

FIFRA SCIENTIFIC ADVISORY PANEL (SAP)

OPEN MEETING

THE POTENTIAL FOR ATRAZINE TO AFFECT  
AMPHIBIAN GONADAL DEVELOPMENT

U.S. ENVIRONMENTAL PROTECTION AGENCY  
CONFERENCE CENTER- LOBBY LEVEL

One Potomac Yard (South Building)  
2777 S. Crystal Drive  
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October 11, 2007

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1 U.S. ENVIRONMENTAL PROTECTION AGENCY  
 2 FIFRA SCIENTIFIC ADVISORY PANEL  
 3 OPEN MEETING  
 4 OCTOBER 11, 2007  
 5 MR. BAILEY: Welcome to the third day of  
 6 the FIFRA SAP on the Potential Affects of Atrazine on  
 7 Amphibian Development.  
 8 I'll be very brief, keeping it in trend  
 9 with yesterday afternoon's schedule.  
 10 My name is Joe Bailey, I'm the DFO for  
 11 the meeting. And for the panel you've received a few  
 12 more handouts. First was a replacement slide for  
 13 Doctor Van Der Kraak's presentation, page 15.  
 14 A couple of other public comments have  
 15 come in, one from the New York State Attorney General's  
 16 Office, one for Partners in Amphibian and Reptile  
 17 Conservation and the, let's see, the final thing was  
 18 Jennifer Sass' reference list, it's a complete  
 19 reference list of references that she had in her  
 20 opening remarks.  
 21 All the materials that have been  
 22 provided so far should be in the docket today so if  
 23 anybody has any interest in seeing those they should be  
 24 there.  
 25 Again, just as a reminder the meeting is

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1 the permanent panel.  
 2 DR. HANDWERGER: Stuart Handwerker,  
 3 Departments of Pediatrics and Cell and Cancer Biology,  
 4 University of Cincinnati College of Medicine. I'm a  
 5 member of the permanent panel.  
 6 DR. ISOM: Gary Isom from Purdue  
 7 University, Professor of Toxicology and also a member  
 8 of the permanent panel.  
 9 DR. GREEN: Sherril Green, Stanford  
 10 University, Department of Comparative Medicine and I'm  
 11 an ad hoc member of the SAP.  
 12 MR. PAULI: Bruce Pauli, Environment  
 13 Canada, Ottawa, Ontario.  
 14 DR. SCHLENK: David Skelley, Professor of  
 15 Ecology, Yale University.  
 16 DR. DENVER: Bob Denver, University of  
 17 Michigan, Professor of Molecular and Cellular  
 18 Developmental Biology.  
 19 DR. FURLOW: David Furlow, Section of  
 20 Neurobiology, Physiology and Behavior, University of  
 21 California, Davis.  
 22 DR. YEATER: Kathy Yeater, Statistician  
 23 with the U.S. Department of Agriculture, Agricultural  
 24 Research Service.  
 25 DR. BAILEY: Ted Bailey, Iowa State

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1 recorded so please state your name before you make any  
 2 comments.  
 3 And I think that is pretty much it for  
 4 me this morning. I'll turn it over to our Chair,  
 5 Doctor Heeringa.  
 6 DR. HEERINGA: Good morning everyone and  
 7 welcome back to the third day in our meeting on the  
 8 topic of the Potential for Atrazine to Affect Amphibian  
 9 Gonadal Development.  
 10 I'm Steve Heeringa of the University of  
 11 Michigan, Chair for this session.  
 12 I want to ask the other members of the  
 13 science advisory panel here this morning to introduce  
 14 themselves and give their affiliation as well.  
 15 DR. PORTIER: Ken Portier, Director of  
 16 Statistics of the American Cancer Society, National  
 17 Home Office, Atlanta.  
 18 DR. CHAMBERS: Jan Chambers, College of  
 19 Veterinary Medicine, Mississippi State University and  
 20 I'm a member of the permanent panel.  
 21 DR. SCHLENK: Dan Schlend, Department of  
 22 Environmental Sciences, University of California,  
 23 Riverside and also a member of the permanent panel.  
 24 DR. BUCHER: John Bucher, Associate  
 25 Director, National Toxicology Program. I'm a member of

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1 University, Department of Statistics.  
 2 DR. DELORME: Peter Delorme, Pest  
 3 Management Regulatory Agency of Health Canada.  
 4 DR. LEBLANC: Gerry LeBlanc, Department  
 5 of Environmental and Molecular Toxicology, North  
 6 Caroline State University.  
 7 DR. MILLER: Debra Miller, the University  
 8 of George, I'm a Veterinary Pathologist.  
 9 DR. PATINO: Reynaldo Patino, U.S.  
 10 Geological Survey Texas Cooperative Fish & Wildlife  
 11 Research Unit.  
 12 DR. HEERINGA: Thank you very much  
 13 members of the panel.  
 14 Good morning, Doctor Steeger. I would  
 15 like you to introduce your team at this point. Will  
 16 you do that?  
 17 DR. STEEGER: Good morning and once again  
 18 thank you for the opportunity to present to the FIFRA  
 19 SAP panel.  
 20 To my right is Mary Frankenberry. She's  
 21 a statistician with the Environmental Fate and Effects  
 22 Division.  
 23 To my left is Doctor Sigmund Degitz, a  
 24 research biologist with the Mid-Continent Ecology  
 25 Division of the Office of Research and Development.



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1 Seated next to him is R.D. Williams who  
 2 is the Acting Director of the Environmental Fate and  
 3 Effects Division.  
 4 Followed by Doctor Stephanie Irene, a  
 5 senior advisor in the Environmental Fate and Effect  
 6 Division.  
 7 And Ms. Eda Peace who is a senior  
 8 biologist in the Environmental Fate and Effects  
 9 Division.  
 10 DR. HEERINGA: Thank you very much,  
 11 Doctor Steeger.  
 12 At this point in the agenda for this  
 13 week's meeting, we suspended our coverage of the charge  
 14 questions yesterday afternoon a little early because we  
 15 had made very good progress and I felt we were  
 16 beginning to move ahead of the point where I think a  
 17 lot of the panel members had anticipated the agenda  
 18 would be and felt it would be appropriate to return  
 19 this morning and pick up again.  
 20 And at this point, Doctor Steeger, I  
 21 don't know if you have any additional comments to  
 22 introduce things that came to you overnight that you'd  
 23 like to say to the panel or should we just proceed with  
 24 the charge questions?  
 25 DR. STEEGER: Actually a couple of things

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1 came to me overnight. Only a couple of them though  
 2 were relative to this SAP.  
 3 With respect to question number 1,  
 4 yesterday's discussion sounded as though the panel  
 5 concurred with the Agency's evaluation criteria for  
 6 open literature.  
 7 These same criteria were applied to the  
 8 registrant's submitted studies as well.  
 9 The panel also seemed to agree that the  
 10 open literature consisting of both laboratory and field  
 11 studies did not across multiple evaluation criteria,  
 12 meet the standards of acceptability.  
 13 It was unclear after yesterday's  
 14 discussion whether the panel believes that the open  
 15 literature continues to have some utility in refuting  
 16 or confirming my hypothesis that Atrazine exposure  
 17 causes amphibian gonadal developmental affects.  
 18 Yesterday Doctor Jim Carr from Texas  
 19 Tech University and Doctor Jim Wolfe from the  
 20 Experimental Jeff Wolfe, I'm sorry, from the  
 21 Experimental Pathology Laboratories provided a brief  
 22 overview of their re-analysis of tissues which were  
 23 initially reported as inter-sex tissues in the open  
 24 literature.  
 25 This re-analysis concluded that none of

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1 the animals originally reported as inter-sex were  
 2 indeed inter-sex. Therefore to our knowledge the only  
 3 literature reviewed to date claiming to result in  
 4 inter-sex is that of Doctor Hayes.  
 5 If the panel believes that open  
 6 literature has some utility relative to the DCI  
 7 studies, do they believe that multiple lines of  
 8 evidence are consistent with the outcome of the DCI  
 9 studies indicating that Atrazine is not affecting  
 10 amphibian gonadal development?  
 11 With respect to question number 8, it's  
 12 unclear whether the panel's final recommendation is for  
 13 the Agency to require a review of sub-samples of slides  
 14 from the DCI studies by a pathology review board or  
 15 whether the panel is simply noting that such a review  
 16 board would be of an added benefit.  
 17 If the latter, is the panel concerned  
 18 regarding the identification of the apical end points  
 19 or mixed sexed or are they concerned regarding the  
 20 secondary measurement end points such as aplasia and  
 21 mineralization?  
 22 If it is the latter, has the panel  
 23 determined the biological relevance of these secondary  
 24 measurement end points?  
 25 How much would these secondary

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1 measurement end points have to change before the  
 2 conclusions regarding the apical end points would be  
 3 affected?  
 4 And finally, with respect to the  
 5 discussions regarding Atrazine's degradate exposure  
 6 potential in the flow through study, data from the  
 7 Health Effects Division indicates that in vivo  
 8 metabolism results in the formation of diammino  
 9 chloroatrazine, DACT, deisopropylatrazine, DIA and  
 10 deethylatrazine, DES, those are the principal  
 11 degradatives of Atrazine that are also found in the  
 12 field.  
 13 So if that is indeed the case, then  
 14 exposure in a flow through system, those animals would  
 15 be expected to be producing those metabolites in vivo.  
 16 And the question would be, what  
 17 additional benefit would be gleaned from having a  
 18 static renewal study to examine those, rather than  
 19 having formal flow through studies that would indeed  
 20 test whether each independent degradate was causing an  
 21 affect?  
 22 DR. HEERINGA: Doctor Steeger, with your  
 23 permission I think that what I would like to do is if a  
 24 member of your staff could maybe put those up so that  
 25 we could get those on the screen and we will return to



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1 those during the questions this morning.  
 2 DR. STEEGER: Okay.  
 3 DR. HEERINGA: I'd like to do it  
 4 systematically rather than sort of right off the bat  
 5 here.  
 6 DR. STEEGER: That's fine, that's just  
 7 DR. HEERINGA: But definitely we will  
 8 systematically review each of those and I think  
 9 certainly in some of the points I recognize the issues  
 10 that you're raising here.  
 11 So what I'd prefer to do is maybe return  
 12 to our question 9, if we could have those put up so we  
 13 could see them and consider them systematically,  
 14 because I think it's taking us back to a few issues,  
 15 but those are excellent points of clarification and I  
 16 think getting us a good discussion of each of those  
 17 points would also clarify our report on those matters  
 18 too.  
 19 What I would like to do at this point  
 20 Doctor Irene, I'd like to return to charge question 9,  
 21 and would you read 9a into the record again please?  
 22 DR. IRENE: That's great. After an  
 23 evaluation of the laboratory based studies submitted in  
 24 response to the DCI, the Agency has concluded that  
 25 these sutides do not provide sufficient evidence to

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1 support the hypothesis that Atrazine causes adverse  
 2 gonadal developmental affects in amphibians.  
 3 A, in light of the responses to  
 4 questions 3 to 8, please comment on whether the results  
 5 from the study in response to the DCI are sufficiently  
 6 robust to address the hypothesis that Atrazine exposure  
 7 causes gonadal abnormalities in Xenopus laevis. If the  
 8 SAP concludes that these results are not sufficiently  
 9 robust, what recommendations can the SAP provide to  
 10 efficiently and reasonable address remaining  
 11 uncertainties?  
 12 For example, if the SAP does not believe  
 13 the DCI study is sufficiently robust to assess the  
 14 hypothesis, does the SAP believe either of the two  
 15 experiments or a specific component of the two  
 16 experiments should be re-analyzed or repeated?  
 17 Please provide the rationale for  
 18 recommending any additional analyses and/or  
 19 experiments.  
 20 DR. HEERINGA: I'd like to return to  
 21 Doctor Delorme again to review his comments oR add  
 22 additional comments.  
 23 DR. DELORME: I think we're a little bit  
 24 more on the ball this morning having been able to put  
 25 our thoughts in a little bit better order.

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1 I'm just going to go over some of what  
 2 was talked about yesterday and then go back to the  
 3 corespondents to see if they have anything to add.  
 4 Just start it off by saying that the  
 5 panel noted the question was somewhat confusing in that  
 6 it presents two hypotheses. In the original question  
 7 is refers to adverse gonadal development affects in  
 8 amphibians. Well within sub-bullet A question, it  
 9 refers to the DCI studies and uses the words, causing  
 10 gonadal, the hypothesis refers to, causing gonadal  
 11 abnormalities in Xenopus laevis.  
 12 In order to provide a clear response the  
 13 panel has restated the hypothesis being considered in  
 14 this question to better reflect the result of the DCI  
 15 study as follows: Exposure to the parent compound  
 16 Atrazine causes adverse gonadal development in Xenopus  
 17 laevis within the range of concentrations tested, i.e.,  
 18 0.01 to 100 micrograms per liter.  
 19 Responses to the more general hypothesis  
 20 concerning adverse gonadal development in amphibians  
 21 are addressed in questions 12 and 13.  
 22 In general the panel believes results are  
 23 sufficiently robust to test or address the restated  
 24 hypothesis based on the discussions and considerations  
 25 identified in responses to questions 3 to 8.

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1 In brief the panel concluded that the study  
 2 design was appropriate for testing the parent, testing  
 3 parent Atrazine and that the study design addressed  
 4 many of the concerns regarding water quality, loading  
 5 rates, et cetera that were identified by the '03 panel.  
 6 Panel members agreed that the use of a flow  
 7 through exposure system and lack of measurement that  
 8 did not allow for testing of the hypothesis related to  
 9 effects of transformation products on adverse gonadal  
 10 development. And we're probably going to talk to one  
 11 of the points Doctor Steeger just brought up.  
 12 Parent Atrazine exposure concentration  
 13 profiles are well characterized and sufficient for  
 14 documenting the potential affect of Atrazine over a  
 15 broad range of exposure concentrations.  
 16 Actual concentrations were generally stable,  
 17 although the panel had concerns about low concentration  
 18 values at the two lower doses for the IGB study  
 19 compared to the target exposure concentrations. These  
 20 concerns are balanced by the robustness of the measured  
 21 concentration data which allows analysis.  
 22 It was suggested that results could be stated  
 23 in terms of measured rather than nominal  
 24 concentrations.  
 25 The panel generally agreed that primary



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1 apical end points were well characterized, both  
 2 technically and statistically for negative control,  
 3 positive control and Atrazine exposed groups.  
 4 There remains uncertainty with respect to the  
 5 biological ecological relevance of secondary end  
 6 points.  
 7 With respect to the histological analyses the  
 8 panel recommended a verification of results by  
 9 independent pathologists.  
 10 In addition, some other comments or some  
 11 other points. The strength of the concentration  
 12 response relationship, studies provided no evidence,  
 13 and these are more related to the results in general,  
 14 studies provided no evidence for a concentration  
 15 response relationship between Atrazine and primary end  
 16 points such as sex ratios and inter-sex testes. One  
 17 study provided significant evidence for concentration  
 18 response relationships with several secondary end  
 19 points, and they're listed here.  
 20 Strength of cause/effect relationship, the  
 21 effects observed with Atrazine were modest despite  
 22 robust responses in the positive control. Furthermore  
 23 the noted concentration response relationships were not  
 24 reproducible between two studies performed in the same  
 25 study protocol.

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1 natural life history of Xenopus laevis, pointing out  
 2 that flow through, the flow through paradigm is likely  
 3 father away from what a Xenopus tadpole experienced in  
 4 the wild than is static renewal.  
 5 Another concern expressed by some panel  
 6 members was based on information presented by Syngenta  
 7 related to the specific strain used and the apparent  
 8 differences in the presence of testicular ovarian  
 9 follicles in different strains of Xenopus laevis. It  
 10 was not clear if the differences in the presence of  
 11 TOF's are the result of differential sensitivity or  
 12 differential presence of other factors which could  
 13 cause them.  
 14 The Xenopus laevis used in the DCI studies  
 15 were derived from strains with no reported TOF's  
 16 apparently. While the DCI studies included positive  
 17 control the possibility of differential sensitivity  
 18 introduces added uncertainty to the interpretation of  
 19 the results.  
 20 And yesterday, Doctor Steeger, you mentioned  
 21 that you wanted, you would like some input on this and  
 22 you noted that there was a positive control. I'm not  
 23 sure whether or not sex reversal and TOF are the same  
 24 thing. So whether or not the positive control is  
 25 relevant for this question or not. Perhaps other

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1 Mechanistic plausibility, no mechanistic  
 2 plausibility. The predominant hypothesis for the  
 3 purported action of Atrazine is the induction of  
 4 aromatase but while the aromatase gene is inducible in  
 5 some cell lines by exposure to high concentrations, we  
 6 are aware of no precedence for the induction of  
 7 aromatase by Atrazine, in Atrazine exposed frogs.  
 8 Failed attempts to induce aromatase in frogs  
 9 by Atrazine have been reported.  
 10 The ecological relevance of effect, end  
 11 points for which there exists weak evidence for an  
 12 effect of Atrazine are not recognized as relevant to  
 13 reproductive fitness.  
 14 Conversely, end points that are more likely  
 15 to impact reproductive fitness, sex ratios, intercepts  
 16 were unaffected by 100 micrograms per liter of  
 17 Atrazine.  
 18 Now, despite the robustness of the DCI  
 19 studies for addressing the hypothesis, several other  
 20 concerns have been identified by panel members.  
 21 Some of the members were concerned by the  
 22 total rejection of the hypothesis based on negative  
 23 data, i.e., no affect and only two studies effectively.  
 24 In part their concern was based on the uncertainty  
 25 caused by the relevance of the exposure system to the

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1 members of the panel can comment on that.  
 2 But I would suggest that perhaps a comparison  
 3 of the responses to a positive control by the different  
 4 strains could help reduce the uncertainty.  
 5 As noted earlier the panel concluded the  
 6 current study did not address potential affects caused  
 7 by exposure to transformation products. The panel  
 8 recommended that the Agency could use existing  
 9 monitoring data which includes information on  
 10 environmental concentrations of transformation products  
 11 to determine the extent to which they might want to  
 12 consider transformation products in the future.  
 13 In other words, look at the monitoring data.  
 14 If the exposure in the environment is reasonably high,  
 15 that you might want to pursue that or not. That's a  
 16 call that EPA would have to make.  
 17 In addition a literature search could be  
 18 conducted to determine if information exists on the  
 19 potential for transformation products that interact  
 20 with the endocrine system, for example, receptor  
 21 binding assays and such.  
 22 And I'll go back to my fellow inputs to see  
 23 if they have anything to add.  
 24 DR. HEERINGA: Let's go back to Doctor  
 25 Denver and see if he has anything to add?



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1 DR. DENVER: No, I don't have anything to  
 2 add. I think you've summarized our comments.  
 3 DR. HEERINGA: Doctor LeBlanc?  
 4 DR. LEBLANC: I have nothing to add.  
 5 DR. HEERINGA: Doctor Furlow?  
 6 DR. FURLOW: I have nothing to add. I  
 7 look forward to a continued discussion about strain  
 8 usage and things like this that I think will continue  
 9 throughout the rest of the questions.  
 10 DR. HEERINGA: Agreed, thank you. Yes,  
 11 Doctor Patino?  
 12 DR. PATINO: Reynaldo Patino. I agree  
 13 with everything generally with what's been said.  
 14 One additional comment I would make and  
 15 this discussion came up I think when we were talking  
 16 about questions 3 and 6, that, you know, the way the  
 17 question is posed seemed very limited in the sense that  
 18 it said in part A, that it talks about gonadal  
 19 abnormalities and somebody suggested that additional  
 20 information to that question should be added to  
 21 response to that question and add, within the range of  
 22 concentrations tested.  
 23 I would add to that too that probably we  
 24 should also say that we had no actual terminated Stage  
 25 66 frogs because on the questions 3 and 6 we talked

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1 about the long terms affects, functional affects that  
 2 are known.  
 3 The question does not address that so I  
 4 just, within the, if you add that parameter to the  
 5 question I would agree that it would clearly show, or  
 6 answer that question.  
 7 DR. HEERINGA: Yes, Doctor Miller please.  
 8 DR. MILLER: Debra Miller. I agree with  
 9 that and I would probably even make it more specific in  
 10 saying *Xenopus laevis* and I know we'll get into this  
 11 later but amphibians are a class and there are many  
 12 species and there are many orders. And this is a great  
 13 lab frog but just like the lab mouse is to mammals you  
 14 don't say in mammals.  
 15 And I just don't think that you can make  
 16 such a broad statement and say that it's the same in  
 17 all amphibians.  
 18 DR. HEERINGA: Doctor Delorme?  
 19 DR. DELORME: Yeah, that was why we  
 20 wanted to restate the hypothesis, it was ambiguous.  
 21 DR. HEERINGA: Doctor Delorme again.  
 22 DR. DELORME: I was just wondering if  
 23 anybody could help us out on Doctor Steeger yesterday  
 24 asked the question, with respect to the strains what  
 25 our concern was given that there was a positive

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1 control?  
 2 Now the positive control was E2  
 3 estradiol and that causes sex reversal. The  
 4 differences in the strains was with respect to the  
 5 presence of testicular ovarian follicles. And I was  
 6 just wondering if somebody could help us out on what,  
 7 if that's a valid concern or not?  
 8 DR. HEERINGA: Members of the panel?  
 9 DR. PATINO: Could you restate the  
 10 question, I didn't this is Reynaldo.  
 11 DR. DELORME: In the presentation by  
 12 Syngenta on Tuesday they indicated that there were  
 13 differences in certain genetic strains of *Xenopus* with  
 14 respect to the presence of testicular ovarian follicles  
 15 with some populations having them in areas that are  
 16 unexposed to Atrazine and other populations in  
 17 unexposed areas not having them.  
 18 The strain that was used for the test  
 19 was derived from the populations that do not have them  
 20 in their background.  
 21 Is that a concern, should that be a  
 22 concern? And it goes to state, is there a differential  
 23 sensitivity to some factor in the environment and could  
 24 that impact the results of the test?  
 25 If we don't think it does then it's a

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1 nonissue and we can take it out.  
 2 DR. HEERINGA: Doctor Green, or Doctor  
 3 Patino.  
 4 DR. PATINO: Reynaldo Patino. I would  
 5 say my experience with fish and reading of the  
 6 literature and I don't have a specific paper in mind,  
 7 but just general knowledge of both sex reversal and  
 8 presence of testicular oocytes are often the cause of  
 9 feminizing, when animals are exposed to feminizing  
 10 agents. You can see both.  
 11 So I would say, you know, perhaps that  
 12 if you find testicular oocytes or inter-sex or mixed  
 13 sex they generally indicate the same or their symptoms  
 14 are the same phenomena which is feminization.  
 15 DR. HEERINGA: Doctor Green.  
 16 DR. GREEN: There is a textbook called,  
 17 *The Biology of Xenopus* by Tinsley and Kobel which is  
 18 published I think, the last edition came out in 1996  
 19 and in that textbook they do describe multiple sub-  
 20 strains of *Xenopus laevis* that are geographically  
 21 distributed around the world in different places.  
 22 And I don't think there is any data  
 23 regarding those specific sub-strains about sensitivity  
 24 differences to stressors. However there are very  
 25 subtle differences on the phenotype, some of which are



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1 secondary sex characteristics which I think, given the  
 2 fine nuances by which we are interpreting differences  
 3 in gonadal development and the low incidence and the  
 4 negative results, that could come into play if you are  
 5 using one of these different sub-strains that has very  
 6 subtle difference like a different snout to vent  
 7 length, a different from metamorphosis to sexual  
 8 maturity.  
 9 And some of those sub-strains are  
 10 characterized and in the last 10 to 15 years I believe  
 11 there have been even more reported and described.  
 12 So that would be something to consider  
 13 in terms of using a different sub-strain of Xenopus  
 14 laevis in studies such as this.  
 15 DR. HEERINGA: Any additional input on  
 16 that particular. I appreciate those two contributions  
 17 yes, Doctor Furlow.  
 18 DR. FURLOW: I just guess I can add to  
 19 this, just one point. We all consider Tamoxifen to be  
 20 an antagonist for the exteroceptor, everybody  
 21 believes that in terms of subculture experiments,  
 22 binding to the receptor, et cetera and yet it has  
 23 different affects on different tissues. It can be an  
 24 agonist in bones and it can be an antagonist on the  
 25 uterus.

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1 At this point I'll ask Doctor Irene to read the second  
 2 part of question 9, or Doctor Steeger, sorry.  
 3 DR. STEEGER: Just as a point of  
 4 clarification, each one of our risk assessments that  
 5 the Agency produces makes a, has a boilerplate language  
 6 in it to indicate to the public that we rely on  
 7 surrogate species in order to conduct risk assessments.  
 8 The, traditionally we don't even look at  
 9 amphibians, we use fish to estimate the risks to  
 10 aquatic phase amphibians. We use birds to estimate the  
 11 risk to reptiles and terrestrial phase amphibians.  
 12 We acknowledge that there are thousands  
 13 and thousands of species out there. But the reality is  
 14 that we get two birds, two bird species to represent  
 15 risks to all bird species, all reptiles, all  
 16 terrestrial phase amphibians. We get two fish to  
 17 represent the risks to aquatic phase amphibians and  
 18 most of the vertebrates that are in water.  
 19 That's the reality that we face. We  
 20 don't really have the luxury of testing every one  
 21 because no pesticide could be rather strict. So the  
 22 reality that we face is we were lucky to get amphibian  
 23 data at all. And yes, there are uncertainties, there  
 24 are incredible uncertainties in terms of whether the  
 25 strain of the animal that's used is more or less

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1 In addition, if you compare rats and  
 2 mice, if you give Tamoxifen to a rat it acts as a pure  
 3 antagonist in the uterus. You give Tamoxifen to a  
 4 mouse and it's an agonist. It has a completely  
 5 opposite affect.  
 6 Xenopus is a very ancient species. You  
 7 know, you could say, okay, come on, you know, Xenopus  
 8 from different areas of South Africa can be as  
 9 different as rats and mice. But I don't know that we  
 10 know that in terms of their ability to handle these  
 11 different compounds.  
 12 The use of the positive control also  
 13 implies to some degree, even though Doctor Steeger was  
 14 careful to mention this previously, but there is some  
 15 underlying implication that the mechanism between  
 16 Atrazine versus the positive control would be common  
 17 and that's given the aromatase, the lack of aromatase  
 18 data I think that's pretty far from clear.  
 19 It's entirely possible that differences  
 20 in strain may result in differences in metabolism  
 21 binding to receptors, et cetera. It's unclear what  
 22 those strain differences might be. And so I think  
 23 there is uncertainty underlying these results because  
 24 of the strains.  
 25 DR. HEERINGA: Thank you, Doctor Furlow.

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1 sensitive than what's out there.  
 2 But the data that we have, we're just  
 3 making the best with what we can work with, suggesting  
 4 this was data that was presented yesterday representing  
 5 the work of Doctor Hayes shows that Xenopus laevis is a  
 6 sensitive indicator to estrogenic compounds. It's one  
 7 of the most sensitive.  
 8 Does the strain difference play a role  
 9 in our assessment? It's a consideration but we have a  
 10 positive control that suggests that the test system was  
 11 sensitive to an estrogenic compound and that it could  
 12 demonstrate that a chemical could impact amphibian  
 13 gonadal development.  
 14 In that test system, did Atrazine show  
 15 an affect or didn't it? That is the question that as a  
 16 risk assessor I have to be evaluating.  
 17 In the context of how we do regulatory  
 18 science here at EPA and the limitations that we have  
 19 that we do not have the luxury of testing every species  
 20 out there and addressing every uncertainty, we can  
 21 caveat those uncertainties, but the likelihood of our  
 22 getting data is becoming increasingly difficult.  
 23 I'll just let it go at that.  
 24 DR. HEERINGA: Thank you, Doctor Steeger.  
 25 At this point I would like to move on to question 9b.



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1 DR. IRENE: Stephanie Irene, 9b. Please  
 2 comment and provide recommendations on alternate  
 3 statistical analyses if any to evaluate the data  
 4 derived from the study. If alternative approaches are  
 5 suggested, please comment to the extent possible on the  
 6 rationale for these approaches and how they represent  
 7 improvements in the existing statistical  
 8 interpretations.

9 DR. HEERINGA: Doctor Bailey is our lead  
 10 discussant on this subpart.

11 DR. BAILEY: We recommend that a combined  
 12 analysis of the data from the two studies be completed.

13 The usual procedure for analyses when an  
 14 experiment is repeated two or more times, the study  
 15 usually involved two phases.

16 First, analyze and interpret each study  
 17 separately. This was done for the most part very well  
 18 in this study.

19 Secondly, carry out an analysis of the  
 20 combined data from both studies. Important advantages  
 21 in the combined analysis include stronger, more  
 22 powerful tests of hypotheses can be made than in each  
 23 experiment.

24 For example the dose relationship of  
 25 Atrazine.

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1 Secondly, more importantly the combined  
 2 analysis allows us to ask the questions like, do  
 3 differences between controls and levels of Atrazine  
 4 differ in the two studies? Does the dose response  
 5 relationship differ in the two studies? Does the  
 6 unexplained variability, the experimental error in the  
 7 two studies differ? If so, why?

8 Answers to these questions provide  
 9 information on the repeatability of affects of interest  
 10 in the study.

11 Second item for comment, we recommend  
 12 the use of blocking be considered in the design of lab  
 13 studies like this one. There are many reasons to  
 14 introduce blocking in the design of experiments,  
 15 including the control of experimental error.

16 It is surprising to us that none of the  
 17 lab studies reviewed in preparation for this panel took  
 18 advantage of the benefits of blocking.

19 We strongly encourage more and better  
 20 interpretation of statistical tests. To state that a  
 21 test is statistically significant or that it is not  
 22 significant is seldom sufficient. One wants to learn  
 23 what the magnitude of the differences between the  
 24 treatments are or we want to learn the magnitude and  
 25 the strength of the dose response relationship.

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1 Making a test of hypothesis is not the  
 2 same as interpreting the result of a test.

3 The use of competence intervals are  
 4 especially recommended for presenting and interpreting  
 5 results from the studies.

6 We recommend that in designing  
 7 experiments the essential choices of experimental unit,  
 8 treatment design, experimental design and the method of  
 9 randomization of treatments to experimental units be  
 10 clearly specified.

11 Application of these principles in  
 12 design not only leads to efficient experiments, they  
 13 also ensure unbiased estimates of treatment effects and  
 14 estimates of experimental error.

15 The information with respect to the  
 16 design of the experiment should be shared with all  
 17 relevant individuals.

18 DR. HEERINGA: Thank you, Doctor Bailey.  
 19 Doctor Yeater.

20 DR. YEATER: Kathy Yeater. In addition  
 21 to those comments with which I concur, I would also  
 22 like to add in that I really feel that there is a high  
 23 quality of data collected in these two studies.

24 And there was a previous mention during  
 25 this SAP meeting was that the idea of perhaps

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1 developing a standard protocol from this, and so that  
 2 leads me to suggest and recommend that more  
 3 sophisticated statistical methods be considered.

4 And I sometimes think this is a failure  
 5 of statistical education in the applied sense is that  
 6 we don't get beyond a standard ANOVA t-test. And I  
 7 want to suggest that well, let me get into this here.

8 Specifically the data analysis presented  
 9 for the DCI study reveals no information on any  
 10 associations that may or may not be present between the  
 11 measured variables.

12 Also there should be more consideration  
 13 given towards the male/female ratio in the tank. From  
 14 the data reported in the DCI study it is observed the  
 15 differences between male and female means are  
 16 significant in several of the end points. However the  
 17 overall tank means are not weighted or standardized for  
 18 this differential which could be influenced by having a  
 19 skewed male/female ratio.

20 These two methods can be approached by  
 21 transposing the data set into a multi varied data sets  
 22 where each larva and its corresponding measurements are  
 23 the units of analysis. This is not such a stretch  
 24 considering we have already accepted that the  
 25 individual tanks are the unit of analysis.



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1 By using each larva as an observation we  
 2 can incorporate all measurements to that sample from  
 3 which it was measured as well as incorporating the  
 4 observed sex of each sample at metamorphosis.  
 5 This would enable a multi varied  
 6 approach such as an ANOVA which is a multi varied  
 7 analysis of variance of even a canonical analysis and  
 8 having some better understanding of possible  
 9 associations and correlations between the measurements  
 10 and observations within and across treatment affects.  
 11 It would also enable the easy inclusion of the  
 12 male/female as an appropriate measure variable.  
 13 DR. HEERINGA: Thank you very much,  
 14 Doctor Yeater. Doctor Portier.  
 15 DR. PORTIER: I don't have much to add.  
 16 We talked about this among ourselves and since I'm  
 17 third I didn't have to add a lot.  
 18 The one thing I will point out is that  
 19 even with a more sophisticated analysis that we're  
 20 recommending, a multi variate look at the data, and  
 21 there's a lot of benefits to doing the multi variate  
 22 because I feel a lot of the responses that were  
 23 observed as significant are probably significant  
 24 together, so there's some underlying mechanisms that  
 25 are causing those events to be significant.

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1 And we haven't really looked at those.  
 2 We've talked about them.  
 3 But I don't think it's going to change  
 4 and increase the number of significant findings that we  
 5 have in the data. So we're not really criticizing the  
 6 analysis, we don't think you missed anything. The only  
 7 opportunity you've missed with a high quality data set  
 8 like this is just doing a better statistical analysis  
 9 that uses more powerful tools to look at it.  
 10 But I think my colleagues would agree, I  
 11 don't think you're going to find some things, magically  
 12 find some additional affects here that were  
 13 significant. And in fact my own personal feeling is  
 14 that some of these are going to go away, some of the  
 15 things that are not consistent are going to be lost in  
 16 the even though we're increasing the power of the  
 17 test by combining the two results, some of these  
 18 findings are just not going to hold up.  
 19 DR. HEERINGA: Thank you to each of you  
 20 for those contributions. Other members of the panel,  
 21 do you want to contribute on the statistical design and  
 22 analysis, they go hand in hand obviously?  
 23 Yes, Director Williams.  
 24 MS. WILLIAMS: R.D. Williams, thank you.  
 25 I just need to try and get something clarified in my

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1 mind if I may.  
 2 One of the things that was mentioned is  
 3 that by combining the analyses it gives you a better  
 4 indication of whether the results are repeatable. Is  
 5 that did I hear that correctly?  
 6 DR. BAILEY: Ted Bailey. It does because  
 7 with the combined analysis you are able to see if the  
 8 same result is obtained in two different labs. If so,  
 9 that reinforces the results.  
 10 And also you're able to look at  
 11 interactions if you combine both, interactions of the  
 12 factors that are in the study that you cannot do  
 13 without a combined analysis.  
 14 MS. WILLIAMS: And I do not, I'm not a  
 15 statistician either, or on t.v. so I guess I'm a little  
 16 confused, because I know one of the things that we  
 17 always look for when we're using data, is whether the  
 18 study has been repeated and the results are repeatable.  
 19 And one of the reasons that this study was done at two  
 20 separate labs was so we could, at the same time have  
 21 the repeated study.  
 22 So I guess I'm confused about why we now  
 23 would combine everything and make it like one study.  
 24 DR. BAILEY: Yeah. During this panel  
 25 what we've seen is a thorough study and interpretation

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1 of each of the studies separately.  
 2 But you can gain some things by doing  
 3 the combined analysis that you cannot do by looking at  
 4 the individual studies separately. And those, that is  
 5 what is to be gained from the it's a very standard  
 6 procedure when studies are repeated in different  
 7 locations or in different labs in many situations.  
 8 It's a very standard thing to do to come  
 9 back and look at be able to make these comparisons  
 10 when you have the data combined.  
 11 DR. PORTIER: This is Ken Portier. I  
 12 think Doctor Bailey had a good example.  
 13 In both studies you talk about a dose  
 14 response and you can see that it's not significant in  
 15 either one, but when you put it together you have more  
 16 power. So one, you have a more powerful test of  
 17 whether there is a dose response. But one of the  
 18 things you could test is whether that dose response was  
 19 the same in both studies.  
 20 Now if you knew it were the same that's  
 21 a more powerful finding, right? You could say, well,  
 22 we've repeated not just the finding of a dose response,  
 23 but we've repeated a finding of the same dose response.  
 24 And that's something you cannot get by  
 25 looking at them separately, right? You have to put



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1 them together.  
 2 We found in one study that there were  
 3 some differences in some of the treatments for one of  
 4 the responses, I forget which one it is, and we didn't  
 5 find that in the other one. When you put them together  
 6 you have more degrees of freedom for residual  
 7 variability, you have a more powerful test.  
 8 Now we can say, you know, when you  
 9 combine the data, are those things that we saw in one  
 10 study, is it still important? If it's important that's  
 11 a study by affect interaction that we can actually test  
 12 and put a P value to and say that we had differences in  
 13 this responses by the studies with this level of  
 14 significance.  
 15 DR. HEERINGA: Yes, Doctor Steeger.  
 16 DR. STEEGER: I have a couple of  
 17 questions. With regard to the idea of combining these  
 18 studies, keep in mind that they were intended to be an  
 19 effort to duplicate or reproduce the study in two labs  
 20 so we could get at the issue, that we wouldn't be  
 21 dealing with a single study but we would actually have  
 22 more than one study.  
 23 In suggesting that they be combined,  
 24 does that compromise in any way the interpretation of  
 25 the studies as being independent and as being intended

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1 discriminate statistical differences would be increased  
 2 by combining them, I will presume it would be  
 3 increased, and then there would be the concern whether  
 4 statistical differences that might appear were driven  
 5 by sample size as opposed to what might have been a  
 6 biologically significant affect.  
 7 The white paper does go into an analysis  
 8 where there was a significant effect, particularly  
 9 related to body weight and body size at IGB in female  
 10 animals, did look at the percent of the affect and did  
 11 discuss whether that is of biological significance.  
 12 In doing so we noted that first of all  
 13 there wasn't a dose response, the affect was skipping  
 14 every other dose. And for weight, the weight did not  
 15 change, the animals were .52 grams in all three  
 16 significant affects. It was a decrease of 7 percent.  
 17 It wasn't, because it wasn't a dose dependent increase  
 18 the weight was constant across all three concentrations  
 19 that were significant and it skipped every other dose.  
 20 It did not appear to be a biologically relevant  
 21 measurement end point.  
 22 It is true that if you were to combine  
 23 the studies that might become, what might have been  
 24 even more subtle affects in the other concentrations  
 25 might have shown a concentration dependence.

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1 to be reproduced?  
 2 DR. BAILEY: Ted Bailey. No.  
 3 DR. STEEGER: Okay.  
 4 DR. BAILEY: The integrity of the studies  
 5 remains. I think it's good to analyze each study  
 6 separately first to be sure we understand what's  
 7 happened in each study. But then we have the  
 8 advantages that have been mentioned that you can do  
 9 other tests about the repeatability of effects and so  
 10 forth, which would be very important.  
 11 You could confirm that you're getting  
 12 similar results in the different labs which would be  
 13 important to know, but you may also find out that the  
 14 effects, the dose response relationship may not be  
 15 exactly, may not be the same in the first lab as the  
 16 second lab. It's entirely possible.  
 17 DR. STEEGER: This is Tom Steeger again.  
 18 I think one of the difficulties that we had in  
 19 originally combining or deciding whether to combine the  
 20 studies was that they are using different animals, they  
 21 are not from the same 10 breeding pairs and completely  
 22 different set of breeding pairs that were used in the  
 23 IGB study compared to the Wildlife studies.  
 24 My concern would be, and I can  
 25 appreciate the fact that the power of the test to

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1 But the fact that the weights weren't  
 2 changing at all, that would be of concern to us.  
 3 Let me mention one other thing. It's  
 4 not in the white paper. When Mary Frankenberry was  
 5 doing the analysis, and I would add that Lisa  
 6 Eisenhower was also a statistician with the  
 7 Environmental Fate and Effects Division, contributed  
 8 greatly to the statistical analysis, I did request that  
 9 they take many of the apical end points and secondary  
 10 end points and do a correlation analysis to determine  
 11 whether any of the changes that were occurring across  
 12 the different treatment groups were correlated with  
 13 other end points.  
 14 So those analyses all proved to be  
 15 negative. But they were conducted although they are  
 16 not included in the white paper.  
 17 DR. PORTIER: You know, I just wanted to  
 18 address the issue of statistical significance versus  
 19 biological significance, we're always aware of that.  
 20 You know, the statistics can only point  
 21 you to where we think something might be happening, but  
 22 you also have to look as Doctor Bailey pointed out, you  
 23 have to look at the magnitude of the affect through  
 24 your biologist's eyes, not your statistical eyes, to  
 25 say, yeah, that might be a statistical difference of .1



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1 but who the heck cares, right? Because that's not a  
 2 biologically important thing.  
 3 But if you look at the power analysis  
 4 you saw for some of the outcomes you needed to observe  
 5 like a 10 percent affect size, right, for any one of  
 6 these experiments. You put it together and it might be  
 7 more like a 7 percent affect size.  
 8 Well 10 percent sounds like a big affect  
 9 to me and that's kind of a biologically big difference  
 10 to be shooting for. I'd be more interested, there  
 11 might be some findings, unlikely, it might be some  
 12 findings that we'd see statistically significant that  
 13 were still in the biological affect area.  
 14 The second thing is, you know, in  
 15 agriculture we've been doing studies like this for at  
 16 least 60 years where, you know, you raise a new variety  
 17 of corn, you don't just depend on one field trial in  
 18 one location to establish that that's a better variety,  
 19 it's got to be planted in three or four or five  
 20 different varieties that have different soil types,  
 21 different climates to establish that you actually have  
 22 an affect here.  
 23 And nobody ever challenges that these  
 24 things are independent field trials even though they  
 25 may be done by the same ag experiment station or a set

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1 different treatments, then you have to be very careful  
 2 because those effects can effect, can influence what  
 3 the magnitude of the correlation is.  
 4 And I'm sure you know that.  
 5 DR. FRANKENBERRY: This is Mary  
 6 Frankenberry. Just two thoughts and we thank you for  
 7 your suggestions definitely and frankly did think about  
 8 a lot of other things that we might have done with more  
 9 time and we're grateful for the ideas.  
 10 But I think also the idea with  
 11 reproducing something in two labs was one of  
 12 reproducibility and not replication originally. And I  
 13 think we've heard a lot of talk about we didn't see the  
 14 affect in both labs and my personal opinion was simply  
 15 that if we saw it in one lab, that was good, if we saw  
 16 it in two, that was better. But it did not detract  
 17 from seeing it in one, no.  
 18 I think there's more to gain if we  
 19 wanted to look at them together but my concern was I  
 20 think with Doctor Portier I was afraid that the  
 21 increased variability we may have between the two labs  
 22 would do away with any increase in power that we might  
 23 have.  
 24 But again we would have an increase in  
 25 information so we can look at that.

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1 of scientists that are working together.  
 2 And the same thing in clinical research,  
 3 we do clinical trials for new drug therapies, not in  
 4 one hospital or one clinic, but in multiple clinics  
 5 with multiple researchers with multiple sets of  
 6 patients and then we have study centers and data  
 7 centers that combine these to look and establish the  
 8 true affect.  
 9 And all we're saying is you've done the  
 10 same thing here. You've done two different studies in  
 11 two different locations with different scientists but  
 12 the same protocol. Different feed stock, high quality  
 13 data, you have an opportunity to actually address with  
 14 more power what affects are there.  
 15 You still have to bring a panel together  
 16 to look at the affects and say whether they are  
 17 important or not. But that's the question here is how  
 18 to improve the statistics and I think combining it does  
 19 improve the statistics.  
 20 DR. HEERINGA: Doctor Bailey.  
 21 DR. BAILEY: Ted Bailey. You just  
 22 mentioned a correlation analysis and we didn't discuss  
 23 that here. But I'd have to be sure that you to say  
 24 to you that when you, if you use correlations when  
 25 you've got structure in your data, structure like the

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1 With regard to anything dose response  
 2 related I think part of that was a time element, but  
 3 also we never saw anything very strongly in either lab  
 4 along those lines to inspire us to go much further.  
 5 But, you know, any other ideas you have  
 6 we're happy to listen to.  
 7 DR. BAILEY: Ted Bailey. The, this is  
 8 the general process when you've got data collected in  
 9 two or more different locations or whatever. This is  
 10 just the regular procedure recommended is to go ahead  
 11 and analyze it individually and then come back and do a  
 12 combined analysis.  
 13 And Doctor Steeger gave a really great  
 14 example of where that could be beneficial. You had the  
 15 different strains in the two labs and if you did the  
 16 combined analysis and then you found an interaction  
 17 between the sex and the treatments, one explanation for  
 18 that interaction would be that there were different  
 19 strains.  
 20 You wouldn't have been able to get a  
 21 test on that unless you did the combined analysis,  
 22 that's the reason for doing it.  
 23 DR. STEEGER: Just as a clarification,  
 24 they had different parentage, the were the same strain.  
 25 DR. HEERINGA: Thank you very much. I



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1 think certainly in terms of the design aspect the two  
 2 independent laboratories repeating the experimental  
 3 process, I think the panel is in complete agreement  
 4 with that.  
 5 We'd be at a very different point in  
 6 this discussion if it hadn't been done that way I  
 7 believe. And so I think these are all additional  
 8 analyses that are proposed as Doctor Bailey suggests  
 9 that in a typical sequence of independent analyses and  
 10 then a combined analyses and with the potential  
 11 benefits as he just discussed.  
 12 But I think that certainly there is, I  
 13 don't see, or haven't heard any critique on the two  
 14 laboratory design from any members of the panel.  
 15 Additional input on the statistical  
 16 analyses that could be added to what has already been  
 17 done in preparation of other reports or the white  
 18 paper?  
 19 Again we'll have a chance to revisit  
 20 these things if new ideas do arise, but at this point  
 21 I'd like to move on then to charge question number 10.  
 22 DR. IRENE: This is the first of the  
 23 concluding questions. Is the SAP aware of any other  
 24 laboratory based or field based studies not included in  
 25 this white paper that contradict the Agency's

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1 conclusions that one, the design associated with  
 2 current studies available in the open literature are  
 3 not appropriate for evaluating the hypothesis that  
 4 Atrazine affects amphibian gonadal development?  
 5 And two, the available data in the open  
 6 literature combined with the results of the DCI study  
 7 indicate that Atrazine does not cause adverse affects  
 8 on gonadal development in Xenopus laevis when  
 9 investigated under conditions consistent with those  
 10 recommended by the SAP in its previous report in 2003.  
 11 If so, please identify the studies and  
 12 briefly outline how the results from these studies  
 13 would contradict the conclusion that Atrazine in  
 14 concentrations up to 100 micrograms per liter does not  
 15 cause adverse affects on amphibian gonadal development.  
 16 DR. HEERINGA: Doctor LeBlanc is our lead  
 17 discussant on this response.  
 18 DR. LEBLANC: Gerry LeBlanc. This charge  
 19 question is divided into two sub-questions and I'll  
 20 address the first and then proceed into the second.  
 21 And to paraphrase the first question,  
 22 are there studies available in the open literature that  
 23 challenge the design of the studies that were submitted  
 24 in response to the DCI request?  
 25 Such studies for example might indicate

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1 that Xenopus does not perform well under flow through  
 2 conditions. Alternatively there may be studies  
 3 available in the literature that would indicate that  
 4 initiating these studies at Stage 46 was inappropriate.  
 5 This is the way at least that I  
 6 interpreted this part of the question.  
 7 And in response I'm aware of no such  
 8 studies that would call into question the design of the  
 9 DCI studies.  
 10 The second part of the question gets  
 11 more to the meat of the issue, that is, are there any  
 12 other published studies available in the literature  
 13 that would contradict the conclusions reached by the  
 14 Agency with respect to the DCI studies? That is, are  
 15 there other studies that were conducted according to  
 16 the recommended guidelines provided from the 2003 SAP  
 17 that come up with conflicting results?  
 18 And again I am aware of no such studies.  
 19 DR. HEERINGA: Doctor Delorme.  
 20 DR. DELORME: I don't have anything  
 21 further to add.  
 22 DR. HEERINGA: Doctor Skelley.  
 23 DR. SKELLEY: Doctor LeBlanc and I  
 24 discussed the response to this question before the  
 25 meeting today and I have nothing to add.

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1 DR. HEERINGA: Any other comments from  
 2 panel members in response to the two parts of this  
 3 question? We've had some conversation on this earlier  
 4 too.  
 5 Doctor Steeger, are you, do you feel  
 6 that you understand the response of this panel and if  
 7 so, do you have any comments or requests for  
 8 clarification?  
 9 DR. STEEGER: No, I understand the  
 10 comments clearly, thank you.  
 11 DR. HEERINGA: Okay. Doctor Irene, would  
 12 you read question 11 into the record please?  
 13 DR. IRENE: Yes. The Agency is not aware  
 14 of data that establish a mechanistic basis for how  
 15 Atrazine could affect amphibian gonadal development.  
 16 Please identify and comment on any studies that  
 17 demonstrate the mechanistic steps by which amphibian  
 18 gonadal development could be affected by Atrazine and  
 19 thereby contradict the Agency's overall conclusions  
 20 based on the studies evaluated for this SAP.  
 21 If the SAP is aware of any relevant  
 22 studies, please comment on the data from this or these  
 23 studies and how the data indicate and quantify a  
 24 mechanistic pathway from Atrazine's molecular site of  
 25 action to histological and apical end points associated



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1 with adverse affects on amphibian gonadal development.  
 2 Please also comment on any dose response  
 3 relationships associated with the steps in the reported  
 4 toxicity pathway.  
 5 DR. HEERINGA: Doctor Furlow is our lead  
 6 discussant on this question.  
 7 DR. FURLOW: So to begin with it's, when  
 8 you're faced with the evidence that the Atrazine alone  
 9 with *Xenopus laevis* and these nicely studies doesn't  
 10 seem to have an affect directly on gonadal development,  
 11 it's difficult to say, okay, well then what's the  
 12 mechanism?  
 13 The prevailing working hypothesis often  
 14 cited in the open literature is that Atrazine increases  
 15 the activity of aromatase, gene expression activity  
 16 during critical periods of gonadal development,  
 17 shifting gonadal steroid synthesis in males from  
 18 primarily testosterone to estradiol.  
 19 As we have discussed previously, both in  
 20 the public comment and in Doctor Steeger's  
 21 presentation, the previous evidence has been indirect,  
 22 such as comparing the reported affects of Atrazine to  
 23 the affects receptor antagonists and estrogen receptor  
 24 agonists or reported reductions in plasma testosterone  
 25 which actually appear to be the most consistently

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1 manner which is a morphonuclear receptor, known to be  
 2 an important physiological regulator of aromatase.  
 3 The authors also suggest that aromatase  
 4 acts as a drug ligand but the exact nature of the  
 5 interaction is unclear at this time.  
 6 The concentrations used to induce  
 7 aromatase activity in these line cell lines in these  
 8 new papers appear to be higher than those reported to  
 9 cause gonadal abnormalities in the open literature,  
 10 although significant induction can be observed in both  
 11 sets of studies with as little as 10 to -7 Atrazine.  
 12 In addition the dose response curves in  
 13 both studies are monotonic rather than u-shaped as  
 14 expected for a simple mass action driven interaction.  
 15 It is formally possible that Atrazine  
 16 under certain conditions has affects on *Xenopus* gonadal  
 17 that alternative mechanisms other than the induction of  
 18 aromatase or its activity may be at play.  
 19 SF1 for example has other gene targets  
 20 other than aromatase, it's expressed in the  
 21 hypothalamus as well as the adrenal glands like gonads.  
 22 Again this point is highly speculative  
 23 so at this point there is no new data on the potential  
 24 mechanisms of Atrazine affects not mentioned by the  
 25 white paper, other than the aforementioned cell culture

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1 reported affect of Atrazine in the literature.  
 2 EPA correctly points out that the best  
 3 evidence supporting the aromatase hypothesis remains  
 4 the studies in cultured cell lines.  
 5 Direct evidence for induction of  
 6 aromatase in vivo in tadpoles is conflicting and may be  
 7 confounded by the low expression levels in the tadpoles  
 8 and the same issues suggest to explain the variability  
 9 in gonadal phenotypes observed with Atrazine.  
 10 There are a couple of papers regarding  
 11 this issue that are not contained in the open  
 12 literature review. But again these are using cell  
 13 culture based assays and I will only mention them  
 14 briefly.  
 15 Earlier this year Holloway, et al  
 16 reported in the Journal of Applied Toxicology that  
 17 aromatase activity, but apparently not gene expression  
 18 can be induced and cultured, primarily in human  
 19 granulosis cells two to threefold by Atrazine, so this  
 20 affect is not solely limited to transformed cancer cell  
 21 lines.  
 22 Secondly a pair of papers by Fan, et al,  
 23 one in Environmental Health Perspectives and one in  
 24 BBRC, presented data to demonstrate that Atrazine can  
 25 activate the aromatase gene expression in one dependent

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1 experiments.  
 2 While these results should be considered  
 3 by the EPA they are in and of themselves insufficient  
 4 to explain Atrazine's potential detrimental affects on  
 5 *Xenopus* gonadal development if they exist at any dose  
 6 at all.  
 7 DR. DELORME: I agree with David's  
 8 statements and I don't have much to add but I want to  
 9 point out that if we just simply ask the question does  
 10 Atrazine affect aromatase activity in amphibian  
 11 tadpoles, I don't think the question has been tested  
 12 sufficiently. I don't think that there sufficient data  
 13 to either accept or reject that hypothesis.  
 14 But I agree that the only data that  
 15 really support the idea that Atrazine can affect  
 16 aromatase are the data from the cell lines, the cell  
 17 culture.  
 18 DR. HEERINGA: Doctor LeBlanc.  
 19 DR. LEBLANC: I feel that David covered  
 20 all of the issues quite well and I have nothing to add.  
 21 DR. HEERINGA: Additional input or  
 22 comments from members of the panel on this particular  
 23 topic, this particular question? I appreciate those  
 24 contributions, Doctor Furlow.  
 25 Doctor Steeger.



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1 DR. STEEGER: So I understand correctly  
 2 there, in response to the question there are no  
 3 additional data other than the mammalian cell culture  
 4 studies that were done at higher concentrations than  
 5 what have been previously demonstrated to results in  
 6 affects in amphibians?  
 7 DR. FURLOW: This is David Furlow.  
 8 That's correct. You can get by ANOVA analysis anyway,  
 9 affects at 10 to -7 but those are marginal. So you  
 10 typically have to go to 10 micromolar but I didn't do  
 11 the calculation, is that how many parts per billion and  
 12 how many micrograms per liter, but that could be done.  
 13 DR. STEEGER: Thank you.  
 14 DR. HEERINGA: Doctor Portier.  
 15 DR. PORTIER: Doctor Furlow, you know, we  
 16 had this discussion on these for transformation  
 17 products.  
 18 Is there nothing, I mean what you talked  
 19 about was the parent compound, right?  
 20 DR. FURLOW: Right. So far I didn't see  
 21 much on the degredates. The SF1 data was screened  
 22 against Atrazine and Simazine and there was interaction  
 23 with Simazine as well. They did test 55 different  
 24 pesticides and those were the only ones that showed  
 25 statistical significance by their analysis and again

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1 brought back this morning for clarification and we'll  
 2 also get to those, certainly before the end of the  
 3 discussion this morning.  
 4 But I'd like to move on to charge  
 5 question number 12 for the panel. Ms. Peace, if you  
 6 would read that into the record please.  
 7 MS. PEACE: In its 2003 white paper the  
 8 Agency proposed a research approach using focused  
 9 empirical laboratory studies based on the initial  
 10 investigations with *Xenopus laevis*, potentially  
 11 followed by selective confirmatory laboratory studies  
 12 with frog species native to North America.  
 13 However the 2003 SAP did not identify  
 14 any important differences between amphibian species to  
 15 conclude that any affected development and/or  
 16 mechanistic processes observed in *Xenopus laevis* would  
 17 not be applicable to indigenous species.  
 18 Please comment on the Agency's  
 19 recommendation that data derived from *Xenopus laevis* in  
 20 the studies evaluated for this review are sufficient to  
 21 conclude that additional testing with indigenous  
 22 species is not warranted.  
 23 DR. HEERINGA: Doctor Skelley.  
 24 DR. SKELLEY: David Skelley. Let me  
 25 start by acknowledging Doctor Steeger's comments this

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1 the raw data wasn't available.  
 2 DR. PORTIER: A one-way ANOVA on 55?  
 3 DR. FURLOW: I'll show you, you can look  
 4 at it and decide.  
 5 DR. HEERINGA: We'll have citations for  
 6 those papers and that work?  
 7 DR. FURLOW: Yes, I'll add those.  
 8 DR. HEERINGA: Okay. At this point in  
 9 time I think we're making very good progress so let me  
 10 suggest that we take a fifteen minute break and we will  
 11 reconvene at 10 o'clock.  
 12 (WHEREUPON, there was a recess.)  
 13 DR. HEERINGA: Welcome back everyone to  
 14 the second half of our Thursday morning session of the  
 15 FIFRA Science Advisory Panel meeting on the Potential  
 16 for Atrazine to Affect Amphibian Gonadal Development.  
 17 One administrative note, the panel has  
 18 been provided with a packet that I believe contains the  
 19 draft manuscript or report of the re-analysis of the  
 20 Carr, et al data from 2003, so that's available and I  
 21 presume it's also part of the docket too for this  
 22 meeting.  
 23 At this point we have made very good  
 24 progress in the review of the charge questions. There  
 25 are some additional questions that Doctor Steeger

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1 morning about the challenges that EPA faces in trying  
 2 to maintain a healthy environment for the more than  
 3 thousands of species that live out there, hundreds of  
 4 thousands if not millions.  
 5 And having acknowledged that I guess our  
 6 job as dumb scientists is just to give you our best  
 7 read on these questions and allow you as risk assessors  
 8 to decide which of our concerns and criticisms are  
 9 worthy of notice.  
 10 So having said that I have to disagree  
 11 with the conclusion that testing with native North  
 12 American species is not warranted.  
 13 The Agency's decision is based on the  
 14 presumption that *Xenopus laevis* is a suitable surrogate  
 15 for native North American species. However there are  
 16 reason to question such a conclusion.  
 17 Unlike North American species, *Xenopus*  
 18 *laevis* is a fully aquatic amphibian in both larval and  
 19 adult stages. Aspects of its biology are suggestive of  
 20 pedomorphosis, that is the retention of larval  
 21 characters in the adult form. And again this is unlike  
 22 North American anurans.  
 23 These and other points were raised  
 24 during the 2003 SAP meeting as well. I guess the  
 25 Agency's question to this SAP suggests an interest in a



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1 more specific response and I'm going to rely on my co-  
 2 discussants to add to what I'm going to say.  
 3 I'm going to focus on one example of a  
 4 comparative study between *Xenopus laevis* and native  
 5 species *Rana pipiens* that Doctor Bob Denver, a member  
 6 of this SAP authored. The study is entitled,  
 7 Developmental Changes in Interrenal in Anuran  
 8 Amphibians, and I will include the full citation to  
 9 this reference in my response, written response.  
 10 The research focused on the development  
 11 of responsiveness to stressors by the hypothalamic  
 12 pituitary interrenal or HPI axis.  
 13 During development tadpoles of different  
 14 stages were subjected to one of two stressors, either  
 15 shaking, physical agitation or injection of adrenal  
 16 corticotrophic hormone, ACTH or a control treatment.  
 17 The investigators then measured whole  
 18 body corticosterone concentrations or sorry, whole  
 19 body content as an index of HPI activity. The patterns  
 20 of whole body corticosterone content during development  
 21 differed strongly between the species.  
 22 Corticosterone content in *Rana pipiens*  
 23 was low during pre-metamorphosis and pro-  
 metamorphosis  
 24 and then increased greatly during metamorphic climax.  
 25 By contrast, corticosterone content was

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1 at it maximum in *Xenopus* during pre-metamorphosis and  
 2 then declines in pro-metamorphosis and then increased  
 3 again during metamorphic climax and remained high.  
 4 While both species responded to  
 5 experimental stressors, the pattern of response  
 6 differed. As an example, elevation of corticosterone  
 7 content in response to ACTH injection was maximal in  
 8 *Rana pipiens* in pre-metamorphic stages and decreased in  
 9 later stages.  
 10 In *Xenopus laevis* elevation of  
 11 corticosterone in response to ACTH did not differ  
 12 statistically among stages.  
 13 And I don't present this example to  
 14 suggest that this bears directly on any specific  
 15 hypothesis about gonadal development, but it does  
 16 suggest that an axis that is involved in development,  
 17 the HPI axis, is affected and affected differently in  
 18 these two species by stressors.  
 19 In the following quotation from the  
 20 discussion of the paper the authors compared the  
 21 responses of their focal study species to other North  
 22 American species that have been studied. They say,  
 23 "While changes in whole body corticosterone content in  
 24 *Rana pipiens* follows those observed in the blood of  
 25 other species, (and that's North American species),

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1 *Xenopus laevis* exhibits a somewhat different pattern.  
 2 Our findings with *Xenopus laevis* largely confirmed  
 3 those of Cloross and colleagues who reported whole body  
 4 corticosterone content to be highest at early lembut  
 5 stages but decreasing to lower values during pro-  
 6 metamorphosis?"  
 7 During this SAP we have heard evidence  
 8 that the tendency to form testicular ovarian follicles  
 9 may differ among populations within the species *Xenopus*  
 10 *laevis*. Based on our knowledge of variation among  
 11 species in response to environmental stressors, it is  
 12 reasonable to predict that specific differences in  
 13 response to stressors in important end points will also  
 14 exist.  
 15 Concerns about ecological relevance to  
 16 North American species and ecosystems prompted the  
 2003  
 17 SAP to suggest that studies of native species be  
 18 carried out as early as possible and those concerns  
 19 remain.  
 20 DR. HEERINGA: Thank you, Doctor Skelley.  
 21 Doctor Green.  
 22 DR, GREEN: So to address the question  
 23 specifically that additional testing with indigenous  
 24 species is not warranted, I spent some time yesterday  
 25 afternoon on the web.

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1 In the short amount of time that I had,  
 2 in doing very simple searches like amphibian  
 3 comparative toxicity studies on amphibian and *Xenopus*  
 4 *laevis* versus *Rana pipiens*, and just those simple  
 5 database broach net casting searches can turn up three  
 6 to four papers on developmental differences between  
 7 *Xenopus laevis* and *Rana pipiens*, neuro plate forms for  
 8 example, differences in acidity of the water that would  
 9 prohibit the development of *Rana pipiens* and not  
 10 *Xenopus laevis*.  
 11 And so I think those differences are  
 12 well characterized in the vertebrate and embryology  
 13 literature that will take time to map out and form a  
 14 comparative table. But it's certainly out there.  
 15 I also came across another useful URL  
 16 which is a database and there is a movement about  
 17 amphibians, there is a movement afoot to address the  
 18 issues concerning species' differences in  
 19 susceptibility to exposure to different stressors.  
 20 And I'd like to just read a short  
 21 paragraph here.  
 22 Researchers are finding that there are  
 23 wide variations in tolerance levels among amphibians,  
 24 even between closely related species. And they cite a  
 25 references, Bridges, et al in 2002 which I'll make



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1 available when we write our report as well as this URL.  
 2 Therefore conclusions drawn from studies on only a few  
 3 species cannot reveal the full effects of potentially  
 4 harmful chemicals to amphibians in general. And this  
 5 reference cited at the end of this sentence is, Diamhed  
 6 and Mitchell in 2000.  
 7 And then they go on to support  
 8 differences that are known between various species of  
 9 Leopard frog tadpoles and boyo tadpoles to different  
 10 chemicals from copper to PCP to permethrin. Additional  
 11 information in this particular URL, they do provide a  
 12 very superficial overview of species' differences in  
 13 response to chemical contaminants. There's nothing in  
 14 this particular document that reviews the quality of  
 15 the papers that have been cited here as references.  
 16 But they do bring up important points  
 17 that there are, even within species, very different  
 18 responses in terms of sexual development and LC50's to  
 19 common contaminants, heavy metals, coal ash and  
 20 whatever. Xenopus is frequently used in this list as  
 21 is Rana species and the Bufo toad.  
 22 So I will make all this available when  
 23 we write our report but I just want to reiterate what  
 24 David said, is that I think that we cannot in good  
 25 conscious say that studies with Xenopus laevis alone on

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1 and Doctor Green's comments and I do also want to  
 2 recognize for Doctor Steeger that amphibians are not  
 3 typically included in risk assessments for pesticides  
 4 and it's been an ongoing challenge to try and get that  
 5 to happen.  
 6 On the sort of I guess biodiversity side  
 7 of things we would be interested in having amphibians  
 8 included in the pesticide regulatory system and I think  
 9 it's to a great credit that there's so much attention  
 10 being paid to amphibians in this particular issue.  
 11 Just very briefly, I would also like to  
 12 comment that we can start to study native species,  
 13 including Rana pipiens, Leopard frogs, we do now have a  
 14 certain amount of understanding of these animals in the  
 15 laboratory. We have ongoing breeding efforts for them  
 16 going on as we speak so that we don't have to take  
 17 animals from the wild.  
 18 And these protocols are being worked on  
 19 and developed on an ongoing basis.  
 20 Certainly there are limitations in terms  
 21 of the number of species that could be included in a  
 22 pesticide risk assessment for regulatory purposes. I  
 23 think we still need, in order to protect the resources  
 24 that we have, to make sure that we include native  
 25 species in those risk assessments.

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1 the Atrazine of ours, to make the statement that  
 2 studies on indigenous species are not warranted.  
 3 And that said, I can certainly be  
 4 sympathetic with the Agency about the logistics and the  
 5 practicality of trying to conduct these studies on  
 6 species which may be in danger and certainly on species  
 7 which would have to be wild caught and then protocols  
 8 developed in the lab to try and grow them up and keep  
 9 them alive during the studies.  
 10 As a laboratory animal veterinarian I  
 11 recognize the difficulty with this and the mortality  
 12 will be high and certainly it would not be good for the  
 13 environment to go and collect native indigenous species  
 14 and try to do this. The protocols simply aren't out  
 15 there.  
 16 But nevertheless I think it would be  
 17 appropriate to revise the wording on this particular  
 18 point under 12a to reflect what I believe is the  
 19 general consensus from the SAP, that additional testing  
 20 would be highly desirable in native indigenous species.  
 21 And other than that I have nothing else  
 22 to add.  
 23 DR. HEERINGA: Bruce Pauli.  
 24 MR. PAULI: Bruce Pauli, Environment  
 25 Canada. I certainly concur with both Doctor Skelley's

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1 And for the remainder, just to preface  
 2 my comments, for the remainder of my comments I'm  
 3 going  
 4 to be talking to a certain about differences in  
 5 species' sensitivity.  
 6 Following on Doctor Skelley's talk and  
 7 the information we just heard about differences in  
 8 sensitivity, not in terms of a difference between  
 9 Xenopus and native species, but we've actually done a  
 10 little bit of work in looking at different native  
 11 species.  
 12 Despite the fact that we can probably  
 13 assume that some of the mechanisms are conserved and  
 14 development pathways are similar between species,  
 15 between Xenopus potentially and native species, we do  
 16 have some data on native species and gonadal  
 17 development.  
 18 And we have conducted a study which gave  
 19 us some evidence that even native species can respond  
 20 differently to compounds that influence gonadal  
 21 development.  
 22 So this is not, we're not trying to  
 23 address, I'm not trying to address here the difference  
 24 in gonadal, in affects on gonadal development between  
 25 Xenopus and native species, this is just between two  
 native species. It's a paper that was published in



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1 2003 in Environmental Toxicology and Chemistry and I'll  
 2 get the citation in my written comments.  
 3 In that work what was studied was  
 4 gonadal differentiation in two native frog species.  
 5 This was the Northern Leopard frog, Rana pipiens and  
 6 the Wood frog, Rana sylvatica. And these two frog  
 7 species were exposed to estrogenic and anti-estrogenic  
 8 compounds.  
 9 Basically the study was conducted to try  
 10 to determine whether or not in a laboratory situation,  
 11 given exposure to an exogenous compound that might  
 12 influence gonadal development, could we see impacts on  
 13 the native species? And this was basically getting  
 14 familiarity with these compounds that might influence  
 15 gonadal development, differentiation in native species.  
 16 The studies assessed the response of the  
 17 two native North American amphibian species to  
 18 exposures to estradiol, Nonylphenol, and aromatase  
 19 inhibitor and anti-estrogen. Various end points were  
 20 assessed histologically and in the end it was concluded  
 21 that the Northern Leopard frog in comparison to the  
 22 Wood frog, Rana sylvatica, was much more susceptible to  
 23 sex reversal and development of inter-sex gonads  
 24 following these laboratory static exposures, than were  
 25 the Wood frogs.

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1 The Wood frogs did show alterations in  
 2 the gonads but these were much less traumatic than  
 3 those that were seen in the Northern Leopard frog.  
 4 So we do have a basis of information  
 5 with which to do some studies on native species. I  
 6 think we're interested in obtaining information on  
 7 native species, possibly more information on native  
 8 species that are exposed to Atrazine in order to, as we  
 9 say, try to potentially protect the environment from  
 10 the possible affects of Atrazine.  
 11 Thank you.  
 12 DR. HEERINGA: Comments from other  
 13 members of the panel on this particular question? Yes,  
 14 Doctor Patino.  
 15 DR. PATINO: Reynaldo Patino. I would  
 16 also like to qualify my comments by saying that I guess  
 17 our job here is to have a scientific discussion about  
 18 these issues and EPA's job is to just take what they  
 19 think is appropriate in the context of their mission.  
 20 But I think I agree and also to some  
 21 extent, perhaps a minor extent, disagree with at least  
 22 one of the comments made, and that is that, you know,  
 23 it is very, you know, it's not surprising that there  
 24 are species differences. My understanding in this case  
 25 was that the hypothesis being evaluated was one of

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1 feminizing affects and I do remember the table or the  
 2 figure that was shown that on the scale of, when you  
 3 look at that feminization, the sensitivity to  
 4 feminizing substances, and I don't know what the  
 5 substances were that were used in those studies, but  
 6 there was a table shown that Xenopus was on the  
 7 sensitive side. If you're looking for feminizing  
 8 affects it's really not a hard species to see that  
 9 phenomenon when you expose them to a feminizing  
 agent.  
 10 So in that again I recognize there is  
 11 species differences and depending on what your end  
 12 point of interest is, Xenopus may be a bad species to  
 13 be looking at, or not an appropriate species.  
 14 But in the context of feminizing affects  
 15 what I saw in that figure that was shown, I think it  
 16 was the EPA that showed that figure, that Xenopus seems  
 17 to be a sensitive species if that is your interest.  
 18 Now the question I have, another  
 19 question, a follow up I guess is if fishes are really  
 20 the model that is used for determining aquatic affect,  
 21 and I was not present, I was not part of the panel in  
 22 2003 but I do know, and again I don't know the quality  
 23 of the studies because there's only abstracts, but at  
 24 the last CTAC meeting in Montreal there were a number  
 25 of posters that were presented by people from my own

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1 agency that showed that we're looking at Atrazine  
 2 affects on fish and there were some affects if I  
 3 remember correctly. But again I hesitate to rely on  
 4 those studies because they have not been published.  
 5 But I'm just bringing them to your  
 6 attention, that there are some studies, recent studies,  
 7 that as far I can tell, I did a search, a recent  
 8 search, have not been published but they're showing  
 9 some affects of Atrazine I guess on fish reproduction  
 10 using probably some models, you know, models that  
 maybe  
 11 are the ones that the Agency is using for assessing  
 12 affects in an aquatic environment.  
 13 So I just wanted to bring that to your  
 14 attention.  
 15 DR. HEERINGA: Doctor Steeger.  
 16 DR. STEEGER: Just to comment, the Agency  
 17 is aware of the presentations that were presented in  
 18 CTAC in Montreal last year. And on at least two  
 19 occasions now we have requested access to the data to  
 20 better understand it and we have not received those  
 21 data.  
 22 DR. HEERINGA: Comments from other  
 23 members of the panel on this particular question? Yes,  
 24 Doctor Delorme.  
 25 DR. DELORME: Yes, I agree with pretty



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1 well everything that David, Bruce and Sherrill said,  
 2 and I just want to point out that from the 2003 panel  
 3 there was concern at that time that although Xenopus  
 4 was a good model, there needed to be some sort of  
 5 information to allow bridging to native species.  
 6 And I appreciate Tom, that surrogate  
 7 test organisms are used, I work in the same area as  
 8 you, but just a note that all those surrogates that are  
 9 used currently are North American species.  
 10 And I also appreciate that we're  
 11 probably on the front edge here for amphibians. The  
 12 reality is as you've stated they're not part of the  
 13 normal data packets that we would receive when we do  
 14 our pesticide risk assessments.  
 15 We do use a number of assumptions in  
 16 order to cover off amphibians in our risk assessments.  
 17 But perhaps maybe it's time that we take a look at  
 18 those assumptions and whether or not they're valid.  
 19 I know for example that within  
 20 Environment Canada there is a researcher who is doing  
 21 side-by-side acute toxicity tests between to see  
 22 whether or not there is a concurrence.  
 23 So, you know, I appreciate that but I'm  
 24 from the 2003 panel and if you go over the responses  
 25 from the panel there are a number of indications there

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1 that stated that there was a concern there.  
 2 DR. HEERINGA: Yes, Director Williams.  
 3 MS. WILLIAMS: Thank you. Obviously  
 4 amphibian, the whole arena of amphibians is one that's  
 5 not been well researched, at least not for our  
 6 regulatory context.  
 7 And it's something that we actually have  
 8 on our mental research agenda that needs more research.  
 9 But I guess one of the things that I  
 10 want to kind of probe here a little bit is whether you  
 11 can help me understand why for Atrazine in particular  
 12 this would be a recommendation, given that the  
 13 statements that developmental pathways and mechanistic  
 14 things are probably similar among frogs, amphibians,  
 15 versus whether we're talking here about a more broad  
 16 agenda of research on frogs and amphibians.  
 17 Because I guess what I'm trying to get a  
 18 firmer grasp on is what additional testing would do in  
 19 the context of the Atrazine action that we're studying  
 20 and trying to take as opposed to what additional tests  
 21 would do to give us more broad information about, you  
 22 know, overall susceptibility of different species and  
 23 subspecies to chemical stressors I guess is my  
 24 question?  
 25 DR. HEERINGA: Director Williams, with

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1 that question are you referring to gonadal development  
 2 and the apical end points that we've considered  
 3 MS. WILLIAMS: Yes.  
 4 DR. HEERINGA: or more generally in  
 5 terms of reproductive success and population?  
 6 MS. WILLIAMS: Just the issue on the  
 7 table here, gonadal development.  
 8 DR. HEERINGA: I think question 13 opens  
 9 it a little bit more, but Doctor Green?  
 10 DR, GREEN: I'd like to clarify, you made  
 11 the statement at the beginning that developmental  
 12 processes were the same amongst all amphibians and I  
 13 think the panel has just presented documentation that  
 14 it's known that it is very different between different  
 15 amphibian species, and within the species itself there  
 16 are differences.  
 17 So why would that relate specifically to  
 18 Atrazine and susceptibility differences? At some point  
 19 along the way during metamorphosis there may be points  
 20 where say Rana pipiens is much more vulnerable to a  
 21 stressor such as Atrazine. They may stay in a  
 22 particular stage such that the exposure is longer  
 23 during that period which would results in changes in  
 24 gonadal development. But you might not see it manifest  
 25 in another species, or manifest in exactly the same

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1 way.  
 2 So I think that there is enough evidence  
 3 and a long history in both Rana pipiens and Xenopus  
 4 laevis development and embryological studies that they  
 5 are very different within the amphibian class.  
 6 MS. WILLIAMS: Well I appreciate your  
 7 explanation and just so you don't think I was making it  
 8 up, I think it was maybe Doctor Denver who said, and I  
 9 wrote it down when he said it, that developmental  
 10 pathways and mechanisms are probably the same among  
 11 species.  
 12 So maybe I took it out of context, I  
 13 apologize if I did, I wasn't trying to imply something  
 14 that wasn't said. I may have taken it out of context.  
 15 SPEAKER: Could I clarify?  
 16 MS. WILLIAMS: Sure.  
 17 SPEAKER: So we are, we including us, are  
 18 descended from a common ancestor and  
 19 MS. WILLIAMS: That's one theory.  
 20 DR. HEERINGA: That question is not on  
 21 the table.  
 22 SPEAKER: Okay, but that's one  
 23 MS. WILLIAMS: I apologize.  
 24 SPEAKER: the point is, and this was  
 25 made in the 2003 SAP was that the panel at the time did



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1 not have evidence that there were significant  
 2 differences between *Xenopus laevis* and native species  
 3 like *Rana pipiens* that would preclude the use of  
 4 *Xenopus laevis* as a model organism.  
 5 MS. WILLIAMS: Okay.  
 6 SPEAKER: However, it was also pointed  
 7 out in the same paragraph that there weren't sufficient  
 8 data to exclude the possibility that there were  
 9 difference, important differences.  
 10 MS. WILLIAMS: Uh-huh.  
 11 SPEAKER: And as has been discussed here  
 12 today, clearly there are.  
 13 MS. WILLIAMS: Thank you, I appreciate  
 14 the clarification.  
 15 DR. HEERINGA: Bruce Pauli.  
 16 MR. PAULI: Bruce Pauli. I think also we  
 17 were asked whether or not there is any specific reasons  
 18 to look at amphibians in relation to exposure to  
 19 Atrazine and I think that's what you were saying, are  
 20 we generally talking about amphibians in the risk  
 21 assessment paradigm or are we talking about a specific  
 22 need to look at amphibians because there may be  
 23 interest in them with respect to Atrazine specifically?  
 24 And I think the latter is the case. I  
 25 think we have gone through, there is suggestive

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1 evidence I might call it at this point, that because  
 2 these animals appear to be able to be influenced by  
 3 their exposure to exogenous compounds that would  
 4 influence their sexual development and differentiation.  
 5 And there is a possible unproven mechanism through  
 6 which Atrazine might influence this, either aromatase  
 7 or alpha reductase or something like that.  
 8 We have a specific interest in examining  
 9 these species that are possibly sensitive to this  
 10 insult as their response to exposure to Atrazine.  
 11 MS. WILLIAMS: Thank you.  
 12 DR. HEERINGA: Doctor Delorme.  
 13 DR. DELORME: The risk assessment that we  
 14 use suggest that in order to have affects you have to  
 15 have exposure. I don't think there is any argument  
 16 that large portions, or a lot of the water in the  
 17 United States and in areas of Canada have an Atrazine  
 18 presence. So I don't think it's a potential for  
 19 exposure, there is exposure there in a lot of frog  
 20 habitat.  
 21 And perhaps, it's perhaps an unfortunate  
 22 coincidence that it's Atrazine in frog gonadal  
 23 development, but I mean as I said before I think we're,  
 24 you know, on the front edge of something.  
 25 MS. WILLIAMS: May I?

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1 DR. HEERINGA: Director Williams, please.  
 2 MS. WILLIAMS: Thank you. Yeah, I  
 3 obviously don't argue that at all, that's been an issue  
 4 for a long time. It's in a lot of different places in  
 5 the water habitats.  
 6 I guess more specifically my question,  
 7 maybe I stated it too broadly, was that we obviously  
 8 have a concern and there was hypothesis that Atrazine  
 9 was going to result in certain affects in amphibians  
 10 and we've tested the hypothesis and our conclusion  
 11 anyway is that the hypothesis was not supported by the  
 12 data.  
 13 And so I guess what I'm wondering is  
 14 kind of, if you go down that line, then I mean if we do  
 15 another frog and it's not, the hypothesis is not  
 16 supported are we going to, is it going to be suggested  
 17 that we do yet another one and another one?  
 18 So I guess what I was trying to get at  
 19 in my own mind was maybe the question is why maybe  
 20 it's even more basic, why is what we have done to try  
 21 to prove or disprove the hypothesis inadequate? And I  
 22 guess I'm hearing that there are species differences  
 23 that people are concerned about and there are new data  
 24 or information that shows that perhaps the  
 25 developmental pathways and mechanisms are not the  
 same

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1 now.  
 2 So maybe I did get my answer. I wasn't  
 3 meaning to suggest that, gee, why are worried about  
 4 Atrazine in frogs?  
 5 So I apologize if that's the impression  
 6 I left.  
 7 DR. HEERINGA: Steve Heeringa, let me  
 8 make a comment. I think a number of us have commented  
 9 that this is really the scientific process at work and  
 10 in my own personal judgement it's probably about as  
 11 good as it gets in terms of the sequence of what we're  
 12 doing. But it is a process that continues.  
 13 And I think if you come to a panel such  
 14 as this and ask, is the door closed, is the book  
 15 closed, it's like saying is the scientific process  
 16 terminated? And it doesn't.  
 17 And so I think the types of answers that  
 18 you're going to hear from us represent, you know,  
 19 pursuing that scientific process beyond the  
 20 intermediate results. And we certainly have an  
 21 excellent set of intermediate results.  
 22 And then the next question, is that the  
 23 end of the process? No. And from our standpoint, from  
 24 a regulatory standpoint you'll have to make decisions  
 25 that incorporate the best available science at this



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1 point.

2 MS. WILLIAMS: Absolutely. My reason for

3 asking is to try and frame kind of your, this group's

4 perception or thoughts on what the degree of

5 uncertainty is in all of this so we can make that kind

6 of a decision. That's why I'm probing along those

7 lines.

8 DR. HEERINGA: Yeah, excellent, no,

9 that's, and that's clearly something that you need to

10 incorporate.

11 So any comments, Doctor Skelley, on the

12 magnitude of the uncertainty associated with the

13 position?

14 DR. SKELLEY: David Skelley. So I did

15 try to pick the example that I focused on carefully.

16 And to break it down, what Doctor

17 Denver's study shows, and I'm sure you will correct me

18 or hit me if I get this wrong, is that you have a

19 hormonal axis in which the response to a stressor in

20 one species shows a different pattern of sensitivity in

21 another species and we also have a developmental time

22 line when gonadal differentiate, limb differentiation,

23 all that stuff happens in certain windows.

24 And so if the sensitivity and gonadal

25 development line up differently, you could get a

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1 best evidence says they are concerned, but how

2 sensitive those pathways are to perturbations and at

3 what window, can differ, right?

4 So I just want to make that point.

5 DR. HEERINGA: Doctor Bucher.

6 DR. BUCHER: So coming at this from the

7 mammalian physiology perspective I'm sure that

8 everybody who has looked at Atrazine and the cancer

9 data can clearly show the, or understands all of the

10 work that's gone into determining the differences

11 between the carcinogenic response of this rat versus

12 the Fisher rat and the mouse.

13 So I think all of that literature is

14 pertinent here. It simply points out that strain

15 specific differences of response certainly exist for

16 Atrazine.

17 DR. HEERINGA: Doctor Delorme.

18 DR. DELORME: I think that you hit it on

19 the head when you brought in the word uncertainty.

20 For me that's what this is all about.

21 How uncertain are we with the assumption that Xenopus

22 is a representative model of North American amphibians?

23 And to my mind there is a lot of

24 uncertainty there. As an environmental risk assessor

25 in pesticides, you know, I find that there is a lot of

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1 different response, perhaps a qualitatively different

2 response. So we have evidence of that and that's the

3 state of scientific knowledge.

4 Now, that doesn't bear directly exactly

5 on proposed Atrazine pathways that ecologists

6 understand, at least what I understand. Perhaps

7 someone else could comment on that I guess. But it, to

8 me that raises concerns that the biology of these

9 species and Xenopus relative to North American species

10 in particular is different enough so that I can't agree

11 with the Agency's statement.

12 DR. HEERINGA: Other comments

13 particularly relating to Doctor Williams' interest in

14 assessments of the degree of uncertainty with this?

15 Doctor Furlow.

16 DR. FURLOW: Well just a quick point and

17 just to amplify something Doctor Skelley said, and that

18 is there's a difference between how concerned the basic

19 mechanisms are and how sensitive the animal might be to

20 different exposures and the windows.

21 Just to make that clear, right, that we

22 can say, yeah, I mean the basic, the SF1 and all these

23 things, right? So all these activation pathways and

24 biochemical pathways that say, am I going to be a

25 testes or am I going to be an ovary, yeah, I mean the

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1 uncertainty there, certainly for the other surrogate

2 species. We have a body of data that we can go to and

3 look at to compare a species' sensitivity distributions

4 to look at relative responses to different groups of

5 pesticides or chemicals.

6 So we can go to that and draw comfort

7 from that or draw certain assumptions from that.

8 We don't have that in this case. And I

9 think that's where some of the concern comes from, from

10 this group, coupled with widespread occurrence of

11 Atrazine in water, coupled with the fact that Xenopus

12 is not a native species.

13 I think that some of that came out in

14 the 2003 SAP as well.

15 Now, is there a way to deal with that

16 uncertainty other than going and doing more tests?

17 Possibly. Safety factors and what not, that's

18 something that is part of the risk assessment process.

19 It's not something that's necessarily part of the

20 science process although it has been subject to SAP's

21 before on the human health side.

22 So there are things to consider.

23 DR. HEERINGA: Doctor Green and then

24 Doctor Steeger.

25 DR, GREEN: I just, this is more of a



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1 personal feeling as a scientist. You know, the  
 2 original Hayes' papers reported affects in both Xenopus  
 3 and Rana pipiens, correct? And after sitting through  
 4 and listening to the data and looking at the DIC study,  
 5 I feel fairly comfortable about the results that have  
 6 been reported for Xenopus laevis.  
 7 And they're certainly not an endangered  
 8 species all over the world and they certainly have been  
 9 exposed to Atrazine in the wild. And there were  
 10 problems with the study that we reviewed in Doctor  
 11 Hayes' original study for both the experimental design  
 12 for both Xenopus laevis and Rana pipiens.  
 13 When it comes to Rana pipiens I'd have  
 14 to echo the sentiment of Peter, that I have a real  
 15 sense of uncertainty about the original data and  
 16 because it hasn't been tested or investigated further,  
 17 I still am very uneasy about leaving it as what we  
 18 found in Xenopus laevis would apply to Rana pipiens.  
 19 They are a threatened species in certain parts of the  
 20 world and they are exposed to Atrazine.  
 21 And is there a way to address that  
 22 question now? What about Rana pipiens? Without  
 23 spending three years and thousands and hundreds of  
 24 thousands of dollars repeating these experiments. And  
 25 so I'm thinking about that and we have a few more hours

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1 potentially answer whether Atrazine exposure could  
 2 affect amphibian gonadal development.  
 3 The protocol the Agency doesn't tell a  
 4 study, it doesn't a registrant how to develop a  
 5 protocol. We can suggest design elements but we cannot  
 6 dictate to them what they ultimately do. That is their  
 7 choice. Whether it flies afterwards is our choice but  
 8 in this, in the case of this study we presented the  
 9 registrant with a number of design elements that we  
 10 would like to see incorporated. We worked very closely  
 11 with them to make sure that they were incorporated,  
 12 even though that's not what we traditionally do, but we  
 13 did. And in that process it took two years to develop  
 14 a protocol and test it, that would work on a regularly  
 15 tested laboratory species.  
 16 And my concern is that I understand, I'm  
 17 fully aware or cognizant of the idea that the SAP  
 18 recommended in 2003 that indigenous species be tested.  
 19 But after standing in those labs for the umpteenth  
 20 time, listening to yet another problem that has come up  
 21 with a regularly tested species, and recognizing how it  
 22 would impact the outcome of the study, I thought, gee,  
 23 if they bring up the idea of another species I am  
 24 hoping that if we proceed down this track there will be  
 25 some willingness to provide input on how to actually

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1 in the day, so if there's a way that perhaps, and I  
 2 could only make the recommendation that with the help  
 3 of statisticians, looking at the most reproducible, the  
 4 most solid experiments that we could and the  
 5 information that we got from the Xenopus laevis  
 6 studies, maybe repeat those studies in a small subset  
 7 of Rana pipiens.  
 8 DR. HEERINGA: Doctor Steeger.  
 9 DR. STEEGER: I can appreciate the  
 10 concerns that have been voiced and recognize that the  
 11 SAP is providing their scientific perspective on what  
 12 would be the right thing to do.  
 13 I'm a risk assessor, I'm a biologist,  
 14 I'm not a risk manager. We only tell them, we tell  
 15 risk managers what our assessment of the biology and  
 16 the environmental fate of a compound is.  
 17 And we also define, or try to define  
 18 what kind of uncertainties there are with those  
 19 estimates of risk and the effects. And in doing so we  
 20 try to define additional, what data gaps may exist and  
 21 what kind of studies would be necessary to address  
 22 them.  
 23 And in 2003, working with the Office of  
 24 Research and Development we defined some study  
 25 elements  
 26 that would address the sources of variability and

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1 conduct the study with an indigenous species that will  
 2 have mortality that falls within the range that's  
 3 acceptable to this Agency and provide data that has  
 4 some hope of being used to regulate.  
 5 I do not typically comment or commend a  
 6 registrant on the conduct of a study but the contract  
 7 labs that were used for these studies in my opinion did  
 8 an excellent job in starting from scratch and pulling  
 9 together a GLP study that may serve as the paragon of  
 10 amphibian studies for looking at this particular end  
 11 point.  
 12 That might have been the luck of the  
 13 draw. Whether they could pull it off for a native  
 14 species has yet to be determined. But I suspect that  
 15 if it took two years to pull this regularly tested  
 16 species study off, I can't begin to guess now many  
 17 years it might take to pull off one with a native  
 18 species.  
 19 DR. HEERINGA: Well let me throw that  
 20 challenge back to the panel. It's a fair question. I  
 21 mean clearly scientifically and ecologically there is a  
 22 strong interest or willingness to sort of extrapolate  
 23 from Xenopus to all native species.  
 24 But the next question is, if we were to  
 25 propose additional research is it feasible to conduct



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1 an experiment say without confounding mortality? It's  
 2 an experiment of a type and quality that we've seen  
 3 with the Xenopus study.  
 4 Doctor Green?  
 5 DR, GREEN: I won't belabor the point but  
 6 Rana pipiens is a well established laboratory animal,  
 7 frog model. It was only eclipsed in the 1980's by  
 8 Xenopus laevis when cancer research and vertebrate  
 9 developmental embryology studies came to the forefront  
 10 in terms of funding.  
 11 So I do believe that there are well  
 12 established protocols for Rana pipiens in the  
 13 laboratory and Doctor Pauli might have some that he'd  
 14 be willing to share.  
 15 Other species, aside from that I do  
 16 agree, you know, it would take longer than two or three  
 17 years to even set up the protocols such that you'd have  
 18 enough live frogs at the end of the day you could  
 19 experiment, only manipulate.  
 20 But I think Rana pipiens would not be  
 21 out of reach in terms of what we know about them in  
 22 terms of housing and husbandry and SOP's for their  
 23 routine care.  
 24 DR. HEERINGA: Bruce, do you want to  
 25 weigh in on this? Is this pie in the sky or is this

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1 mortality.  
 2 DR. HEERINGA: Doctor Skelley.  
 3 DR. SKELLEY: David Skelley. So in the  
 4 last decade or so my laboratory has worked on, I think  
 5 I just counted seven different native species, in all  
 6 cases we're dealing with wild collected, usually  
 7 embryos and reared in the laboratory.  
 8 I don't think the challenge, at least in  
 9 the static renewal context is particularly tough in  
 10 getting them to survive and rearing them to  
 11 metamorphosis. I think that the protocols as Bruce  
 12 Pauli mentioned, I think the protocols, or I guess it  
 13 was Doctor Green mentioned, the protocols are out there  
 14 to do that part, excuse me.  
 15 The distinction is in the ability to  
 16 start experiments at any time of the year. That's  
 17 routine with Xenopus. That's a bit more challenging  
 18 with the native species. It seems to me that that  
 19 would be the big challenge, not the actual laboratory  
 20 rearing and feeding and so on.  
 21 DR. HEERINGA: Doctor Handwerker.  
 22 DR. HANDWERGER: I'm just wondering, what  
 23 would happen if we repeated this whole study in Rana  
 24 pipiens and came back to an SAP meeting in four years,  
 25 three years, would we be then asking again the

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1 MR. PAULI: Well I probably would lean  
 2 towards Doctor Steeger in considering that a completely  
 3 daunting task to established Rana pipiens in a manner  
 4 similar to what was done with the DCI studies that  
 5 we're currently evaluating here.  
 6 They will behave for you in the limited  
 7 experience, relatively limited experience that we have  
 8 with them. We have not, and I should emphasize this,  
 9 ever had them in a flow through apparatus. And that is  
 10 probably one of the things that would cause, you know,  
 11 a fair amount of delays in terms of getting these  
 12 things established.  
 13 In the current, with luck in the current  
 14 set ups that we have, we have reasonably good success  
 15 in both attaining fertilized egg masses in our  
 16 laboratory, that's one lab only and taking animals from  
 17 that stage through metamorphosis.  
 18 It's doable but again, these are static  
 19 renewal experiments of a rather small nature given the  
 20 resources that we have to do these experiments.  
 21 We have done it, we've done it on an  
 22 annual basis for the last eight years. They, given  
 23 good husbandry, acceptable laboratory conditions, you  
 24 can take a lab, Rana pipiens tadpole through  
 25 metamorphosis with fairly good success and acceptable

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1 question, well, is this data adequate, do we need to do  
 2 another species? You know, there are thousands of them  
 3 and we've now done two or are some of us going to  
 4 question the fact that we need to do a third and a  
 5 fourth and a fifth? I mean where do we end, what is  
 6 the point at which we're all going to be satisfied that  
 7 Atrazine use does or does not have an affect?  
 8 So, you know, as a biologist, as a  
 9 pediatrician and I, you know, I always to see  
 10 completion in many, many things done, but only if at  
 11 the end you can make a definitive statement.  
 12 And I don't know how we're ever going to  
 13 be able to generalize to all amphibians whether we  
 14 studied Rana pipiens or not, because we're still going  
 15 to have this same fundamental question that there is  
 16 variation. And maybe we just didn't pick the  
 17 particular, you know, strain or whatever it is that's  
 18 going to be susceptible to Atrazine.  
 19 And I'm sure that if you look, if there  
 20 are thousands and thousands of strains, you'll find one  
 21 that probably is susceptible just as there is probably  
 22 one susceptible to glucose and anything else.  
 23 So I think the real question is, what is  
 24 the end point? I mean if we do Rana pipiens are we  
 25 going to be satisfied with that? Is that going to



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1 answer the question?  
 2 And I don't know the answer to that.  
 3 You people probably should know. I only work with  
 4 homo sapiens.  
 5 DR. HEERINGA: Doctor Miller.  
 6 DR. MILLER: I just want to make a brief  
 7 comment that I am part of a research team that has had  
 8 very good success taking through metamorphosis  
 9 bullfrogs and, you know, I'm sure everybody has their  
 10 opinion on using bullfrogs. But we have done that in  
 11 flow through systems as well as static systems.  
 12 And in regard to bullfrogs there is a  
 13 lot of success with Rana culture systems and I know  
 14 that's not laboratory approved necessarily, but as far  
 15 as growing them out there's a lot of information there.  
 16 DR. HEERINGA: Doctor Steeger.  
 17 DR. STEEGER: I think continuing on on  
 18 the discussions with the species, native species  
 19 testing, we've seen from the work that Doctor Hayes has  
 20 done that even within Rana pipiens he's demonstrated  
 21 affects in one case but in the next there is no affect.  
 22 And so we go back to the, you know,  
 23 being hit or miss on whether we've selected the correct  
 24 strain, so the logistics of pulling this off I think  
 25 again are very daunting for a study that would meet the

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1 goes out the door. Does this study have any likelihood  
 2 of success or are you just having someone spend  
 3 millions of dollars to prove that something can't be  
 4 done to your satisfaction?  
 5 I only mention that because those are  
 6 the realities that I have to face in moving forward  
 7 with working with the recommendations that the panel  
 8 makes. And I mention it to bring some sense of reality  
 9 to where regulatory use of the information deviates  
 10 from the science itself.  
 11 DR. HEERINGA: Thank you, Doctor Steeger.  
 12 And I believe too. That's what I want to spend the  
 13 little time we have as a panel trying to separate the  
 14 sort of scientific motivation for these recommendations  
 15 from the current practicality and logistical difficulty  
 16 of maybe doing it.  
 17 Because hopefully that benefits the EPA  
 18 in their consideration too.  
 19 Doctor Portier?  
 20 DR. PORTIER: As I listen to the  
 21 discussion you've got to throw out a challenge that  
 22 says, you know, how do I design better experiments to  
 23 address these things?  
 24 And then Doctor Handwerger keeps coming  
 25 back saying, how do we make the decision in the final,

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1 standards that EPA looks for from studies submitted for  
 2 regulatory purposes.  
 3 Again, as Doctor Skelley has noted you  
 4 have a limited time window in which to work with the  
 5 animals. Their period for metamorphosis could be  
 6 protracted and as the studies are extended in time the  
 7 potential for errors occur. And as you've seen in the  
 8 studies that were conducted for the DCI, and these were  
 9 conducted by very well known contract labs, errors  
 10 happen.  
 11 And the likelihood of them happening  
 12 increases as the time of the study extends.  
 13 And again you're right, the Agency  
 14 doesn't have to embrace your recommendations, they're  
 15 just simply opinions. But we do take them to heart and  
 16 my job is to try and put those recommendations into  
 17 something that's concrete and workable that we can then  
 18 hand over to the registrants and say we want to see  
 19 these incorporated. And we also have to explain them  
 20 to the Office of Management and Budget as to how do  
 21 these changes, these additional studies affect the risk  
 22 assessment decision to warrant the regulated community  
 23 having to generate those data.  
 24 And where will this stop? Those are  
 25 questions that I will have to answer before it even

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1 you know, do we experiment forever?  
 2 And I think EPA has developed protocols  
 3 to handle these kinds of things for some of the animal  
 4 studies where they go to more physiologically base  
 5 models, right? They use the basic research and the  
 6 understanding of what's happening in the, in specific  
 7 organisms and they incorporate variability at that  
 8 level to be able to handle the broader class of  
 9 animals.  
 10 The problem I see with the amphibians  
 11 and the frogs that we're talking about here is that we  
 12 haven't done the basic research to understand the  
 13 processes to be able to help you design the kind of  
 14 confirmatory experiments that you need to close the  
 15 door on some of these issues.  
 16 And, you know, for a lot of this I feel  
 17 like there's a failure in our society to fund that  
 18 basic research, that basic physiological research  
 19 that'll help you answer these questions.  
 20 And I've been sitting here hoping that  
 21 one of these guys would say, well, we've got this model  
 22 of a frog and I haven't heard that and I've asked that  
 23 individually and I still don't hear that.  
 24 DR. HEERINGA: Doctor Skelley.  
 25 DR. SKELLEY: David Skelley. First I'd



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1 like to reinforce Doctor Portier's comment that there  
 2 is not enough money for research on basic biology  
 3 frogs.  
 4 DR. HEERINGA: That's the other second  
 5 major recommendation we'll submit.  
 6 DR. SKELLEY: Absolutely. The second  
 7 point in response to the comment, when will there be  
 8 enough species?  
 9 I think I'd look at that differently at  
 10 this point in the development of EPA's interests and  
 11 effort with amphibians.  
 12 If looking forward you wanted to bet on  
 13 a horse that's going to help us understand risks to  
 14 North American species and North American ecosystems,  
 15 should we continue to invest in the Xenopus model which  
 16 everyone agrees is very well characterized, or should  
 17 the investment be made to switch to a North American  
 18 species?  
 19 It's my sense, and I'd be interested to  
 20 hear what other panel members think, that the effort  
 21 expended to develop a North American model makes a lot  
 22 of sense in the context of Doctor Delorme's comment,  
 23 that other surrogate species that are used in North  
 24 America, both in Canada and the United States, are  
 25 North American species.

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1 We have some very nice frogs in this  
 2 country and I know that we can work out the details to  
 3 figure out how to do good lab based culture and then  
 4 lab based experiments that get results that everyone  
 5 can be proud of.  
 6 And I think there is some hope that  
 7 those results will be more generalizable to other North  
 8 American species.  
 9 I won't raise the common dissent issue  
 10 again, but certainly Rana pipiens as one example is a  
 11 member of the dominant frog family in North America  
 12 and  
 13 Doctor Denver's paper that I quoted from earlier noted  
 14 that for that particular physiological pathway, the  
 15 results were congruent, not just within Rana, but  
 16 between Rana and another family of Spadefoot toads.  
 17 So, you know, the little bit that we do  
 18 know suggests that there is going to be more congruence  
 19 and that if the future some SAP comes back at you with  
 20 the interest in doing more species, if the work is  
 21 being done on a North American species I think you'll  
 22 be in a much stronger position to push back.  
 23 DR. HEERINGA: Doctor Green and the  
 24 Doctor Chambers.  
 25 DR, GREEN: And just for the record, it  
 was the original recommendation of the panel in 2003

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1 that Xenopus laevis be studied as well as Rana pipiens  
 2 and I believe we recommended that those field, or those  
 3 studies on that particular species, Rana pipiens, be  
 4 taken up immediately, because at that time we  
 5 recognized the utility of looking at a frog species  
 6 that is on this continent and is indigenous to this  
 7 country, or North America.  
 8 So where does it end? That's a really  
 9 tough question but I think I'd have to concur with  
 10 David in that we'll be in a much stronger position when  
 11 the compounded question is tested on a species that is  
 12 relevant to agriculture and the ecosystems in North  
 13 America.  
 14 DR. HEERINGA: Doctor Chambers.  
 15 DR. CHAMBERS: I think Doctor Skelley  
 16 made some very, very good points a few minutes ago and,  
 17 you know, certainly it seems like ultimately we need to  
 18 study some frogs that are more relevant to our  
 19 situation here in North America.  
 20 However at this point in time if those  
 21 procedures are not established enough to give you the  
 22 type of data you need in a regulatory context to have  
 23 the same sort of quality that you're getting out of  
 24 mice, rats, rabbits, Xenopus and all, then it seems  
 25 like it would premature to demand those types of

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1 studies until the protocols and the procedures were  
 2 really established enough to have confidence that the  
 3 studies could be run accurately.  
 4 DR. HEERINGA: Yes, Doctor LeBlanc.  
 5 DR. LEBLANC: During the 2003 SAP meeting  
 6 I don't think anyone was thrilled about doing the  
 7 proposed studies with Xenopus, but I think we all  
 8 recognized that it was the available model, that the  
 9 studies could be done in. And we threw in that caveat,  
 10 we need to look at an indigenous species as well.  
 11 My recollection was not, and but I could  
 12 be wrong, was not that we do it immediately but that we  
 13 do it as soon as possible. And I think the two are  
 14 different. I think we recognized that it wasn't  
 15 possible to work with a Rana species.  
 16 So I think the point is the Xenopus  
 17 species is currently the most appropriate species but a  
 18 significant level of uncertainty remains, having tested  
 19 only that species.  
 20 As to how many species do we test before  
 21 we get the answer? If we keep getting negative answers  
 22 I suppose that's comforting but again it's hard to  
 23 prove the negative.  
 24 So that's an Agency decision, when do we  
 25 have enough information that we can say, okay, we have



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1 enough information to make a valid decision?  
 2 And I think one of the things that  
 3 everyone's struggling with right now is the Agency is  
 4 struggling with the issue of whether or not that  
 5 decision can be made with only a single species and not  
 6 just a single species, but a species that's not  
 7 necessarily representative. Or the uncertainty with  
 8 respect to the degree to which it's representative to  
 9 North American species.  
 10 DR. HEERINGA: Steve Heeringa. Just a  
 11 personal comment again going back to my earlier  
 12 comments about the scientific process.  
 13 Our discussion here is post hoc of some  
 14 findings that are predominantly null with respect to  
 15 the affects of Atrazine on Xenopus. If we had  
 16 conducted the experiment and the experiment had turned  
 17 out to prove major dose response affects, substantial  
 18 affects I think conclusions to progress forward would  
 19 have taken a different path.  
 20 But in the presence of a predominantly  
 21 null results from a well designed experiment on  
 22 Xenopus, now we're still left with this secondary  
 23 question, it's a step forward.  
 24 So again I think the steps taken in this  
 25 process in terms of the resources expended and the

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1 effort put into that protocol were appropriate.  
 2 But now that we are sitting here with  
 3 again a predominantly null result on this particular  
 4 hypothesis test for Xenopus and the door is not  
 5 completely closed, but it then leads us to this other  
 6 question of the species difference.  
 7 Doctor Bailey.  
 8 DR. BAILEY: Ted Bailey. I am listening  
 9 to the discussion here about this species or that  
 10 species. I don't even know if this is possible, but if  
 11 you design an experiment maybe you should have two or  
 12 more species in it so you can make this comparison  
 13 among species.  
 14 That would be better than doing one  
 15 experiment with this species and a second experiment  
 16 with that species.  
 17 DR. HEERINGA: Doctor Delorme.  
 18 DR. DELORME: I think I'd have to agree  
 19 with Doctor Heeringa's remarks that if we had had  
 20 positive results would we have had a different outcome  
 21 on this? And it's a difficult question but I think the  
 22 fact remains that there is a considerable amount of  
 23 uncertainty and I think that's what's causing some of  
 24 us a little bit of angst.  
 25 And in the end EPA is the one and the

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1 Agency is going to have to deal with that uncertainty.  
 2 As I said before there are other ways to  
 3 deal with it. Certainly we deal with it when we use  
 4 other surrogate species. It's not to say that in the  
 5 future data is not going to be developed for Atrazine  
 6 on other data species voluntarily. Who knows?  
 7 But also for other chemicals or other  
 8 pesticides as well. And as I said in my earlier  
 9 remarks which were actually part of my answer for  
 10 question 13, right now we lack a good database that we  
 11 can go to and draw comfort from to support the fact  
 12 that Xenopus is a good surrogate species.  
 13 I don't think we're saying that it's not  
 14 a good surrogate species, I think we have a  
 15 considerable amount of uncertainty of where to place it  
 16 with respect to the native species. And given the  
 17 widespread contamination of water with Atrazine, you  
 18 know, is that a reasonable conclusion to make based on  
 19 a single species? I'm not sure.  
 20 DR. HEERINGA: Thank you. At this point  
 21 I would like to move on to the final charge question if  
 22 we could. And we'll have a chance to come back for a  
 23 general closure and comments as well.  
 24 So I believe it would be Doctor Irene.  
 25 DR. IRENE: Charge question 13. Based on

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1 the available data provided by the DCI studies, the  
 2 Agency has concluded that Atrazine does not adversely  
 3 affect amphibian gonadal development. The Agency has  
 4 further concluded that no additional studies are  
 5 required to address the hypothesis that Atrazine  
 6 adversely affects amphibian gonadal development.  
 7 Please comment on the Agency's  
 8 recommendation that the current body of data is  
 9 sufficient to refute the hypothesis that Atrazine by  
 10 itself can adversely affect amphibian gonadal  
 11 development, and that no additional data are required  
 12 to address this hypothesis.  
 13 DR. HEERINGA: Doctor Delorme.  
 14 DR. DELORME: I think we just spent about  
 15 a half hour answering those questions.  
 16 Anyways, I'm just going to reiterate  
 17 some points that I wrote down and then I think the  
 18 discussion will continue. I believe I'm going to have  
 19 a fun time writing this one up.  
 20 I think that the data is sufficient to  
 21 refute the hypothesis that Atrazine by itself can  
 22 adversely affect Xenopus laevis gonadal development.  
 23 I think the real question is if the data  
 24 are sufficient to extend this conclusion to all  
 25 amphibians at this point in time with that uncertainty.



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1 We acknowledge the use of surrogate  
 2 species as an efficient and logical approach and  
 3 generally accepted. We further acknowledge that  
 4 current toxicity data related to amphibians is not a  
 5 specified data requirement. So we are really on the  
 6 front edge here.  
 7 And there are certain challenges faced  
 8 by the Agency and the registrants with respect to  
 9 conducting amphibian studies.  
 10 But in essence as we've already stated  
 11 we're addressing concerns related to the uncertainty of  
 12 refuting the hypothesis.  
 13 Unlike other tests or other test  
 14 organisms a body of knowledge and research related to  
 15 these types of affects in other amphibian species for a  
 16 range of chemicals does not exist to support the  
 17 assumption.  
 18 So if you make an assumption that's  
 19 based on uncertainty and some of the factors that we've  
 20 already talked about is the relative sensitivity of  
 21 different species is unknown, the different ecologies  
 22 of species and how they're going affect outcomes, the  
 23 nonrepresentativeness of Xenopus to native species,  
 24 that's atypical ecology, totally water living. And  
 25 specifically with respect to Atrazine as I previously

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1 pointed out, the widespread occurrence in water.  
 2 So there's all these factors that are  
 3 going into this that are adding to the uncertainty.  
 4 You know, I wrote down here before the  
 5 previous discussion that at a minimum and consistent  
 6 with the recommendations of the 2003 SAP, the Agency  
 7 should consider tests with a native species for  
 8 accuracy.  
 9 And I think we recognize the  
 10 difficulties in conducting studies given our current  
 11 level of knowledge and technical expertise.  
 12 And as I said just before we started  
 13 answering this question, I think in the future we're  
 14 going to see some of those techniques and methods and  
 15 protocols develop for native species, we're on the  
 16 front edge of that.  
 17 And perhaps in another 10 or 15 years  
 18 there will be more evidence, pro or con for this issue.  
 19 It's going to take time, I recognize that.  
 20 In the interim I'm not sure but I'll go  
 21 to the other discussants, there are several of them on  
 22 this and see what their input is.  
 23 DR. HEERINGA: Doctor Green, Sherril  
 24 Green.  
 25 DR, GREEN: I think I have nothing to add

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1 at this point.  
 2 DR. HEERINGA: Doctor LeBlanc?  
 3 DR. LEBLANC: I agree with everything  
 4 Peter said. The only thing I want to emphasize is that  
 5 any well executed study succeeds in answering the  
 6 questions that are originally posed for which the  
 7 protocol was defined to address those questions and at  
 8 the same time raises new questions.  
 9 And I think that's what we're seeing  
 10 here.  
 11 And it then becomes a judgement call on  
 12 the part of the risk assessors, the regulators as to  
 13 whether the strength of the answers that were answered  
 14 are sufficient to make a judgement, or whether the  
 15 unanswered questions are sufficiently important that  
 16 more studies are warranted.  
 17 And that's a judgement call. It's a  
 18 very difficult question to answer and I know it's one  
 19 that you're, as the Agency is asking for advice on now  
 20 from the experts in the field. But it is difficult to  
 21 answer.  
 22 I think that many uncertainties were  
 23 raised over the course of this SAP meeting and really  
 24 the only one that I felt that the committee felt was of  
 25 significant uncertainty is the issue of species

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1 sensitivity. And I think with respect to the  
 2 conclusions of the DCI studies we can state with some  
 3 degree of certainty that Atrazine does not affect  
 4 gonadal development in Xenopus laevis at concentrations  
 5 as high as 100 parts per billion.  
 6 We can't make judgements about  
 7 concentrations higher than 100 parts per billion in  
 8 Xenopus laevis and we can't make judgements about  
 9 concentrations lower than 100 parts per billion in  
 10 other species because we simply don't know.  
 11 And again that's a judgement call. One  
 12 has to look at the information that's available with  
 13 respect to species' differences in sensitivity, the  
 14 likelihood that there might be an affect. Certainly  
 15 the most scientifically sound and comfortable approach  
 16 is to test another species and see what the information  
 17 says. If that's not practical, if it's not feasible,  
 18 if it's not tenable at this point in time for  
 19 scientific reasons, then alternative approaches need to  
 20 be taken.  
 21 And for example Peter mentions safety  
 22 factors as an approach that's often taken.  
 23 DR. HEERINGA: Doctor Skelley.  
 24 DR. SKELLEY: David Skelley. So I agree  
 25 with the comments of the prior discussants and I just



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1 want to add one point along a different line.  
 2 The 2003 SAP considered two primary  
 3 lines of evidence in making its recommendations. The  
 4 first involved laboratory based evidence that Atrazine  
 5 exposure was related to abnormal gonadal development  
 6 and other responses, and that's what we've spent most  
 7 of our time talking about.  
 8 The second line of evidence was based on  
 9 the detection of gonadal abnormalities in wild  
 10 populations of amphibians. Since 2003 very little new  
 11 evidence has emerged to evaluate the role of Atrazine  
 12 or other stressors in producing these abnormalities  
 13 which are heterogeneous in space and in some cases  
 14 related to gradients of exposure to Atrazine or other  
 15 presiticides.  
 16 Given the possibility of inter-specific  
 17 differences in response to Atrazine exposure, the lack  
 18 of study on native North American species means that  
 19 the role of Atrazine in producing abnormal development  
 20 in field populations of native North American species  
 21 remains unknown, or at least uncertain.  
 22 Even if the Agency concludes that  
 23 laboratory studies provide no basis for further  
 24 exploration of the Atrazine hypothesis, these  
 25 observations of natural populations remain unexplained.

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1 They are still there and we still don't know why.  
 2 And in thinking about the second line of  
 3 evidence I'm reminded of the story of the man who is  
 4 searching under a streetlight for his, on the ground  
 5 and somebody else walks up to him and says, well, what  
 6 are you doing? He says I'm looking for my car keys.  
 7 And the person asks, well, did you lose them over here?  
 8 And he said, no, I lost them over there but it's really  
 9 dark over there.  
 10 And I think that while it's, it can be  
 11 comfortable to stick with a model system, if we're  
 12 really going to figure out what's going on in North  
 13 American ecosystems we're going to have to go where  
 14 it's dark and scary and maybe a little more difficult.  
 15 DR. HEERINGA: Doctor Portier.  
 16 DR. PORTIER: I looked at this just  
 17 slightly different. When you look at the statement  
 18 it's pretty broad and you talk about adversely affect,  
 19 and that, and what I've heard is that there are direct  
 20 and potentially indirect affects. And so I think we  
 21 have a pretty clear statement about a direct affect.  
 22 But these indirect affects which I break into two  
 23 parts, these degradedates or transformation products,  
 24 there seems to be a lot of uncertainty with what's  
 25 going on there and it ties in with whether you're

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1 dealing with a flow through or a static system.  
 2 And the other one that was mentioned,  
 3 and we really haven't talked about is the potential for  
 4 a synergistic affect of this chemical and/or its  
 5 degradate with other chemicals in the environment and  
 6 what is happening there.  
 7 And I put a note here, cocktails based  
 8 on water quality data from ag fields. So we all know  
 9 that the water that's in the environment is not just  
 10 parent Atrazine in H2O, it's a cocktail. And the  
 11 concern that I have is that while we've tested direct  
 12 affects, we haven't even begun to look at any of these  
 13 indirect affects.  
 14 And with a broad statement like that it  
 15 excludes all these indirect affects. So I'm just kind  
 16 of putting on the table that I think a limitation in  
 17 our hypothesis that we can make a positive statement on  
 18 should have the word direct in it.  
 19 DR. HEERINGA: Doctor Schlenk.  
 20 DR. SCHLENK: Well this has been a very  
 21 interesting discussion this morning Dan Schlenk, UCR.  
 22 I wondered again, this is, I'm more of a  
 23 fish toxicologist but I wonder if we had these  
 24 discussions 50 years ago when we were talking about  
 25 utilization of the Fathead minnow if this was something

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1 that was bantered about quite a bit.  
 2 And, you know, the Fathead minnow is  
 3 obviously a surrogate model, it's a native species, but  
 4 if I want to look at genetic toxicology or how things  
 5 affect the geno I'm looking at the Zebra fish. The  
 6 Zebra fish is a well characterized model.  
 7 Now, would EPA use a toxicity test from  
 8 Zebra fish to set a standard or to make a decision? I  
 9 don't know.  
 10 I think the model that you select is  
 11 based upon the question that you're asking, it always  
 12 is.  
 13 And in this particular case I think the  
 14 question you're asking is, are North American  
 15 amphibians going to be affected? And in order to do  
 16 that I think you have to in my opinion, have a  
 17 comparison between your exotic species answering the  
 18 question that you are, and in this particular case, is  
 19 gonadal development, that question. This particular  
 20 exotic model actually answers that question I think in  
 21 that regard.  
 22 Can you apply those data to native  
 23 American species? Maybe, but you can't say for sure  
 24 until you actually test it in the North American  
 25 species.



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1 So again I would concur again with what  
 2 Peter sort of indicated in his responses that, you  
 3 know, I think you have to kind of change the question a  
 4 bit.  
 5 It definitely affects *Xenopus gonadal*  
 6 develop or it does not affect *Xenopus gonadal*  
 7 development. But does that mean that's it and the door  
 8 is closed? I can't agree with that.  
 9 DR. HEERINGA: Other discussants, then  
 10 Doctor Bailey.  
 11 DR. BAILEY: Yeah, I agree with Ted  
 12 Bailey I agree with the previous comment. And again  
 13 if you're going to make that comparison I think it will  
 14 have to be within the same experiment. Otherwise you  
 15 have what statisticians refer to as disconnect  
 16 experiments in which you can't make any comparison.  
 17 And if we can't do that we'll be back the next time  
 18 we're here in the same position of trying to decide if  
 19 you can have any test about, no difference between  
 20 species.  
 21 So it's a very difficult problem to  
 22 handle.  
 23 DR. HEERINGA: Comments from other panel  
 24 members on this. Doctor Delorme.  
 25 DR. DELORME: Just following along on

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1 Doctor Heeringa's earlier observation that had the  
 2 results been positive would we be as concerned?  
 3 Perhaps the panel would be concerned and  
 4 maybe the registrant would have been a bit concerned  
 5 and maybe at that point they would have said, oh well,  
 6 maybe we should do this in a native American species to  
 7 try and see whether or not there is concurrence of  
 8 affects.  
 9 Just an observation. I mean there are  
 10 different ways of looking at this. You know, it's a  
 11 conundrum, I acknowledge that.  
 12 And again it's just the in part I  
 13 think a coincidence of events that's happened. Certain  
 14 papers that have been published in the past number of  
 15 years have focused on frogs and frogs are now on the  
 16 radar.  
 17 And I think from a broader context or a  
 18 longer term perspective, you know, amphibians are,  
 19 you're going to have to do something with them in the  
 20 future.  
 21 At the very least we're going as  
 22 regulatory agencies, I think we're going to have to go  
 23 back and look at the assumptions that we can use fish  
 24 as surrogates, at least for the in life water stages of  
 25 amphibians.

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1 And but as I said it's on the public  
 2 radar, it's on the scientific radar and, you know, our  
 3 job is to do the assessment and make sure that the  
 4 assumptions that we make here are valid.  
 5 And our assumptions with respect to  
 6 uncertainty and our ability to make conclusions based  
 7 on surrogate species I think are going to come under  
 8 scrutiny probably.  
 9 DR. HEERINGA: Steve Heeringa, my  
 10 comments earlier about the sort of post hoc nature of  
 11 our conversations, I think obviously as a statistician  
 12 we want the hypothesis to be followed through  
 13 regardless, but from a regulatory standpoint and a  
 14 practical decision making standpoint, the post hoc sort  
 15 of view of this is different depending on the outcome  
 16 of that first experiment I think.  
 17 So there's a little difference between  
 18 the decision process and what would be a pure  
 19 scientific process.  
 20 Additional comments? Doctor Green.  
 21 DR, GREEN: Could I just raise the  
 22 question, when you referred to had the outcome been  
 23 different in *Xenopus laevis*, do you mean that for  
 24 certain these experiments would have been repeated in  
 25 *Rana pipiens*?

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1 DR. HEERINGA: If the outcome had been  
 2 different  
 3 DR, GREEN: Positive.  
 4 DR. HEERINGA: positive.  
 5 DR, GREEN: So we were able to show  
 6 affects of Atrazine on *Xenopus laevis* gonadal  
 7 development.  
 8 DR. HEERINGA: That point I hadn't  
 9 actually considered, but I think the framework of the  
 10 discussion here in the face of a positive, a strong  
 11 positive affect of Atrazine on *Xenopus laevis*, that in  
 12 fact the whole conversation would have been a review of  
 13 that study and the EPA, I'm speculating that the EPA  
 14 offices would have moved ahead on the basis of our  
 15 judgement about the quality of that *Xenopus* data.  
 16 Now whether that would have led to other  
 17 decisions, I don't know and that's probably neither  
 18 here nor there. But I just wanted to make that point,  
 19 that, you know, in the discussion and the motivation in  
 20 terms of this additional step and apparent  
 21 recommendation from this panel that we not think about  
 22 *Xenopus* as a complete surrogate for the native species  
 23 and that additional work on native species is  
 24 warranted, I'd say we're looking at that decision after  
 25 a set of experimental results and it has to have been



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1 different even when we looked at it in advance.  
 2 DR. GREEN: Maybe I could address Doctor  
 3 Steeger. What is the standard protocol for the Agency  
 4 if you do have a positive study say in one species, do  
 5 you routinely move into a higher species?  
 6 For example if there are positive  
 7 results in rats or mice, do you then repeat the  
 8 experiments in dogs?  
 9 DR. STEEGER: Each pesticide has a  
 10 standard set of data that are required of the  
 11 registrant to submit for the purposes of registering  
 12 the pesticide.  
 13 The human health studies contain a  
 14 battery of tests across a number of species. As I  
 15 indicated though for ecological risk assessments, while  
 16 we make use of the mammalian tox data we have a very  
 17 limited number of species, two birds, two freshwater  
 18 fish, on invertebrate, one freshwater invertebrate and  
 19 up to three saltwater invertebrates and one marine  
 20 fish.  
 21 That's it. We do not, we have to draw  
 22 our conclusions on ecological risk based on that base  
 23 set of data and what we can glean from the open  
 24 literature. Whether it concurs, conflicts, with our  
 25 understanding of the acute and chronic toxicity of the

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1 chemical.  
 2 DR. GREEN: Thank you.  
 3 DR. HEERINGA: Additional comments on  
 4 this particular charge  
 5 question? Doctor Steeger, I think the panel has been  
 6 fairly clear that there is an element of uncertainty  
 7 that remains that will have to be considered. I hope  
 8 we provided enough guidance for you to sort of  
 9 calibrate that level of uncertainty, at least at a  
 10 gross level.  
 11 DR. STEEGER: I do have some follow up  
 12 questions beyond the ones that I asked this morning.  
 13 DR. HEERINGA: Okay.  
 14 DR. STEEGER: I'd like some clarification  
 15 on the issue of the degradedates.  
 16 Is the panel concerned about the  
 17 exposure to the degradedates themselves or the fact that  
 18 it was a flow through as opposed to a static study?  
 19 DR. HEERINGA: I had that as point 3 from  
 20 this morning but maybe it's different.  
 21 Would somebody on the panel, a member of  
 22 the panel like to respond to that particular issue of  
 23 the degradedates and the flow through versus static test  
 24 experimentation?  
 25 Doctor LeBlanc, will you lead off?

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1 DR. LEBLANC: I can try but I don't know  
 2 that I'm the best person to respond because I wasn't  
 3 terribly concerned about it.  
 4 But it was my understanding that not so  
 5 much I don't think the issue was so much whether or  
 6 not the degradedates are themselves problematic because I  
 7 think the issue was raised and I think it was resolved  
 8 that if indeed the degradedates are responsible for  
 9 toxicity, then toxicity would be observed in the in  
 10 vivo studies.  
 11 I think the issue was, as I perceived  
 12 it, was perhaps ambiguities between flow through and  
 13 static renewal studies could be explained in part due  
 14 to degradedates. That is, degradedates are accumulating in  
 15 the static renewal conditions and as such animals in  
 16 those conditions are exposed to higher levels of  
 17 degradedates that might be biologically active and that  
 18 might be why we're not seeing it in flow through  
 19 studies.  
 20 That was my understanding. So if, and  
 21 again if I'm wrong my personal take on that is I'm sure  
 22 it's relevant because it seems to me that's an artifact  
 23 of experimental design and that in my opinion the flow  
 24 through study is a better design.  
 25 DR. HEERINGA: Doctor Denver.

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1 DR. DENVER: Yeah, so the issue that was  
 2 raised I think yesterday and discussed was that we  
 3 don't know if degradedates or metabolites were  
 4 accumulating in the static renewal, that were not  
 5 present in the flow through.  
 6 But the other issue that was brought up  
 7 was that we don't know if there are affects of  
 8 individual degradedates or metabolites on amphibian  
 9 gonadal development.  
 10 There is literature that suggests that  
 11 there are affects of these degradedates on, as I  
 12 mentioned prostate and pubertal development in rats and  
 13 there are some other studies that suggest that there  
 14 may be affects.  
 15 So that's why that issue was raised,  
 16 that we don't know whether there are affects in  
 17 amphibians. And we also don't know whether the affects  
 18 that were potentially seen in the static renewal,  
 19 whether you believe those affects or not, were caused  
 20 degradedates that could have accumulated.  
 21 So I don't know how to directly answer  
 22 your question since we don't know whether these  
 23 degradedates or metabolites have any impact on amphibian  
 24 physiology or development.  
 25 I guess that there are two questions



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1 there.

2 One is whether they do impact amphibian

3 development and the other is whether affects that may

4 have been seen in the static renewal, or people may see

5 in the static renewal, are due to that accumulation.

6 So those are two, I guess two different

7 questions.

8 DR. STEEGER: Are we agreed that because

9 we have data demonstrating that the three primary

10 degradedates, DACT, DIA and DES, I'm sorry, it's just too

11 much to mention those chemicals again, that they do

12 form in vivo and that the mass balance if you will of

13 chemical in and chemical out would have been occurring

14 in the flow through study in the Xenopus and presumably

15 that those animals would have been exposed to the

16 degradedates as well as the parent in the flow through

17 study, and that the study would be accounting for

18 potential affects of the degradedate plus the parent in

19 the Xenopus study?

20 DR. DENVER: Well I guess the question

21 that goes back to the static renewal is one of

22 concentration and if they have accumulated to a higher

23 level than they would have in the flow through system

24 and does that have an impact?

25 But I don't know the answer to that, but

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1 that is the question that is posed.

2 DR. CHAMBERS: This is Jan Chambers, I

3 have a response to that too.

4 There's a little bit of a semantic

5 problem here I think, because those of us who study

6 metabolism would call those metabolites and degradedates

7 would be environment breakdown products in my opinion.

8 But as was mentioned yesterday I think

9 the animal if it's producing metabolites is going to be

10 exposed to those in the study and therefore if they are

11 exerting any toxicity, then the in vivo study would

12 demonstrate that.

13 However I think the concern level on

14 this needs to be leveled against what the environment

15 is accumulating. I assume you're doing some

16 environmental monitoring studies on the parent

17 compounds and the environmental degradedates. If the

18 degradedates are prominent then there may be a greater

19 level of concern. If they're pretty diluted then I

20 don't know how much of a concern there needs to be

21 about that.

22 But the metabolites really should take

23 care of themselves in the in vivo study as being

24 present in the organism.

25 DR. STEEGER: I understand this is Tom

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1 Steeger our understanding is that one of the primary

2 routes of degradation in Atrazine is by biotic

3 degradation and that the degradedates are equivalent to

4 the metabolites that the animal was forming, so that

5 the exposure through a flow through study to the

6 metabolites would likely be as great as they would have

7 been in a static system, because they're the same

8 compounds.

9 DR. HEERINGA: Doctor Delorme and Doctor

10 Green.

11 DR. DELORME: I think if that's the

12 assumption you're making you need to look at it with

13 respect to what you see in the environment, okay? And

14 I think that we've already made that comment.

15 And, you know, I think that Doctor

16 Chambers has covered it off, saying that with respect

17 to the metabolites, i.e., the in organism produced

18 degradation products, it's encompassed in the design.

19 But I think the concern is those

20 degradedates probably have different physical chemical

21 properties than the parent compound. They may be more

22 or less persistent and therefore there could additional

23 concentrations in the environment that come from either

24 bacterial degradation or other biotic transformation.

25 And it has to be considered.

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1 DR. STEEGER: This is Tom Steeger again,

2 so you would not be recommending that metabolites, if

3 you indeed found that they were higher concentrations

4 of the degradedates in the environment, that a static

5 renewal study would be required to look at that, you

6 could do it with a flow through study.

7 DR. DELORME: I'll have to think about

8 that. It just depends, Tom. You really have to look

9 at the first part of the risk assessment framework is

10 the exposure, right?

11 And given that we know Atrazine does, is

12 out in the environment, are the degradedates accumulating

13 a little bit, are they sticking around a little bit

14 longer than the parent? In which case they may have

15 reached an elevated concentration than you would

16 normally find.

17 I don't know, you have to look at the

18 data.

19 DR. STEEGER: Right, but the question for

20 approaching the study itself

21 DR. DELORME: Uh-huh.

22 DR. STEEGER: did not require a static

23 renewal study to accomplish

24 DR. DELORME: No, not necessarily. If

25 you had access to the degradedates and the chemicals you



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1 could expose them to them.  
 2 And I think that earlier I suggested you  
 3 might want to even look and see if there's any receptor  
 4 assays that have been done to see if there's even any  
 5 indication that they could interact with the endocrine  
 6 system.  
 7 DR. HEERINGA: Doctor Isom and then  
 8 Doctor Green.  
 9 DR. ISOM: I just might add, I think in  
 10 the 2003, in our discussion at that panel meeting there  
 11 was some concern about interaction of the degradedates of  
 12 the metabolites with the receptor system, estrogen  
 13 receptor and there were some comments. They may even  
 14 be anti-estrogens in activity. There was some, I think  
 15 that was written up in the report also.  
 16 And there was so much concern about that  
 17 comment on it that it was recommended that that be  
 18 studied in a little more detail, or at least come data  
 19 be generated there.  
 20 DR. HEERINGA: Doctor Green.  
 21 DR, GREEN: Just a point about the flow  
 22 through system. In terms of degradedates and metabolites  
 23 and exposures, I feel pretty confident with a flow  
 24 through system you have exposure and those exposures  
 25 are occurring in the absence of additional stressors

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1 that relate to poor water quality, which certainly  
 2 would maybe I wouldn't say certainly, would have the  
 3 potential to intensify negative affects of the parent  
 4 compound, the metabolites, the degradedates.  
 5 So the fact that the studies were  
 6 conducted in flow through systems I think the first  
 7 study is a good thing, because we have a pretty clear  
 8 picture of exposure in the absence of say nitrate and  
 9 nitrite, ammonia and anything else.  
 10 So moving into a static system now where  
 11 those compounds may hang around just a little bit  
 12 longer, but in the presence of additional water quality  
 13 parameters that are already known to stress frogs in  
 14 captivity in the laboratory environment, might enhance  
 15 the affects that they have.  
 16 And those affects would in terms of  
 17 water quality may be closer to what happens in the  
 18 environment in a static system versus the beautiful  
 19 water quality that you get in a nice well managed flow  
 20 through system.  
 21 DR. HEERINGA: Doctor Steeger.  
 22 DR. STEEGER: Not to beat this poor dead  
 23 horse to death, but the difficulty that I have is that  
 24 the Agency relies on very strict standards for  
 25 conducting studies. And those studies are under, are

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1 derived from ASTM guidelines and ASTM guidelines, the  
 2 most modern ones rely on flow through conditions  
 3 because you are able to eliminate the confounding  
 4 effects that can influence the outcome of a study.  
 5 At some point you lose the ability to  
 6 detect whether it's the chemical or all these other  
 7 factors.  
 8 And where we digress into how much our  
 9 standardized studies reflect reality, that's an  
 10 uncertainty that we, EPA staff scientists wrestle with  
 11 on a daily basis.  
 12 But in order for us to move forward and  
 13 be able to say with some reason of certainty that it is  
 14 the chemical and not environmental factors that are  
 15 causing the affect, we rely very heavily on flow  
 16 through systems and not the static.  
 17 And that's why I raised this issue as if  
 18 you felt that it was necessary to address the degradedate  
 19 issue, does it have to be addressed under static flow  
 20 through conditions, or static conditions, because that  
 21 is not consistent with our process.  
 22 DR, GREEN: Yeah, and I agree and that  
 23 point is well taken. And I think if there is a way to  
 24 expose them to degradedates in a flow through system that  
 25 would be ideal because then you eliminate all the other

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1 possibilities with all the water quality issues that  
 2 come up otherwise.  
 3 DR. HEERINGA: No comments on this point?  
 4 Yes, Doctor LeBlanc.  
 5 DR. LEBLANC: Just a quick comment. In  
 6 reading over the charge questions I think the Agency  
 7 was very careful to whenever they made a statement with  
 8 regards to conclusions based on the DCI study and  
 9 Atrazine and its affects on gonadal development, they  
 10 seem to have gone out of their way to always state  
 11 Atrazine, by itself, and you know, I think that  
 12 qualifying statement is very, very important.  
 13 There are a lot of other, as I mentioned  
 14 earlier, considerations that could impact the affect of  
 15 Atrazine on gonadal development but I think it's beyond  
 16 the purview of this SAP.  
 17 We can discuss them but I don't think  
 18 it's part of the charge questions.  
 19 DR. HEERINGA: Doctor Steeger, we have  
 20 several other issues, I wrote, maybe we could turn to  
 21 the issue of the reliability study or would you have an  
 22 order that you would like to pick up these final  
 23 points?  
 24 DR. STEEGER: Tom Steeger. We can, I  
 25 have hard copies of each of the items that were brought



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1 DR. HEERINGA: Great.  
 2 DR. STEEGER: up this morning.  
 3 DR. HEERINGA: Okay, good. Those will be  
 4 distributed.  
 5 DR. STEEGER: I'm wondering, Doctor  
 6 Heeringa, if it would better if we wait until after  
 7 lunch to get into this?  
 8 DR. HEERINGA: Doctor Portier just  
 9 suggested the same thing and since we have confirmatory  
 10 replication, let's do that.  
 11 I have twenty minutes of twelve. Let's  
 12 rejoin here at 1:00 p.m. if that suits. A good  
 13 suggestion for everybody. A very productive morning.  
 14 I think we'll be fresh to pick these up and any final  
 15 closing items.  
 16 Thank you, Doctor Steeger. We'll see  
 17 everyone at 1:00 p.m.  
 18 (WHEREUPON, there was a recess.)  
 19 DR. HEERINGA: Welcome back everyone. I  
 20 invite you to return  
 21 with us to the final I think afternoon session of our  
 22 multi day meeting of the FIFRA Science Advisory Panel  
 23 on the topic of the Potential for Atrazine to Affect  
 24 Amphibian Gonadal Development.  
 25 At this point we have completed our

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1 panel's response to the 13 charge questions but we are  
 2 revisiting some points related to the earlier  
 3 responses, points of clarification.  
 4 And Doctor Steeger and the scientific  
 5 staff of EPA have provided us I think with a list in  
 6 writing of some of those questions.  
 7 And one of them we had addressed prior  
 8 to the break which related to the degradedates I believe  
 9 of Atrazine and the potential experimental process that  
 10 might be applied to study their affects. And I think  
 11 the panel was quite clear in its responses to that  
 12 particular follow up question.  
 13 Doctor Steeger, let me have you take  
 14 them in the order that you'd like. There are some  
 15 residual questions that you have, so if you would just  
 16 point us to the question you'd like to address and  
 17 we'll pick it up.  
 18 DR. STEEGER: Let me just start at the  
 19 top of the page. That's with respect to question  
 20 number 8. I'm unclear whether the panel in its final  
 21 recommendation to the Agency is to require their review  
 22 of the sub-samples of slides from the DCI studies or  
 23 whether that is simply a added benefit that could be  
 24 derived to help reduce uncertainty.  
 25 If it's the latter, if you feel that

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1 there is an actual need to conduct this pathology  
 2 review board, is that based on uncertainty regarding  
 3 measurements that were made or observations that were  
 4 made relative to the apical end points or is it  
 5 relative to secondary measurement end points such as  
 6 aplasia and mineralization?  
 7 If it's the latter, has the panel  
 8 determined the biological relevance of the secondary  
 9 measurement end points and/or, how much would these  
 10 secondary end points really have to change before  
 11 conclusions regarding the apical end points would be  
 12 affected?  
 13 DR. HEERINGA: Doctor Miller, would you  
 14 like to address that first?  
 15 DR. MILLER: Debra Miller. Yeah,  
 16 basically what we're going to do is recommend that you  
 17 bring in two additional pathologists.  
 18 And the main reason for this is because  
 19 you're doing it for regulatory purposes and you wanted  
 20 to follow the general laboratory practices with quality  
 21 assurance.  
 22 And to do that it's a good idea to bring  
 23 in two additional pathologists.  
 24 And the sub-sample that we are talking  
 25 about is the sub-sample of whole animals. And you'd

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1 probably need some statistical testing to determine the  
 2 proper number that will give you what you need as far  
 3 as the number of animals to look at.  
 4 And then in that sub-sample you take the  
 5 whole slide set from those animals and using those same  
 6 slides you have two other pathologists review  
 7 everything. We're not breaking it out into, you know,  
 8 primary or secondary things. Everything that was  
 9 reviewed from those slides should be reviewed again for  
 10 quality assurance. And should be read and the lesions  
 11 scored in the same manner, using the same parameters.  
 12 And then as far as biological  
 13 significance of the secondary end points, do we know  
 14 that they are biologically significant or at what point  
 15 they're biologically significant? We can't always say  
 16 that but we also cannot say that they're not, because  
 17 we don't necessarily know.  
 18 And until you look at them and include  
 19 those scorings in your analysis, we're not going to  
 20 know. So we need to see, how do the different scores  
 21 factor in and do they relate to anything?  
 22 And then also just to go back to that,  
 23 at what point are they significant? Until you test  
 24 function we also don't know.  
 25 So you need to do both.



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1 DR. STEEGER: Thank you.  
 2 DR. HEERINGA: Doctor Miller I think was  
 3 the lead discussant on that question too, so that  
 4 response would reflect at least the tenor of the  
 5 current collective response from the group.  
 6 Any other contributions from panel  
 7 members on that particular question of clarification?  
 8 Go on to the next question, Doctor  
 9 Steeger.  
 10 DR. STEEGER: With respect to question  
 11 number 1, yesterday's discussion sounded as though  
 12 panel members concurred with the Agency's evaluation  
 13 criteria for open literature.  
 14 These same criteria were applied to the  
 15 registrant's submitted studies as well. The panel also  
 16 seemed to agree that the open literature consisting of  
 17 both laboratory and field studies did not across  
 18 multiple evaluation criteria meet the standards of  
 19 acceptability.  
 20 It was unclear after yesterday's  
 21 discussion though, whether the panel believes that the  
 22 open literature continued to have some utility in  
 23 refuting or confirming the hypothesis that Atrazine  
 24 exposure causes affects on gonadal developmental  
 25 affects.

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1 Yesterday Doctor Carr from Texas Tech  
 2 University and Doctor Jeff Wolfe from Experimental  
 3 Pathology Laboratories provided a brief overview of the  
 4 re-analysis of the tissues which were initially  
 5 reported as inter-sex animals. This re-analysis  
 6 concluded that none of the animals originally reported  
 7 as inter-sex were indeed inter-sex.  
 8 Therefore to our knowledge the only  
 9 literature reviewed to date claiming to result in  
 10 inter-sex is that of Doctor Hayes.  
 11 If the panel believes that open  
 12 literature has some utility relative to the data call  
 13 in studies, do they believe that the multiple lines of  
 14 evidence are consistent with the outcome of the DCI  
 15 studies indicating that Atrazine is not affecting  
 16 amphibian gonadal development? And I understand that  
 17 that would be more refined now based on earlier  
 18 conversations today that Atrazine does not affect  
 19 amphibian gonadal development in *Xenopus laevis* at  
 20 concentrations up to 100 micrograms per liter.  
 21 DR. HEERINGA: With those qualifications  
 22 as Doctor Steeger has just presented them, would anyone  
 23 from the panel like to comment on this point in  
 24 response to that question?  
 25 SPEAKER: Could I just get a

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1 clarification please on those data?  
 2 The re-analysis that was conducted on  
 3 the Carr data set was on the animals that were  
 4 originally classified as inter-sex. And there is  
 5 another, according to the paper there is another data  
 6 set which discusses discontinuous, a measure or at  
 7 least a categorization of in my understanding, abnormal  
 8 gonads which were classified in the study as  
 9 discontinuous gonads. And it's also a significant end  
 10 point in the study.  
 11 I was wondering if those data were, they  
 12 were not re-analyzed because they were not classified  
 13 originally as inter-sex. The data stands as a data set  
 14 that suggests that there is some gonadal abnormalities  
 15 in those animals at significance level of 25.  
 16 I just wanted to clarify if those two  
 17 data sets are still being treated separately?  
 18 DR. STEEGER: We could have Doctor Carr  
 19 or Doctor Wolfe come back up and present a more  
 20 detailed presentation on what their analysis consisted  
 21 of if the panel would benefit from that.  
 22 DR. HEERINGA: I'm turning to the panel  
 23 here, Bruce?  
 24 MR. PAULI: I guess so, if we can just  
 25 have a determination that, maybe even a clarification

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1 of what this abnormality, which I think it is,  
 2 represents. It's a discontinuous categorization of  
 3 those gonads was discontinuous and it's a separate data  
 4 set. It's a separate data set from the inter-sex  
 5 animals.  
 6 DR. CARR: I'm Doctor Carr, Texas Tech  
 7 University. To answer the first question, we did not  
 8 pull the slides that were from animals that were  
 9 identified by gross morphologies, discontinuous testes  
 10 and have those analyzed by EPL, just the animals that  
 11 were originally scored as inter-sex.  
 12 And part of the rationale there was to  
 13 try to harmonize terminology from 2001 which was when  
 14 our study was done with some of the newer findings on  
 15 how the term inter-sex is used.  
 16 The question about what discontinuous  
 17 gonads were at the gross morphology level, the original  
 18 description in the paper discussed this and it really  
 19 has to do with uniform shape of the ovary, the ovary in  
 20 Stage 66 animal is longer than the testes. Whether  
 21 there is a uniform shape throughout the gonad at the  
 22 gross morphology level in either the testes or the  
 23 ovary.  
 24 So there might have been for example a  
 25 testes with a small butt of tissue at the end or



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1 something that the readers felt was just not uniform in  
 2 shape as a discontinuous gonad. And those were based  
 3 on two naive readers who went through all of the gross  
 4 morphology of the animals that were studied.  
 5 MR. PAULI: Bruce Pauli, so just to  
 6 clarify then, those readers compared to the control  
 7 gonads or their understanding of what a controlled  
 8 gonad would look like, they might classify it as  
 9 abnormal?  
 10 DR. CARR: They would not compare them to  
 11 the controls because they were blinded to the  
 12 treatments. They would just identify whether they look  
 13 uniform in shape or were discontinuous as kind of an  
 14 absolute.  
 15 You know, part of your identification is  
 16 male or female and at the gross morphology level it's a  
 17 pretty easy thing to do in Stagee 66 animals. So was  
 18 the ovary normal looking in terms of its uniform shape,  
 19 was the testes normal looking in its uniform shape or  
 20 were there things that looked like they were butting  
 21 off or discontinuous in the gonad.  
 22 It's not an end point that we know has  
 23 any biological relevance at the point, at the time but  
 24 it was something that they did write down and score in  
 25 the raw data when they evaluated it.

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1 MR. PAULI: And yeah, I guess I'm happy  
 2 with that. It clarifies that that's a separate data  
 3 set and it's basically a, I guess you could say a  
 4 qualitative score of abnormality and it's, there is a  
 5 dose response in that data set with significance at 25.  
 6 But it is as you say a qualitative score  
 7 based on a blind reading of  
 8 DR. CARR: Right.  
 9 MR. PAULI: the gross morphology of  
 10 those  
 11 DR. CARR: Right.  
 12 MR. PAULI: -- gonads.  
 13 DR. CARR: Right.  
 14 MR. PAULI: And it's the inter-sex  
 15 animals only that were reevaluated.  
 16 DR. CARR: Well  
 17 MR. PAULI: Those animals that were  
 18 identified through gross morphology as potentially  
 19 ambiguous sex.  
 20 DR. CARR: Right.  
 21 MR. PAULI: That were reevaluated at DPL.  
 22 DR. CARR: That's correct.  
 23 DR. HEERINGA: Other questions for Doctor  
 24 Carr at this point on the research and the re-analysis  
 25 or the review? Thank you very much, Doctor Carr.

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1 Back to the question. Bruce, have you  
 2 had time to can we put you on the spot here?  
 3 MR. PAULI: Bruce Pauli. I guess the  
 4 thing that I was maybe doing there, maybe not  
 5 effectively, was there is certain I think when on  
 6 Tuesday we discussed the possibility that there are  
 7 some, what I'm calling suggestive evidence I guess,  
 8 that there are some things going on.  
 9 And when the data was presented  
 10 yesterday as a re-analysis of the inter-sex animals to  
 11 take that bit of evidence away from consideration, I  
 12 think it in my opinion it was important for me to try  
 13 to understand what that actually meant in terms of this  
 14 study and whether or not I know that we've already  
 15 discussed this particular study and the fact that there  
 16 might have been some water quality issues with it my  
 17 interest I guess was to say, is there any other  
 18 confirmatory or even suggestive evidence out there that  
 19 would provide some information on whether or not there  
 20 is an affect in amphibians?  
 21 And I think in this case there is data  
 22 from one other study I suppose in my opinion that might  
 23 have some suggestion that there is something going on  
 24 in terms of exposure of these animals to Atrazine. And  
 25 just to get some clarification on how that data set was

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1 more recently assessed was good for me to hear.  
 2 Thanks.  
 3 DR. HEERINGA: Additional comments from  
 4 panel members on this particular question as to whether  
 5 beyond the Hayes studies, whether there is any other  
 6 evidence in the open literature that you would like to  
 7 bring?  
 8 Doctor Steeger, I don't know if we have  
 9 actually addressed this.  
 10 DR. STEEGER: So is that concurrence that  
 11 the open literature is not, has little utility in  
 12 refuting and confirming the hypothesis?  
 13 DR. HEERINGA: Bruce, I think  
 14 MR. PAULI: Bruce Pauli. I guess, yeah,  
 15 I mean we've already agreed that the open literature  
 16 has flaws and we agreed that the way that you evaluated  
 17 that open literature was appropriate and that there are  
 18 some methodological issues and things like that in the  
 19 open literature.  
 20 So I guess in my opinion alone we'd have  
 21 to agree that there aren't any open literature studies  
 22 which would be useful to you based on the evaluation of  
 23 the literature that you do.  
 24 Any further ones I'm not aware of. I  
 25 was just trying to get a clarification on this one



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1 particular study which is as has been noted, is oft  
 2 cited as something that provides to a certain extent a  
 3 little bit of confirmatory evidence to Doctor Hayes'  
 4 studies.  
 5         And to see that there is an affect, a  
 6 significant affect in this study while at the same time  
 7 recognizing that it isn't completely in consideration  
 8 because of the methodological or the data quality  
 9 issues, I think is something that I would like just to  
 10 recognize, that the data set is there.  
 11         There's been a reevaluation of that data  
 12 but not the entire data set which took away from what  
 13 we're dealing with here is a question of whether or not  
 14 we are seeing inter-sex ova testes or testicular  
 15 oocytes in these animals exposed, whereas there is  
 16 another question, can you see gonadal abnormalities?  
 17 Does Atrazine affect gonadal development?  
 18         And I think in this case there is some  
 19 suggestion that it did affect gonadal development.  
 20 We've taken away the inter-sex animals by the re-  
 21 analysis but there is some suggestion that there is  
 22 some affects on gonadal development.  
 23         And then again, then we have to bring in  
 24 these qualifications in terms of the way the study, the  
 25 way the methodological flaws of the study or the data

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1 quality, the water quality issues had to be factored  
 2 into the assessment of that.  
 3         So in the end I think because we have  
 4 accepted the fact that the review and assessment of the  
 5 studies based on the criteria that were applied to them  
 6 were acceptable, then we're left with the one study,  
 7 the DCI study to determine whether or not the  
 8 hypothesis is true, that there is no affect on the  
 9 production of ova testes in Xenopus laevis by Atrazine  
 10 at the exposure concentrations that were assessed.  
 11         DR. HEERINGA: Would any other panel  
 12 members like to contribute on this particular topic?  
 13 Yes, Doctor Schlenk.  
 14         DR. SCHLENK: Yeah, I mean Dan Schlenk  
 15 here I think as memory serves I think Doctor Denver  
 16 had mentioned something about the fact that we wanted  
 17 to not throw the baby out with the bath water, that I  
 18 think some of the studies that were present should not  
 19 be disregarded entirely, but be utilized as a  
 20 comparison after the fact.  
 21         Correct me if I'm wrong, that's sort of  
 22 what you had mentioned before.  
 23         DR. HEERINGA: Doctor Denver.  
 24         DR. DENVER: No, that's right, that was,  
 25 the point that I was trying to make is that the fact

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1 that a study doesn't adhere to EPA standards for GLP it  
 2 opens important significant questions about the  
 3 validity of the findings.  
 4         But the point I was trying to make is  
 5 that those 30-odd studies have, potentially have some  
 6 data in them that could form a basis for developing  
 7 hypotheses, not confirming or refuting the hypothesis.  
 8         I'm not sure if I'm being entirely  
 9 clear. Is that  
 10         DR. STEEGER: Yeah, I this is Tom  
 11 Steeger I understand what you're saying and yes, and  
 12 that's why we're here is because there were sufficient  
 13 data to formulate hypothesis, but at this point it's  
 14 the Agency's position that based on those available  
 15 studies and the flaws that were identified in them or  
 16 the limitations I should say that were identified in  
 17 them, we are in a position that we feel that the only  
 18 study that we can use to test that hypothesis that  
 19 Atrazine exposure results in affects on Xenopus laevis  
 20 at concentrations between the level of detection and  
 21 100 micrograms per liter, have to be based on the  
 22 studies that were responsive to recommendations made to  
 23 the registrant in 2003 by both the Agency and the SAP.  
 24         DR. DENVER: Yes, and with that  
 25 definition I agree.

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1         DR. HEERINGA: Next point, was there a  
 2         DR. STEEGER: That was it I believe.  
 3         DR. HEERINGA: Okay. Okay, at this point  
 4 I think that we have addressed each of the charge  
 5 questions but what I would like to do before we wrap up  
 6 this meeting is I would like to go around the panel.  
 7         Doctor Portier just pointed out to me, I  
 8 think in your notes, Doctor Steeger, just to make sure  
 9 that we've covered everything, on the second page of  
 10 your notes in reference to number 11, question number  
 11 11 follow up I have it as the tiered stage of testing  
 12 from 2003 indicating going forward with mechanism  
 13 studies only if apical affects were observed.  
 14         Does the SAP still support that  
 15 recommendation?  
 16         DR. STEEGER: It's my understanding that,  
 17 and correct me if I'm wrong, that the SAP does still  
 18 support that recommendation.  
 19         DR. HEERINGA: Is that the consensus of  
 20 the panel? Would anybody like to yes, Doctor Green.  
 21         DR. GREEN: Honestly I have to review the  
 22 tiered stage testing that we proposed form 2003, so if  
 23 you could give me just a minute to look at that,  
 24 because was testing in indigenous species part of that  
 25 tier?



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1 And I can't actually recall, I'll have  
 2 to dig that diagram out. So otherwise I guess, is that  
 3 part of the apical affect that we'd be looking at, the  
 4 response of that species, the Rana pipiens?  
 5 DR. STEEGER: The mechanistic studies  
 6 were proposed as a tier two study. The testing of an  
 7 additional species for whether there is an affect or  
 8 not would be a tier one study.  
 9 DR. HEERINGA: Okay, I think individuals  
 10 are thinking here. Yes, Doctor LeBlanc?  
 11 DR. LEBLANC: It's certainly my  
 12 understanding and I think it was the agreement of the  
 13 SAP that tier two testing was warranted only if affect  
 14 were observed in a tier one.  
 15 DR. STEEGER: Thank you.  
 16 DR. HEERINGA: Yes, Doctor Patino.  
 17 DR. PATINO: Reynaldo Patino. I have  
 18 already said I was not part of the 2003 SAP but just  
 19 generically I can say too that, just confirm that if  
 20 there is no phenomenon to study the mechanisms, there's  
 21 no reason to study mechanisms. I mean that's as simple  
 22 as you don't have to explain why.  
 23 DR. HEERINGA: Okay, at this point oh,  
 24 Doctor Denver please.  
 25 DR. DENVER: I have just one additional

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1 general comment. And that is that in light of the re-  
 2 analysis I do hope that the published record will be  
 3 corrected.  
 4 DR. HEERINGA: There was a distribution  
 5 to the panel this morning under a cover from Syngenta  
 6 and Doctor Carr as well with the I think draft report  
 7 and I don't know whether that's actually a manuscript  
 8 or just a report at this point.  
 9 So it's a good point.  
 10 At this stage what I would like to do is  
 11 to go around the panel just to see if there are any  
 12 additional closing comments that the panel would like  
 13 to make based on their participation in this panel  
 14 meeting or the materials that you have seen.  
 15 Maybe we can begin with Doctor Furlow.  
 16 DR. FURLOW: Right, so just to summarize  
 17 some of the thoughts I've had earlier, the testing  
 18 system that was devised and funded by the registrant is  
 19 in fact impressive in its ability to maintain the  
 20 animals in a healthy state and to get them through  
 21 metamorphosis, and I think has real potential to serve  
 22 as a paradigm for testing in at least one amphibian  
 23 species.  
 24 One I guess nagging issue that I guess  
 25 is mollified a little by the statements by the EPA that

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1 they will consider new data as it comes, but this is  
 2 always an ongoing situation and I suppose if not us,  
 3 someone will hold you to that I'm sure.  
 4 MR. WILLIAMS: I think our law holds us  
 5 to that.  
 6 DR. FURLOW: Yeah, exactly. So, that  
 7 there were observations that were not consistent  
 8 between the two laboratories, but were in fact  
 9 reminiscent of some of the findings that the earlier  
 10 Hayes' studies had examined and reported on in terms of  
 11 pigmentation and translucent gonads that we couldn't  
 12 assign to a phenotype, but that's because we don't know  
 13 enough about what that means.  
 14 You know, one can't help but think that  
 15 it is still formally possible that above the 100  
 16 micrograms per liter that something is going on and I  
 17 understand that at least that, you know, with this flow  
 18 through system that this was a system, a situation  
 19 where the animals were not particularly sensitive to  
 20 Atrazine, and that's fine.  
 21 You can argue either, there's no  
 22 evidence one way or the other to support that at this  
 23 point.  
 24 But I just hope that, you know, the EPA  
 25 and as you say, the law requires you to do so. We'll

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1 keep an open mind and keep looking at the open  
 2 literature to see if that in fact higher levels may in  
 3 fact cause gonadal issues, whatever that may mean for  
 4 the animal and that if surface water or drinking water  
 5 reaches those levels, despite the best practice  
 6 management issues that I believe was sincerely  
 7 presented by the Farm Bureau, et cetera, despite, you  
 8 know, their best practices, you know, these things  
 9 happen.  
 10 So I wish, I guess that sums up most of  
 11 my concerns.  
 12 DR. HEERINGA: Thank you, Doctor Furlow.  
 13 Doctor Denver, any additional you take a pass.  
 14 Doctor Skelley? Bruce Pauli?  
 15 MR. PAULI: I agree with that and I think  
 16 there's, I think that the 2003 white paper statements  
 17 where there's insufficient evidence to either support  
 18 or refute the hypothesis that Atrazine has affects on  
 19 amphibian gonadal development, and we're now basing a  
 20 decision or an evaluation on whether or not Atrazine  
 21 alone causes gonadal inter-sex in Xenopus laevis and in  
 22 the DCI experimental setup and there are slightly  
 23 different things there.  
 24 And I think I agree with and I like  
 25 Dan Schlenk's, Doctor Schlenk's statement that we don't



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1 want to throw out the baby with the bath water and I  
 2 think I would concur that as evidence or as new studies  
 3 are published, that it will be interesting to see how  
 4 we can use those open literature studies and further  
 5 assessment of environmental impacts.  
 6 DR. HEERINGA: Doctor Green? Doctor  
 7 Isom?  
 8 DR. ISOM: Right, I'd just like to make a  
 9 comment and commend the EPA and the registrant for  
 10 conducting the studies and interpretations of them. I  
 11 think that the conclusions are very logical and  
 12 certainly have a great deal of bearing on future types  
 13 of analysis.  
 14 With that caveat though I'd like to  
 15 point out that there is kind of a, I guess uneasiness  
 16 among the panel of a clear interpretation that answer  
 17 the questions directly, the main question of whether  
 18 there was an affect or was not.  
 19 I guess from just observing this as a  
 20 scientist that we're really kind of stuck at a point  
 21 where we need some really good basic science and we  
 22 need to continue to monitor the field studies which I  
 23 think have an important contribution in any of these  
 24 pesticide management and decisions.  
 25 And we kind of got away from that, but

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1 in the past the SAP has considered toxicological  
 2 evaluations of pesticides in the field studies so I  
 3 guess you could say post-marketing did play an  
 4 important role to continue to follow the toxicological  
 5 analysis of the pesticides, and certainly that would be  
 6 true here.  
 7 DR. HEERINGA: Thank you very much,  
 8 Doctor Isom. Doctor Handwerger.  
 9 DR. HANDWERGER: I'd just like to say how  
 10 much I appreciate the difficult position that you're  
 11 in.  
 12 It's so, on the one hand reassuring to  
 13 have negative data but negative data is often so  
 14 difficult to interpret because there are so many  
 15 reasons why it could be negative. I really think it's  
 16 so difficult to make regulatory decisions based on  
 17 negative data.  
 18 I mean in the field of good old homo  
 19 sapiens of the position of the FDA approving a drug  
 20 after it's gone through 500 patients and having the  
 21 501st and 502nd patient developing fatal complications.  
 22 It's really a very difficult position,  
 23 giving you a little bit of a hard time. I hope it'll  
 24 be taken in perspective. We realize the tremendous  
 25 pressure on you and the difficulties. And the

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1 selection of an appropriate model is always a difficult  
 2 situation. I've never seen a model system that  
 3 couldn't be criticized except the actual species you're  
 4 pertaining to, and then you can always find something  
 5 wrong with that.  
 6 Hypotheses are only there to be tested  
 7 and they're only as good as the next piece of data that  
 8 comes along.  
 9 So thank you very much for this meeting.  
 10 DR. HEERINGA: Doctor Schlenk? Doctor  
 11 Portier? Doctor Patino?  
 12 DR. PATINO: Reynaldo Patino. And I  
 13 would just like to reiterate some comments I think I  
 14 made earlier. And in the context of the way I  
 15 understood our charge, my charge was to address or  
 16 assess the evidence for Atrazine affects on amphibian  
 17 gonadal development.  
 18 And, you know, using the I didn't  
 19 comment when the question number 13 came up, but  
 20 using  
 21 the way the question was posed by the EPA that the  
 22 first conclusion being that Atrazine does not have  
 23 adverse affects on amphibian gonadal development, I  
 24 think as a scientist I cannot answer that question in  
 25 the, positively or negatively, I don't think there's  
 sufficient evidence for that.

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1 But if you phrase the question as we  
 2 discussed yesterday, does Atrazine affect Xenopus  
 3 gonadal development within the range of concentrations  
 4 tested, as it says during Stage 66, the answer is no,  
 5 there is no evidence for that.  
 6 So I just wanted to make sure that I can  
 7 answer some questions but I cannot answer others. It  
 8 depends on how the question is phrased.  
 9 DR. HEERINGA: Doctor Delorme?  
 10 DR. DELORME: I just wanted to echo  
 11 Doctor Isom's comments with respect to the quality of  
 12 the review and the quality of the study that was done.  
 13 I think it's rare and given that this  
 14 was the first attempt I think Syngenta should be  
 15 commended as well as EPA for their review of the  
 16 information and the presentation.  
 17 I also appreciate the position you're in  
 18 with respect to trying to deal with the uncertainty and  
 19 I look forward to discussing it with you later.  
 20 DR. HEERINGA: At this point I think that  
 21 we've reached at least the end of our general input.  
 22 I'll turn back to Doctor Steeger to see if there are  
 23 any final closing comments or questions of the EPA  
 24 scientific staff.  
 25 DR. STEEGER: I just wanted to take this



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1 opportunity to thank the SAP for their time and  
 2 dedication to helping provide input to the Agency on  
 3 what is a very important issue for us and we look  
 4 forward to reading your final report.  
 5 Thank you.  
 6 DR. HEERINGA: Thank you, it's Steve  
 7 Heeringa here. On behalf of the panel I believe this  
 8 has been a very productive three days and I want to  
 9 thank the panel members, members of the EPA scientific  
 10 staff for all of their contributions, the public  
 11 commenters, representatives from Syngenta for their  
 12 detailed presentations.  
 13 At this point in time the panel will  
 14 compile its minutes of this meeting in the form of an  
 15 edited report which should reflect the discussions and  
 16 the comments made during this meeting. It shouldn't  
 17 reflect things that weren't covered or you shouldn't  
 18 expect to see a point of view stated that was not  
 19 expressed in these meetings. That's the nature of the  
 20 open meeting setup that we have for this Science  
 21 Advisory Panel.  
 22 I want to again thank everybody for  
 23 their participation and obviously this is a large  
 24 issue, a very important issue to the Agency and also to  
 25 the industry as well and to the general public in the

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1 prepared to call this meeting to a close.  
 2 Again, thank you everyone and safe  
 3 travels.  
 4 (WHEREUPON, the Meeting was concluded at 1:40 p.m.)  
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1 United States and Canada. And I thank our Canadian  
 2 representatives for participating in this process as  
 3 well, it's very, very helpful to have that perspective.  
 4 So at this point in time before we close  
 5 the meeting I'd like to turn back to the Designated  
 6 Federal Office, Joe Bailey, to see if there are any  
 7 final closing administrative comments.  
 8 MR. BAILEY: No administrative comments.  
 9 In closing I just want to thank everybody for their  
 10 participation, in particular the public commenters who  
 11 came forward offering remarks and to EPA for their  
 12 thorough compilation of the background materials and  
 13 the presentation slides.  
 14 I want to thank the panel for agreeing  
 15 to take the time out from their busy schedules to do  
 16 the work that's necessary to come to the meeting in  
 17 such a prepared state as you were. So thank you very  
 18 much.  
 19 And I look forward to working with you  
 20 on completing the final meeting minutes. And they will  
 21 be completed within 90 days after the meeting and will  
 22 be available both in the docket and on the SAP website.  
 23 And finally I'd like to thank Doctor  
 24 Heeringa for chairing the meeting for us.  
 25 DR. HEERINGA: Thank you. With that I'm

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1 CAPTION  
 2  
 3  
 4 The foregoing matter was taken on the date,  
 5 and at the time and place set out on the Title  
 6 page hereof.  
 7 It was requested that the matter be taken by  
 8 the reporter and that the same be reduced to  
 9 typewritten form.  
 10 Further, as relates to depositions, it was  
 11 agreed by and between counsel and the parties that  
 12 the reading and signing of the transcript, be and  
 13 the same is hereby waived.  
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1 CERTIFICATE OF REPORTER  
 2 COMMONWEALTH OF VIRGINIA  
 3 AT LARGE:  
 4 I do hereby certify that the witness in the  
 5 foregoing transcript was taken on the date, and at  
 6 the time and place set out on the Title page  
 7 hereof by me after first being duly sworn to  
 8 testify the truth, the whole truth, and nothing  
 9 but the truth; and that the said matter was  
 10 recorded stenographically and mechanically by me  
 11 and then reduced to typewritten form under my  
 12 direction, and constitutes a true record of the  
 13 transcript as taken, all to the best of my skill  
 14 and ability.  
 15 I further certify that the inspection,  
 16 reading and signing of said deposition were waived  
 17 by counsel for the respective parties and by the  
 18 witness.  
 19 I certify that I am not a relative or  
 20 employee of either counsel, and that I am in no  
 21 way interested financially, directly or  
 22 indirectly, in this action.  
 23  
 24 MARK REIF, COURT REPORTER / NOTARY  
 SUBMITTED ON  
 25 October 11, 2007



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