Dr. Greenwood, you

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1 suggested potentially answering A and B together, and
2 Dr. Krishnan raised to that, too. So if we could read
3 Part A and also Part B into the record.
4 **DR. CHESTER RODRIGUEZ:** Thank you. I
5 guess I have to read this. So Question 3.1 Part A,
6 please comment on the analysis of the pharmacokinetic
7 data that is obtained in the Thede 1987 study to
8 estimate internal dose reflective of atrazine and its
9 metabolites in rat plasma.
10 **DR. STEVEN HEERINGA:** And then also Part
11 B.
12 **DR. KANNAN KRISHNAN:** And Part B, so
13 based on Figure 5.5 in the Draft Paper, the Agency has
14 concluded that plasma levels of atrazine and its
15 metabolites reach or nearly reach pharmacokinetic
16 pseudo-steady state levels in rat plasma after
17 approximately four daily oral exposures over a wide
18 range of doses. Please comment on the extent to which
19 the data do and do not support this finding.
20 **DR. STEVEN HEERINGA:** Okay. I will
21 follow the order for Question Part A in terms of our
22 discussion we covered with Dr. Greenwood.
23 **DR. RICHARD GREENWOOD:** Well, first of
24 all, I think we're in agreement when we discussed this
25 amongst the three of us involved that the use of area

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1 under the plasma concentration time curve is a totally
2 appropriate measure of internal exposure. We feel it's
3 probably the best way to approach the problem of trying
4 to relate exposure in rats to response and then
5 extrapolating or predicting human exposure of this
6 ideally for the physiologically based pharmacokinetic
7 model but in its absence, this is a good start. We
8 feel this is going in the right direction.
9 Now, it's particularly useful because at
10 the minute, we have no idea really of the exact
11 critical sight of action and what this area under the
12 curve does is to provide a measure of the opportunity
13 of a material to be distributed to other tissues,
14 target and non-target tissues. And certainly, if you
15 look at the studies of Dulley what he published in 2008
16 looking at rat pituitary in the brain, he looked at
17 preoptic area, medial basal hypothalamus cortex and I
18 think he found some 19 proteins leveled in the
19 pituitary between two strains of rats, and about 30 in
20 the brain, and these are just an indication. He gives
21 no idea of whether the binding of the Di-D agent
22 atrazine or the binding has any impact at all. We
23 don't know if it's anything to do with the mode of
24 action; we don't know. All we know is that it binds.
25 It could activate proteins, deactivate them or do

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1 nothing at all. We haven't got a clue but we do know
2 that it's scattered everywhere.
3 So the area under the curve is a good
4 approach and I think in the absence of good data on the
5 plasma concentrations of phenol compound and individual
6 metabolites, then we give it on its way with elapsed
7 time. Then the use of total chlonotriazine based on
8 the C14 compounds that's in the study is a very
9 reasonable first step, particularly as there's an
10 absence of information on the relative pharmacodynamic
11 activity of the parent compound and some of the
12 metabolites.
13 However, having said that, the data of
14 Thede from 1987, there are some limitations and these
15 need to be kept in mind when interpreting the
16 pharmacokinetic analysis. One of the big problems with
17 it is that the plasma samples were taken every 24
18 hours, so the data sets are really sparsely populated
19 and it means there's a big gap of 24 hours between each
20 points, each turn points.
21 This means that the profile is very
22 defined. And because of the very widely separated
23 sample points, it's bound to appear smooth. There are
24 a few points on the washout period really to obtain
25 sound estimates of the elimination properties. That's

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1 one of the problems.
2 The Agency's interpretation of the data
3 involves the assumption that the parent compound and
4 individual metabolites, DACT, DEA, DIA, are all
5 toxicologically active. And there's no evidence to
6 gain some. There is evidence that the DACT and
7 atrazine, DACT is the way you want are actually
8 important in some areas.
9 So it doesn't need to be borne in mind
10 when looking at the interpretation. But when we look
11 at the way that atrazine behaves, atrazine on the two
12 model of the Alcott is done are very rapidly depleted
13 by primary detoxification. And the major end product,
14 the DACT dominates the plasma profile. So in
15 interpretation, and I think it's fair, there is an
16 assumption that none of the pharmacokinetic processes
17 such as absorption, distribution and the detoxification
18 and elimination is saturated.
19 And so, it may be assumed in the first
20 instance that the proportions of parent compound
21 metabolites are in dependable dose. But of course, the
22 composition of the total radiolabel will vary with
23 time. So as soon as you've administered the next order
24 of gavage, then there will be atrazine present to model
25 the outcome agent compounds that biochemically, we get

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1 four hours and it will be virtually all back to the
2 DACT, and then you give another gavage.
3 So during that time, it's not a constant
4 dose in terms of this constant mixture that is being
5 distributed around the body. I think what this pseudo-
6 steady state implies, there's good evidence it is being
7 reached. These absorption and distribution processes
8 have been matched by elimination. And so, if we look
9 at the levels presented in Figure 5.5, this is why we
10 wanted to consider the two together; they are linked.
11 It's a bit misleading in the way that they're being
12 described because all of the samples were taken at 24
13 hours after the previous dose.
14 So the points we find in the profile on
15 Figure 5.5 or the minima in this whole truth. They're
16 not the average; they're the minimum because they're
17 taken just before the next dose. So those will be
18 underestimated in the area under the curve and if you
19 look at the figures from Syngenta's study where they've
20 got a much better definition of the individual spikes,
21 what you'll see is that there is quite a large area by
22 all of gavage, there's a dietary application around
23 that to a large extent. But by all of gavage, there's
24 a large area in that too, both the level of which being
25 measured by the team.

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1 And in fact, if samples are being taken
2 say 12 hours after dosing, you would put a different
3 profile with a different problems and mistakes, if you
4 take them randomly, you probably wouldn't have seen a
5 plateau at all with those few data points that would be
6 available.
7 So I don't think we're arguing that
8 pseudo-steady state is not being achieved. I think
9 it's the way that that plateau is being interpreted
10 because it's not like the theoretical figure that is
11 shown in Figure 5.5 of the paper because all of the
12 points, it's much more spiky than you would think from
13 that theoretical picture.
14 The good thing in a way is that although
15 there is a bias there, it's going to be approximately
16 across the plateau. So actually, your conclusions are
17 okay. It doesn't affect the goodness of fit of the
18 area under the curve when you've plotted it against the
19 administered dose. But it could give you a false sense
20 of security, so I think we need to think about that and
21 something will come back to Part C of Question 3.1.
22 I think the other problem -- so getting
23 back to the Part 3.1 A, is that the estimates of the
24 elimination were in constant on the basis of the last
25 three points. Remember it's a single animal that is

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1 going to be associated with some uncertainty because
2 there is a very rapid fall from the level -- at the
3 time of the last dose. And actually, if you consider
4 that that would have risen before it fell, again after
5 that time, it's just unfortunate releasing the data
6 you've got, you've done the best you can with it, but
7 it's difficult because of the lack of definition I
8 think in the watch-out period.
9 But having said that, you do what you
10 can. You've got the best estimates you can from those
11 data. But this morning when I questioned Syngenta,
12 they said in fact it is -- they've got a study out of
13 the four and they felt it was first order rather than a
14 double exponential process. So maybe what you've done
15 is actually giving you a reason to investigate and do
16 an elimination of being constant. But I think it's
17 something that needs to be looked at carefully that
18 there are in fact two phases in the elimination.
19 So I think to some -- I think the
20 approach taken by the Agency is not the correct way but
21 I think you just need better data than the Thede's data
22 set before you start to take it seriously in terms of
23 regulatory matters.
24 I think the pharmacokinetic study that
25 Syngenta have got underway -- and the preliminary

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1 results are in Report TK0040016. We'll provide the
2 data of the quality you need because it uses frequent
3 sampling and mass spectrometry for identifying, which
4 is the method of choice for the different analites and
5 it's going to give tight pharmacokinetic profiles for
6 individual compounds. And this type of study will lend
7 itself to the analysis of relationships between some
8 area under the curve for the different metabolites and
9 the parent compound, and trying to relate those two
10 biological responses.
11 So I think this, combined with good
12 estimates of plasma partition coefficients, should
13 allow really a good physiologically-based
14 pharmacokinetic model being developed and I'm quite
15 excited about that. I think it could well provide a
16 good basis for extrapolating to humans once that's
17 developed, but that we'll see what pre-judges that.
18 It's an exciting turnout.
19 Now, there is another limitation in
20 terms of interpreting the pseudo-steady state because
21 in the pharmacokinetic experiments that the team has
22 determined, the same dose is used throughout, so you've
23 got a constant level in the area of pseudo-steady state
24 over four days, and that's proportional to the gavage
25 dose which is shown in Figure 5.6. But when you come

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1 to interpret this, really the conclusions you can draw
2 are limited by this experimental design. It's very
3 difficult because if you are trying to use that pseudo-
4 steady state to get some area or area under the curve,
5 it doesn't tell you in the way the experiments are
6 being done whether there's a critical time. And then
7 if there is and you have to maintain a constant level
8 over a critical time, say three days, two days, four
9 days, then what you're going to do when you calculate
10 the area under the curve, you just multiply the
11 concentration by a constant. So you're back to the
12 plasma concentration rather than the area under the
13 curve. And this is kept with time because all you're
14 doing is multiply it by a constant if there is a fixed
15 critical period of exposure.
16 We don't know that that's the case but I
17 think it's something that's worth investigating. Would
18 you get a different result if you had a high dose on
19 day one, low doses on day three and four, you establish
20 a pseudo-steady state at the low level, and then you're
21 putting a big spike on the two or three? Measure the
22 area under the curve. IS it the area under the curve
23 that's related to the responses we get or not are
24 equally susceptible on all this exposure? There are
25 lots of questions about that.

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1 The only interpretation you can get
2 really, you're limited by the way in which the
3 experiment is done. To do it in the other way would be
4 quite difficult and quite challenging. But if you
5 really wanted to tie it down to an area under the curve
6 rather than plasma concentration for a fixed time so
7 the time is just constant and the area under the curve
8 was triggered with calculation, you really need to know
9 whether if you change the time window and change the
10 area under the plasma period for that timetable whether
11 you'll actually get a different response, or if you
12 have the same area around the curve achieved in
13 different ways, do you always get the same response?
14 So at the minute, I think there are some
15 limitations in there. But I think maybe the way to go
16 in future studies, I think it is clear with dietary
17 administration, it's possible. One, you get a smoother
18 plateau. That's what is needed. And certainly, I
19 think you can avoid some of the stress associated with
20 daily oral gavage, unless of course there are problems
21 with the dietary in oncology. And it goes to those
22 cells, you get a bit more realistic in terms of what
23 you might expect to see with the human exposure to
24 drinking water. But even there, depending on the
25 presence of food in the digestive tract, it could be

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1 sort of good between the equivalent of all of gavage
2 and dietary exposure. So I'll leave my comments there.
3 **DR. STEVEN HEERINGA:** Thank you Dr.
4 Greenwood. Dr. Krishnan.
5 **DR. KANNAN KRISHNAN:** I think he
6 essentially covered everything. All I can do is say
7 the same thing in a different accent. Well, maybe in
8 different words.
9 First of all, to begin with, I think it's
10 important that I do say in public as well that I agree
11 with my colleague's conclusion that EPA is taking an
12 approach of using the daily AUC as a matter of internal
13 dose. That is quite reasonable and it's definitely the
14 right direction. As it reiterates their relevant
15 pharmacokinetic exposure to atrazine. And this section
16 was a pleasure to read, not that the EPA and others
17 weren't. It's very well written and I appreciate the
18 clarity and the presentation, even though we share the
19 same concerns.
20 Number one, about the steady state, once
21 again thinking about the steady state pharmacokinetics,
22 particularly in the context of chronic assessment is
23 relevant and it's in the right direction that it allows
24 you to perform simple calculations that help go a long
25 way with less uncertainty essentially. When you think

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1 about for example rat to human extrapolation, you're
2 thinking that it's essentially the ratio of clearance
3 and adjustment for bioavailability if that's relevant.
4 But for a chemical like atrazine, the dosing
5 with humans are under consideration. It may not result
6 in the constant steady state concentration. I think
7 you already alluded to it that there's a peak or a
8 maximum concentration and a minimal on a trial. On the
9 12 concentrations which were essentially recorded or
10 that you got from the key paper, it most likely
11 represents concentrations of DACT on the metabolites
12 rather than the others. Still, the fact that these 12
13 concentrations that were part of the new figures that
14 did not vary between the days clearly indicate that
15 there's no increased accumulation due to subsequent
16 doses. I think that's -- that comes out clearly in
17 there.
18 So no Sequa non increase in accumulation are
19 performed by days. That's essentially like getting
20 into the steady state, and the document also, the key
21 paper I think brings to line that plasma is a
22 reasonable biological metric that reflects the internal
23 dose. They do present some ratios of concentrations
24 including plasma and tissues or RBCs.
25 An RBC is essentially it would represent a

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1 challenge given the extent of binding and so forth. So
2 the measurements in the plasma would appear to be
3 reasonable and the consideration of steady state would
4 appear to be fine. And the conclusion of linearity on
5 Page 68 of Section 525, that figure on the associated
6 discussions, I'll make it clear that there's no
7 saturation in those ranges. That's what I see rather
8 than, in your terms, linearity. You know there was a
9 problem with an aggressive attempt as we talked about
10 this.
11 And there's a concern that in those different
12 points that the proportions of metabolites might vary
13 since it's a total of C14. There are very high doses
14 that are not brought up in this figure. Maybe those
15 proportions could be different. And also, you may be
16 aware the DACT, the higher concentrations, and one has
17 to appreciate the difference in molecular weight. In
18 the study we heard that that might not be a problem,
19 but that might be a problem. Atrazine molecular weight
20 is 215.7 whereas DACT is 145.5. It's 50% or so in
21 difference. But for others, it may be much less of a
22 difference.
23 So once you take -- once you consider them on
24 the basis of molecular equivalence of atrazine, I think
25 you always have to be conscious of the molecular weight

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1 differences, especially when you're taking the numbers
2 down like 24 hours of exposure and assuming that to be
3 atrazine, milligrams of atrazine. It would not be
4 appropriate.
5 And I think I've got two more comments. One
6 -- the next one is about the internal dose, the choice.
7 Here, the measures are presented based on triazine
8 equivalence, which time to be conservative, which I
9 thought was not warranted. In this context, I can see
10 rather -- it's essentially a letter to the current
11 extent of the knowledge or the database; that's what it
12 needs rather than conservatism.
13 Here, the choices are the total metabolism of
14 atrazine, total amount of calories produced. I mean in
15 terms of the semantics that you can think of. Our
16 total metabolism minus the GSH conjugation put a sum of
17 DIA, DEA and DACT or the sum of DIA and DEA. You
18 haven't tried to make any differentiation among these
19 potential dose metrics. One thing that will be useful
20 is to state very clearly what the assumptions are,
21 which is basically counting atrazine and the GSH
22 conjugate out, calculating the total. At least that's
23 what it represents in most cases. The other two would
24 be very minor.
25 But some use of the observations from the

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1 papers of Susan Lars in 2003, Stopper 2002 and McMullen
2 2004 might help co-add some collaborative or non-
3 contradictory evidence for using some of the
4 metabolites in atrazine or for using the atrazine
5 equivalence. Like there'll be some things there that
6 could be drawn upon to strengthen the use of the kind
7 of dosing already.
8 My last comment relates to the potential use
9 of this kind of -- here, the calculations are made
10 using the dose surrogate which is the total triazine
11 equivalence. I think you have to keep in mind as to
12 the ultimate use of that, then how would one do the
13 inter-species extrapolation based on the kind of
14 totality of the triazine equivalence. So hopefully
15 there will be more and better information to
16 characterize that rather than summing all of them, or
17 you have to define more clearly one of these
18 alternative dose metrics.
19 If one does that and uses a PBPK model for
20 human or some PK information or clearance information,
21 I think consideration has to be given to differences
22 and bioavailability, the GSH conjugation in rats versus
23 humans. We didn't hear very much about it yesterday,
24 the role of intestinal metabolism and then the red
25 blood cell to plasma partition coefficient that I

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1 didn't see here at the meeting, but there was one in
2 the paper. That seems to be critical, at least with
3 the metabolites. I think some of those considerations
4 would be very critical if the position used to derive
5 HEDs or the human equivalent doses weighing from any of
6 these internal dose measures that lump together.
7 At some point I was confused, so let me talk
8 about that before I conclude, which are some of the
9 pharmacokinetic data and so on were on the Sprague-
10 Dawley rats and there were some presentations about
11 Long-Evans being more sensitive than the Sprague-Dawley
12 rats particularly to the measures of LH. I tried to
13 get some clarification, but I should admit that I may
14 refuse. So I do see that there is some increase to
15 susceptibility that came through in reference to the
16 2000 paper and so forth. But then in your plots where
17 you put everything together, it seems like there's no
18 difference in sensitivity and so forth.
19 The reason why I bring that up is that that
20 shouldn't, at the end of the day, become a factor -- a
21 limiting factor for the use of the PK data because at
22 the end of the day, if the key study ends up being
23 along the Long-Evans rat considered more sensitive than
24 the SD rats and then you end up having a lot of PK data
25 in the SD rats, which is the case of Thede as well as

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1 the presentations of the other scientist.
2 So in conclusion, the use of the daily AUC
3 seems to make more sense. It's excellent. And the use
4 of total triazine equivalence or refinement data based
5 on some of the alternative dose metrics that we talked
6 about, which you might be able to do if there is a PBPK
7 or another PK model that use those alternative metrics.
8 So the use of that kind of triazine equivalence
9 consistent with the assumptions and use of plasma as
10 metrics seem fine, whether it's based on -- and when I
11 went to that, I said to myself these calculations and
12 the strategy can be followed either using the PK data
13 or PK model but that assessment would be determined by
14 what's going to be available to allow you to resolve
15 the level of detail of the internal dose level because
16 you don't have to resolve it more than what the data
17 would allow me to do at this point.
18 **DR. STEVEN HEERINGA:** Thank you, Dr.
19 Krishnan. Dr. Meek and then we'll go to Dr. Mumtaz.
20 **DR. BETTE MEEK:** Well, I don't think
21 there's a lot more to say. We were in conclusion
22 before these comments. But I just wanted to add that I
23 very much appreciate the work the Agency is putting in
24 this particular aspect. Pursuing dose response
25 analysis based on the internal dose metric as an

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1 alternative to the ministered dose metric we may just
2 reduce it. It's really, really important. It's really
3 -- you've attempted a maximum use of limited and
4 available data. You've made many conservative choices
5 in the absence of information and you verified the
6 estimates that stand possible. I think that the issue
7 really here is, how do you deal with the residual
8 uncertainties associated with the constraints of the
9 data that were available to you.
10 And I think it would be great to have a
11 PBPK model. I think we all heard of it. We all do it.
12 But I think that understanding well the constraints
13 with regulatory programs having been employed in one
14 most of my, I think -- I wonder if there is some way to
15 prioritize the collection of data that most inform in
16 the current analysis, so to move us forward, kind of --
17 you may not get to the whole PBPK model at the time
18 that you need to do current decisions, but we might be
19 able to do something in current analysis and the
20 information that's being collected.
21 So I would strongly suggest that perhaps
22 that would be considered. I would also suggest that
23 the analysis has been extremely valuable in another
24 context, just making it distinct about what's actually
25 driving the dynamics of -- so just think about how we

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1 relate all these things.

2 **DR. STEVEN HEERINGA:** Thank you, Dr.

3 Meek. Dr. Mumtaz.

4 **DR. MOIZ MUMTAZ:** Kannan did it, so I

5 will give you the accent, too. I I think I agree with

6 what has been presented in the report, is that the AUC

7 -- what we're trying to do is a concept which we can

8 live with. And the point or order of the mixtures

9 issue that is -- it would be interesting to see what

10 happens if we could get an SCR analysis to give them

11 the potency of other chemicals and use that in the

12 greater that all these are equal. So to define a

13 common currency or matrix is an issue that makes us,

14 people always deal with, in this particular time that

15 might be useful. So I would suggest that that can be

16 used as a data to support what we're going to use.

17 **THE CHARIMAN:** Thank you Dr. Mumtaz.

18 Dr. Schlenk.

19 **DR. DANIEL SCHLENK:** I'm going to sort

20 of contrast. I think that his comment here being --

21 I'm going to claim na Academic isn't here for this but

22 in terms of the politics, in terms of coming up with a

23 PBPK, I just -- sitting on this Panel, we've seen PBPKs

24 from other compounds that are probably less data rich

25 in terms of what we have for atrazine. I just find it

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1 actually a little disappointing that there hasn't been
2 pursuance towards the PBPK model since 2007, which
3 since -- at least that's when the last McMullen model
4 is published.
5 So again, I would recommend that that
6 would be a high priority. I think that you'll
7 definitely be able to reduce a lot of the uncertainties
8 that have been raised already by some of the other
9 comments that have been made. And I guess at least my
10 hope that in putting this at least in writing that
11 maybe within five years from now that maybe when re-
12 registration comes in that maybe we might have a PBPK
13 model. So at least again, I would push towards that.
14 I'd also say to that, given the
15 differences, species differences with the Long-Evans
16 and Sprague-Dawley rats and its LH response that that
17 particular species be targeted for the PBPK model. I
18 think most of everything I've seen has always been
19 Sprague-Dawleys but there's been a limited sort of
20 focus on Long-Evans. There are obviously some species-
21 specific issues there which may be related to dynamics.
22 I don't know, maybe kinetics, too. But I think that
23 needs to be explored. I would also recommend that
24 again, intestinal biotransformation be considered in
25 this metric when the model is actually put forward.

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1 This again could either be done through Caco cells or
2 through microsomes, although I would warn based upon
3 the podocyte data that Syngenta presented that there
4 are some differences in microsomal metabolism,
5 particularly when you don't see DACT formed in
6 microsomes, but you do see it form in the podocyte,
7 which I think is very interesting.
8 So therefore, the Caco cells
9 particularly in the intestinal system may have actually
10 warranted, particularly given this microsomal
11 inconsistency in the form of the DACT, and DCT seems to
12 be this ultimate metabolite that seems to be formed. I
13 think that's probably important. And again, I think
14 with these models, particularly using the podocyte,
15 even now I think you could probably do in vitro studies
16 with mixtures to get an idea of what's going on in
17 terms of an addition and at least in the max KM data,
18 it can actually be employed in certain model that's
19 already present. At least Syngenta has presented it.
20 And again, I would highly recommend that there would be
21 some interaction there perhaps and maybe that model
22 could be again modified and refined to something that
23 might be useful here in the near future. If not, next
24 year at least. Again, whenever the next assessment
25 takes place.

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1 Again, I think this is a great system,
2 particularly you got a target that you already
3 identified, so I think it's a very powerful tool that
4 can be used not only in low-dose extrapolation but also
5 I think maybe in your toxicity assessments, too.
6 **DR. STEVEN HEERINGA:** Thank you, Dr.
7 Schlenk. Comments from other Panel members? Okay.
8 Well, thank you very much for that presentation. Let's
9 turn to Question 3.1.c, and if we could read that into
10 record, Dr. Rodriguez.
11 **DR. CHESTER RODRIGUEZ:** So Figure 5.8 of
12 the draft paper shows a plot of the LH attenuation
13 versus those of atrazine across different exposure
14 durations which range from four days all the way up to
15 six months. This data contained on this figure were
16 collected from several different labs and involved two
17 modes of oral administration of the dietary versus oral
18 gavage in two different rat strains. Attenuation of LH
19 as measured by percent of control is remarkably similar
20 across studies, strains, labs, again most notably of
21 the duration of exposure. The Agency has concluded
22 that the findings on Figure 5.8 strongly support the
23 hypotheses that pseudo-steady is achieved or nearly
24 achieved in adult rats after four daily consecutive
25 oral exposures.

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1 The Agency also believes that pseudo-
2 steady state is strongly associated with the
3 attenuation of the LH surge following atrazine exposure
4 in rats. Please comment on the analysis in the
5 Agency's preliminary conclusions as it relates to these
6 findings in rats.
7 **DR. STEVEN HEERINGA:** Dr. Akana.
8 **DR. SUSAN AKANA:** Hello, this is Figure
9 5.8 on page 71 of the Issue Page and our working group
10 met and I believe it's correct to say we have a general
11 consensus that this is a good start, a model to work
12 with. It's nice to have a visual graphic to start to
13 test ideas.
14 And the group as a whole found that they
15 would like to really reconsider how it's scaled above
16 the X and Y axis because it's linear here.
17 Also, that there was some desire --
18 actually, quite a lot of desire. They have the highest
19 -- the higher dose is spotted on this, the ones that
20 were not included in the study. And we had a very
21 eloquent group and they had very specific comments of
22 the scaling and on the quality of the LH data. So I
23 would prefer to differ to the other members of the
24 group who are very expert in that.
25 So on personal comments that are unique

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1 to me, one of my concerns was looking at the Y-axis, LH
2 surge attenuation presented and unfurled and I did ask
3 this to the group, and the answer was -- the question
4 was, "Was this peak LH?
5 Was this LH at 1800 hours or was this
6 varying under the curve?" because the answer they gave
7 us, the peak -- or excuse me, the amount of LH at 1800
8 hours, what the studies included include three older
9 studies in Morseth, Minima, and McMullen, and then the
10 more current Cooper study. And my apologies and
11 sympathy to everyone on the committee because I did
12 request the two older studies, which was an additional
13 1500 pages.
14 Now, why did I do that? Okay, my
15 personal interest was I was very concerned about the
16 food and body weight. These are legs, which mean that
17 I can interpret well, and my eyeball scan -- my eyeball
18 scan looking over the more set Minima data and the
19 McMullen data that were available, is that food and
20 body weight were not touched, were not different in the
21 doses shown on this spot. And so that was very
22 reassuring to me. However, I do want to add the
23 comment that they are very much hit when you hit the
24 higher doses.
25 So when you look at this curve which is

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1 LH attenuation to atrazine, there's actually a mirror
2 image curve that emerges for food and body weight in
3 the other direction and I think that's something to
4 keep in mind to not just look at the LH surge
5 attenuation and isolation.
6 My second point of concern was the --
7 oh, I mentioned the Y-axis, the actual nature of the
8 LH. You go back to these older studies. If you look
9 at LH at 1800 hours, in some space, that is a peak. In
10 many studies, it's not. So sometimes the peak, the
11 highest level is at 1600 hours or 2000 hours.
12 Now, why that's significant to me is how
13 much precision do you have at these very low points.
14 Now, if you were to look at it as the
15 absolute peak overall time, you're going to get a
16 different figure. And since these points are so
17 sensitive, you get a different body. Those are my
18 unique points that I wanted to raise and I wanted to
19 let the other Panel members expound.
20 **DR. STEVEN HEERINGA:** Thank you Dr.
21 Akana. Dr. Delclos.
22 **DR. BARRY DELCLOS:** I conducted a
23 sophisticated pattern analysis and noticed that the
24 discussions were listed by alphabetical order rather
25 than whether they contribute to the questions, and the

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1 other members who are eloquent
2 **DR. STEVEN HEERINGA:** Does eloquence
3 increase in alphabetical order?
4 (Laughter.)
5 Okay. Well, Dr. Greenwood, you're going
6 to own up here.
7 **DR. RICHARD GREENWOOD:** I think what we
8 were looking at was normally instead of percentages,
9 you would expect to see maybe a normal probability
10 scale used on the Y-axis to replace those percentages
11 which will, if anything else, spread out to the points,
12 but also making quite clear that the confidence
13 associated with the points of the upper or near the
14 upper percentile, 100 percentile are very, very much
15 less reliable with those in the middle.
16 And I think maybe it will be clear to
17 see also if we used a log scale and included some of
18 the higher dosage. But I think if we would need to do
19 that scaling in order to build it and then hopefully,
20 get the data around that plot in a scale that is useful
21 and that we could actually see what's going on.
22 I think it is important to remember that
23 when there is a lot of uncertainty anywhere around some
24 of these influences that already Dr. Akana has pointed
25 out, it makes a big difference maybe sometimes of two

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1 hours when you look at the LH surge.
2 It's important to remember that when you
3 are trying to the upper and lower percentiles, you do
4 have a very large uncertainty and I think you've got to
5 think in terms of the probability scale and there, I've
6 been wrong.
7 **DR. STEVEN HEERINGA:** Thank you, Dr.
8 Greenwood. Dr. Legan.
9 **DR. SANDRA LEGAN:** I have some specific
10 comments relative to my numerous years in measuring LH
11 surges. But first, I'd like to also mention first, a
12 formal data said that this construct is really
13 appealing to me and I really like the way this approach
14 has been attempted to carry out to see if in fact there
15 is a pseudo-steady state and call data from other
16 experiments.
17 That's really a nice approach here. But
18 as you said, we feel that it really maybe doesn't -- it
19 isn't the strongest support and it's probably because
20 you're having a pool of data from different studies.
21 In any case, aside from the differences in rat strains
22 and so forth that were mentioned, when I got those
23 thousands of pages for the Morseth and Minima studies
24 that had not been originally provided, and I had also
25 sort of wanted to have -- get a hold of those but I

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1 started on the other mammary gland question first. I
2 didn't get that question out.
3 But I started to really look carefully
4 at the LH data and yes, there is a great deal of
5 imprecision in measuring LH peak as I talked about
6 earlier and it seems
7 So I looked at the LH data and it's
8 great to see ends of 20 in a group and I looked through
9 the data in both of those group studies. And when you
10 look at the individual rats, there are tables you could
11 use and columns of LH. So whenever you're measuring an
12 LH surge and looking at your data, all rats' biology,
13 all the rats don't surge all the time.
14 So you first have to define what data
15 you're going to accept as -- you have to define the LH
16 surge within the data set. And the most common in the
17 literature that has been used is its -- you look at the
18 level of LH at the first time point at this baseline
19 and you do the main standard deviations of that and you
20 take two standard deviations of that mean, which is the
21 95% limit.
22 And you say any animal that's had LH
23 levels up at any -- above that for at least two
24 consecutive time points because we're talking about a
25 68-hour duration to that, will be defined as an LH

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1 surge.
2 And so I went back and I saw a lot of
3 zeros and 1.2s in the data and I -- so that's what
4 triggered this whole comment in my going back, so I
5 calculated the mean and standard deviation and so forth
6 and did this.
7 And what happens is that a significant -
8 - a large number of rats in some cases, 10 out of 20 in
9 one group -- and I just went through the controls. I
10 didn't have the time to go through every dose levels
11 and so forth. But there were a number of animals whose
12 LH didn't achieve LH sequence of data, did not over the
13 afternoon achieve an LH surge under that definition
14 that I just described. And those data should have
15 dropped from the analysis.
16 The problem is maybe they were but I
17 couldn't -- there was no description of that that I
18 could find in these thousands of pages. It was hard to
19 know where to look in the sets of information. So that
20 needs to be corrected.
21 Then for the McMullen data, it's not
22 possible to tell whether this is done. And in the
23 Cooper study, they, as everyone heard, have three
24 conditions to determine whether the animals were
25 crossed. This was a sacrifice study so they have

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1 sequential samples.
2 So when they went and -- before they
3 sacked the rats, they had to know whether they were in
4 process or they were not. So that is not a problem
5 with the Cooper study because they looked at
6 progesterone. They looked at vaginal smears, right?
7 They didn't have the levels of progesterone they had
8 the uterine wave and vaginal smear.
9 And later on, post-op, I think they
10 verified their progesterone levels when they got them
11 to make sure all the data were corrected and all the
12 animals have surge.
13 So when we mentioned about the precision
14 around the values at the low end of the curve here, the
15 precision, it may well be quite a bit tightened up if
16 those animals who have been surged are taken out of the
17 data set, if in fact that is true of those two data
18 sets.
19 What that does in addition however is
20 that changes -- that may change where the NOEL and the
21 LOELs are. It might be a different data because the
22 numbers that I calculated -- and I can show you. I
23 brought some xeroxes and calculations with me. I don't
24 want to go into the details, but I can show you later
25 that instead of having an LH peak value of 3.4, it goes

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1 to 4.5 or 6 or such. In a standard deviation, it gets
2 smaller.
3 So this data, if they re-plotted mine
4 and maybe on a log scale as was suggested, you might
5 get a better estimate of what this -- where this data
6 fit and if they support the pseudo-steady state. You
7 just couldn't -- you could maybe tighten up the data.
8 Having said that, if these data are incorrect and in my
9 mind -- I looked at this and said I can't count on the
10 3 Ms data, the Morseth, Minima and McMullen studies
11 because of this issue.
12 But the Cooper study, they were counting
13 data from the animals that had it. And so, that's the
14 only data on the graph, so that weakens it and I think
15 you need more data. The other thing is that also,
16 according -- Dr. Akana mentioned that the better way to
17 analyze it is to take the highest level in each rat
18 rather than just give the 1800 time point.
19 If there are a significant number of
20 rats, he'd get 1600 or 2000 or whatever is available
21 and the data consider these, you should use the peak
22 level and that will tighten up this data set also. And
23 then, you should use more midrange doses and at the
24 higher, and maybe you would get a whole lot better
25 construct from which you can much more strongly say

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1 that the pseudo-steady state is associated with these
2 types of attenuations of LH surges.
3 I guess I was a little confused about --
4 in the Cooper report, the NOEL level was 1.56
5 milligrams per kilogram per day when you use the data
6 from all the times in those groups in the analysis.
7 But if you only use the 1800 time point, the NOEL was
8 doubled, brought into the next dose, 3.12 milligrams
9 per kilogram per day.
10 So I didn't know which ones were -- I
11 guess I could have figured it out. But if the NOEL can
12 change, having on which groups were put into the data
13 set, you have to come up with a decision about that,
14 which is, do you want to use all the LH data from the
15 whole afternoon or do you just want it as the peak
16 level? Or do you want -- I don't think you should use
17 the 1800 only.
18 I think you should use the peak level,
19 which could occur at 1800 plus or minus two hours, and
20 you could read through this graph and it might come out
21 stronger because of those data sets, but I think you
22 still need midpoint levels between say 5 and 25.
23 There's no -- there's not much data. And maybe beyond
24 that, there are some data or -- I don't know, the
25 higher doses. I mean we have a -- I think it would be

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1 better. So that was my main point.
2 **DR. STEVEN HEERINGA:** Thank you, Dr.
3 Legan. Dr. Roby.
4 **DR. KATHERINE ROBY:** Okay, let me jump
5 in and respond first to a couple of these comments
6 before I forget them. First of all, in regard to
7 normalizing to the peak, I do think that is a good
8 idea. I think you might enhance your sensitivity if
9 you can do that.
10 However, in regard to kind of throwing
11 out the data from the animals that do not surge, I
12 think in fact you would be reducing your sensitivity
13 because part of the response is the lack of the surge
14 and just maybe it means that the data needs to be
15 thought about in a different manner instead of cooling
16 20 animals and averaging their surge.
17 Maybe it needs to be reported such that
18 15 animals did not surge and of the animals that did,
19 there was a surge. I think that will allow you to
20 really make a strong point that a significant number of
21 animals did not surge. I think that will strengthen
22 the overall data.
23 I think like several of us, I would also
24 like to see the higher data points included in part
25 because those are the dose levels that are more closely

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1 associated with a downstream fertility end point. But
2 secondly, I think you made a comment in your discussion
3 yesterday or the day before that that after about five
4 or milligrams per kilogram, the curved plateau -- and
5 I'm not entirely sure if all those higher data points
6 are added that that will actually be the case.
7 Further, I think that if it's not the
8 case, it might represent either a different or
9 secondary mode of action that needs to be addressed or
10 a different PK profile at higher dose levels and that
11 would be very interesting.
12 I guess my other point was that we're
13 thinking about different life stages throughout this
14 whole assessment and most of this data really is in
15 mature cycling animals.
16 I think it's been showing a little bit
17 of data with prepubertal exposure and I think no data
18 actually under the aging or senescent or perisenescent
19 setting, and I wonder if this representation will look
20 different in those studies. This kind of associates
21 with the discussion about the LE versus the SD strains
22 and maybe some of the information we saw with the
23 prepubertal exposure, the results might look different
24 if it was done in the LE strain first.
25 And then secondly, again repeating

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1 myself, this response curve might look different in a
2 perisenescent animal where we believe anyway the
3 sensitivity to the estrogen and the response of surge
4 is a little different, and that might give us some
5 information later on to human exposure and sensitivity
6 at different life stages.
7 **DR. STEVEN HEERINGA:** Thank you, Dr.
8 Roby. Any additional comments on this particular
9 charge question? Dr. Greenwood.
10 **DR. RICHARD GREENWOOD:** Just really
11 again to remind you, I wouldn't get too hung up on the
12 pseudo-steady state per se. That may not be important.
13 What might be important is just maintaining a minimum
14 concentration of the--
15 We keep saying pseudo-steady state but
16 that may not actually be what is needed. It can then
17 just be -- as long as you got the exposure of a
18 critical field, a minimum exposure, you're going to get
19 an attenuation of surge.
20 **DR. STEVEN HEERINGA:** Dr. Horseman and
21 Dr. Roby.
22 **DR. NELSON HORSEMAN:** Maybe this --
23 maybe I can be educated here. It seems to me that all
24 we're being asked to do here is based on the cooling on
25 a number of these studies, is to draw a line to these

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1 data ourselves. Imagine a kind of uncertainty around
2 that one. I wonder why the Agency didn't do that for
3 us.
4 (Laughter.)
5 And maybe the statisticians here could
6 talk about the strengths and weaknesses of maybe doing
7 that kind of analysis, but what it seemed to have done
8 is draw a line through one -- the data from one
9 experiment and dribble other data on to the same graph
10 and ask us to interpret the strength of that kind of
11 enhancement. So I'm sorry if that may be a crass
12 characterization.
13 (Laughter.)
14 Maybe you can help me here.
15 **DR. KATHERINE ROBY:** I think you're
16 asking me to respond or affirm to this one. In
17 response to Dr. --
18 **DR. NELSON HORSEMAN:** I may be asking as
19 well for a response from some of the other more
20 statistically apt members of the panel.
21 **DR. CAROL CHRISTENSEN:** I'm sure they
22 would be obliged because they're always willing to --
23 the statisticians will always step up.
24 (Laughter.)
25 **DR. STEVEN HEERINGA:** Dr. Portier and

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1 Dr. Lee are thinking right now.
2 **DR. CAROL CHRISTENSEN:** I can tell from
3 their faces. One comment before we get back to that,
4 Dr. Roby, on that plot, the splattery one, there is --
5 the more set data set on there is six-month because
6 those are the six-month graphs.
7 So you're implying that they're aged --
8 aging, except they were exposed over that six-month
9 time frame.
10 **DR. KATHERINE ROBY:** Yes.
11 **DR. CAROL CHRISTENSEN:** And I think one
12 of our goals is to understand an exposure time frame
13 related to an effect or response, and this is really in
14 my opinion, very long-term exposure. And even though I
15 think some call four-days a long-term, you could also
16 consider it short-term, especially in relationship to
17 the event that it can cause biologically.
18 So I guess what I was talking about is a
19 lot of these studies are normalized to basically
20 inducing a surge exogenously or looking at the
21 endogenous surge and impact of atrazine over a pretty
22 short period of time, over one cycle in fact. And this
23 is really a long-term study.
24 I think the data is -- I'm not
25 questioning the data and I think that the results are

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1 very realistic, but I was thinking more along the line
2 of kind of repeating the studies that had been done in
3 the adult cycling mature animal in a kind of
4 perisenescent animal where at least the data we have
5 already would indicate that the responsiveness should
6 be already altered based on aging.
7 So you actually might see -- you might
8 hypothesize that there would be a greater sensitivity
9 in the perisenescent, i.e. perimenopausal setting. I
10 guess that's what I was --
11 **DR. KATHERINE ROBY:** Thank you for that
12 clarification because I didn't hear that point --
13 **DR. CAROL CHRISTENSEN:** Okay. But I'm
14 going to add one more before -- and that is, as Dr.
15 Greenwood reminded me, I think the other important
16 issue that needs to be thought about and that also
17 relates to the six-month versus the four-day exposure,
18 and that is period of exposure with relation to stage
19 of the cycle.
20 And I think that it's very clear that
21 exposure throughout one entire estrocycle has an
22 effect; that's clear. But that's exposure through two
23 days of the estrocycle. What about the first two days
24 versus the last two days?
25 Because I think there is data to show

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1 that on pro-esterase, there is not an effect. A dose
2 given earlier in the cycle that are very high dose will
3 have an effect. This kind of gets to the area under
4 the curve versus for a six-time duration exposure
5 issues also.
6 And I only -- I think it's very
7 difficult in a rodent because of the short cycle, but I
8 think it's relevant when you start to address questions
9 related to exposure in humans or women with a longer
10 cycle and it doesn't matter if the first five days of
11 the menstrual cycle have any exposure versus days 8 to
12 14, and that's where I'm thinking not just the duration
13 but the timing within the cycle is maybe an important
14 issue to think about.
15 **DR. KATHERINE ROBY:** I hope you hold
16 those thoughts for the last question.
17 **DR. CAROL CHRISTENSEN:** I know. They're
18 all really tied together.
19 **DR. KATHERINE ROBY:** So in response to
20 Dr. Horseman, if you recall Dr. Rodriguez's
21 recollection of the events that led up to this question
22 you have in front of you, after the April SAP, we heard
23 from the Panel these deliberations to think about
24 moving to an internal dose metric.
25 We heard that loud and clear, and

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1 proceeded -- I mean, as you can tell, fairly
2 aggressively after that point. And he began those
3 plots with the Thede study to show this very nice
4 plateau and we all simultaneously have the same
5 question, what about the LH data? And started out with
6 a plot and we drew on another plot and drew on another
7 plot.
8 It's actually not far from the way you
9 described it in fact, which is really funny. But
10 that's not a bad thing to create a process that works
11 in different ways.
12 And after the fact, we've asked
13 ourselves those questions. Does it make sense to do --
14 for example Dr. Lucciani has benchmarked those analysis
15 as a single end point.
16 Our program, we have a precedent for
17 taking multiple studies and combining these single
18 analysis across -- particularly things at the steady
19 state. We have a strong -- we've done that on 30 some
20 chemicals and organophosphates. Is this another case
21 for doing that? Actually doing a more sophisticated
22 analysis across, which would involve calculated
23 confidence balance.
24 We withheld doing that analysis until
25 we've got some feedback on the direction that we were

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1 headed not only on the pseudo-steady state ideas but
2 thinking about looking at the LH data in this way
3 because it's a unique way that people have taken.
4 We're not aware that anyone else has taken all this
5 atrazine, LH data and done this before.
6 So we were reserving a lot of
7 sophisticated analysis until we got feedback on where
8 we were at that point.
9 **DR. STEVEN HEERINGA:** Steve Heeringa,
10 just maybe to start the discussion, I think it deserves
11 a little bit of discussion, and that is -- I'm actually
12 glad that they did it this way because as Dr. Legan has
13 pointed out, we really don't know much other than the
14 Cooper data, but what happens between 5 milligrams per
15 kg and 25 milligrams per kg.
16 And if you remove the Cooper data, which
17 is the Long-Evans rat, so the first covariate, I would
18 put in this analysis. If I was going to try to combine
19 this, it's the rat type and immediately, you get two
20 different curves.
21 And if you had -- so in short answer to
22 you and maybe it's a copout is that I think that the
23 covariate space is partitioned here. We say
24 essentially you don't have overlapping covariate space.
25 Dr. Legan says you don't have enough

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1 observations on the two different types of rats between
2 5 mg and 25 kg. So I think it's a great idea. I think
3 that the way that they presented it now actually
4 generates better statistical hypothesis about the next
5 stage than if they try to combine them.
6 If we had enough data pool -- I mean
7 theoretically, we like to not only know the variances
8 of these estimates, but we'd like to know their biases
9 relative to some pure measure, and we don't know the
10 latter and we never will but we could maybe assume some
11 of those away.
12 But I think this rat strain covariate
13 and the fact that it's only one study that's defined in
14 the shape of this curve between 5 kg and that it's a
15 unique rat type, to me biologically I don't know if
16 there's anything to that at all. But statistically, I
17 couldn't sort out the rat strain from the shape of this
18 curve at this point. I don't know, Dr. Lee, do you
19 have any thoughts?
20 **DR. HERBERT LEE:** I agree that the rat
21 strain is an issue here, although one approach we did
22 at the hierarchical model, it certainly gets more
23 traction that way combining across the two strains.
24 But as you pointed out, there's not any information
25 though between the 5 and 30 on the Sprague-Dawley rats

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1 so that the shape of the curve is what would be
2 determined by Long-Evans rat study.
3 And with only six different levels, even
4 there you're not going to get a lot of information
5 about what the shape should be to get a model with
6 actual confidence. Hence for a whole curve, you're
7 going to have to make some fairly strong assumptions
8 about the shape of that curve. And then of course all
9 your results depend on those assumptions.
10 **DR. STEVEN HEERINGA:** I think if you
11 look at the figure, there's a faint dash line which
12 draws a straight -- between two points for the Sprague-
13 Dawley rats, and my guess is that we did some sort of
14 merged analysis that what you would see emerge as a
15 curve somewhere between that straight line and the
16 sublinear curve that you're seeing for Dr. Cooper's
17 data. It's a great idea but -- other thoughts on that?
18 **DR. KENNETH PORTIER:** Well, I think
19 since I've recommended this study, Dr. Cooper should go
20 do a six-month exposure --
21 (Laughter.)
22 It will only take, what, three or four
23 more years, right? But I'm looking at this and I'm
24 thinking the same thing. It would be really nice to
25 know -- I wish to see this, but it would really be nice

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1 to know for more dose levels for the six-month exposure
2 exactly what we look at in the Long-Evans rat.
3 And right now, we just don't -- what was
4 the word used? Gestalt this map gives you a gestalt
5 but it's definitely not going to provide you confidence
6 bands on some kind of dose response thereof.
7 **DR. STEVEN HEERINGA:** Other
8 contributions on the Question -- I guess 3.1? Well, I
9 know that Dr. Meek has a plane to catch later and we
10 want to get to her charge questions, so let's turn to
11 Question No. 3.2 before our break. Dr. Rodriguez, do
12 you have a comment? Please. I'm sorry.
13 **DR. CHESTER RODRIGUEZ:** Yeah, thank you.
14 I just wanted to add that I tried plotting this data in
15 many different ways and this was the way that should
16 make the most sense to at least four other scientists
17 here. So yeah, we think that I should feedback sort of
18 the best way to show this data.
19 But for us, I think it's remarkable how
20 similar the four studies are in open plotted, as per
21 se, control and how that correlates within
22 pharmacokinetics. So we were partly ecstatic when we
23 saw this because it gives you a chance to link the PK
24 and PD and that's something that is not commonly seen
25 in science.

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1 **DR. STEVEN HEERINGA:** Stephen Heeringa.
2 I agree it's a nice picture and I think we all agree
3 the picture would change. We would be less ecstatic if
4 at 20 milligrams per kg, there was 85% controlled LH
5 value sitting out there for four different types of
6 rats.
7 I think that's what we're -- but
8 nevertheless, I think it's effective and the
9 presentation certainly stimulated the right type of
10 discussion. Thank you.
11 At this point, if we could read Question
12 3.2 into the record.
13 **DR. CAROL CHRISTENSEN:** Please comment
14 on the BMD analysis summarized in Section 5.3 of the
15 draft Issue Paper with details provided in Appendix C.
16 **DR. STEVEN HEERINGA:** Dr. Meek.
17 **DR. BETTE MEEK:** Michael has the
18 shortest question, right? Okay, so this is a great
19 general question and I think just to provide some
20 general comments to start, I am very much in agreement
21 that it's important to consider early key or precursor
22 events that might quantify modes of action as the basis
23 for characterization, the critical response,
24 relationships, more relevant to prevention of adverse
25 effects in the human population.

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1 In fact, we have evidenced consideration
2 the mode of action the context of this source to
3 adverse outcome have we really assisted in
4 transitioning our focus in toxicology and risk
5 assessment from the lead adverse effects which occur at
6 high doses to the earlier precursor events of doses
7 that are more relevant.
8 Often data on these earlier precursor
9 key events lend themselves to much better
10 characterization in the response analysis as well.
11 Then have in traditionally -- and that's really owing
12 to the availability incidence data and more involved in
13 these levels under the commission could have more
14 return studies as we've seen on the plot.
15 So I appreciate very much that EPA is
16 following up on the recommendation of the previous
17 Panel in this context. And the advantages of
18 developing benchmark doses over effects are also well
19 documented and all the dose response data are much more
20 robust. There's accounting for those selections based
21 in the sample size.
22 A benchmark dose based on special LH
23 surge also appears to be protected where the end points
24 occurring more doses that have a wide range of effects
25 investigated in a rather extensive toxicological

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1 database, so it has many advantages.
2 However, and there's always a however,
3 the biological significance and adversity of the effect
4 for the benchmark value in my mind remains to be
5 robustly addressed and necessarily will need to be
6 considered carefully in relation to more severe end
7 points.
8 It seems important to consider levels of
9 effect which would be considered adverse on continued
10 exposure based on the totality of the data, including
11 from the more traditional studies. And this would
12 permit consideration of the degree, a protection
13 offered by this proposed point of departure compared to
14 those based on traditional toxin for which we all can
15 have a larger database.
16 I think that -- and you haven't gotten
17 there yet in the assessment. I think that that will
18 need to be taken into account and consideration the
19 application of example and certainty factors, as well
20 as the advocacy, particularly kinetic and also dynamic
21 data to inform intermediate species extrapolations.
22 It may be helpful then to rank potential
23 points of departure for various ends points with a view
24 to characterizing their degree of protection in
25 relation to biological significance of the observed

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1 effect and associated uncertainty.
2 This is rather critical as a basis to
3 interpret the derived benchmark dose in context not
4 only a biological significance but the traditional risk
5 assessment construct as a basis to comparatively
6 consider uncertainties associated with various options.
7 So comparative uncertainty analysis would include
8 consideration of appropriate intraspecies and
9 interspecies adjustments in the context of their
10 associated degree of protection and available and some
11 of us involving kinetic and dynamic information at both
12 ends, so it would be a better basis for comparison of
13 the benchmark doses overall. I'll leave it at that.
14 **DR. STEVEN HEERINGA:** Thank you, Dr.
15 Meek. Dr. Delclos.
16 **DR. BARRY DELCLOS:** My slight
17 interpretation of this question is to whether the
18 analysis have been chosen the way the end point, the
19 right study to use for the analysis, and I think that
20 coming in here, I thought that the day we submitted our
21 case that this is, right now the most extensive end
22 point and the most protected end point as you enroll
23 the level of change that's unclear what it would mean
24 in terms of adverse output.
25 But it's clear that this sensitive end

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1 point study that was selected is certainly -- again,
2 the Agency made a good case in the document that it was
3 the best study to use. It's been criticized here and I
4 don't know what would make that criticism.
5 Frankly, I think that's a matter for the
6 statisticians and the Agency to work out what to do to
7 with the blocking time of the experiment, whether there
8 are certain chores. I don't know how to evaluate those
9 criticisms, but certainly it would need to be ironed
10 out. That's really all I have to say.
11 **DR. STEVEN HEERINGA:** Thank you, Dr.
12 Delclos. Dr. Penelope Fenner-Crisp.
13 **DR. PENELOPE FENNER-CRISP:** I want to
14 confirm my opinion. I agree with what Bette said and
15 what Barry said about what I thought before I got here.
16 And in fact that there were some discussions of
17 criticism offered and of the day that it had been --
18 well, it's clarified some of them and one of the
19 criticisms was that the subset of controlled data
20 weren't included in the analysis but it says it was.
21 So if that's the case, then that criticism is not
22 appropriate.
23 At that time, I was looking if that was
24 a valid criticism and if it were appropriate to
25 criticize the wide range of age of the animals and the

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1 three blocks, then what would the analysis look like if
2 you only use the third block compared to what it would
3 look like using all three provided agents what happened
4 if you used all three combined, so that was just a
5 curiosity.
6 And then of course we've only seen the
7 summary of a new data set from Syngenta and I don't
8 know exactly what that means in the context of the
9 Agency's data because of the different results. It's
10 interesting to see the analysis of similarity and
11 differences between those two data sets and how they
12 make their way in the quantitative assessment.
13 You would think that they would want to
14 echo it is appropriate to use the benchmark dose rather
15 than an old break level. You get a lot more
16 information out of it. It's right for you to know.
17 **DR. STEVEN HEERINGA:** Dr. Cooper.
18 **DR. COOPER:** Yeah, I would like to make
19 a clarification about what Dr. Legan and the Sulken
20 paper discussed in the statistics. That was on the
21 analysis of areas that was included in my report to the
22 program office.
23 Those statistics are not being used in
24 benchmark dose. I mean the same data is being used but
25 it's a different -- it's the same data but whether that

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1 third control group was included or not is moved now
2 because we're not using my graph pad analysis. That
3 was I think the second point to whether we should
4 analyze different blocks separately. That I think is a
5 matter of cranking through different data sets.
6 **DR. STEVEN HEERINGA:** Thank you, Dr.
7 Cooper. Dr. Roby.
8 **DR. KATHERINE ROBY:** Okay, just quickly,
9 I concur with everyone. I do believe that the
10 benchmark is the appropriate approach and I think given
11 the body of data that is out there right now, LH is the
12 appropriate end point at this point. I think
13 everything else goes into next question.
14 **DR. STEVEN HEERINGA:** Dr. Legan.
15 **DR. SANDRA LEGAN:** I agree about the
16 benchmark dose in being the appropriate measure to use
17 as opposed to NOEL end support. And I took this
18 question sort of like delicate in terms of this is the
19 right end point for calculating a benchmark and that
20 was mentioned by the other commentators on this
21 question, on this issue.
22 And of course, I had talked about -- I
23 have raised an issue a couple of days ago about whether
24 a small decrease in the amplitude in the LH surge it is
25 really physiologically meaningful thinking in terms

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1 back to the mode of action of atrazine in attenuating
2 LH surge or the LH peak. I guess we've had a lot of
3 discussion about that and I guess some of those
4 comments should be I think seriously taken in
5 consideration.
6 Right now, based on all the historical
7 data and the way this was developed, the LH surge
8 attenuation continuation is in fact at this point the
9 most sensitive. So I agree with having pursued that
10 and maybe even continuing with it a bit.
11 However, in light of the evidence from
12 20-planned that the LH surge is controlled differently
13 in the rat and the human. We might think - and even
14 before I heard these comments, I was thinking the LH
15 surge peak is maybe not the best end point partially
16 because it's so variable.
17 And you're trying to pull out a
18 significant small difference which may not be
19 physiologically important but it's a variable. You're
20 fighting this large variability in the event that
21 you're measuring.
22 I kind of hate to say this, but basal LH
23 which is controlled by estrogen negative feedback might
24 well, as Tony suggested -- I agree with him that that
25 might be something you should start looking into as

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1 another alternative marker to derive
2 DMD from.
3 And there were two pieces of evidence.
4 I was concerned about the small attenuation in the LH
5 surge at the lower levels whether - I mean that's not
6 enough to stop the cycle. But Dr. Akana and Dr. Cooper
7 both have said in the last couple of days that they
8 agree this may not be physiologically important thing
9 and that may not be driving the mechanism of what mode
10 of action is beyond this.
11 But it's part of that mode of action.
12 It's a small part and maybe there are the places in the
13 brain and other things that we're not looking at. It's
14 like you've got a ton of vision about this. It's a
15 very sensitive end point that we have -- or that you
16 have found and I think to this point, it's valid but
17 you can't keep the blinders on. I think there are
18 little bits of the data that don't all fit into this.
19 For example, we know that there is a
20 decrease in general pulsatility as atrazine's effect.
21 That certainly can explain the decrease in amplitude of
22 LH surge but there's no change in a couple of papers.
23 There was no change in FSH and that's odd because when
24 you suppress the GnRH frequency, that is a change
25 generally. So there is a little bit of red flag there.

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1 There is a paper that came out this year
2 that indicated that atrazine finds or competes with
3 finding growth hormone releasing hormone to the growth
4 hormone releasing hormone receptor.
5 So if atrazine -- and there's no data
6 other than that that I knew of, and that was in vitro
7 data and there may be problems with that data. You can
8 always criticize some papers and experiments. However,
9 there's a hint there that maybe there's a decrease in
10 growth hormone as a result of atrazine.
11 There might be. I don't know that there
12 is. No, I don't know of any. But if there's a change,
13 as an endocrinologist, if there's a change in growth
14 hormone, it has to do with onset of puberty.
15 The growth hormone has a lot to do with
16 GnRH pulse frequency and LH growth. Growth hormone has
17 a lot to do with metabolism, mammary gland development,
18 etc. So I think that we can't just look at the LH
19 surge attenuation. I don't think we should throw it
20 out or stop with that.
21 But I like the Agency to keep looking
22 for other things that might -- I know it's very complex
23 but I guess I was just -- keep your open. And the
24 growth hormone receptor paper, actually what triggered
25 that study according to the introduction was they did

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1 not change it. They treated some animals with atrazine
2 and they did some kind of change of analysis and they
3 found this transcript that they blasted and figured out
4 they have the most similarity to growth hormones
5 receiving receptor and they jumped on that and did
6 several different studies.
7 Well, this is kind of a relevant
8 approach. There's not been any molecular data here. I
9 think maybe someone should be involved in generating a
10 BMDI. I know increasing workloads and -- and I realize
11 that, but it's a thought that one should keep in mind.
12 Basal LH is going to be something and I'm not sure
13 that's a realistic suggestion, but stuff like that has
14 to be kept in mind.
15 There are other possible mechanisms that
16 certainly have been ruled out, and it also could -- to
17 completely explain much of the changing -- many of the
18 changes that we have seen. Totally, I think easily if
19 the growth hormone story is the one I'm thinking about
20 is -- so I'd say don't throw away the LH surge but I
21 think there's probably many other issues and it's
22 probably one component among a number of things.
23 Like Bob Hom's data on the POS
24 localization, in generic terms, he had to see changes
25 in the CRH event. But you know, if there is an effect

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1 -- if he still got sections, then he's not prepared and
2 I would want to get up and look at him because maybe
3 there's a cause related activation of neurons elsewhere
4 in the brain that would give us another hint.
5 Things like that that could be explained
6 and keeping our eyes open on what is a sensitive end
7 point that can also be used not only in the LH surge.
8 And I think we all agree and you said earlier that
9 these changes may be controlled in the brain. You said
10 the hypothalamus. Maybe other neurons that have input
11 to the GnRH or the CRH growth hormone releasing hormone
12 bias and those kinds of things.
13 So you know, the catecholamine and
14 energy sort of from and you do see changes in
15 catecholamine with atrazine. We haven't even -- I
16 don't remember that you said that, but once -- so there
17 are these little bits of pieces of data in your draft
18 paper that maybe -- and again, in a literature, it
19 wasn't mentioned there. I don't know if it did come
20 out afterward, but keep looking for other mechanisms if
21 possible.
22 **DR. STEVEN HEERINGA:** Dr. Legan, you can
23 provide the reference for the --
24 **DR. SANDRA LEGAN:** Absolutely. That
25 paper is actually included in our analysis.

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1 **DR. STEVEN HEERINGA:** Okay.
2 **DR. SANDRA LEGAN:** And the big appendix.
3 **DR. STEVEN HEERINGA:** Thank you. Any
4 other comments or response to Question 3.2 for the
5 Panel? Yes, Dr. Krishnan.
6 **DR. KANNAN KRISHNAN:** I just want to add
7 a couple of minor comments in some of the analysis.
8 Some of the BMD analysis also are based on the internal
9 dose just for the record since we mentioned it
10 yesterday, but there is a negative intercept in the
11 analysis culminating with the administering of internal
12 dose and that's what fits in to the BMD analysis, so
13 it's a bit problematic but it's coming with that, and
14 number two, the internal dose measure once again as
15 it's used is residual or minimal triazine equivalent in
16 the system for all the reasons that Richard and I
17 discussed before.
18 The AUC on the concentration that's
19 being used in the residual concentration were a minimal
20 one during the steady state condition. One thing that
21 was a bit surprising is to see different BMD models on
22 the basis of administered versus internal dose, even
23 though those are supposedly linear or proportional, so
24 maybe that needs some ratification. I haven't been
25 able to rerun the models but that's just -- that caught

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1 my eyes.
2 **DR. STEVEN HEERINGA:** Thank you very
3 much Dr. Krishnan. Other comments on this particular
4 one? We could come back afterwards, but let's take a
5 15-minute break and reconvene at 3:20. Again, I would
6 have to excuse myself for the balance of the afternoon,
7 but Dr. Portier will take over chairing the meeting.
8 So back here at 3:20.
9 **(WHEREUPON,** a Break was taken.)
10 **DR. KENNETH PORTIER:** Okay, I'm Ken
11 Portier. I'll be chairing this last session. My plan
12 is to go until about 5:10, 5:15. It's 3:20 at this
13 point. I'm hoping we'll get through 4.1 and of course,
14 if not all, or 4.2 today to get us back on schedule, so
15 just kind of warning, hydrology and modeling people.
16 I think we've kind of started actually
17 the discussion of 3.2 in some of the last
18 conversations, so why don't we read question 3.2.b and
19 we'll continue with the conversation on that question.
20 **DR. CHESTER RODRIGUEZ:** Question 3.b
21 says to please comment on scientific factors important
22 for establishing a benchmark response for attenuation
23 of LH as part of the BMD analysis for atrazine. Notice
24 that that's not what is there -- what's here, sorry.
25 **DR. KENNETH PORTIER:** Okay. Dr. Roby,

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1 you're the lead.
2 **DR. KATHERINE ROBY:** Okay. So I think
3 this is a key question and maybe paradoxically it can
4 be answered or addressed really simply or really
5 complicated -- complexity.
6 So the question is what's important in
7 establishing a benchmark response specifically with
8 regard to LH, and I think the short answer is we really
9 do not know. We do know that -- well, personally --
10 first let me back up a second.
11 We have to establish events with a
12 benchmark response. That's key to the analysis. But
13 in specific regard to LH, which again I think is the
14 key end point to be measuring in this situation, we do
15 know that various significant changes in the LH surge
16 result in significant downstream effects related to
17 fertility.
18 It's well established what the LH surge
19 controls from rodents up to humans and we know that if
20 the LH surge is lost, there are significant effects on
21 fertility. That's key. That's very clear from a huge
22 body of data.
23 What we really do not know is how much
24 of the LH surge is important. Actually, we kind of
25 know. We know that we need 20 something percent of the

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1 LH surge. We know that but that means shutting down
2 the LH surge at 80% and that's significant.
3 What we don't know is what is the effect
4 of diminishing 30%, 40%, 25% -- actually, there's
5 really no information on the literature to indicate
6 there's a significant downstream effect of loss of LH
7 surge peak or area under the curve or duration really
8 by -- what I'm going to say is a small effect but
9 statistically, it's a big effect.
10 It's a statistical effect but
11 biologically, there doesn't seem to be a downstream
12 effect. So that's what makes this question simple and
13 complex. So the simple thing is we can't really
14 establish X percent decrease in one LH surge, this is
15 also a key, having a biological downstream adverse
16 effect on fertility.
17 Now, my bias -- my personal bias is this
18 is a measure of an effect, an ultimate effect on
19 fertility. Now, if you would hit at one LH surge, it
20 doesn't matter in the scheme of things. One LH surge
21 doesn't matter.
22 I believe if you would hit the LH surge
23 over the duration or over a critical time, onset of
24 puberty or during critical time during one cycle, it
25 might produce one LH surge but over a critical period

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1 of a lifetime, there may be an adverse effect on say
2 onset of menopause or change in its timing of onset of
3 menopause.
4 But that's my personal bias. There is
5 no literature to suggest that that's true. That's
6 where the difficult thing comes.
7 So really, I think the question, the
8 scientific importance of establishing an actual percent
9 change in the LH surge I think cannot be addressed
10 directly because there's no literature to help us look
11 at that.
12 So I think based on your guidance that
13 you have to go to the approach that you've taken and
14 look at the mean and the standard deviation, again,
15 with the caveat that one or two standard deviations
16 from the mean may not have a biological type than that
17 one cycle that you're looking at, it might have a long
18 term biological effect.
19 So there's really a big disconnect I see
20 in looking at ammunition of the LH surge and what's
21 happening downstream. That's just in these small yet
22 significant changes in the surge amplitude.
23 And if I should -- I've already
24 indicated the idea that change in effect throughout the
25 lifetime is also a consideration and there's no

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1 information. We already know that the spike in the LH
2 surge changes with aging in women and in rodents.
3 But again, there are changes in the
4 amplitude of the LH surge as a woman enters menopause,
5 that perimenopausal period where there is still
6 ovulation with every cycle. So again, that means that
7 the downstream -- what we would consider negative
8 effect is not there with changes in the amplitude of LH
9 surge.
10 So again, there's a big disconnect and
11 now I'm repeating myself, and it takes you to the
12 conclusion that the Agency came to in using the mean
13 and so much data..
14 **DR. KENNETH PORTIER:** Okay. Dr. Roby,
15 are you done?
16 **DR. KATHERINE ROBY:** I think that would
17 be it for now.
18 **DR. KENNETH PORTIER:** Dr. Bucher's got a
19 question for you.
20 **DR. KATHERINE ROBY:** Oh, for me? Yeah.
21 **DR. JOHN BUCHER:** So I'm reminded of the
22 cancer study long ago that started this whole thing
23 about the LH suppression and the fact that the LH
24 suppression was seen early in the Sprague-Dawley rat
25 that caused early senescence and caused the --

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1 according to the dogma, an increase in estrogen
2 stimulation and mammary onset the onset of mammary. So
3 are you speaking only in terms of the humans or are you
4 speaking in terms of the fact that there's no adverse
5 effect of LH surge suppression through our lifetime?
6 **DR. KATHERINE ROBY:** Well, no. In fact,
7 the opposite. I think that there is evidence over the
8 lifetime but all of this is looking at short-term
9 exposure and then short-term effect. In other words,
10 can we relate a change in LH surge in one cycle in an
11 adverse effect?
12 Now, if we shut down the LH surge and
13 have no LH surges, the data is there. If there's a 50%
14 reduction in the amplitude of the LH surge, the data is
15 not there. That's where I think the difficulty comes
16 in. Does that make sense? No?
17 **DR. JOHN BUCHER:** Well, if you're
18 speaking -- if you think there's a distinct difference
19 between short-term and the long-term exposure, yeah, it
20 makes sense.
21 **DR. KATHERINE ROBY:** Well short, and
22 then -- but I think the issue question is to define a
23 percent change that we're going to call a significant
24 change related to subsequence fertility event in this
25 situation, or it can be cancer event, too.

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1 And that's where the problem is. I
2 don't think that we have information on the given
3 percent change that will elicit that secondary effect.
4 **DR. KENNETH PORTIER:** I think what
5 you're saying is the percent change for how many cycles
6 is going to produce what downstream effect, right? So
7 you're saying a percent change in one cycle, it's
8 unlikely to see anything.
9 But a percent change in the next 15
10 cycles may produce cancer or other effects underlying.
11 **DR. NELSON HORSEMAN:** Just for
12 clarification, this model or notion suppression of the
13 cycles leading through the sequence of events to cancer
14 is complete suppression in the cycle or a large
15 fraction of the cycles.
16 In other words, a large fraction and
17 other cycles I believe as opposed to just the issue of
18 decrement in the LH surge. At least that's my
19 understanding.
20 I'm sorry, John Bucher, this is -- I
21 look at it in a different way. I look at it sort of in
22 a way that you're going to have senescence in a
23 Sprague-Dawley rat no matter what rat's life is like.
24 Any addition in the LH surge could bring that
25 senescence on earlier.

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1 **DR. KATHERINE ROBY:** Well, I think you
2 can hypothesize that but I don't think there's any data
3 to support that hypothesis. Is that -- does someone
4 else have -- yeah?
5 **DR. KENNETH PORTIER:** Dr. Akana, I'm
6 going to ask you to wait in on this discussion.
7 **DR. SUSAN AKANA:** I tried. I thought
8 real hard about this and I honestly have nothing to
9 add.
10 (Laughter.)
11 **DR. KENNETH PORTIER:** Okay, Dr. Legan.
12 **DR. SANDRA LEGAN:** I think Dr. Roby put
13 it in a very articulate way and I think it is obviously
14 generating a lot of thought about this, and it's really
15 tough. It's a tough issue but I have some additional
16 thoughts.
17 In response to your question, if a
18 diminution in the LH surge happens naturally in the rat
19 physiologically with aging, doesn't that mean that over
20 time that that would shut off cycles?
21 And think a way to think about this, not
22 to figure -- so we as measuring LH, when you have 10%
23 or whatever continuation at peak physiologically within
24 that cycle and it just doesn't change the compliment of
25 the old ovulation, the number of eggs ovulated -- in a

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1 short-term, that is -- so the problem is we keep
2 running up against it.
3 This isn't physiologically important to
4 the rat cycle or to the fertility probably because some
5 rats only have a very small LH surge and they function
6 fine through their whole lives. Okay, and that
7 individual variation. Maybe that's not important, but
8 the way I think of it is that this attenuation of the
9 LH surge that occurs in rats as they age and in women
10 as they become perimenopausal is the canary in the
11 coalmine.
12 Forget about the absolute attenuation of
13 the LH surge and how much that's going to affect
14 whatever. It's part in nature, in biology. It's part
15 of a process in both species that we know this is just
16 one of the steps that we've been measuring, the
17 mechanism.
18 There's something else going on that
19 started this that is now going to overtime result in
20 infertility and possibly cancers, and possibly all
21 these things we're thinking about because atrazine is
22 maybe sometimes causing this in a non-destructive way.
23 So with the loss of cyclicityin the
24 middle aged rat, the theory has been proposed, although
25 I don't know if there's -- there's not real solid data

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1 for it that the reason that the LH attenuates is that
2 there is a decrease in response to the positive
3 feedback of estrogen and that's happening up in
4 hypothalamic and higher centers.
5 So in my mind, that's the kind of thing
6 where we can't measure those things easily yet and we
7 haven't identified what that is because this is really
8 a complex process.
9 So atrazine may be doing some of those
10 things that cause that attenuation of LH surge
11 naturally in the rat and naturally in women, and that's
12 the only -- that's our canary. And so there is
13 something else here where we're measuring the canary's
14 survival rate. Does that help?
15 It's another way to look at it. I think
16 you alluded to that with talking about the drop in the
17 amplitude of the daily surge in one cycle where we have
18 a short term. It isn't physiologically -- so for us to
19 say here's a dose of atrazine with a certain percent
20 attenuation that's probably -- we can't because the
21 measurements haven't been done over in the long term
22 and we don't know what caused this attenuation.
23 In that thing, we may be able to connect
24 better. But it's chronically going to take place over
25 a long period of time.

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1 The problem with -- maybe you could
2 design that experiment new with chronic atrazine and
3 you could define thresholds, so we've talked about
4 that.
5 But in the human who's drinking water in
6 the spring or a few days they have hot and you know,
7 you have all these kinds of different patterns and the
8 chemographs that we're going to talk about, I don't
9 know how we'll ever get that experiment done. But to
10 benchmark those analysis, getting back to the question,
11 I think you go with the standard D.
12 I agree with Dr. Roby. We don't have a
13 number we can put on this. We could lose the event as
14 a measure and we should go with the standard deviation
15 percent as the benchmark.
16 **DR. KENNETH PORTIER:** Dr. Mumtaz, I
17 think you're next up.
18 **DR. MOIZ MUMTAZ:** I'm going to defer my
19 time to Kannan Krishnan.
20 **DR. KANNAN KRISHNAN:** I'm just going to
21 ask a question. One standard deviation or two?
22 **DR. SANDRA LEGAN:** We're just
23 reiterating the problem in that there is no information
24 to say what a significant change is, one or two or
25 three, until we get to about 80%.

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1 And I don't -- I think in the desire to
2 be conservative, which I think is the right approach, I
3 don't think that you can go to that level. And I do
4 think that the small inhibition ultimately may have an
5 effect but we do not know what that effect is and we --
6 there is no literature to support that hypothesis.
7 I suppose studies could be designed to
8 over a long-term inhibit 30% or 50% and look at some
9 long-term effects. Those studies could be designed and
10 carried out. They're very long term studies.
11 I do believe that inhibition is a
12 signal. It's a biological response to trigger. So you
13 have to -- you do have to set a benchmark. That's the
14 difficulty in the question and there's no biological
15 reason to say one or two SD, but you have to set that.
16 You have a guidance and you need to set it, and you
17 already have a guidance in place to use, right?
18 And since the other approach can't
19 really be supported by any data, then you take the
20 guidance with that, unless other studies are carried
21 out in the long-term. It's a long-term side effect.
22 **DR. KENNETH PORTIER:** I'm going to let
23 Dr. Schlenk come in, but we also -- Dr. Krishnan, you
24 asked a question rather than made a statement, so I do
25 want to come back to your question.

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1 **DR. DAN SCHLENK:** Yeah. Actually, this
2 reminds me. Carrie and I were talking about this
3 during the break and it reminds of the OP choline
4 esterase sort of story. I mean, how much choline
5 esterase inhibition do you need before you actually see
6 development neurotoxic effects or something like that.
7 It's the same question.
8 I think the relevance here, the positive
9 sides of this is that you did a very nice dose response
10 curve that you can actually somewhat get a nice
11 calculation of a BMD.
12 So the logic is there in terms of its
13 approach but again, quantitative and qualitatively it's
14 there because it fits the theory in terms of what it's
15 -- the question really boils down in actually being
16 more of an ecological person. One of the things we
17 always deal with is asking so what because we have
18 biomarker data all the time and says, "Well, so what?
19 We see Sequa-non induction in animals.
20 So what? What does that really mean?"
21 And this has all been kind of fascinating to me,
22 particularly with the choline esterase thing as well.
23 But I think in terms of for 2011 and what the time
24 frame has actually required here, it seems to fit a
25 nice dose response curve that allows you to do a BMD

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1 response.
2 Now, in the long term, I think you got
3 to calibrate that response to a higher apical end point
4 at some point somehow, either using again a
5 gonadotropin antagonist or something like that with a
6 low enough dose that you could say, "Okay, if we
7 inhibit 20% or 30% or 40%, what does that do to vaginal
8 opening or what does to do the reproductive fertility
9 end point that's you're actually concerned about?" and
10 you can calibrate to that then you'd be much more
11 certain about what your data mean and what your
12 benchmark is at that point.
13 But anyway, it seems to me that it seems
14 very similar to the choline esterase OP situation.
15 **DR. KENNETH PORTIER:** Dr. Krishnan, did
16 you want to elaborate on the one or two standard
17 deviation? And then we'll come back --
18 **DR. KANNAN KRISHNAN:** Well, I could just
19 ask --
20 **DR. KENNETH PORTIER:** Dr. Roby, would
21 you turn off your mic?
22 **DR. KANNAN KRISHNAN:** I don't have any
23 particular task but rather I just wanted to see your
24 real view point on this, and some of it is pertinent
25 because it's not an adverse effect for states of

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1 precursor and there's no calibration on the precursor
2 levels with the downstream effects, particularly at the
3 organism level of things.
4 Now, the science doesn't allow us to
5 really define the level or the delta of the precursor.
6 Personally, we're here actually talking about the NOEL
7 instead of the LOEL that the Agency has started this
8 for several years. But it may be transcending in light
9 of the recent NAS work and so on.
10 Is there any way that data from several
11 studies in terms of the controls and so forth could
12 somehow allow a characterization of how much deviation
13 might be still normal or that's not a realistic thing
14 in such an analysis --
15 **DR. KATHERINE ROBY:** You mean to
16 standardize a normal surge? Is that what you mean, to
17 standardized a normal surge? Well, I think there's a
18 lot of data in the data packages we've received right
19 here to indicate that there's a huge range of what
20 normal is. That's apparently the problem in defining a
21 percent change. The surge can be very small and
22 minimal or very large and still result in normal
23 fertility and that's true in rodents and women.
24 **DR. KANNAN KRISHNAN:** So there's no way
25 of normalizing them and pulling them --

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1 **DR. KATHERINE ROBY:** Not when you're
2 talking about absolute level. If you have --
3 **DR. KANNAN KRISHNAN:** No, I mean
4 somehow --
5 **DR. KATHERINE ROBY:** If you had
6 sequential cycle serial samples, yeah. It's possible.
7 **DR. KENNETH PORTIER:** But that implies
8 then that the one standard deviation means it's going
9 to drop it right there, right? If the standard
10 deviation is big, one standard deviation in the mean is
11 going to take you on your way out.
12 **DR. KATHERINE ROBY:** Well, you see in
13 the previous figure we were talking about, you see the
14 standard errors. That's because that's inherent of the
15 data that's on there.
16 **DR. KENNETH PORTIER:** Dr.Legan?
17 **DR. SANDRA LEGAN:** I was going to answer
18 that question, one standard D or two. My comment was
19 that given the highly variable nature of the
20 measurement of the LH surge, the amplitude of the LH
21 surge, I have just an opinion about that that normally,
22 I would -- to see a significant difference, I would go
23 with two standard Ds because it's a 95% content limit.
24 But when I think about LH surge peaks and how they're
25 measured and how variable that is, one standard D is

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1 more than enough in my opinion to use from -- to have a
2 difference from the controls.
3 Plus adding in a thought about the fact
4 that the doses that are being tested just could get the
5 lowest dose -- benchmark dose, right? How many orders
6 of magnitude below what humans are exposed to, so given
7 those two things in my head, I think one standard D is
8 fine with this specific instance. And everything else
9 I do in science I will use, too.
10 But when I think of the variability of
11 the LH peak and measuring it and I say -- and we're so
12 far below a dosage, it's probably going to be unhinged
13 upon, or that any human would be exposed to-- is that
14 not correct? I kept hearing that. Then I think one is
15 fine, and that's just my reasoning and I can be
16 overruled.
17 **DR. KENNETH PORTIER:** Yeah. I think you
18 mean the human dose is much lower than what the animals
19 are exposed to, right? You had it -- you were saying
20 it backwards but --
21 **DR. SANDRA LEGAN:** Well, that's what I
22 meant.
23 **DR. KENNETH PORTIER:** Yeah. Dr. Lowit,
24 do you want to jump in at this point?
25 **DR. ANNA LOWIT:** Yeah. I had one

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1 question on -- I'm pretty sure I know the answer but I
2 just want it on the record to make sure it's part of
3 the question. I've heard a lot of conversation about
4 the female fertility and the cycling.
5 Can we take a minute and cover the late
6 puberty and anything in the male? I'm sure I know the
7 answer. I just want it on the record.
8 **DR. KATHERINE ROBY:** So same thing with
9 the delayed puberty. Again, we don't really know. You
10 can shift to puberty by shifting when -- let's see, I
11 guess the frequency of the generic surges increase,
12 pulses necessary. But is there an amount change that
13 relates to a shift on the onset of puberty? And did
14 you say "male" at the second part?
15 **DR. ANNA LOWIT:** Yeah. I think you
16 covered it. I just want to make sure that the response
17 to the question is a little broader than just the
18 cycling.
19 **DR. KATHERINE ROBY:** Yeah. It goes over
20 also over life span and onset of menopause or
21 senescence.
22 **DR. KENNETH PORTIER:** Did I hear a
23 discussion on the male?
24 **DR. KATHERINE ROBY:** Do you want me to
25 come on the male? The male is going to be the same.

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1 **DR. SANDRA LEGAN:** Correct, that's
2 right.
3 **DR. KATHERINE ROBY:** A little change in
4 LH is not going to have a significant change in
5 testosterone, which is going to be driving the
6 spermatogenesis and the secondary sexual
7 characteristic.
8 **DR. SANDRA LEGAN:** As it relates in the
9 question, there's an unknown fact, there's an unknown
10 amount of change that work into those stuff.
11 **DR. KATHERIN ROBY:** Correct.
12 **DR. KENNETH PORTIER:** Anyone else who
13 want to jump in on this? That was a good conversation.
14 I learned a lot. Dr. Greenwood.
15 **DR. RICHARD GREENWOOD:** I just don't
16 think it would be an appropriate -- I know that this
17 is a little out of place just at the moment but it's
18 just for the record really to go back to our previous
19 conversation where a growth hormone was introduced.
20 And actually, this was discussed at length and in the
21 ending minutes of the April- it was in response to
22 Question 1.3.
23 There was a discussion around growth
24 hormone and how that might be actually something we
25 should look at because it does have impacts for both

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1 males and females, the very general effects that might
2 actually, it's some of the general syndromes with
3 atrazine exposure.
4 **DR. KENNETH PORTIER:** So Dr. Roby and
5 Dr. Legan, you weren't at that meeting but we probably
6 had the whole afternoon of discussion on that. That
7 doesn't mean that -- I remember it. I didn't
8 understand any of it, but I remembered.
9 Dr. Horseman.
10 **DR. NELSON HORSEMAN:** This could be an
11 instantaneous response. Is there a program or some
12 follow-up to that? I think that's the critical issue
13 in this, is whether given that discussion at the April
14 meeting, has the Agency program into their planning
15 actually addressing this growth hormone issue? That's
16 all. I will --
17 **DR. KENNETH PORTIER:** Dr. Lowit.
18 **DR. ANNA LOWIT:** That's new. I would
19 just reiterate what I started out this morning around
20 9:00 or 9:15 that there are many investigators
21 worldwide who continue to do atrazine research on a
22 variety of topics.
23 I'm not aware that EPA is pursuing that
24 per se and certainly by 2011, those ideas will -- it's
25 highly unlikely it will be mature to an extent. It

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1 would be -- the science is immature enough for moving
2 into the regulatory arena. But as that grows, we'll
3 continue to watch it
4 **DR. KENNETH PORTIER:** And I think if
5 there's one guarantee a year from now, there would be
6 150 more papers on atrazine out there for us to -- any
7 additional comments? Very good.
8 Dr. Lowit, do you think you got it from
9 this? I think all that discussion kind of came down to
10 your characterization a minute ago that no, we can't
11 tell you what percent is the threshold.
12 **DR. ANNA LOWIT:** At least we know why we
13 had trouble coming up with the value.
14 **DR. KENNETH PORTIER:** Okay. I think at
15 this point we're going to kind of change gears on the
16 other side of the table or the far end of the table,
17 and this side is going to get more involved in the
18 discussion and we're going to start talking about the
19 water sampling strategies. So if you will read -- I
20 guess Mr. Nelson?
21 **DR. NELSON THURMAN:** Okay. The ultimate
22 utility of pesticide monitoring data for drinking water
23 exposure estimations in human health risk assessments
24 depends on how well the monitoring data characterize
25 the spatial and temporal variability of pesticide

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1 concentrations in drinking water with an emphasis on
2 the upper end of the exposure distribution.
3 In addition, the method used to estimate
4 concentrations from monitoring data depends on the
5 duration of concern and how critical it is to estimate
6 peak concentrations.
7 A well-designed drinking water
8 monitoring study takes into account both spatial and
9 temporal patterns of exposure.
10 Please comment on the USEPA's
11 recommended framework for designing a monitoring study
12 by targeting the most vulnerable areas, targeting
13 seasonal times for more intensive sampling, basing
14 sampling frequency on the toxicological exposure
15 duration of concern and using autosamplers to
16 supplement monitoring data.
17 **DR. KENNETH PORTIER:** Dr. Coupe.
18 **DR. RICHARD COUPE:** First off, let me
19 apologize. You think after sitting here every week I
20 have something profound to say.
21 I really don't. I just want to
22 compliment the USEPA in the April meeting. It sounded
23 like things were disorganized and this time, it looks
24 like we're on target. So what we want to do is compare
25 it to treatment with atrazine, make some dose that does

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1 not do anything to rats or whatever.
2 Sampling for atrazine in the water is
3 really --
4 **DR. KENNETH PORTIER:** Dr. Coupe, would
5 you pull your mic a little closer? I think people in
6 the back might be -- they're not able to hear you.
7 **DR. RICHARD COUPE:** Okay. Compliments
8 to Syngenta, too. I think Paul went through his
9 presentation pretty quickly. They've kind of lowered
10 the impact of Syngenta on the time frame, but he had
11 some really good information in there and they had some
12 really good suggestions even when we look at it
13 critically, you did a nice job on that.
14 Just a little note, I saw on the heading
15 for Section 7.2 as a General Strategy for Designing a
16 Monitoring Study to Characterize Drinking Water
17 Exposure and that's a little different from the stated
18 purpose on the Issue Paper in Section 3.7.3.2 that
19 gives the rationale for sampling source water versus
20 finished as we get more protection.
21 I think if the purpose of the monitoring
22 program because it is truly estimating exposure, then
23 you might have to sample the finished water. It's
24 probably more appropriate.
25 The work I've seen generally shows the

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1 statistically reduction of atrazine between the source
2 water and finished water, although there's atrazine
3 still left in the finished water after it goes through
4 the treatment plant most of the time.
5 But I would -- in general, I would like
6 to see the source water completely sampled. We could
7 only do one but if you want to, you'd be able to go
8 back and do a study on the population that's drinking
9 the water and probably even the finished water.
10 So this question is broken into four
11 parts, so it's targeting and monitoring the most
12 horrible areas. Yeah, this is certainly appropriate as
13 an additional method for inclusion here, inclusion into
14 the monitoring approach.
15 So right now, it's included when the
16 community water system trigger currently 1.6 parts of a
17 billion in the Source Water Drinking Act and that's a
18 good one. So including, when we borrow the ones, using
19 the models and looking in front of a community water
20 system certainly is a way to do it.
21 Additionally, I just looked at where
22 atrazine is used, applied at the old layer of the cross
23 drainage bases and see which bases have an awful lot of
24 atrazine use in them and make sure that they're
25 included in the variability model and also Source Water

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1 Drinking Act.
2 As I mentioned before, agriculture is
3 not a static enterprise that can change quickly, much
4 more quickly than you would think and in any given
5 year. So any monitoring program I think needs to have
6 a little flexibility to be able to move around.
7 The second part of this target intends
8 at sampling to the high occurrence period. I think
9 that's definitely a good idea and you get the most
10 tainted blood by sampling one that have pesticides out
11 there.
12 But in addition to following up on that,
13 you can also target the timing and the amounts of
14 samples of a tiered approach based on expected
15 concentrations in the screening. So as we are
16 targeting certain vulnerable areas, you can also target
17 your sampling regime and having that flexibility with
18 who's collecting the sample.
19 So if you think about it, atrazine in
20 water can be explained by sort of a function that's
21 kind of like source strength which is a function of
22 time. So that the amount of atrazine that's been
23 applied and even how long it takes for water to move it
24 off, and then the second part would be hydrology.
25 Using these two terms, you can predict pretty close to

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1 where your atrazine is going to be moving into your
2 screening.
3 You can also use things like the low
4 percent of use. We've talked a little bit about how
5 well characterized atrazine is, how many studies there
6 are of it, the ecological part of it.
7 But man, there are a lot of studies on
8 the safe transport of atrazine, so it's pretty well
9 characterized. We know how much atrazine is going to
10 move off, know how much water moves off, so you kind of
11 look at it in the backwards way and say, "If I have
12 this much atrazine being applied in this basin, how
13 much are going with my range of concentration?" They
14 kind of worked those anyway.
15 And then you can do sampling based on
16 flow, so I think Syngenta had a little suggestion of
17 this. You can kind of look at--we've gota small screen
18 and it's really flashy. Then you could sample when it
19 first comes through and you got a small screen.
20 If you got a larger screen and the
21 screen takes a long time to reach the peak flow and it
22 takes a long time to go down, you need to sample a lot
23 less. One the smaller screen, they up and go down on
24 one day or two days. You could actually set your
25 sampling regime to sample twice the first day, twice

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1 the second day and give you a little bit more
2 characterization on how far up that sample was.
3 If you take a sample in the middle of
4 the day, facilities water base, if we dug in that, it
5 would give you the peak concentration. It could change
6 quite a bit. The third part and fourth part really was
7 base sampling frequency on the toxicological exposure
8 duration of concern.
9 That's a good idea if we actually knew
10 what the duration of concern was. And then, use other
11 samplings to collect data for exposure of impurities,
12 that's a really good idea if you can do that, but the
13 only thing I wanted to point out here was that you
14 actually don't even need to get that complicated.
15 If you have a water treatment plant
16 operator who's collecting the samples for you, you just
17 have them collect one sample everyday at the same time.
18 He just has to go to the water tap and pour it into a
19 bottle. If he could just put that in a refrigerator or
20 a freezer, you could just hold on to the sample and
21 decide later if -- I want to look at this four-day
22 period, so I'm going to take these four samples and
23 post it together in a subsample and I'd get an average
24 concentration on those four days, or I could take one
25 sample every four days and something like that. You

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1 can do a lot more.
2 You don't need to be as complicated with
3 all the samples if you don't have the opportunity.
4 Usually, automatic samplers is a little bit more
5 tricky, so you need a little more experienced personnel
6 to -- that's all I have at this point.
7 **DR. KENNETH PORTIER:** Dr. Lee.
8 **DR. HERBERT LEE:** I don't have too much
9 to add to that. I just want to reiterate something we
10 brought up in the April SAP meeting, which is if you
11 are trying to estimate shortened time periods or trying
12 to estimate an area under the curve or some sort of
13 average over time period, you really need at least sort
14 of two points per time period unless you're going to
15 use some really enhancing modeling, which we could talk
16 about in a bit.
17 So the basic idea is if you can get two
18 samples per time period, that will get you pretty much
19 all the way there, not quite but most of the way there.
20 And so, the idea of basing a number of samples on the
21 exposure duration concern seems like a really good
22 idea.
23 **DR. KENNETH PORTIER:** Mr. Stone.
24 **MR. WESLEY STONE:** Yeah, I don't have
25 too much to add other -- one point that Dr. Henley

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1 brought up yesterday was source of the water is very
2 critical, whether -- and it's something that I had
3 overlooked. I've looked at the AMP data as well as the
4 AEEMP data.
5 But whether it's flowing, static, I
6 think you had bio up there, that's going to be critical
7 as far as designing your plan to get representative
8 sites that you can then relate to other clean water --
9 or excuse me, drinking water and clean water supplies.
10 The other thing in the sampling plan was
11 the period of application or the growing season. And
12 typically if you think about that in terms of corn now,
13 you should be looking at April through August for your
14 sites, start turning south.
15 You're going to need to move out a
16 little earlier in the year. The case in point would be
17 -- I think I've seen data from one of the studies. I
18 think it's ATEMP sites in Tennessee that April wasn't
19 quite early enough to characterize a chemograph there.
20 My colleague is from Mississippi, so he might have to
21 move further south.
22 I think they've covered the issue about
23 the exposure duration. Just to add to what Dr. Coupe
24 was saying, you could consider using mineral assays at
25 the stream level if you have multiple samples to look

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1 at it and see which ones you may want to target.
2 Having done some of these transport studies, it gets
3 frustrating to be sampling a high intensity when you're
4 at base level for a long period of time.
5 But also note it's very hard sometimes
6 to capture when things missed its off of the function
7 of the street sites.
8 The only thing about the other samplers
9 having used them, I do see that they were a great help
10 in the AEEMP study, adding to the data by triggering
11 on, I believe it was flow and the data deposits.
12 I think the point that Dr. Coupe brought
13 up about it essentially different because there's a
14 facility there. Maybe they're not -- may not be as
15 needed. And whenever you involve more technology,
16 there are robots collecting samples.
17 Odds are pretty high that something will
18 go wrong when you don't want it to go wrong and that's
19 what we're seeing. That's all.
20 **DR. KENNETH PORTIER:** Any other
21 comments? This is getting pretty I wanted to point
22 out when I've talked to these guys about this thing,
23 one of the things that comes up is that what you're
24 really proposing here kind of deviates from the typical
25 sampling designs that we've done probably over the last

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1 50 years which is to take your sampling effort and kind
2 of uniformly distribute it over the growing season and
3 tell the operator, "Give me a sample every seven days."
4 But what we're really seeing now is if
5 you're going to take that sampling effort, you want to
6 be smarter about where you want to put it. And in this
7 situation, the amount of data, amount of understanding,
8 the amount of modeling that's going on for these
9 situations means that we're very smart about knowing
10 what goes on. And we really don't want to put samples
11 at times and situations where we expect nothing to
12 happen.
13 Why would we want to spend our effort
14 there? And so, all of these things you're recommending
15 seem to indicate that you're moving toward a much more
16 -- what statisticians would call an adaptive sampling
17 design and the adaption means you're adapting your
18 sampling to which you know or expect in the system.
19 And a model doesn't have to be perfect for this to be a
20 very good sampling design.
21 In risk assessment, you're working on
22 probabilities and all we're saying is that when you're
23 doing your sampling, you're going to be working on the
24 same probability. So there's going to be a chance that
25 you've going to miss a peak every once in a while.

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1 But maybe from a public health point of
2 view, that's not as critical. It's not wasting a lot
3 of dollars, on the other end, sampling and tiring up
4 your workforce collecting samples that don't produce
5 results. So I'm personally glad to see this moving in
6 this direction.
7 Any additional comments on the sampling?
8 Okay. Nelson, does that kind of answer your question?
9 I see a smile, so --
10 **DR. NELSON THURMAN:** Yes.
11 **DR. KENNETH PORTIER:** Let's go on to
12 Question 4.2.
13 **DR. NELSON THURMAN:** Okay, there are two
14 parts, so I'm going to read one part at a time so you
15 could actually ask two different things.
16 Please comment on the Agency's proposal
17 to use chemograph shapes (number, duration and
18 magnitude of peaks) to manage Community Water Systems
19 with more intensively monitored data sets.
20 In particular, the Agency is interested
21 in recommendations on approaches for matching
22 chemograph shapes given the loss of short-duration
23 peaks that occurs with less frequent sampling.
24 **DR. KENNETH PORTIER:** Mr. Stone.
25 **MR. WESLEY STONE:** You know, chemograph

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1 shapes influenced by many factors other than the
2 watrershed characteristics. They're influenced by
3 factors that vary annually such as precipitation,
4 amount of pesticide applied spatially. And so, you can
5 have chemograph shapes, the magnitude, length of -- the
6 foresight varying from year to year.
7 So it's not really something that I've
8 ever considered kind of a fingerprint foresight or an
9 identifier. So the concept of trying to match to that
10 -- when I first read the question, I never really ever
11 considered it before and I thought, "Well, maybe that's
12 something we should look at."
13 The other thing with the chemograph
14 shapes is the question itself kind of brings up the
15 larger questions. You don't know if you're missing
16 something when -- you have a beautiful match between
17 high frequency, high -- a site of sample with high
18 frequency to less frequency but it still didn't tell
19 you if you missed them.
20 So alternatively, I would think more in
21 terms of matching these sites based on first, the
22 source water where there's flowing or static or
23 whatever, any hydrologic information that will hold up,
24 water shed, pesticide use, climate, precipitation
25 characteristics, as well as their geographic locations.

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1 And you create these groups because you
2 should be able to get a better understanding of what
3 you're looking at there and getting an idea of when
4 these sites fall into these troops, what the magnitude
5 of a less frequently sample site might miss.
6 In case of static waters, I think it's
7 also important to look in terms of reservoirs and in
8 terms of retention time, turnover time because if
9 you're looking at a site's impoundment that actually
10 it's a low dam or something that the water is flowing
11 by quickly, it may behave like a stream water, so
12 residence time is very, very critical. That's all I
13 have.
14 **DR. KENNETH PORTIER:** Dr. Coupe.
15 **DR. RICHARD COUPE:** I don't have much.
16 **DR. KENNETH PORTIER:** I can quote you on
17 that, okay. Dr. Lee.
18 **DR. HERBERT LEE:** I just want to add a
19 little bit more on the idea of matching the shapes.
20 This relates to the literature on registration and
21 functional data analysis.
22 In registration, it's lining up curves.
23 It happens a lot in biological events or neurons and
24 stuff like that where they have a pulse at a certain
25 time and you want to line up similar curves based on

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1 them starting at the same time.
2 And I think there's the same idea here
3 in that you have an application and you have rainfall
4 and you get a particular pulse.
5 And so I would recommend in the
6 literature the functional data analysis. For example,
7 the Bransen and Silverman have two books out that are
8 listed in the April 2010 SAP report.
9 And so, those references are already
10 there. The key to keep in mind is that here, you have
11 missing data. You know that people are only sampling
12 once a week. You don't have measurements for the next
13 six days. So you may completely miss the peak. So
14 when you're talking about an actual shape, you got to
15 keep in mind that you may not know what your shape
16 looks like if you're trying to match.
17 So I'm a little bit concerned from the
18 presentation. For example, when Figure 7.7 is on the
19 112 of the Issue Paper that's put up, it was discussed
20 as -- you still get the general shape, even sampling
21 once every seven days. But for that particular one,
22 you're really missing the main peak. You get the
23 initial peak but you miss the second peak, which is the
24 large peak of the two.
25 And so, if you're just looking at

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1 general shapes of chemographs, that one is going to
2 look quite different from what you actually want to
3 match it to. And so, just keep in mind that you have
4 missing data and you may -- that can affect.
5 You can still match things with only
6 partial data, but you're going to have more
7 uncertainty. You're going to have a range of different
8 shapes which could match. And so, you can build that
9 into your confidence assessments based on the ranges of
10 shapes which could match.
11 **DR. KENNETH PORTIER:** Anyone else who
12 wanted to comment? Anybody?
13 You know, when I think about this idea
14 of pattern matching as a statistician, I'm really
15 thinking of that shape as a function. It's
16 parameterized.
17 In 2007, we saw a lot of these
18 chemographs but they don't have the same shape. Where
19 they're different was in peak and duration or the main
20 body, area under the curve, all these kinds of things
21 and to me, you're never going to get enough data to
22 really do a great job of matching not just the pattern
23 but putting it in the right location and time.
24 And really, this pattern matching has to
25 link in with the modeling that's being done because the

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1 modeling is going to tell you kind of where it fits in
2 time and roughly it's going to give you half your
3 parameters and if you're lucky, the data you're
4 actually collecting and monitoring is going to help you
5 fill in the other half of the parameters to put the
6 shape into place.
7 I think I did for a little bit for them
8 in that typically, they're thinking kind of a little
9 more non-parametric the data in some kind of a
10 smoothing process is going to give me that shape.
11 And I tend to think more in terms of a
12 parameterization of a function that you're trying to
13 estimate those parameters for a certain location,
14 certain situation or a certain point in time. And I
15 find it much easier for me to think about it in that
16 way. Dr. Lee.
17 **DR. HERBERT LEE:** I think we're going to
18 come back to that because I think that's essentially
19 what the SEAWAVE model is doing. And so, we'll discuss
20 that in the following two questions.
21 **DR. KENNETH PORTIER:** So I think we can
22 move on to B.
23 **DR. NELSON THURMAN:** Please comment on
24 the strengths and weaknesses of using more intensively
25 samples data sets from Heidelberg and the Atrazine

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1 Ecological Exposure Monitoring Program for analysis of
2 flowing water and PRZM/EXAMS for lakes and reservoirs.
3 **DR. KENNETH PORTIER:** Dr. Lee.
4 **DR. HERBERT LEE:** Alright, so first, I
5 do want to say that the analysis given and it's deep,
6 with all the chemographs looking at weekly samples from
7 a daily analysis of Heidelberg data and AEEMP data very
8 nicely shows the problem of trying to draw inference
9 for an exposure when the interval is only sampled with
10 a single point per interval.
11 Sometimes you get lucky and your timing
12 is good and you get a good estimate, and sometimes you
13 get unlucky. You miss the peak and you just grossly
14 underestimate your exposure. So it is really important
15 to have true daily data when developing methodology, or
16 I guess on some flashy streams, you may even want more
17 than daily data.
18 But in general, having true daily data
19 is really important to be able to understand what
20 you're trying to estimate and be able to test the
21 methodology. And so, what I learned in the AEEMP data
22 sets are good for that, although they are representing
23 particular types of watersheds.
24 The PRZM/EXAMS modeling can also be
25 useful providing Halberd curves for simulated daily

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1 values. Again, that's giving a more parameterized
2 approach to giving a curve.
3 It should be noted that the PRZM/EXAMS
4 model is not necessarily true data. It's simulated
5 data, so any conclusions drawn should be taken as
6 approximation. But they certainly would be expected to
7 give more accurate results than say linear or stair-
8 step interpolation of less frequently sampled data.
9 There is a substantial literature on the
10 use of pure models to augment physical data and were
11 properly calibrated, so meaning adjusted to match the
12 available partial real data. In the population, it can
13 be very good, and so I think that the concept in using
14 PRZM/EXAMS is a good one with a lot of backing in the
15 statistical literature.
16 However, my understanding -- and I think
17 my colleagues can contest to this further, is that
18 PRZM/EXAMS is not built for later reservoirs and that
19 may not be the right model. Dr. Henry brought up the
20 very late data set and that might be a more relevant
21 one for reservoirs, and depending on what the reservoir
22 is. Some reservoirs are essentially stream-based and
23 there's a dam or something.
24 And so, they do exhibit a behavior more
25 similar to flowing water whereas larger reservoirs

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1 generally have multiple input sources that would be
2 blending different inputs, different concentrations of
3 pesticides that also tend to have exposure over time.
4 And so, the pesticide concentration tend
5 to be much more smooth, lot less spiky in a larger
6 reservoir compared to a flowing stream, which is what
7 most of the data we've been looking at as also flowing
8 stream data. In such a case, the sparser such as
9 weekly sampling may actually be representative enough
10 of the overall chemograph as was demonstrated by the
11 Perry Lake example that Dr. Henley showed.
12 So you can think of that maybe in those
13 cases and you had to take it in a case by case basis.
14 But for certain reservoir base systems, weekly may be
15 sufficient.
16 On the other hand, you can also think of
17 -- if we're always thinking about flowing water sources
18 that can be seen as a conservative approach, being able
19 to predict the peak of the flowing water source will
20 generally then -- whatever methods will work for that
21 should give you good enough results as well on the
22 larger reservoir.
23 **DR. KENNETH PORTIER:** Dr. Coupe.
24 **DR. RICHARD COUPE:** Is it always in
25 alphabetical order? Sorry. So just a comment on the

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1 Heidelberg data, certainly it's a great data set and
2 one that's used, but it's kind of unique in the sense
3 that you never see a scale difference in it. Usually,
4 when you go from a very small base to a larger greater
5 base, you have a reduction in the load or the percent
6 of use there.
7 Well, now there's not a reduction there
8 but a reduction in the amount that's coming because you
9 incorporate more areas that are not agricultural.
10 In the Heidelberg data set, they
11 actually manage to keep the almost 80% to 90% of the
12 agriculture from the very small base into the larger
13 ones. You kind of miss out on that scale difference.
14 There's a little -- we don't match up always with some
15 of the stuff we see elsewhere.
16 Most of my comments, I think I'm going
17 to stay out with PRZM/EXAMS or PRZM -- I have used PRZM
18 and it's a very detailed model. It's not an easy model
19 to use. There's another talk about using SWAT. I
20 mostly use SWAT. SWAT is a nice model.
21 I don't know that you want to or have
22 the people available to put together a PRZM or a SWAT
23 model on all of the reservoirs that you have in
24 Midwest. They're very data-intensive, take rainfall
25 slower. They're just taking an awful lot of work to

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1 get going.
2 Additionally, I don't really think you
3 need a model of that scale to do what you need to do.
4 One thing you need to keep in mind with reservoirs is
5 to make reservoirs different.
6 So it makes a big difference whether
7 it's a small -- one of the river reservoirs, or it's
8 just a reservoir with a low head dam and the water is
9 backed up, or whether that only has a small retention
10 time of just a couple of days, or the large reservoir
11 which has a large retention time of months and years.
12 Or even they some that are offstream storage reservoirs
13 where they can pump from the river into an offstream
14 storage that they could control when the water comes in
15 the reservoir.
16 To kind of finish that up, I think you
17 could actually get a better idea of how a reservoir --
18 how pesticides act in the reservoir by just looking at
19 random basin characteristics and reservoir
20 characteristics, potential time and size, those kinds
21 of things.
22 I think you can do a much better job
23 with that given the idea that reservoir tends to lower
24 the peak concentration and attenuating concentration.
25 So given the reservoir's -- the different reservoirs

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1 and streams, I think you have a much better opportunity
2 to use a model of the reservoir to do a screen. You
3 should be able to do it fairly easy.
4 **DR. HERBERT STONE:** I'm going to leave
5 the reservoir stop with Dr. Coupe. I'm going to just
6 talk about the Heidelberg and just kind of switch back
7 and forth. Heidelberg data set is a very good data
8 set. I've used it in the work I've done with wash
9 aggressive pesticides. It's very intensive.
10 There are some limitations in fact that
11 only represents a select geographic area that atrazine
12 was used in, and this is kind of highlighte when the
13 AEEP -- and I always get stuck on the acronym. It's
14 too easy, but I think they understand what I'm saying.
15 When it spread throughout the entire
16 corn belt, one thing that's very, very important to
17 understand is that it highlighted some watershed
18 characteristics and I'm specifically talking about the
19 depth to limiting or a restrictive layer that really
20 hadn't been thought of or seen, and that's an issue of
21 not having a certain data.
22 Certainly, the folks in Northwest or
23 Northeast Missouri knew about it and wrote quite a bit
24 of papers about it. I mean, that's a case in point
25 that Heidelberg may not represent all of the areas, all

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1 the water supplies that could potentially be that and I
2 think that's a limitation that if you look at the
3 Heidelberg and draw conclusions, you run the risk of
4 being overconfident, which is being shown here.
5 **DR. RICHARD COUPE:** Let me add one more
6 thing. Some USCS people have done work on pesticides
7 on reservoirs, especially atrazine.
8 **DR. KENNETH PORTIER:** Anyone else who
9 want to comment? I don't know why the physiologists
10 aren't just jumping out.
11 Okay, let's -- question?
12 **MR. WESLEY STONE:** Actually, I have a
13 couple of follow-up questions. Dr. Coupe struck me
14 because we've been talking about size of the basin and
15 I'm wondering, is it really the size or is it the land
16 use? Should that be your focus?
17 **DR. RICHARD COUPE:** Well, I think you've
18 got to do both-- I mean unfortunately -- I mean, the
19 size of the basin is going to control the water. The
20 land use is going to control the input of the atrazine.
21 So that's why I had to two functions, the source
22 strength and how the hydrology relates to the basin.
23 You probably need both.
24 **MR. WESLEY STONE:** This is Wes Stone.
25 One of the first iterations actually looked at basins

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1 or reservoirs. In the percentiles, it largely aired on
2 being biased as far as underpredicting because the
3 residence time.
4 Reservoirs may not have a sizeable peak
5 but they can carry their concentrations for a longer
6 period of time in the stream.
7 So being in terms of the chemograph that
8 it's a wider and a sharp peak, but you can look at that
9 as well. You might have some insight into those
10 characteristics.
11 **DR. NELSON THURMAN:** And then one last
12 follow-up. One of the reasons we haven't focused too
13 heavily on Perry Lake is because it never really got
14 concentrations greater than four parts per billion, so
15 didn't really think there was a high exposure example.
16 I know we're aware of the USGS monitoring and weekly
17 sampling for some reservoirs, but in terms of anything
18 in between there, that's one of the problems we've
19 struggled with on that. So if you're aware in
20 providing a report of anything that might be more
21 frequent than that, we'd appreciate that.
22 **DR. RICHARD COUPE:** So reservoirs are
23 really ugly animals so no one really wants to do any
24 work there.
25 **DR. NELSON THURMAN:** I've noticed that.

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1 **DR. RICHARD COUPE:** There are a lot of
2 issues involved with the reservoir sampling, where you
3 sample, what you sample. It's very difficult to know
4 because there's not a lot of work has been done there.
5 **DR. KENNETH PORTIER:** Why don't we just
6 finish Question 4.b?
7 **DR. NELSON THURMAN:** You know what, I'd
8 like that. Please comment on the strengths and
9 weaknesses of proposed -- wait a minute, I think there
10 may be -- okay, I might give you the preamble part of
11 that question to put some context.
12 Once the magnitude and duration of
13 exposure of toxicological concern are identified, USEPA
14 will determine which methods to use to analyze the
15 existing atrazine Community Water System monitoring
16 data for use in drinking water exposure estimates.
17 Based on the April 2010 SAP recommendations, the Agency
18 is focusing on regression-based modeling combined with
19 random function modeling.
20 For example, WARP model coupled with
21 kriging the USGS SEAWAVE-Q Model.
22 Please comment on the strengths and
23 weaknesses of these proposed approaches and provide any
24 recommendations for improving the model applications.
25 **DR. KENNETH PORTIER:** Dr. Lee.

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1 **DR. HERBERT LEE:** Well, really the
2 easiest thing to do is just sampling twice for each
3 period of interest, then you're fine. If they conclude
4 that the duration of interest is 14 days or longer,
5 then we've got two samples per interval and we can just
6 go ahead with everything and not worry about modeling.
7 On the other hand, supposing that we get
8 an interval of concern which is shorter than 14 days,
9 then we're going to need to go to some sort of modeling
10 and the idea of combining deterministic model like
11 SEAWAVE or PRZM, PRZM with a regression-based model
12 like WARP appears to be the most promising approach to
13 deal with sparse data with flowing water, which is the
14 scenario that these models were designed for.
15 This approach makes use of information
16 about halfway as an aggregate data that are not
17 incorporated by purely statistical methods such as
18 creating our neural networks. And so, bringing in more
19 information should give you better results of course if
20 you use the models correctly.
21 On the other hand, combining a model
22 such as WARP with a purely statistical method like
23 kriging will still give better interpolations than
24 simple methods like a linear interpolation but it fails
25 to make use of the information about the expected shape

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1 of the concentration curves that could be predicted by
2 deterministic model.
3 Oh, there's a trade-off in the
4 difficulty implementing these methods. It would likely
5 be easier to implement a combination of WARP and a
6 relatively simple statistical approach such as kriging
7 instead of combining WARP with a deterministic model.
8 So this may be more practical to do in a short amount
9 of time, or if say this needs to be done more out in
10 the field, I think it would be nearly impossible to get
11 WARP calibrated with SEAWAVE for every community water
12 system in the field.
13 Something like rigging doesn't allow
14 this small estimation of compost vents and that can be
15 useful for guessing what might be happening in between
16 observations. But please do note that empirical
17 diagrams are highly variable.
18 I saw you looking at empirical diagram
19 and you're estimating something from it and that's
20 sometimes the best you can do, but the variability in
21 variograms is much higher than most people think it is.
22 So one thing to do is you take a
23 variogram, generate data from it, and then fit the
24 empirical diagram and see what you get on that. If you
25 do this ten times, you'll get ten weekly different

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1 variogram estimates.

2 **DR. RICHARD COUPE:** That's fun to do.

3 **DR. HERBERT LEE:** Okay, it can be

4 enlightening, let's put it that way. Slide 94 in the

5 presentation shows -- it shows looking at different --

6 doing rigging at different sampling intervals and this

7 shows -- for the interval, you get some instant results

8 but when you get to 16-day sampling, you hardly have

9 anything there. I think this really highlights the

10 need for doing joint estimation of variograms. You can

11 learn a lot about the shapes and the correlation

12 structures approximately more than one water system at

13 a time.

14 I think it's not necessarily that

15 they're all going to have the same shape but

16 correlation structures will be more similar across

17 different watersheds than individual shapes are.

18 And so, I think there is a lot more to

19 be learned by providing information in correlation

20 structures across watersheds and that's going to be

21 really important to get good kriging estimates because

22 you need to have that correlation structure to get

23 anything out of that 16-day sample. And if you do have

24 a good estimate, what you're going to get there is

25 really Y-competence bands.

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1 You'll get the same mean as you got
2 right there but your confidence should be a lot wider
3 and that should give you some more reasonable way of
4 estimating what's probably exceeding a threshold over
5 four days or something like that.
6 The last thing I want to say about
7 rigging is that correlation structure here seems
8 clearly non-stationary. Earlier I asked a little bit
9 about the Galian correlation structure that was
10 estimated and I didn't think that that was appropriate
11 for the peak. And on further the question, I think
12 what's going on is that it is non-stationary.
13 Around the time of the peak, it has one
14 correlation structure and then sort of the tails which
15 comprise much of the curve where you're getting very
16 low levels or close to zero or zero levels, it's a
17 different correlation structure. It's very smooth at
18 these low levels for most of the time period of
19 sampling.
20 And then, there are these short
21 intervals where there are peaks. And so, the
22 correlation structure is actually quite different
23 around the peaks than it is for the low level areas.
24 And in fact, you got a lot more points at the low
25 level.

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1 It's driving you to estimate a much
2 smoother correlation structure than you want around the
3 peaks. And so, if you use that sort of correlation
4 structure, it's going to underestimate the peaks.
5 So you may want to actually estimate a
6 correlation structure from shorter snippets of the
7 chemographs concentrating more tightly around the peak
8 areas and use that correlation structure.
9 You could use that for the whole thing.
10 It will give you sort of wider bands than you need on
11 the boring areas. But those are the boring areas.
12 You're not really worried about it as much anyway.
13 **DR. KENNETH PORTIER:** Dr. Coupe.
14 **DR. RICHARD COUPE:** So I'll leave the
15 fun stuff to Herbert. I don't have too much to say.
16 Not to be a naysayer but after this week, the genesis
17 of toxicology is coming up where there is a concern on
18 -- we know it's less than 90 days, probably more than a
19 day.
20 I think -- I think if you go forward
21 with the dark wave sampling that we're talking about,
22 you can actually lead the way for toxicology. You can
23 actually have the characteristics of the atrazine in
24 these streams and community water systems already done
25 by the time they come up with the duration of concern.

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1 And so, they'll be able to move right into it.
2 **DR. KENNETH PORTIER:** Mr. Stone.
3 **MR. WESLEY STONE:** I'm going to talk
4 more just about WARP, SEAWAVE view and some of the
5 efforts with that. But I want to first say to watch
6 your aggression for pesticides to the WARP, the intent
7 there is this national, it's nationwide -- it's more or
8 less the guide, more intensive efforts of sampling to
9 show you where you might have a probability of a
10 seeding criteria, so you should look more closely at
11 it.
12 So in terms of guiding more intensive
13 efforts, it's a good approach. Now, it is national to
14 look at in terms of what you're keying in perhaps. It
15 would be more appropriate to scale it to the area of
16 interest such as corn mill and that's been talked about
17 and the progress is on its way. It's being worked on.
18 But a part of that would be adding in
19 the data from the AMP program and we'll try to do that.
20 But I think that the issues there, it's trying to get
21 the watershed ancillary data.
22 This is a huge enough data when you add
23 in all the 40, 50, 60 traditional variables for all of
24 the water supplies together and put them all into one
25 package.

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1 Earlier on in work development, I think
2 they looked at doing data simulations report and it's
3 in the references I believe. I'll make sure it gets
4 there. It's back in Crawford 2006. They've built the
5 time series model and that simulated daily pesticide
6 concentrations.
7 They did use the Heidelberg data set as
8 part of the development and checking of this model.
9 And it performed fairly well but one of the keys in
10 that effort was that their intent was not to predict
11 daily concentrations. They wanted to just do that in
12 order to look at long term trends and that's the key.
13 Dr. Vecchia went on to develop the
14 SEAWAVE-Q models that we've talked about more recently
15 and again, the intent of that model is to look at long-
16 term trends. It does generate daily pesticide
17 estimates but it's more intended to look over trends in
18 years.
19 The next logical step would be to go
20 back or revisit the joining of those two models again
21 then maybe change the focus back to more of a data of
22 the time set. That has a lot of promise.
23 One of the key weaknesses I think Dr.
24 Henley brought up yesterday is that these models, the
25 empirical models are based on the data collected on the

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1 stream and if our data that we're using in the models
2 is not adequate to address the short-term exposure,
3 then the model is not going to behave that well.
4 So if we're looking at short-term
5 durations, the models are set to do that such as WARP
6 and its models.
7 Adding in data such as the data which is
8 collected on weekly basis will help it, and that will
9 certainly key it that way, but that's one of the
10 caveats, it's making sure. And Dr. Lee was referring
11 to that, using it appropriately in the discussion.
12 To build in this adaptive or iterative-
13 as this data becomes available and incorporating them
14 back into the model's improvement and to keep this
15 phase going. That's all I have.
16 **DR. KENNETH PORTIER:** I've been giving
17 this some thought, too. This is Kenneth Portier and I
18 wanted to kind of read what I've got here because it
19 took me a while to kind of put this altogether. So I
20 recognize that the focus of the exercises and atrazine
21 concentration, modeling atrazine concentration and
22 community water system source and output of treated
23 water is the support that's brought risk assessment
24 goals, right?
25 But there's also been a discussion about

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1 how this exercise will inform broader monitoring
2 efforts around atrazine in the environment as we move
3 out. So you're going to do the risk assessment.
4 A lot of the data we're collecting is to
5 try to help set these thresholds of concern but at some
6 point, you can also move this out into how we monitor
7 atrazine in the environment to ensure from a public
8 health point of view that we're not exceeding these
9 levels.
10 And I would point out that -- with
11 apologies to Dr. Bailar that in this case, we have vast
12 and complex data but it's exactly the data we want.
13 It's not the data we don't have. We have the data that
14 we want here. We just need to figure out how to use
15 it.
16 At the April 2010 SAP, the Panel
17 recommended the use of statistical models incorporating
18 environmental explanatory variables and geostatistical
19 correlations that simulate chemographs for input waters
20 for community water systems.
21 With such a system, the exposure end
22 points of interest can be estimated in proposed
23 sampling procedures evaluated for their statistical
24 properties. It's clear for the presentations before
25 the Panel that both the AUC and Syngenta continue to

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1 pursue this approach and we're happy to see that and we
2 continue to see progress.
3 It seems that a lot of time and effort
4 is being concentrated on properly modeling the
5 magnitude of concentrations in source raw waters
6 realizing that the source waters will eventually be
7 modified through the community water system treatment
8 process and that the ultimate exposure metrics for the
9 human risk assessments are derived from the levels of
10 atrazine in community water system output or drinking
11 waters.
12 It's comforting to see that again, EPA
13 and Syngenta are making advances in characterizing the
14 community water system's water treatment processes as
15 they affect of atrazine concentrations.
16 As EPA and Syngenta continue to explore
17 sampling plants for monitoring, some thought should be
18 given to actually using these simulation models and
19 community water system characterizations as part of the
20 monitoring process.
21 In particular, it's feasible that models
22 will eventually be accurate enough to provide
23 predictions of atrazine concentrations in source waters
24 to community water system for the coming crop season,
25 so I'm thinking in terms of being able to use these

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1 models to kind of predict ahead.
2 Instead of requiring a community water
3 system to collect and analyze water samples in their
4 output drinking water stream in some predefined
5 frequency, say daily or weekly in the case of some
6 sites, it should be possible to use these models to
7 facilitate targeted sampling for periods of time most
8 likely to experience an exceedance. The sampling plan
9 might look something like the following.
10 A prediction of expected concentrations
11 for raw and drinking water for a CWS would be running
12 at the beginning of a crop year using available long-
13 term climate predictions within the area of the water
14 system and expected cropping practices in this area and
15 the CWS site-specific characteristics.
16 It's not exactly required that one know
17 the exact days of rainfall or atrazine applications.
18 Just having distributions for the expected number of
19 heavy rainfall events, expected duration and likelihood
20 that these events would coincide with new atrazine in
21 the field would be sufficient data probably for this
22 exercise.
23 For most community water systems, the
24 expectation would be that there would be no predicted
25 exceedances. Sites with high likelihood of exceedances

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1 might be required to implement interventions under
2 specified conditions to mitigate these expected
3 exceedances.
4 The CWS would be required to collect
5 water samples on a periodic basis, say daily, and store
6 them in a form that would preserve atrazine
7 concentrations. At the end of the season, the model
8 would be again run but this time, the actual rainfall
9 patterns and crop and chemical application and used
10 information would be used.
11 The post-season model run will identify
12 periods in the season just past where high atrazine
13 concentrations would have been predicted. The stored
14 water samples in this period are then retrieved and
15 analyzed to get actual atrazine concentrations in the
16 CWS output waters to determine actual concentrations
17 for exposure.
18 This information can then be used to
19 assess the water system's performance and the need for
20 further system management changes to ensure atrazine
21 concentrations in the future are below maximum
22 allowable concentrations. The plant follows closely
23 sampling protocols that are typically used for
24 obtaining information on rare events. It has the
25 benefit that sampling effort can be more easily

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1 controlled and planned for.
2 The community water systems would know
3 that they would be responsible for say only X water
4 sample analysis for any one year so they could do
5 better planning.
6 But they would know exactly which time
7 period is going to be analyzed, so there is always
8 this, "I have to do a good job because I'm not sure
9 when they're going to ask for my data and grade me."
10 They would be responsible for collecting and storing
11 water samples for the season, but I think this is more
12 of a minor clause than anything else. This is an
13 economic issue that we heard of in the public comments
14 and it's of high concern for community water system
15 managers.
16 You control sampling effort and at the
17 same time focus the sampling on periods with the
18 highest likelihood of actually seeing measurable
19 concentrations. It acknowledges the fact that for most
20 community water systems and for most times, there is no
21 atrazine concentration in output waters.
22 It also allows for random selection and
23 analysis of stored water samples to estimate the extent
24 to which the models might be missing peak periods or
25 high concentration areas, if any.

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1 It's recognized that this method of
2 organizing sampling effort deviates from the
3 traditional approach which specifies sampling effort to
4 be distributed uniformly over a time period of
5 interest.
6 But it has been made clear in the
7 presentations before the Panel, and I'm talking about
8 the SAP in 2007, the SAP in April 2010 and today's SAP,
9 that this traditional thinking will lead to intensive
10 and expansive sampling with high frequency with the
11 expectations that the vast amount of the analysis will
12 indicate no detect concentrations.
13 While this may provide confidence to
14 many that there is little or no atrazine in these
15 community water system output waters, it also
16 represents an unnecessary expensive approach that will
17 not provide better results than this more focused and
18 less expensive sampling that I'm suggesting here, so
19 I'll include that in.
20 Sorry for reading the whole thing but it
21 was really -- I wanted to get it right. Any additional
22 comments? Yes, Dr. Horseman.
23 **DR. NELSON HORSEMAN:** Well, since you
24 can't challenge this side of the table, they have
25 something from this.

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1 I'm welcome to contribute. We did have
2 some information and quality information can be argued
3 and so forth that one or more environmentally generated
4 metabolites, in this case since hydroxyatrazine came up
5 a couple of times, might end up having some relevant
6 role.
7 And I haven't heard anything in the
8 discussion of characterizing these systems for that
9 kind of metabolite. I'm just wondering if -- and
10 obviously, we're not going to recommend based upon this
11 little bit of data that every sample being measured.
12 But even the possibility that the profiles, and we're
13 talking about these profiles in shapes and curves,
14 might be quite different for a metabolite that's
15 leeching from a validly generated source.
16 It might be quite different. Is there a
17 reason to include a subject to amount possibility of
18 measuring that sort of product? Did I make any sense?
19 **DR. KENNETH PORTIER:** Mr. Stone?
20 **MR. WESLEY STONE:** Yeah. I think we're
21 if I hear what you're saying correctly, is the
22 chemograph or degradation product the same as the
23 parent product.
24 And in some of the smaller systems, like
25 you said, I've seen certain soils in a degree and you

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1 get different phases of water movement through soils
2 and you may see more of one component coming through
3 than the other.
4 But I think that needs to be looked at.
5 And if that becomes something of an interest, one in
6 particular comes more interesting then you have to
7 target it.
8 **DR. RICHARD COUPE:** A comment to that-
9 Nelson we only regulate the atrazine, not the
10 components, correct?
11 **DR. NELSON THURMAN:** We are modeling for
12 all the chlorotriazine which includes atrazine,
13 cenozine and the DEA, DIAA and DACT. As far as I know,
14 hydroxyatrazine was not included in the monitoring.
15 **DR. RICHARD COUPE:** So as far as the
16 AAEMP program, which --
17 **DR. NELSON THURMAN:** It's part of --
18 yeah, the community water system data, we get more of
19 those metabolites as well, so we get it. All the
20 components are measured individually, at least for the
21 last --
22 **FEMALE:** 2005.
23 **DR. NELSON THURMAN:** Since 2005, yeah.
24 **DR. RICHARD COUPE:** Do you have DACT
25 also?

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1 **DR. NELSON THURMAN:** Yes.
2 **DR. RICHARD COUPE:** Well, just to finish
3 up, the metabolites of atrazine are not really easy to
4 analyze. The diethylatrazine is -- our labs had
5 trouble with it and its recoveries are 20%, 30%, 40%,
6 something like that.
7 So we don't have a really good idea of
8 what diethylatrazine is the one that you normally see
9 in surface waters. We don't do DACT on a regular basis
10 and we don't do hyrdoxyatrazine on a regular basis
11 also. They're very expensive and you take it little
12 different approach to them.
13 **DR. KENNETH PORTIER:** Dr. Chambers.
14 **DR. JANICE CHAMBERS:** Really, the reason
15 we're not speculating about the hydroxyatrazine is
16 because of that one study that showed extremely low
17 biological effects and the only real good explanation
18 is the hydroxyatrazine was never been studied and the
19 other studies was the actor, but I don't think there's
20 any database at this point to suggest that it would
21 really be worth studying at this point.
22 **DR. KENNETH PORTIER:** Dr. McManaman?
23 **DR. JAMES MCMANAMAN:** So would you
24 expect that the hydroxyatrazine would be really
25 different in the community water system given the way

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1 that water is handled versus the catchment areas
2 because it's dehydroxylated and that's a chemical --
3 I mean, that form of atrazine is being
4 generated by chemical processes rather than biological
5 processes, so it might actually be harder to measure.
6 But it might actually really give you some interesting
7 information with regards to what is going on.
8 **DR. RICHARD COUPE:** Yes, that's very
9 true. But I don't have any information
10 hydroxyatrazine. We didn't measure for that, just the
11 diethylatrazine. My only response to Dr. Chambers is
12 if we can dismiss that result out of hand, then we can
13 ignore the possibility of measuring this.
14 But I don't know that we can dismiss
15 that result out of hand at this point. That's a matter
16 of science whether or not we can.
17 Like I said, I'm not -- certainly nobody
18 is to construe this as advocating that, you know, run
19 out and measured this metabolite on every sample, but
20 they are getting some data that might inform that
21 analysis. That's all.
22 **DR. KENNETH PORTIER:** Dr. Chambers, a
23 follow-up?
24 **DR. JANICE CHAMBERS:** But what I'm
25 hearing from Dr. Coupe and others is that their

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1 technology is not really in place right now. It would
2 be very expensive and it really might not be a very
3 practical approach until there is some biological
4 information that that degradate is really atrazine.
5 **DR. RICHARD COUPE:** So I -- I'm sorry,
6 Richard Coupe. I'm just talking about our lab and our
7 lab tries to package together some 50 pesticides
8 together, so we're doing our best to do a solid phase
9 extraction. I think there are lots of techniques that
10 would be better as you go for it.
11 This is a really cheap one, cheap in the
12 sense that it's not very expensive but it's a good way
13 of doing it. There are other ways to do it.
14 **DR. KENNETH PORTIER:** Dr. Lee.
15 **DR. HERBERT LEE:** So my personal
16 speculation on these chemographs would be that in
17 flowing water systems like most of these water systems,
18 you're going to see similar shapes because it is a
19 flowing water system.
20 There's continual turnover in the water,
21 whereas the reservoirs would be a whole different ball
22 game and no idea what they're going to look like.
23 **DR. KENNETH PORTIER:** Mr. Stone.
24 **MR. WESLEY STONE:** At one -- and this is
25 kind of moving off subject a little bit, but we spent

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1 several days talking about lab PC and QC in
2 experiments, quality assurance and that was one of the
3 things that we didn't touch on in framework of the
4 study for the sampling, is we can do a lot of work on
5 characterizing how well we're capturing a certain
6 exposure duration by changing our sampling frequently.
7 But there also needs to be a component that tells you
8 how confident you are in that sample that you took,
9 whether it's through applying some replicates. So I
10 think the QC plan should be used in all of that. I
11 mean, I don't think that was in there.
12 **DR. NELSON THURMAN:** This is Nelson
13 Thurman, I just want to add, I know they do -- Syngenta
14 have that analysis issues. I'm not sure we've got a
15 final report on the paper report but I know that's part
16 of what is collected on there.
17 **DR. KANNAN KRISHNAN:** I just want to
18 make a comment on the hydroxy metabolite. The study
19 authors used some of the survey results, I could be
20 wrong , their effort to see the monitored results when
21 they chose the percent that they were using in their
22 study, which was about 20% I think.
23 But again, stepping back and looking at
24 this assessment, essentially it's an assessment of
25 atrazine and you could within the context include the

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1 metabolites that are found within the mammalian system.
2 I don't necessarily see us leaving any more talks to
3 the current evalutation of the hydroxy metabolite, even
4 though that could be on its own.
5 **DR. KENNETH PORTIER:** Dr. McManaman?
6 **DR. JAMES MCMANAMAN:** Given the fact
7 that the hydroxyatrazine looks like it's implicated
8 from the mixture study, it would seem like it would be
9 something recommended to do. And given that the
10 fragmentation pattern of the hdyroxyatrazine versus the
11 chloroatrazine, mass spec would be greatly different
12 that it would just seem like a -- as a mass spec
13 analysis, you should be able to pick it up pretty
14 easily but I don't do that sort of thing.
15 I mean I do mass spec but I don't do the
16 kinds of things that you guys do. So just a comment
17 whether is it really -- could it be that hard to
18 develop those kinds of operating procedures that's the
19 expensive part of it, or is it you have to give an
20 analysis?
21 **DR. RICHARD COUPE:** Richard Coupe, so we
22 have a standard analysis to do it. I'm not a
23 laboratory person so I'm not an expert on the aspect
24 and we have analysis to do it. I just know that when
25 you add in hydroxyatrazine, you add a lot of ammonia on

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1 your analysis, so we have done a lot of that.
2 To kind of answer the question about --
3 I wasn't really sure. I was surprised when she said it
4 was a mixture from USGS.
5 I just quickly went through and looked
6 at the references and I'm not sure she could have
7 gotten all of those -- or the authors could have gotten
8 all of the mixtures from USGS references they put in
9 the table. There were some other papers that they had
10 listed as far as this where we have a mixture of only
11 one USGS and I think there were other mixtures. So
12 they might have gotten the hydroxy from someone else.
13 **MR. WESLEY STONE:** This was on the --
14 recently in the last couple of years, we spent some
15 work, Greg Ellsworth at USGS looking at treated and
16 untreated drinking water. And I believe
17 hydroxyatrazine is one of the components they're
18 looking at.
19 I could find the reference and try to
20 get it, if it's published. It could provide more
21 information about hydroxyatrazine, but they looked at
22 sampling from on the river, at the intake and then at
23 the finis. And then they also tried to time the
24 samplings and get to cohort so you have the same water
25 coming in and out, which is extremely difficult to do.

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1 It sounds easy but it's not. I'll see if I can find
2 the reference.
3 **DR. JAMES MCMANAMAN:** First I want to
4 apologize for even bringing this up due to the amount
5 of discussion, but I guess in the back of my mind, the
6 reason for bringing it up is I just hate for people to
7 be put in a position of an issue being brought up but
8 appears to be toxicologically an interesting outlier in
9 terms of the data we've seen.
10 I think we can agree to the stat, right?
11 And if there's any confirmation that -- if someone
12 asked whether you ever looked at it and the answer is
13 "no", that would be sort of a hard answer to get.
14 That's my own reason for bringing it in.
15 **MR. WESLEY STONE:** I think bringing it
16 up is actually very useful.
17 **DR. KENNETH PORTIER:** Dr. Lowit.
18 **DR. ANNA LOWIT:** Yes. Of course, the
19 one reason I didn't bring my bag of atrazine thinking I
20 would just sit here all day and take notes. In 2003,
21 atrazine risk assessment does have a component of it
22 where we're evaluated hydroxyatrazine. I don't know
23 that data off of my head. I don't see anyone in the
24 room who have knowledge -- you do.
25 There are some guideline type studies

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1 submitted for hydroxyatrazine. It's what we would
2 consider a limited database for food use but we've got
3 a good amount of data for a lot of other chemicals in
4 the world.
5 And there's at least one study from ORD
6 looking at I think the puberty onset of hydroxy, but I
7 do know that none of those studies have shown hydroxy
8 to be more potent than the parent atrazine. But
9 anyway, I have it referenced right here on the
10 computer.
11 **DR. PENELOPE FENNER-CRISP:** I do. I
12 have the RFD for hydroxyatrazine here. Its NOEL was
13 actually lower than the NOEL for the chronic number for
14 atrazine. It's 1.0 with an uncertainty factor of 100
15 is based upon results from the chronic carcinoegenicity
16 study in a rat and the end point are histopathological
17 lesions of the kidney.
18 But the tox profile isn't in here. I
19 was looking for the results from the double battery of
20 the registration but you don't have them in here
21 anymore.
22 **DR. ANNA LOWIT:** I think you need to be
23 careful about saying that the one is different than one
24 point at using the rat. I think they're in the same
25 line I think.

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1 **DR. PENELOPE FENNER-CRISP:** Exactly, but
2 -- it's near it but the point is -- this conversation
3 has been, "Oh yeah, hydroxy is so much less toxic."
4 Then you look at the choice of studies for the RFD
5 andit's comparable. What id doesn't say anything about
6 is what you know about it in terms of being hormonally
7 hormonally active. None of those, it's just plain,
8 old --
9 **DR. KENNETH PORTIER:** That was Dr.
10 Fenner-Crisp and Dr. Lowit.
11 **DR. PENELOPE FENNER CRISP:** Oh, sorry.
12 **DR. KENNETH PORTIER:** Are you going to
13 bring up another topic here at 5:00?
14 **DR. MCMANAMAN:** No, I just want to make
15 a final statement about this. Don't ever ask for
16 comments from physiologists.
17 **DR. KENNETH PORTIER:** Dr. Legan.
18 **DR. SANDRA LEGAN:** I just want to
19 comment on what you said Penny. It may be that a given
20 chemical has a totally different effect at different
21 dose levels in different tissues.
22 So it doesn't matter that in the kidney
23 toxicity study or whatever, the dose -- how they drive
24 an RFD you said, they use that data. In the mammary
25 gland that's developing, it made it a totally different

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1 -- you might get a totally different RFD.
2 **DR. PENELOPE FENNER-CRISP:** Well,
3 absolutely. You might -- well, if you have ever tested
4 this, this is some of the systems that Ralph has used,
5 you will probably get are very different numerical
6 profile when you do it for the parent and the DIADA. .
7 **DR. ANNA LOWIT:** I think an important
8 point that gets lost in the numbers is that the agency
9 has put some effort into thinking about hydroxy so we
10 haven't forgotten it or ignored it in any way.
11 **DR. KEN PORTIER:** And we've gotten all
12 of the topic. Somehow we got packed to the physiology.
13 We're finishing up the questions on sampling. Any
14 additional comments on Question 4 or any components to
15 report? Yes, Mr.Thurman?
16 **DR. NELSON THURMAN:** I'd actually like
17 to go back to Question 4.3 and just ask just a little
18 bit different because some of the recommendations I've
19 heard are things people are thinking about, some are
20 going to be taking a little bit to develop.
21 Given what Dr. Lowit said earlier that
22 we're probably looking at -- at least for determining
23 doing more frequent monitoring or how we're going to do
24 the monitoring, I know the recommendation, the points
25 of what you're talking about is.

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1 But in terms of some of the modeling and
2 some of these things we look at is possible exposure
3 estimation methods, possibly saying take -- here's what
4 we have, here's how we might estimate the exposures by
5 some type of a comments bound or a safety factor, and a
6 spring 2011 time frame. What would you -- would your
7 recommendations stay the same as what you've done or
8 what would you recommend?
9 **MR. WESLEY STONE:** This is Wes - How
10 exactly are you going to use these models?
11 **MR. WESLEY STONE:** In terms of doing
12 exposure estimation for the drinking water, there are
13 different ways of looking at it. A lot of it is going
14 to come down to what the duration of concern is.
15 If we end up with a short, much shorter
16 duration we have now and we're trying to estimate have
17 we -- and not knowing what the magnitude is, but do we
18 have sites that based on their existing weekly
19 monitoring may actually exceed the level of concern?
20 We'd like to do some way -- at least
21 doing a -- one of the ways we might do is a triage of
22 looking at we have sites based on how we -- given a
23 weekly sampling in terms of estimating exposures, we
24 don't necessarily want to do linear interpolation in
25 that regard.

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1 So we would probably be looking at in
2 terms of evaluating maybe as a first shot. Given the
3 monitoring we have on these sites, these high, more
4 vulnerable sites, are we seeing anything based on a
5 weekly monitoring that might suggest that we could
6 triggering.
7 Exposure duration is a concern because
8 we're not on anything that might lead us in one
9 direction. But if there is something that may be
10 exceeding that level of concern, it might lead us in a
11 different direction.
12 So I think that's kind of giving us a
13 way of how confident are we that given the estimates
14 that we might be exceeding or not exceeding whatever a
15 duration and timing comes up to be.
16 **MR. WESLEY STONE:** So let me ask in a
17 slightly different- this is Wes Stone again. So if you
18 run a model and it shows that a site has a higher
19 probability to perceive, what does that mean to you?
20 What is the subsequent end? What is the use of --
21 **DR. NELSON THURMAN:** I think it means of
22 a more intensive monitoring a little more intensive
23 focus on those sites.
24 **MR. WESLEY STONE:** Okay, and we were
25 talking about this before this morning to make it more

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1 obvious to ourselves. Now, to get back to your
2 original question, if your exposure duration as Dr. Lee
3 pointed out, it turns out to be anywhere from three
4 weeks or greater and I think we're pretty good. Once
5 that exposure duration starts getting shorter than
6 that, then at least in terms of the WARP models, they
7 would need to be reevaluated.
8 But the data that will support that type
9 of estimation, if it got down to a four-day, then we're
10 talking about we would need the data from your first
11 study to try 7.2 to go back.
12 So all of this is a feedback mechanism
13 as far as all are connected including data you're
14 collecting back into the models and development to
15 improve that. So in the time frame that you're talking
16 about, you're not having data by spring obviously.
17 So depending on what exposure duration
18 you come up with, you're going to have to look at-- I
19 haven't had a chance to talk with Dr. Vecchia on the
20 SEAWAVE-Q and what can be done with that. And moving
21 back to this page on where we talked about chemograph
22 shapes but it's loosely based on atrazine.
23 It's not giving you what you would --
24 there has to a refinement of that to actually zero in
25 on that daily estimate to better characterize that.

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1 And from earlier toxicology-
2 So break it down to a further -- in
3 terms of the corn belt, we can move there and hopefully
4 have something to use for at that time. But the other
5 parts, I just don't have an idea right now as far as
6 characterizing for those.
7 And one of the key unknowns with these
8 models, if you're doing a type of that exposure
9 duration and it's real down tight, it's really going to
10 change the model and throughout the plots data that
11 don't support that type of model.
12 Did that answer your question?
13 **DR. NELSON THURMAN:** Probably not.
14 **MR. WESLEY STONE:** Did I talk long enough
15 to confuse you?
16 **DR. RICHARD COUPE:** This is Richard
17 Coupe. I'll reserve the right to come back tomorrow
18 morning after I've thought about it.
19 But are you familiar with what Patagalan
20 did with the reservoirs and what Gould and Patagalan
21 did? That would be some low hanging fruit because they
22 developed a regression equation based on a number of
23 variables in the 90's. You should be able to pick that
24 up and move right with it.
25 **DR. NELSON THURMAN:** I'm familiar with

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1 some of the work. I have to go back to --
2 **DR. RICHARD COUPE:** Yeah, that was a
3 while ago.
4 **DR. KENNETH PORTIER:** I think we're
5 reaching the witching hour here, ten after five. What
6 I'm going to do is I'm not going to end this question.
7 I'm going to allow a couple of these thought to
8 percolate over the evening and we'll revisit just
9 briefly in the morning just in case you --
10 A new question came up or whether the
11 trio on the end over here comes up with some new areas.
12 I think at this point, we're going to call it quits for
13 the day and we're starting again tomorrow morning at
14 8:30 with finalizing Question 4 and Questions 5 and 6.
15 Thank you very much.
16 **(WHEREUPON,** the meeting was recessed at 5:07 p.m.)
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0

0.09 117:10 121:24

0.77 40:1

0.79 39:22

0.87 121:24

1

1 13:7 59:24

1% 13:8 62:6 62:7

1.0 278:14

1.1 57:19 57:19

1.2 57:20 58:4 58:6 65:1 65:4

1.2s 180:3

1.3 227:22

1.56 183:4

1.6 232:16

1:15 140:2

10 9:11 20:1 87:1 180:8

10% 216:22

100 60:13 87:25 92:12 95:12 101:24 102:7 104:10 137:11 138:16 177:14 278:14

100% 26:21 29:13

100%--I 29:13

100mg 90:6 90:10

100mg/kg/day 117:8

104 119:22

105 27:1

11 91:2

112 243:19

12 157:2 163:9 163:12

12/12 6:19 6:24 9:13 92:10 95:22

120 26:16

1200 31:10

126 26:20

13 90:10 90:11 90:20 92:15

14 9:11 190:12 255:4 255:8

14/10 6:25 7:1 88:1 95:21

1400 31:10

1410 6:12 6:12

14-10 8:24

145.5 164:20

15 20:10 90:11 90:11 184:18 215:9

150 229:6

1500 175:13

150mg/kg 22:13

15-minute 209:5

15th 34:21

16 2:3

160 124:15

1600 176:11 182:20

16-day 257:8 257:23

17 90:11 90:11

18 61:25

1800 26:22 32:7 175:5 175:7 176:9 182:18 183:7 183:17 183:19

19 16:12 54:6 54:10 69:16 74:12 90:11 90:11 90:20 92:15 109:8 153:18

1987 152:7 154:14

2

2 24:2 24:3

2% 19:25 110:3

2.0 87:5

2.1 87:7 87:8 117:2 117:6 140:15 140:25 149:12 149:21

2.2 117:1 117:4 137:8 140:11 140:15 140:25

2.3 140:12

20 59:24 86:25 107:6 107:7 179:8 180:8 184:16 196:4 210:25

20% 7:25 15:11 222:7 271:5 274:22

20/80 9:18

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200 31:7

2000 27:18 32:11 167:16 176:11 182:20

2002 166:1

2003 34:2 166:1 277:20

2004 70:25 87:11 87:23 117:6 166:2

2005 87:11 89:19 90:4 117:6 270:22 270:23

2006 71:1 261:4

2007 21:19 117:9 171:2 244:17 268:8

2008 153:15

2010 2:3 38:7 67:17 87:11 92:6 117:7 243:8 254:17 263:16 268:8

2011 34:8 35:6 35:17 221:23 228:24 281:6

20-planned 203:12

20's 86:12

21 106:9

215.7 164:20

22 88:25 90:20

24 154:17 154:19 156:12 165:2

24-hour 8:17

25 30:13 90:20 183:22 192:15 193:2

25% 211:4

28th 10:11

29 54:6 55:3

3

3 57:1 63:2 182:10

3.0 58:8

3.1 151:23 151:24 152:5 157:21 157:23 195:8

3.1.c 173:9

3.12 183:8

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3.2.b 209:18

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3.4 181:25

3.7.3.2 231:18

3.b 209:20

3:20 209:5 209:8 209:12

30 153:19 191:19 193:25

30% 211:4 220:8 222:7 271:5

30-40 98:5

31 39:22

32 76:23

324 55:2

33 89:5

350 98:3 98:4

354 40:20

36 76:23

362 42:25

37 61:25

38 54:8

4

4 90:20 280:14 285:14

4.0 65:7

4.1 209:13

4.2 209:14 240:12

4.3 280:17

4.5 182:1

4.b 254:6

40 8:19 260:23

4-0 127:16

40% 211:4 222:7 271:5

40-50 106:10

43 8:21

44 8:21

46 55:18 90:21

47 90:21

5

5 60:14 183:22 192:14 193:2 193:14 193:25 285:14

5% 59:22 60:1

5.3 196:14

5.5 152:13

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156:9 156:15 157:11

5.6 159:25

5.8 173:11 173:22 174:9

5:00 7:18 279:13

5:07 285:16

5:10 209:12

5:15 209:12

50 8:16 94:6 94:21 94:23 95:12 105:22 137:12 239:1 260:23 273:7

50% 164:20 214:13 220:8

502 97:20

50mg/kg 90:9

525 164:5

58 64:9

6

6 27:2 182:1 285:14

6% 19:25

60 105:22 127:18 260:23

67 90:23

68 164:5

68-hour 179:25

7

7.2 231:15 283:11

7.7 243:18

71 174:9

75 30:14

77 26:19

8

8 18:4 30:14 190:11

8.72 121:24

8:30 285:14

80 19:24

80% 15:11 211:2 219:25 249:11

80:20 17:20

84 27:1

85% 27:1 196:4

87 20:12

87% 20:14

9

9:00 228:20

9:15 228:20

90 259:18

90% 249:11

90's 284:23

94 257:4

95% 60:1 179:21 224:23

97% 39:8

9th 15:21

A

A.10 117:14

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abandon 113:21

abdominal 62:20

ability 37:14 40:12 42:18 49:22

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absorb 55:25

absorbed 12:25 75:23 123:7

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12:18 13:18 14:3 23:16 23:18 23:23 23:24 155:17 156:7

absurd 80:19

Academia 101:11

academic 101:15 170:21

accent 162:7 170:5

accept 179:15

accepted 142:10

access 5:9 125:20 125:21

accomplish 19:6

according 182:16 205:25 214:1

account 28:8 76:9 79:2 143:16 198:18 230:8

accounted 18:20

accounting 46:25 47:2 63:19 197:20

accounts 105:15

accumulation 134:14 163:15 163:18

accuracy 110:20 111:17 114:7

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achieve 8:15 8:16 68:16 180:12 180:13

achieved 28:21 33:14 157:8 161:12 173:23 173:24

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